THE MARFAN FOUNDATION

The Marfan Foundation Presents

SCIENCE in SPAIN

October 4-7, 2026

Meliá Barcelona Sarrià Hotel, Spain

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GENERAL INFORMATION

Hotel Address and Airport Logistics: Meliá Barcelona Sarrià, Avinguda de Sarrià, 50 Barcelona The distance from Barcelona Airport (Barcelona-El Prat, BCN) to the Meliá Sarrià Barcelona hotel is approximately 16 km (9.3 miles). Taxis and Uber are readily available at the airport and are a convenient option, costing around €30-35 for the journey. While not as direct, the train and airport shuttles are also available.

Networking Dinner: Join colleagues for dinner and an evening of connection and collaboration on October 5, 2026, at El Xalet de Montjuïc. This event is open to all meeting attendees and their guests. Advance ticket purchase is required.

Speaker Presentation: Presentation timers will be used. All speakers will be required to load their presentations onto a single computer between 7:00 and 7:45 AM or during the breaks. Please bring your presentation on a USB. International Symposium presentations are to be 8 minutes in length, followed by a 7-minute Q&A. Genetic Aortic Network and ESC Aorta and Peripheral Artery Working Group presentations are to be 10 minutes in length, followed by a 10-minute group discussion after several presentations.

Poster Presentation Instructions: A poster presentation session is planned for October 4-6, 2026 and will take place in Barcelona A/B rooms. Posters have been assigned a number and a poster presentation session. This information can be found on the Poster Presentation List included in this booklet. Place your poster on the appropriate numbered board prior to the start of the session. Please remove your board after the poster session ends.

WELCOME

Welcome to **Science in Spain 2026**. This year's meeting marks an exciting milestone as we bring together the **12th International Symposium on Marfan, Loeys-Dietz, Vascular Ehlers-Danlos and Related Conditions,** our **Genetic Aortic Network (GAN) division,** and, for the first time, the **European Society of Cardiology (ESC) Working Group on Aorta and Peripheral Vascular Diseases.**

Throughout its history, the Marfan Foundation has believed that scientific progress is accelerated when experts from around the world come together to share ideas, challenge assumptions, and build lasting collaborations. Many of tomorrow's breakthroughs will begin with the discussions that take place during this meeting.

This gathering reflects the extraordinary progress our field has made through collaboration. By uniting the world's leading scientists, physicians, surgeons, geneticists, and allied health professionals, we are creating an unparalleled forum to advance research, improve clinical care, and accelerate discoveries. Your dedication continues to redefine what is possible in genetic aortic medicine. Your research, innovation, and commitment to excellence are driving meaningful advances in diagnosis, treatment, and patient outcomes.

This year's scientific program highlights the remarkable breadth of our field—from fundamental discoveries in disease mechanisms to emerging therapeutic strategies, genomic editing technologies, artificial intelligence, emergency cardiovascular care, and advances in imaging, surgery, and patient-centered care.

Dedicated sessions on Vascular Ehlers-Danlos syndrome, maternal health, pediatric management, and international research collaborations reflect both the complexity of these conditions and the multidisciplinary approach required to improve lives.

We extend our sincere gratitude to our meeting chairs, planning committee, moderators, speakers, and abstract presenters for creating such an outstanding program. We are also deeply grateful to our sponsors, **DEFY Foundation** and **W. L. Gore & Associates,** and to our valued partner, **Annabelle's Challenge**, whose commitment to research and education helps make this meeting possible.

We hope this week inspires new collaborations, bold ideas, and discoveries that will ultimately improve the lives of genetic aortic and vascular condition community members around the world.

Josephine Grima, PhD
Chief Science Officer

Michael Weamer
President & CEO

The Marfan Foundation

Lauren May, MPH
Senior Vice President of Research

Bert Medina
Chair, Board of Directors

SCIENCE IN SPAIN HOSTS

Arturo Evanglelista, MD, PhD

Gisela Teixidó Turà, MD, PhD, Hospital Vall d'Hebron

PLANNING COMMITTEES

12th International Symposium on Marfan, LDS, and VEDS and Related Conditions

- **Peter Byers**, MD, University of Washington (Co-Chair)
- **Bart Loeys**, MD, PhD, University of Antwerp (Co-Chair)
- **Hal Dietz**, MD, Johns Hopkins University (Co-Chair)
- **Catherine Boileau**, PharmD, PhD, Hôpital Bichat
- **Gustavo Egea**, PhD, University of Barcelona
- **Arturo Evanglelista**, MD, PhD, Hospital Vall d'Hebron
- **Alberto Forteza**, MD, Quirónsalud Madrid Hospital and the La Luz University Hospital
- **Jared Griffin**, Annabelle's Challenge
- **Josephine Grima**, PhD, The Marfan Foundation
- **Xavier Jeunemaitre**, MD, PhD, Centre de Recherche Hôpital European Georges-Pompidou
- **Marlies Kempers**, MD, PhD, Radboud University Nijmegen Medical Centre
- **Mark Lindsay**, MD, PhD, Massachusetts General Hospital
- **Lauren May**, MPH, The Marfan Foundation
- **Gretchen MacCarrick**, MS, CGC, Johns Hopkins University
- **Gisela Teixidó Turà**, MD, PhD, Hospital Vall d'Hebron
- **Lynn Sakai**, PhD, Oregon Health & Science University
- **Fleur S. van Dijk**, MD, PhD, London Northwest University Healthcare
- **Tony Yasick**, MD, DEFY Foundation
- **Maya Brown Zimmerman**, MPH, CGC, Norton Healthcare

Genetic Aortic Network & ESC Aorta and Peripheral Vascular Working Group Meeting

- **Julie De Backer,** MD, PhD, Ghent University (Co-Chair)
- **Shaine Morris**, MD, MPH, Texas Children's Hospital (Co-Chair)
- **Kim Eagle**, MD, University of Michigan (Co-Chair)
- **Alan Braverman**, MD, Washington University
- **Arturo Evanglelista**, MD, PhD, Hospital Vall d'Hebron
- **Josephine Grima**, PhD, The Marfan Foundation
- **Marion Hofmann Bowman**, MD, University of Michigan
- **Kathryn Holmes**, MD, MPH, Oregon Health & Science University
- **Guillaume Jondeau**, MD, PhD, Hôpital Bichat
- **Lauren May**, MPH, The Marfan Foundation
- **Dianna Milewicz**, MD, PhD, University of Texas at Houston
- **Sherene Shalhub**, MD, MPH, Oregon Health & Science University
- **Gisela Teixidó Turà**, MD, PhD, Hospital Vall d'Hebron
- **José F. Rodríguez Palomares**, MD, PhD, Hospital Vall d'Hebron

CELEBRATING EXCELLENCE

in Aortic and Cardiovascular Science

Throughout our four-day meeting, we are honored to recognize four individuals whose leadership, dedication, and contributions have advanced cardiovascular and aortic science and strengthened our global community.

Charging Forward Together Award

Jared Griffin

Annabelle's Challenge

Global Vision Award for Cardiovascular Science and Medicine

Valentin Fuster, MD, PhD

The Mount Sinai Hospital

Lifetime Achievement Award in Aortic Medicine

Arturo Evangelista, MD, PhD

Hospital Vall d'Hebron

The Distinguished Contribution to Aortic Science Award

John Elefteriades, MD

Yale University

SCHOLARSHIPS AWARDS

We are happy to announce the top-ranked abstracts for scholarship awards. Congratulations!

Iván Alcaron-Ruiz – Centro de Biología Molecular Severo Ochoa (CBM-CSIC)
Targeting Fibronectin Accumulation Reverses Marfan Syndrome-Related Aortic Disease in Mice

Apoorva Bhandari – Oregon Health & Science University
Dermal Extracellular Matrix Abnormalities Reflect Genotype-Associated Substrate Vulnerability in Vascular Ehlers-Danlos Syndrome

Emily Bramel – The Broad Institute of MIT and Harvard
High-Throughput Functional Profiling of Arterial Fragility Genes Reveals Shared Mechanisms of Extracellular Matrix Dysfunction and Vascular Instability

Lucia Buccioli – University of Antwerp
Striking Phenotypical Difference Between Ipo8 Knock-Out Mouse Models on Different Genetic Backgrounds Explored by RNA-Sequencing

Ernesto Calderon Martinez – The University of Texas Health Science Center at Houston
Gene and Sex-Specific Risk for First Aortic Events in Heritable Thoracic Aortic Disease: Insights from the Montalcino Aortic Consortium (MAC)

Luna Chetrit – Université Paris Cité, Inserm
TREM-1 Aggravates Marfan Syndrome Aortopathy

Maarten Dhaese – Ghent University
Unmasking Immune Cells in Marfan Syndrome: The Hidden Culprits Behind Aortic Disease?

Simon D'hulst – Ghent University Hospital
Myocardial Recovery After Mitral Valve Surgery in Children with Marfan Syndrome: A Multicentre European Study

Axel Hernandez-Pineda – Vall d'Hebron University Hospital
Do Echocardiographic Thresholds Underestimate True Aortic Size? A Multimodality Analysis

Andrew Huang – University of Michigan
The Impact of Time Spent Normotensive on Surgically Managed Aortic Dissection Outcomes

Yogesh Karnam – Vall d'Hebron University Hospital
Quantitative 3D Aortic Shape Analysis Detects Heritable Thoracic Aortic Disease in Non-Dilated Aortas

Peter Lauffer – Amsterdam UMC
Further Delineation of the Vascular and Connective Tissue Phenotype of the LOX Gene and Screening Recommendations

Tiffany Lian – Oregon Health & Science University
Sex Differences in Aortopathy, Arteriopathy, and Mortality in Vascular Ehlers-Danlos Syndrome

Gerard Merino – Universitat de Barcelona
Multi-Targeted Oxidative Stress Pathways as a Complementary Strategy to Current Medical Treatment Against Aortopathy Progression in Marfan Syndrome

Ester Galiana – Vall d'Hebron Hospital, Catalunya, Spain; Institute of Sports Medicine and Science, CONI, Rome
Cardiac Magnetic Resonance Assessment of Marfan Patients Undergoing a Supervised Exercise Program: Insights into Myocardial Strain and Intraventricular Flow Dynamics

Gian Luca Ragazoni – Great Ormond Street Hospital
Mitral Annular Disjunction and Aortic Phenotype in Adults with Marfan Syndrome

Bita Salamat – Baylor College of Medicine / Texas Children's Hospital
Longitudinal Aortic Root Growth and Outcomes in Pediatric Marfan Syndrome Compared by Baseline Dilation Status: A Multicenter Study From CLARITY

Pepijn Saraber – The Cardiovascular Research Institute Maastricht (CARIM)
From Variant to Vessel: Patient-Specific VSMC Dysfunction Mirrors Aortopathy Severity

Emiel Van Wetter – Ghent University
Decoding Marfan Syndrome Cardiomyopathy Using Advanced Stem Cell-Derived Heart Models

Andrea Vosberg – Oregon Health and Science University
Impact of Attention Deficit Disorder (ADHD) Among Children with Marfan Syndrome: A Multicenter Study from CLARITY

PROGRAM

- **12th International Research Symposium**
  Sunday & Monday, October 4 & 5
- **Joint Session of the Genetic Aortic Network and the ESC Working Group on Aorta and Peripheral Vascular Diseases**
  Tuesday & Wednesday, October 6 & 7

PROGRAM 12th International Symposium on Marfan, Loeys-Dietz, Vascular Ehlers-Danlos and Related Syndromes (Day 1)

SUNDAY, OCTOBER 4 – Diamante AB/Ground Floor

15-minute slot = 8-minute presentation + 7-minute discussion

8:00 AM	**Welcome and Opening Remarks** *Josephine Grima; The Marfan Foundation; USA; Bart Loeys; University of Antwerp; Belgium; Arturo Evangelista and Gisela Teixidó Turà; Vall d'Hebron University Hospital; Spain*
SESSION #1: Basic & Translational Studies in Vascular Ehlers-Danlos Syndrome – Moderators: Xavier Jeunemaitre; University Paris Descartes; France and Elena MacFarlane; Johns Hopkins School of Medicine; USA	
8:15 AM	**Sex Differences in Aortopathy, Arteriopathy, and Mortality in Vascular Ehlers-Danlos Syndrome** *Tiffany Lian; Oregon Health & Science University; USA*
8:30 AM	**Femoral Artery Access for Endovascular Intervention in Vascular Ehlers-Danlos Syndrome: Outcomes, Complications, and Technical Considerations** *Tiffany Lian; Oregon Health & Science University; USA*
8:45 AM	**Beyond Collagen Deficiency: Genotype-Specific Extracellular Matrix Alterations in Vascular Ehlers-Danlos Syndrome** – *Apoorva Bhandari; Oregon Health & Science University; USA*
9:00 AM	**Ciprofloxacin Causes Lethal Arterial Complications in a Mouse Model of Vascular Ehlers-Danlos Syndrome** – *Scott LeMaire; Geisinger College of Health Sciences; USA*
9:15 AM	**Manufacturer-Specific Effects of Celiprolol in VEDS Mice: Implications for Clinical Translation** *Janine Meienberg; Swiss Foundation for People with Rare Diseases; Switzerland*
9:30 AM	**GLP-1 Analogue in Hereditable Aortopathy: Effects of Liraglutide on the Aortic Wall in a Murine Model of Vascular Ehlers-Danlos Syndrome** – *Máté Csonka; Semmelweis University; Hungary*
9:45 AM	**Intraluminal Pressure at Aortic Rupture in a Mouse Model of Vascular Ehlers-Danlos Syndrome** *Roland Stengl; Semmelweis University; Hungary*
10:00 AM	**Trainee Awards For Scientific Excellence in VEDS** – *Tony Yasick; DEFY Foundation*
10:05–10:30 AM	**BREAK**
SESSION #2: Mechanistic and Pathogenic Studies in Animal Models – Moderators: Bart Loeys; University of Antwerp; Belgium and Lynn Sakai; Oregon Health & Science University; USA	
10:30 AM	**Targeting Fibronectin Accumulation Reverses Marfan Syndrome-Related Aortic Disease in Mice** *Iván Alarcón Ruíz; Centro de Biología Molecular Severo Ochoa (CBM-CSIC); Spain*
10:45 AM	**TREM-1 Aggravates Marfan Syndrome Aortopathy** *Luna Chetrit; Université Paris Cité, Inserm, PARCC; France*
11:00 AM	**Perivascular Inflammation is Critically Involved in the Progression of Aortic Aneurysms Formation in Marfan Syndrome** *Hiroki Yagi; The University of Tokyo; Japan*

11:15 AM	**Chromatin and Transcriptional Profiling Reveal Senescence Pathways as Therapeutic Targets in Loeys-Dietz Syndrome** – *Elena MacFarlane; Johns Hopkins School of Medicine; USA*
11:30 AM	**Striking Phenotypical Difference Between *Ipo8* Knock-Out Mouse Models on Different Genetic Backgrounds Explored by RNA-Sequencing** – *Lucia Buccioli; University of Antwerp; Belgium*
11:45 PM	**Pain Hypersensitivity and Spinal Redox-Neuroinflammatory Signaling in *Fbn1*$^{C1041G/+}$ Mice** *Francesc Jiménez-Altayó; Autonomous University of Barcelona; Spain*
SESSION #3: Pharmacological and Therapeutic Intervention Strategies – Moderators: Gustavo Egea; University of Barcelona; Spain and Arturo Evangelista; Vall d'Hebron University Hospital; Spain	
12:00 PM	**Key Signaling Events Linking Extracellular Matrix to Aortic Disease in Marfan Syndrome** *Miguel R. Campanero; Centro de Biologia Molecular Severo Ochoa; Spain*
12:15 PM	**Multi-Targeted Oxidative Stress Pathways as a Complementary Strategy to Current Medical Treatment Against Aortopathy Progression in Marfan Syndrome** *Gerard Merino; Universitat de Barcelona; Spain*
12:30-2:00 PM	**LUNCH – Ona Restaurant and Diagonal Room**
02:00 PM	**Opposing Cardiovascular Phenotypes in Fibrillinopathies: A Platform for Drug Target Discovery in Marfan Syndrome** – *Eline Vanaken; University of Antwerp; Belgium*
2:15 PM	**Targeting Oxidative Stress with Allopurinol Attenuates Cardiovascular Remodeling in Marfan Syndrome** – *Rodrigo Barbosa de Souza; Faculdade Santa Marcelina; Brazil*
2:30 PM	**A Novel Transforming Growth Factor-β Vaccine for Aortic Aneurysm Formation in a Mouse Model of Marfan Syndrome** – *Shun Okamura; The University of Tokyo Hospital; Japan*
2:45 PM	**Mechanism-Based Approach in Designing Patient-Specific Combination Therapies for Nonsense Mutation Diseases** – *Yale E. Goldman; University of California, Davis; USA*
SESSION #4: Biomarkers, Modifiers and iPSC Studies – Moderator: Catherine Boileau; Paris Cité University; France	
3:00 PM	**KLF15, a Protective Factor for Thoracic Aortic Aneurysm in Marfan Syndrome** *Bart Loeys; University of Antwerp; Belgium*
3:15 PM	**Decoding Marfan Syndrome Cardiomyopathy Using Advanced Stem Cell-Derived Heart Models** *Emiel Van Wetter; Ghent University; Belgium*
3:30 PM	**Marfan IPSC- Vascular Smooth Muscle Cells (VSMCs) Model Aortic Aneurysm by Recapitulating Their Pathogenic Phenotypic Switching Events Enabling Target Identification to Curb Chondrogenesis in Marfan Aortas** – *Deeti Shetty; University of Cambridge; United Kingdom*
POSTER SESSION	
3:45-5:45 PM	**Room: Barcelona A&B - Ground Floor**

MONDAY, OCTOBER 5 – Diamante AB/Ground Floor

15-minute slot = 8-minute presentation + 7-minute discussion

SESSION #5: Imaging, Diagnostics and AI Tools – Moderators: Gisela Teixidó Turà; Vall d'Hebron University Hospital; Spain and Siddharth Prakash; The University of Texas Health Science Center at Houston; USA	
8:00 AM	**Development of an AI-Powered Mobile Application for Point-of-Care Facial Phenotyping in Heritable Thoracic Aortic Disease** *David Murdock; The University of Texas Health Science Center at Houston; USA*
8:15 AM	**Quantitative 3D Aortic Shape Analysis Detects Heritable Thoracic Aortic Disease in Non-Dilated Aortas** *Yogesh Karnam; University of Wisconsin-Madison; USA*
8:30 AM	**Discriminative Value of Cardiovascular Magnetic Resonance-Derived Pulse Wave Velocity for Aortic Dissection in Marfan Syndrome** *Simon D'hulst; Ghent University Hospital; Belgium*
8:45 AM	**Nanoparticle Contrast-Enhanced Computed Tomography of Aortopathy and Cardiac Abnormalities in a Mouse Model of Marfan Syndrome** *Ketan Ghaghada; Texas Children's Hospital / Baylor College of Medicine; USA*
9:00 AM	**3D Facial Image-Based Morphometric Phenotyping for Diagnosis and Risk Stratification in Heritable Thoracic Aortopathies** *Benedikt Hallgrimsson; University of Calgary; Canada*
SESSION #6: Genetic Determinants of Disease Variability – Moderators: Marlies Kempers; Radboud University; the Netherlands and Julie De Backer; Ghent Unversity; Belgium	
9:15 AM	**From Variant to Vessel: Patient-Specific VSMC Dysfunction Mirrors Aortopathy Severity** *Pepjin Saraber; Maastricht University; the Netherlands*
9:30 AM	**Gene and Sex-Specific Risk for First Aortic Events in Heritable Thoracic Aortic Disease: Insights from the Montalcino Aortic Consortium (MAC)** *Ernesto Calderon Martinez; The University of Texas Health Science Center at Houston; USA*
9:45 AM	**High-Throughput Functional Profiling of Arterial Fragility Genes Reveals Shared Mechanisms of Extracellular Matrix Dysfunction and Vascular Instability** *Emily Bramel; The Broad Institute of MIT and Harvard; USA*
10:00 AM	**SMAD4 Gain-of-Function Disrupts TGF-β and Flow Sensing Pathways in Aortic Hypoplasia** *Emily Bramel; The Broad Institute of MIT and Harvard; USA*
10:15–10:45 AM	**BREAK**
SESSION #7: Patient Experiences, Quality of Life, and Patient-Centered Care – Moderators: Mary Sheppard; University of Kentucky; USA and Gretchen MacCarrick; Johns Hopkins University; USA	
10:45 AM	**Impact of Attention Deficit Disorder (ADHD) Among Children with Marfan Syndrome: A Multicenter Study from CLARITY** *Andrea Vosberg; Oregon Health & Science University; USA*

11:00 AM	**Employment Status and Socioeconomic Deprivation Among Adults with Marfan Syndrome is Related to Aortic Dissection but Not with Preventive Aortic Surgery** *Olivier Milleron; Hôpital Bichat; France*
11:15 AM	**None of Our Doctors Know About This: Stakeholder Perspectives on the Gaps Between Clinical Recommendations and Real-World Care in Heritable Connective Tissue Disorders** *Catherine Isadora Côté; Université de Montréal; Canada*
SESSION #8: Phenotypic Studies and Outcomes – Moderators: Fleur S. van Dijk; Royal Brompton & Harefield NHS Foundation Trust; United Kingdom and Shaine Morris; Texas Children's Hospital; USA	
11:30 AM	**Longitudinal Aortic Growth in Individuals with Filamin A Deficiency** *Christopher Spence; Texas Children's Hospital / Baylor College of Medicine; USA*
11:45 AM	**Myocardial Recovery after Mitral Valve Surgery in Children with Marfan Syndrome: A Multicentre European Study** – *Simon D'hulst; Ghent University Hospital; Belgium*
12:00 PM	**Aortic Events After Proximal Thoracic Aortic Repair in Heritable Thoracic Aortic Disease: Insights from the Montalcino Aortic Consortium** *Ernesto Calderon Martinez; The University of Texas Health Science Center at Houston; USA*
12:15 PM	**Longitudinal Aortic Root Growth and Outcomes in Pediatric Marfan Syndrome Compared by Baseline Dilation Status: A Multicenter Study From CLARITY** *Bita Salamat; Texas Children's Hospital; USA*
12:30-2:00 PM	**LUNCH – Ona Restaurant and Diagonal Room**
SESSION #9: Genotype-Phenotype Correlations – Moderators: Kathryn Holmes; Oregon Health & Science University; USA and Dianna Milewicz; The University of Texas Health Science Center at Houston; USA	
2:00 PM	**Loss-of-Function Variants in ADAMTS6: A Novel Syndrome with Heart Defect, Thoracic Aortic Aneurysm and Neurodevelopmental Features** – *Carine Le Goff; Inserm; France*
2:15 PM	**Beyond Aortic Disease: Preliminary Evidence of Myocardial Dysfunction and Arrhythmias in Pediatric HTAD** – *Simon D'hulst; Ghent University Hospital; Belgium*
2:30 PM	**Gene-Specific Enrichment of Bicuspid Aortic Valve in Heritable Thoracic Aortic Disease: Insights from the Montalcino Aortic Consortium** *Siddharth Prakash; The University of Texas Health Science Center at Houston; USA*
SPECIAL SESSION: Valentin Fuster; The Mount Sinai Hospital; General Director of Spain's National Center for Cardiovascular Research – Moderator: Arturo Evangelista; Vall d'Hebron University Hospital; Spain	
2:45 PM	**The Heart, the Aorta and the Brain: Role of Imaging as Evolving Prevention Approaches**
3:15 PM	**Summary and Conclusion** – *Bart Loeys; University of Antwerp; Belgium*
POSTER SESSION	
3:30-5:30 PM	**Room: Barcelona A&B - Ground Floor**

TUESDAY, OCTOBER 6 – Diamante AB/Ground Floor

8:00 AM	**Welcome and Introduction** – *Josephine Grima; The Marfan Foundation; USA; Alan Braverman; Washington University in St. Louis School of Medicine; USA; Jose Fernando Rodriguez Palomares; Vall d'Hebron University Hospital; Spain*
8:10 AM	**KEYNOTE: Genomic Editing for Genetically-Triggered Arteriopathies** *Mark Lindsay; Massachusetts General Hospital; USA*
8:20 AM	**Discussion**
SESSION #1: Acute Aortic Syndrome Management – Moderators: Julie De Backer; Ghent University Hospital; Belgium and Jose Fernando Rodriguez Palomares; Vall d'Hebron University Hospital; Spain	
8:30 AM	**DEBATE: Ascending Aortic Dilatation Management - ESC Position** *Alessandro Della Corte; University of Campania "L. Vanvitelli"; Italy*
8:40 AM	**DEBATE: Ascending Aortic Dilatation Management - AHA Position** *Elaine Tseng; University of California San Francisco; USA*
8:50 AM	**Discussion**
9:00 AM	**TEVAR Before Discharge in Uncomplicated Descending Aorta Dissection** *Arturo Evangelista; Vall d'Hebron University Hospital; Spain*
9:10 AM	**Risk and Outcomes of Type B Dissection in Marfan Syndrome** *Nupoor Narula; Weill Cornell Medicine; USA*
9:20 AM	**The Impact of Time Spent Normotensive on Surgically Managed Aortic Dissection Outcomes** *Andrew Huang; University of Michigan; USA*
9:30 AM	**30 Years of Patient Care and Management** *Guillaume Jondeau; Hôpital Bichat-Claude Bernard; France*
9:40 AM	**Discussion**
9:50 AM	**Break**
SESSION #2: Maternal and Aortic Health: Insights into Pregnancy in HTAD Moderators: Alan Braverman; Washington University in St. Louis School of Medicine; USA and Mary Roman; Weill Cornell Medicine; USA	
10:10 AM	**The Pregnancy Roadmap with Aortopathy and the Unmapped Territories Between: Comparison of ESC and ACC/AHA Guidelines - ESC Position** *Julie De Backer; Ghent University Hospital; Belgium*

10:20 AM	**The Pregnancy Roadmap with Aortopathy and the Unmapped Territories Between: Comparison of ESC and ACC/AHA Guidelines - ACC/AHA Position** *Melissa Russo; Brown University; USA*
10:30 AM	**Discussion**
10:40 AM	**Registry of Pregnancy and Cardiac Disease III (ROPAC III) Update** *Julie De Backer; Ghent University Hospital; Belgium*
10:50 AM	**Contraceptive Practices and Patterns: A Comparison between Aortopathy and Congenital Heart Disease Individuals** *Melissa Russo; Brown University; USA*
11:00 AM	**Reproductive Decision-Making in Marfan Syndrome: Our Center's Experience** *Miguel Del Campo; Vall d'Hebron University Hospital; Spain*
11:10 AM	**Discussion**
SESSION #3: Imaging and Engineering Frontiers – Moderators: Arturo Evangelista; Vall d'Hebron University Hospital; Spain and Gisela Teixidó Turà; Vall d'Hebron University Hospital; Spain	
11:20 AM	**How to Measure the Aortic Root Using Multimodality** *Jose Fernando Rodriquez-Palomares; Vall d'Hebron University Hospital; Spain*
11:30 AM	**New Tools to Improve Aorta Growth Rate Reproducibility** *Andrea Guala; Vall d'Hebron University Hospital; Spain*
11:40 AM	**Personalized 3D Aortic Z-Scores Identify Heritable Aortopathy from a Single CTA** *Carlos Alberto Campello Jorge; University of Wisconsin-Madison; USA*
11:50 AM	**Discussion**
12:00 PM	**Predicting Aortic Dissection Using Advanced Image Analysis** *Nick Burris; University of Wisconsin-Madison; USA*
12:10 PM	**Descending Aortic Distensibility Is Not Associated with Development of Type B Dissection in Marfan Syndrome** *Nick Burris; University of Wisconsin-Madison; USA*
12:20 PM	**Discussion**
12:30 PM	**Publications & Career Reflections** *Arturo Evangelista; Vall d'Hebron University Hospital; Spain*
12:40-2:00 PM	**LUNCH – Ona Restaurant and Diagonal Room**

SESSION #4: Emergency and Critical Care Management of Acute Aortic Syndrome Moderators: Marion Hofmann Bowman and Rob Pena; University of Michigan; USA	
2:00 PM	**A Tale of Two Patients: Difficulties in Diagnosing AAS in the Emergency Department** *Marion Hofmann Bowman; University of Michigan; USA*
2:05 PM	**Ruling Out AAS in the Emergency Department (ADvISED and AORTAs Algorithms)** *Robert Pena; University of Michigan; USA*
2:15 PM	**Physician Clinical Practices in Evaluating Suspected AAS in the Emergency Department** *Colin Greineder; University of Michigan; USA*
2:25 PM	**Emergency Department Care for vEDS Patients** *Sherene Shalhub; Oregon Health and Science University; USA*
2:35 PM	**Future Directions: Biomarkers for Risk-Stratifying Medically-Managed Type B Aortic Dissections in the ICU** – *Robert Pena; University of Michigan; USA*
2:40 PM	**Discussion**
SESSION #5: AI Applications: From Genes to Populations – Moderators: Siddharth Prakash; University of Texas Health Science Center at Houston and Guillaume Jondeau; Hôpital Bichat-Claude Bernard; France	
2:50 PM	**Linking Genetics and AI-derived Aortic Phenotypes from Clinical Imaging** *Tooraj Mirshahi; Geisinger Health; USA*
3:00 PM	**Creation of Aortic Digital Twin Technology for Prognosis in Loeys-Dietz Syndrome** *Bharath Ambale Venkatesh; Johns Hopkins Medicine; USA*
3:10 PM	**AI-Driven Facial Recognition of HTAD Cases** *David Murdock; The University of Texas Health Science Center at Houston; USA*
3:20 PM	**AortaGPT: An AI-Enabled Clinical Decision Support Platform for Heritable Thoracic Aortic Diseases** *Siddharth Prakash; The University of Texas Health Science Center at Houston; USA*
3:30 PM	**Discussion**
POSTER SESSION	
3:45- 5:45 PM	**Room: Barcelona A&B - Ground Floor**

PROGRAM

Joint Session of the Genetic Aortic Network and the ESC Working Group on Aorta and Peripheral Vascular Diseases (Day 2)

WEDNESDAY, OCTOBER 7 – Diamante AB/Ground Floor

8:00 AM	**Marfan Foundation Partnerships** *Josephine Grima; The Marfan Foundation; USA*
8:05 AM	**Patient to Physician Perspective on Living with an Aortopathy** *Geoff Lester; Monash University; Australia*
SESSION #6: Insights from Registries: Research To Improve Clinical Outcomes – Moderators: Dianna Milewicz; The University of Texas Health Science Center at Houston; USA and Shaine Morris; Texas Children's Hospital; USA	
8:10 AM	**Modeling of Timing of Aortic Replacement (CLARITY)** *Shaine Morris; Texas Children's Hospital; USA*
8:20 AM	**Prevalence of Developmental and Psychological Concerns Among Children with Aortopathy (CLARITY)** – *Kathryn Holmes; Oregon Health & Science University; USA*
8:30 AM	**Previously Unrecognized Syndromic Aortopathies Identified by Postmortem Whole Genome Sequencing in Fatal Aortic Dissection** *Ellen Hostetler; The John Ritter Foundation for Aortic Health; USA*
8:40 AM	**Discussion**
8:50 AM	**Gene-Based Management for Heritable Thoracic Aortic Disease: Translation to Physicians and Patients (MAC)** – *Siddharth Prakash; The University of Texas Health Science Center at Houston; USA*
9:00 AM	**Risk Score for Thoracic Aortic Disease: Genetic Modifier of Aortic Outcomes in Heritable Thoracic Aortic Disease (MAC)** *Dianna Milewicz; The University of Texas Health Science Center at Houston; USA*
9:10 AM	**Genetic Determinants of Aortic Complications After Elective Proximal Aneurysm Repair: Insights from the Montalcino Aortic Consortium (MAC)** *Ernesto Caldron Martinez; The University of Texas Health Science Center at Houston; USA*
9:20 AM	**Discussion**
9:30 AM	**SMAD3 Dataset of 200+ Participants** *Anji Yetman; University of Nebraska; USA*
9:40 AM	**Insights from the Spanish Network on Genetic Aortic Disease (REPAG): Advancing Aortic Risk Prediction and Sex-Specific Prognosis** – *Gisela Teixidó-Turà; Vall d'Hebron University Hospital; Spain*
9:50 AM	**Thoracic Aortic Disease with Bicuspid Aortic Valve: Limited Contribution of Genetic Testing** *Pauline Arnaud; Hôpital Bichat; France*
10:00 AM	**Discussion**
10:10 AM	**BREAK**

SESSION #7: Modern Surgical Strategies Across the Aortic Arch and Thoracoabdominal Aorta Moderators: John Elefteriades; Yale University; USA and Bo Yang; University of Michigan; USA	
10:30 AM	**Bicuspid Aortic Valve Surgery in Women** *Bo Yang; University of Michigan; USA*
10:40 AM	**What Every Surgeon Should Know about Vascular Ehlers Danlos Syndrome** *Sherene Shalhub; Oregon Health & Science University; USA*
10:50 AM	**Surgical Advances in Endo-Bentall Procedure** *Mehrdad Ghoreishi; Johns Hopkins University; USA*
11:00 AM	**Discussion**
11:10 AM	**Open Aortic Arch Surgery: Current Surgical Strategies** *Maral Ouzounian; University of Toronto; Canada*
11:20 AM	**Modern Surgical Strategies Across the Aortic Arch and Thoracoabdominal Aorta** *Sherene Shalhub; Oregon Health & Science University; USA*
11:30 AM	**Thoracoabdominal Aortic Repair: Technical Nuances & Outcomes** *Rafael Rodriquez Lecoq; Vall d'Hebron University Hospital; Spain*
11:40 AM	**Discussion**
SESSION #8: Thrivorship: Incorporating Exercise and Improving Mental Health Moderator: Mary Sheppard; University of Kentucky; USA	
11:50 AM	**Home-based Exercise after Aortic Dissection: Lessons Learned From a Pragmatic Randomized Trial** – *Siddharth Prakash; The University of Texas Health Science Center at Houston; USA*
12:00 PM	**The Aorta in Athletes** *Alan Braverman; Washington University in St. Louis School of Medicine; USA*
12:10 PM	**From Tragedy to Prevention: Caring for the Family After Post-Mortem Aortic Dissection Diagnosis** *Rajani Aatre; University of Michigan; USA*
12:20 PM	**Discussion**
12:30 PM	**LUNCH – Ona Restaurant and Diagonal Room**

SESSION #9: Pediatric Aortopathy Management – Moderators: Shaine Morris; Texas Children's Hospital; USA and Kathy Holmes; Oregon Health & Science University; USA

2:00 PM	**Pediatric Transition in Aortopathy** *Mary Sheppard; University of Kentucky; USA*
2:10 PM	**Exercise Considerations and Limitations: Parent Experience with Schools** *Kathryn Holmes; Oregon Health & Science University; USA*
2:20 PM	**Prophylactic Irbesartan Therapy in Young Patients with Bicuspid Aortopathy: Aortic Growth Rates from a New England Collaborative Registry** *Jonathan Flyer; University of Vermont; USA*
2:30 PM	**Challenges in Medical Therapy for Pediatric Aortopathies: What is the Current Evidence and How Do We Gather More Evidence?** *Ron Lacro; Boston Children's Hospital; USA*
2:40 PM	**Cardiovascular Outcomes and Survival in Patients with Neonatal Marfan Syndrome** *Christopher Spence; Texas Children's Hospital / Baylor College of Medicine; USA*
2:50 PM	**Discussion**
3:00 PM	**Summary and Conclusion** *Alan Braverman; Washington University in St. Louis; USA*

POSTER
PRESENTATION LIST

A select number of abstract submissions were chosen for oral presentations and the date is noted on the following list.

- Posters 1-50B are presented on October 4
- Posters 51-100 are presented on October 5
- Posters 101-145 are presented on October 6

POSTER PRESENTATION LIST

SUNDAY, OCTOBER 4

Poster	Author	Title & Session Topic	Oral Presentation
P1	Lian	**Sex Differences in Aortopathy, Arteriopathy, and Mortality in Vascular Ehlers-Danlos Syndrome** *Basic & Translational Studies in* VEDS	October 4
P2	Lian	**Femoral Artery Access for Endovascular Intervention in Vascular Ehlers-Danlos Syndrome: Outcomes, Complications, and Technical Considerations** *Basic & Translational Studies in* VEDS	October 4
P3	Bhandari	**Beyond Collagen Deficiency: Genotype-Specific Extracellular Matrix Remodeling in Vascular Ehlers-Danlos Syndrome Combined** *Basic & Translational Studies in* VEDS	October 4
P4	Bhandari	**Dermal Extracellular Matrix Abnormalities Reflect Genotype-Associated Substrate Vulnerability in Vascular Ehlers-Danlos Syndrome** *Basic & Translational Studies in* VEDS	—
P5	Boerio	**Barriers in Vascular Ehlers-Danlos Syndrome Care: Characterizing the Interface Between Patient and Providers Through a Cross-Sectional Survey** *Basic & Translational Studies in* VEDS	—
P6	LeMaire	**Ciprofloxacin Causes Lethal Arterial Complications in a Mouse Model of Vascular Ehlers-Danlos Syndrome** *Basic & Translational Studies in* VEDS	October 4
6A	Wilkinson	***COL3A1* Haploinsufficiency: An Evaluation of Disease Course Severity in a UK Vascular Ehlers-Danlos Syndrome Cohort** *Basic & Translational Studies in* VEDS	—
P7	Meienberg	**Manufacturer-Specific Effects of Celiprolol in VEDS Mice: Implications for Clinical Translation** *Basic & Translational Studies in* VEDS	October 4
P8	Meienberg	**Rupture Sensitivity, Pharmacogenetic Profiling and Co-Occurrence of Hereditaryaortopathies** *Mechanistic and Pathogenic Studies in Animal Models*	—
P9	Meienberg	**Losartan in MFS Mice: Reduction of Aortic Dilatation but No Improvement in Aortic Rupture Force** *Pharmacological and Therapeutic Intervention Strategies*	—
P10	Csonka	**GLP-1 Analogue in Hereditable Aortopathy: Effects of Liraglutide on the Aortic Wall in a Murine Model of Vascular Ehlers-Danlos Syndrome** *Basic & Translational Studies in* VEDS	October 4

POSTER PRESENTATION LIST

SUNDAY, OCTOBER 4 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P11	Stengl	**Intraluminal Pressure at Aortic Rupture in a Mouse Model of Vascular Ehlers-Danlos Syndrome** *Basic & Translational Studies in* VEDS	October 4
P12	Campanero	**Key Signaling Events Linking Extracellular Matrix to Aortic Disease in Marfan Syndrome** *Mechanistic and Pathogenic Studies in Animal Models*	October 4
P13	Chetrit	**TREM-1 Aggravates Marfan Syndrome Aortopathy** *Mechanistic and Pathogenic Studies in Animal Models*	October 4
P14	MacFarlane	**Chromatin and Transcriptional Profiling Reveal Senescence Pathways as Therapeutic Targets in Loeys-Dietz Syndrome** *Mechanistic and Pathogenic Studies in Animal Models*	October 4
P15	Yagi	**Perivascular Inflammation is Critically Involved in the Progression of Aortic Aneurysms Formation in Marfan Syndrome** *Mechanistic and Pathogenic Studies in Animal Models*	October 4
P16	Yagi	**Inverse Agonist Activity of Angiotensin II Receptor Blocker is Crucial for Prevention of Aortic Aneurysm Progression in Mice Model of Marfan Syndrome** *Pharmacological and Therapeutic Intervention Strategies*	—
P17	Restrepo	**The Long Noncoding RNA *Meg3* Contributes to Maladaptive VSMC Remodeling in Marfan Syndrome Aortopathy** *Mechanistic and Pathogenic Studies in Animal Models*	—
P18	Yanagisawa	**Dynamic Endothelial Phenotypic Switching During Intimomedial Tear Formation in Fbn1$^{G234D/G234D}$ Aorta** *Mechanistic and Pathogenic Studies in Animal Models*	—
P19	Buccioli	**Striking Phenotypical Difference Between *Ipo8* Knock-Out Mouse Models on Different Genetic Backgrounds Explored by RNA-Sequencing** *Mechanistic and Pathogenic Studies in Animal Models*	October 4
P20	Buccioli	**Development of an IPSC-Derived Vascular Smooth Muscle Cell Model for TGFB3-Loeys-Dietz Syndrome (Type V) Aortopathy** *Mechanistic and Pathogenic Studies in Animal Models*	—
P21	Jimenez-Altayo	**Pain Hypersensitivity and Spinal Redox-Neuroinflammatory Signaling in *Fbn1*$^{C1041G/+}$ Mice** *Mechanistic and Pathogenic Studies in Animal Models*	October 4

POSTER PRESENTATION LIST

SUNDAY, OCTOBER 4 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P22	Jimenez-Altayo	**Perivascular Adipose Tissue Imposes a Sex- and Region-Specific Redox Brake on Aortic Contractility in Marfan Syndrome** *Mechanistic and Pathogenic Studies in Animal Models*	—
P23	Dhaese	**Unmasking Immune Cells in Marfan Syndrome: The Hidden Culprits Behind Aortic Disease?** *Mechanistic and Pathogenic Studies in Animal Models*	—
P24	Mougin	**Activation of YAP or Rho/ROCK in WT SMCs Triggers the Same Phenotypic Changes as Observed in *Acta2*$^{-/-}$ SMCs** *Mechanistic and Pathogenic Studies in Animal Models*	—
P25	Al-Rifai	**Monocyte/Macrophage Infiltration Promotes Marfan Aortopathy Through MMP12 Production** *Mechanistic and Pathogenic Studies in Animal Models*	—
P26	Cohen	**Involvement of *TNXB* in the Pathophysiology of MFS** *Mechanistic and Pathogenic Studies in Animal Models*	—
P27	Salmazo	**Elastic Fiber Remodeling and Limited Structural Recovery in the Lung of Fbn1$^{MG\Delta LPN/+}$ Mice** *Mechanistic and Pathogenic Studies in Animal Models*	—
P28	Verstraeten	**In Vivo Interrogation of the Contribution of *Igfbp2* Upregulation to Thoracic Aortic Aneurysm Development** *Mechanistic and Pathogenic Studies in Animal Models*	—
P29	Barnowski	**Different *Fbn1* Mutations Cause Distinct Pathomechanisms in Mouse Models of Marfan Syndrome** *Mechanistic and Pathogenic Studies in Animal Models*	—
P30	D'hulst	**Context Matters: Genetic Background Modulates Cardiovascular Phenotypes in Marfan Syndrome Mice** *Mechanistic and Pathogenic Studies in Animal Models*	—
P31	Reinhardt	**A Novel Dual Role of Fibrillin-1 in Adipose Tissue Early Development and Late Maintenance** *Mechanistic and Pathogenic Studies in Animal Models*	—
P32	Sheppard	**Mouse Models of Marfan Syndrome Demonstrate Hyperactivation of the Renin Angiotensin System** *Mechanistic and Pathogenic Studies in Animal Models*	—

POSTER PRESENTATION LIST

SUNDAY, OCTOBER 4 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P33	Hebert	**A Single Cell View of Aortic Wall Dysfunction in an AngII-Infusion Biglycan-Deficient Mouse Model** *Mechanistic and Pathogenic Studies in Animal Models*	—
P34	Marcos	**Role of Mitochondrial Supercomplexes in Marfan Syndrome's Pathology** *Mechanistic and Pathogenic Studies in Animal Models*	—
P35	Parker	**Loss of Endogenous Sex Hormones Alters Aneurysm Severity in Both Male and Female MFS Mice** *Mechanistic and Pathogenic Studies in Animal Models*	—
P36	Rochano Ortiz	**Lipotoxicity in Marfan Syndrome** *Mechanistic and Pathogenic Studies in Animal Models*	—
P37	Richard	**Mitochondrial Function in BAPN-Induced Aortopathy is Transiently Rescued by NAD+ Repletion** *Mechanistic and Pathogenic Studies in Animal Models*	—
P38	Egea	**Impact of the Maternal Environment on Cardiovascular Features of the Offspring in a Mouse Model of Marfan Syndrome** *Mechanistic and Pathogenic Studies in Animal Models*	—
P39	de Andrade	**Perlecan Defines Lung Phenotype Severity as a Modifier Gene in Marfan Syndrome** *Mechanistic and Pathogenic Studies in Animal Models*	—
P40	Valdivia Callejon	**Single-Cell RNA Sequencing Reveals Altered Aortic Cellular Composition and Fibroblast Activation with Maladaptive Remodelling in a Mouse Model of Ipo8-Related Thoracic Aortic Aneurysm** *Mechanistic and Pathogenic Studies in Animal Models*	—
P41	Tiedemann	**Fibrillin-1 Activity in the Bone Marrow of Long Bones** *Mechanistic and Pathogenic Studies in Animal Models*	—
P42	Alcaron-Ruiz	**Targeting Fibronectin Accumulation Reverses Marfan Syndrome-Related Aortic Disease in Mice** *Pharmacological and Therapeutic Intervention Strategies*	October 4
P43	Merino	**Multi-Targeted Oxidative Stress Pathways as a Complementary Strategy to Current Medical Treatment Against Aortopathy Progression in Marfan Syndrome** *Pharmacological and Therapeutic Intervention Strategies*	October 4

POSTER PRESENTATION LIST

SUNDAY, OCTOBER 4 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P44	Vanaken	**Opposing Cardiovascular Phenotypes in Fibrillinopathies: A Platform for Drug Target Discovery in Marfan Syndrome** *Pharmacological and Therapeutic Intervention Strategies*	October 4
P45	Barbosa de Souza	**Targeting Oxidative Stress with Allopurinol Attenuates Cardiovascular Remodeling in Marfan Syndrome** *Pharmacological and Therapeutic Intervention Strategies*	October 4
P46	Barbosa de Souza	**Ramipril Outperforms Losartan in Long-Term Rescue of Aortic and Skeletal Phenotypes in Marfan Syndrome** *Pharmacological and Therapeutic Intervention Strategies*	—
P47	Okamura	**A Novel Transforming Growth Factor-β Vaccine for Aortic Aneurysm Formation in a Mouse Model of Marfan Syndrome** *Pharmacological and Therapeutic Intervention Strategies*	October 4
P48	Rosen-blatt-Velin	[redacted]	—
P49	Sips	**A Novel Zebrafish Model of Marfan Syndrome Reveals Immune Involvement and Enables in *Vivo* Drug Screening** *Pharmacological and Therapeutic Intervention Strategies*	—
P50	Galán	**Targeting Mitochondrial and ER Stress as New Therapeutic Strategies to Halt Aortic Dilation in a Murine Model of Marfan Disease** *Pharmacological and Therapeutic Intervention Strategies*	—
P50A	Goldman	**Mechanism-Based Approach in Designing Patient-Specific Combination Therapies for Nonsense Mutation Diseases** *Pharmacological and Therapeutic Intervention Strategies*	October 4
P50B	Alder-weireldt	**GEMS-App: A Web-Based Dynamic Consent Platform Enabling Genome-Wide Epistasis Research in Marfan Syndrome** *Biomarkers, Modifiers and IPSC Studies*	—

MONDAY, OCTOBER 5

P51	Egea Guri	**Introducing Allopurinol to the Medical Treatment of Marfan Syndrome: Advantages, Limitations and Potential Extension to Other Aortopathies** *Pharmacological and Therapeutic Intervention Strategies*	—

POSTER PRESENTATION LIST

MONDAY, OCTOBER 5 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P52	Aizpuru-Gomez	**Allopurinol-Mediated Reduction of Oxidative Stress and Inflammasome Improves Cardiovascular Phenotype in a Williams-Beuren Syndrome Mouse Model.** *Pharmacological and Therapeutic Intervention Strategies*	—
P53	Chiu	**Impacts of Pharmacological Interventions on Aorta Change in Patients with Marfan Syndrome: A Network Synthesis** *Pharmacological and Therapeutic Intervention Strategies*	—
P54	Genot	**Fibrillin-1 Deficiency in Marfan Syndrome Disrupts Endothelial Cell Quiescence** *Pharmacological and Therapeutic Intervention Studies*	—
P55	de Waard	**The AMP-Kinase Activator AICAR Does Not Rescue Aortic Pathology in Two Aneurysm Models** *Pharmacological and Therapeutic Intervention Strategies*	—
P56	Kwak	**Longitudinal Changes in Aortic Root Dilation During GnRH Agonist Therapy in Pediatric Marfan Syndrome** *Pharmacological and Therapeutic Intervention Strategies*	—
P57	Loeys	**KLF15, a Protective Factor for Thoracic Aortic Aneurysm in Marfan Syndrome** *Biomarkers, Modifiers and IPSC Studies*	October 4
P58	Van Wetter	**Decoding Marfan Syndrome Cardiomyopathy Using Advanced Stem Cell-Derived Heart Models** *Biomarkers, Modifiers and IPSC Studies*	October 4
P59	Shetty	**Marfan IPSC- Vascular Smooth Muscle Cells (VSMCs) Model Aortic Aneurysm by Recapitulating Their Pathogenic Phenotypic Switching Events Enabling Target Identification to Curb Chondrogenesis in Marfan Aortas** *Biomarkers, Modifiers and IPSC Studies*	October 4
P60	Marcous	**Implication of Asprosin (Fibrillin-1-Derived Peptide) in Connective Tissue Disorders** *Biomarkers, Modifiers and IPSC Studies*	—
P61	Heymans	**Development of a CRISPRi-Based Functional Genomics Platform to Identify Molecular Modifiers of Marfan-Related Cardiomyopathy in HiPSC-Derived Cardiomyocytes** *Biomarkers, Modifiers and IPSC Studies*	—
P62	Lian	**Skin as a Window to the Artery: A Novel Pilot Study of Extracellular Matrix Concordance** *Biomarkers, Modifiers and IPSC Studies*	—

POSTER PRESENTATION LIST

MONDAY, OCTOBER 5 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P63	D'hulst	**The Role of Fibrillin Fragments in Marfan Aortopathy** *Biomarkers, Modifiers and IPSC Studies*	—
P64	D'hulst	**Discriminative Value of Cardiovascular Magnetic Resonance-Derived Pulse Wave Velocity for Aortic Dissection in Marfan Syndrome** *Imaging, Diagnostics, and AI Tools*	October 5
P65	Asadi	**Investigation of IGFBP2 Serum Levels as a Biomarker for Thoracic Aortic Aneurysm and Dissection** *Biomarkers, Modifiers and IPSC Studies*	—
P66	Fedorysh-chenko	**Generation and Functional Characterization of an IPSC-Derived Endothelial Cell Model for *Ipo8*-Related Syndromic Thoracic Aortic Aneurysm and Dissection** *Biomarkers, Modifiers and IPSC Studies*	—
P67	Karnam	**Quantitative 3D Aortic Shape Analysis Detects Heritable Thoracic Aortic Disease in Non-Dilated Aortas** *Imaging, Diagnostics, and AI Tools*	October 5
P68	Murdock	**Development of an AI-Powered Mobile Application for Point-of-Care Facial Phenotyping in Heritable Thoracic Aortic Disease** *Imaging, Diagnostics, and AI Tools*	October 5
P69	Ghaghada	**Nanoparticle Contrast-Enhanced Computed Tomography of Aortopathy and Cardiac Abnormalities in a Mouse Model of Marfan Syndrome** *Imaging, Diagnostics, and AI Tools*	October 5
P70	Hernandez-Pineda	**Do Echocardiographic Thresholds Underestimate True Aortic Size? A Multimodality Analysis** *Imaging, Diagnostics and AI Tools*	—
P71	Hernandez-Pineda	**Impact of Cusp-to-Cusp Measurement Convention Across Multimodality Imaging on Z-Score-Based Classification of Aortic Root Dilation** *Imaging, Diagnostics and AI Tools*	—
P72	Galiana	**Cardiac Magnetic Resonance Assessment of Marfan Patients Undergoing a Supervised Exercise Program: Insights Into Myocardial Strain and Intraventricular Flow Dynamics** *Imaging, Diagnostics, and AI Tools*	—
P73	Hallgrimsson	**3D Facial Image-Based Morphometric Phenotyping for Diagnosis and Risk Stratification in Heritable Thoracic Aortopathies** *Imaging, Diagnostics and AI Tools*	October 5

POSTER PRESENTATION LIST

MONDAY, OCTOBER 5 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P74	Cartier	**AORTA: A Digital Health Tool to Improve Equitable Access to Guideline-Based Aortic Care** *Imaging, Diagnostics, and AI Tools*	—
P75	Bennett	**Decreased Mass to Volume Ratio on Cardiac MRI in Marfan Syndrome** *Imaging, Diagnostics and AI Tools*	—
P76	Hallgrimsson	**Rethinking Penetrance and Expressivity for Genetic Disease: Leveraging Facial Shape Analyses to Predict Severity of Genetic Disease** *Imaging, Diagnostics, and AI Tools*	—
P77	Richer	**Think Rare-Aortafind: Using Artificial Intelligence to Identify Patients with Undiagnosed Hereditary Aortopathies** *Imaging, Diagnostics, and AI Tools*	—
P78	Richer	**Building a Heritable Connective Tissue Program: The CHEO Genetics Experience** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—
P79	Saraber	**From Variant to Vessel: Patient-Specific VSMC Dysfunction Mirrors Aortopathy Severity** *Genetic Determinants of Disease Variability*	October 5
P80	Calderon Martinez	**Gene and Sex-Specific Risk for First Aortic Events in Heritable Thoracic Aortic Disease: Insights from the Montalcino Aortic Consortium (MAC)** *Genetic Determinants of Disease Variability*	October 5
P81	Bramel	**High-Throughput Functional Profiling of Arterial Fragility Genes Reveals Shared Mechanisms of Extracellular Matrix Dysfunction and Vascular Instability** *Genetic Determinants of Disease Variability*	October 5
P82	Bramel	**SMAD4 Gain-of-Function Disrupts TGF-β and Flow Sensing Pathways in Aortic Hypoplasia** *Genetic Determinants of Disease Variability*	October 5
P83	Lauffer	**Further Delineation of the Vascular and Connective Tissue Phenotype of the *LOX* Gene and Screening Recommendations** *Genetic Determinants of Disease Variability*	—
P84	Yagi	**The Clinical Impact and Genomic Profile of Patients with Nonsyndromic *FBN1*-Related Thoracic Aortic Aneurysm and Dissection** *Genetic Determinants of Disease Variability*	—

POSTER PRESENTATION LIST

MONDAY, OCTOBER 5 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P85	Fernandez Alvarez	**Whole-Gene Sequencing of FBN1: Identifying New Splicing and Deep-Intronic Variants** *Genetic Determinants of Disease Variability*	—
P86	MacCarrick	**Static Panels in a Dynamic Field: Global Variation in HTAD Gene Testing** *Genetic Determinants of Disease Variability*	—
P87	Ágg	**Association of Ocular Features with Mutation Type and Cardiovascular Severity in Marfan Syndrome** *Genetic Determinants of Disease Variability*	—
P88	Vosberg	**Impact of Attention Deficit Disorder (ADHD) Among Children with Marfan Syndrome: A Multicenter Study from CLARITY** *Patient Experiences, Quality of Life, and Patient-Centered Care*	October 5
P89	Milleron	**Employment Status and Socioeconomic Deprivation Among Adults with Marfan Syndrome is Related to Aortic Dissection but Not with Preventive Aortic Surgery** *Patient Experiences, Quality of Life, and Patient-Centered Care*	October 5
P90	Côté	**None of Our Doctors Know About This: Stakeholder Perspectives on the Gaps Between Clinical Recommendations and Real-World Care in Heritable Connective Tissue Disorders** *Patient Experiences, Quality of Life, and Patient-Centered Care*	October 5
P91	Pagel	**Accommodations or Restrictions? Parental Impressions of School Experience in Children with Marfan Syndrome** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—
P92	Alexander	**Rates of Guideline-Recommended Aortic Imaging in Patients with Marfan and Loeys-Dietz Syndrome Following Incorporation of an Adult Aortopathy Specialist Within a Pediatric Hospital.** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—
P93	Kallish	**Comparing Parental Perspectives on Raising Children Affected with Inherited vs. *De Novo* Marfan Syndrome** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—
P94	Kallish	**Optimizing Diagnostic Referrals for Marfan Syndrome: Phenotypic Risk Stratification in the Pediatric Population** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—
P95	Rigelsky	**Electronic Medical Record-Based Tools to Improve Care for Individuals with Hereditary Thoracic Aortic Disease** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—

POSTER PRESENTATION LIST

MONDAY, OCTOBER 5 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P96	Cavallé-Garrido	**Symptoms, Quality of Life and Phenotypic Spectrum of Aortic Disease in Pediatric Heritable Aortopathy in Canada: Preliminary Analysis from the CAN-ACT Registry** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—
P97	Al-Mufty	**From Lived Experiences to Systemic Change: Patient Perspectives on the Diagnostic Journey of Loeys-Dietz Syndrome** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—
P98	Al-Mufty	**Exploring the Interrelationship Between Pain, Exercise, Migraines, Sleep, Fatigue, and Anxiety in Individuals with Loeys-Dietz Syndrome** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—
P99	Dimholt	**Fatigue and Reduced Daily Physical Activity in Heritable Thoracic Aortic Disease: Implications for Healthâ€‘Related Quality of Life** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—
P100	Taylor	**Transforming Clinical Research and Care Quality in Rare Connective Tissue Disorders: A Mixed-Methods, Cross-Community Clustering Study Integrating Patient Perspective** *Patient Experiences, Quality of Life, and Patient-Centered Care*	—

TUESDAY, OCTOBER 6

P101	Adeyanju	**Suspected Marfan Syndrome Presenting with Chest Pains in a 39 Year Old Nigerian Man; a Case Report** *Acute Aortic Management*	—
P102	Adeyanju	**from Chest Pain to Death,Catastrophic Acute Aortic Dissection in a 65year Old Woman; a Case Report** *Acute Aortic Management*	—
P103	Huang	**The Impact of Time Spent Normotensive on Surgically Managed Aortic Dissection Outcomes** *Acute Aortic Management*	October 6
P104	Dinsmore	**AI Risk Stratification and Biomarker Discovery for Thoracic Aortic Dissection Using a Large Clinic Cohort** *AI Applications: From Genes to Populations*	—
P105	Prakash	**AortaGPT: An AI-Enabled Clinical Decision Support Platform for Heritable Thoracic Aortic Diseases** *AI Applications: From Genes to Populations*	October 6

POSTER PRESENTATION LIST

TUESDAY, OCTOBER 6 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P106	Prakash	**Gene-Specific Enrichment of Bicuspid Aortic Valve in Heritable Thoracic Aortic Disease: Insights from the Montalcino Aortic Consortium** *Genotype-Phenotype Correlations*	October 5
P107	Prakash	**The Impact of Sex Hormones on Heritable Thoracic Aortic Diseases: A Montalcino Aortic Consortium Study** *Phenotypic Studies and Outcomes*	—
P108	Aatre	**Cutting Through the Genetic Counseling Waitlist-Queue: A Guideline Based Approach** *Clinical Studies & Registries: Research to Improve Outcomes*	—
P109	Arnaud	**Genetic Contribution to Non-Syndromic Aortic Dissection: The Experience of the French Reference Center** *Clinical Studies & Registries: Research to Improve Outcomes*	—
P110	Arnaud	**Thoracic Aortic Disease with Bicuspid Aortic Valve: Limited Contribution of Genetic Testing** *Clinical Studies & Registries: Research to Improve Outcomes*	October 7
P111	Arnaud	**Loss-of-Function Variants in ADAMTS6: A Novel Syndrome with Heart Defect, Thoracic Aortic Aneurysm and Neurodevelopmental Features** *Genotype-Phenotype Correlations*	October 5
P112	Calderon	**Health-Related Quality of Life in Genetic Versus Non-Genetic Aortic Disease: Preliminary Evidence from the AORTIC-Chile Prospective Cohort** *Clinical Studies & Registries: Research to Improve Outcomes*	—
P113	Chris-tophersen	**Elucidating the Genotype-Phenotype Associations in *SMAD6*-Disorders: Familial Congenital Craniosynostosis and Dilated Ascending Aorta, and a Variant of Uncertain Significance in *SMAD6*** *Clinical Studies & Registries: Research to Improve Outcomes*	—
P114	De Backer	**Telomere Length in Patients with Marfan Syndrome** *Clinical Studies & Registries: Research to Improve Outcomes*	—
P115	Guerin	**Mainstreaming Genetic Testing for Suspected Inherited Aortic Disease: A Quality Improvement Initiative** *Clinical Studies & Registries: Research to Improve Outcomes*	—
P116	Guerin	**Genotype-Phenotype Decision Making in Inherited Aortopathy: A Longitudinal Case** *Genotype-Phenotype Correlations*	—

POSTER PRESENTATION LIST

TUESDAY, OCTOBER 6 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P117	Hostetler	**Previously Unrecognized Syndromic Connective Tissue Disorders Identified by Postmortem Whole Genome Sequencing in Fatal Aortic Dissection** *Clinical Studies & Registries: Research to Improve Outcomes*	October 7
P118	Macera	**Multidisciplinary Approach to Pregnancy in Women with Marfan Syndrome: A Case Series** *Clinical Studies & Registries: Research to Improve Outcomes*	—
P119	Muriel	**HPO-Guided Exome Sequencing Identifies Syndromic and Atypical Diagnoses in Hereditary Connective Tissue Disorders** *Clinical Studies & Registries: Research to Improve Outcomes*	—
P120	Ragazoni	**Mitral Annular Disjunction and Aortic Phenotype in Adults with Marfan Syndrome** *Clinical Studies & Registries: Research to Improve Outcomes*	—
P121	Esmel-Vilomara	**Beyond the Aorta: Extracardiac Morbidity in a Pediatric Loeys-Dietz Syndrome Cohort** *Genotype-Phenotype Correlations*	—
P122	Spence	**Longitudinal Aortic Growth in Individuals with Filamin a Deficiency** *Phenotypic Studies and Outcomes*	October 5
P123	Spence	**Cardiovascular Outcomes and Survival in Patients with Neonatal Marfan Syndrome** *Pediatric Aortopathy Management*	October 7
P124	Spence	**Severe Ocular Manifestations in Neonatal Marfan Syndrome: Case Series and Literature Review** *Genotype-Phenotype Correlations*	—
P125	Vincent	**Loeys-Dietz Syndrome in an Individual of Inuit Ancestry: Expanding Clinical Recognition of a Heritable Thoracic Aortic Disease in Indigenous Populations** *Genotype-Phenotype Correlations*	—
P126	D'hulst	**Beyond Aortic Disease: Preliminary Evidence of Myocardial Dysfunction and Arrhythmias in Pediatric HTAD** *Genotype-Phenotype Correlations*	October 5
P127	D'hulst	**Myocardial Recovery After Mitral Valve Surgery in Children with Marfan Syndrome: A Multicentre European Study** *Phenotypic Studies and Outcomes*	October 5

POSTER PRESENTATION LIST

TUESDAY, OCTOBER 6 *continued*

Poster	Author	Title & Session Topic	Oral Presentation
P128	Shvartsman	**Intrafamilial Variability of Cardiac Abnormalities in Loeys- Dietz Syndrome Patients with Tgfb2 Mutations** *Genotype-Phenotype Correlations*	
P129	Burris	**Descending Aortic Distensibility is Not Associated with Development of Type B Dissection in Marfan Syndrome** *Imaging and Engineering Frontiers*	October 6
P130	Campello Jorge (GAN -ORAL)	**Personalized 3D Aortic Z-Scores Identify Heritable Aortopathy from a Single CTA** *Imaging and Engineering Frontiers*	October 6
P131	Gehle	**Role of [18F]FDG PET/CT in Early Detection and Therapeutic Management of Aortic Graft Infections in Patients with Hereditary Thoracic Aortic Disease** *Imaging and Engineering Frontiers*	—
P132	Del Campo	**Reproductive Decision-Making in Marfan Syndrome: Our Centers Experience** Maternal & Aortic Health: Insights Into Pregnancy in HTAD	October 6
P133	Taylor	**Orthotopic Heart Transplant in a Patient with Arterial Tortuosity Syndrome** *Modern Surgical Strategies*	—
P134	Taylor	**Peri-Anesthetic Considerations for Arterial Tortuosity Syndrome** *Modern Surgical Strategies*	—
P135	Tseng	**First Report of Rapidly Progressive Multisegment Aortic Dissection in Combined *FBN1* and *MYH11* Mutations: A Staged Surgical Strategy** *Modern Surgical Strategies*	—
P136	Flyer	**Prophylactic Irbesartan Therapy in Young Patients with Bicuspid Aortopathy: Aortic Growth Rates from a New England Collaborative Registry** *Pediatric Aortopathy Management*	October 7
P137	Brunet-Garcia	**Neurovascular Risk Stratification in Paediatric Loeys-Dietz Syndrome: Towards a Tailored Surveillance** *Phenotypic Studies and Outcomes*	
P138	Calderon Martinez	**Aortic Events After Proximal Thoracic Aortic Repair in Heritable Thoracic Aortic Disease: Insights from the Montalcino Aortic Consortium** *Phenotypic Studies and Outcomes*	October 5

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P140	Lian	**Anatomic Distribution and Temporal Progression of Aortopathy in Genetically Confirmed Marfan Syndrome** *Phenotypic Studies and Outcomes*	—
P141	Moran, Olivia	**Examining the Clinical Features and Diagnostic Yield Among Pediatric Patients Assessed for Marfan Syndrome and Other Aortopathies** *Phenotypic Studies and Outcomes*	—
P142	Parsons	**Systematic Review of Loeys-Dietz Syndrome: Two Decades of Research Progression** *Phenotypic Studies and Outcomes*	—
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ABSTRACTS
OF POSTER PRESENTATIONS

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SEX DIFFERENCES IN AORTOPATHY, ARTERIOPATHY, AND MORTALITY IN VASCULAR EHLERS-DANLOS SYNDROME

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Introduction: Vascular Ehlers-Danlos Syndrome (VEDS) is a rare autosomal dominant disorder due to pathogenic alterations in type III collagen structure and production which results in increased risk of aortopathy and arteriopathy.

Objectives: Given the documented sex-related differences in aortic and other arterial aneurysms and dissections in non-VEDS populations, the potential influence of sex on the incidence of aortopathy, arteriopathy, and mortality in individuals with VEDS was examined.

Methods: A cross-sectional analysis on a cohort of 557 individuals with VEDS with *COL3A1* pathogenic variants was performed as part of the VEDS Collaborative Natural History Study. Primary outcomes were all-cause mortality and time to first aortopathy or arteriopathy diagnosis.

Results: Males comprised 44.5% of the cohort (n=248) and females 55.7% (n=309). At enrollment, the mean age of males was younger than females (35.8 ± 16.6 vs 39.2 ± 16.0 years; p=.017). Mean age at genetic diagnosis did not differ (30.8 ± 17.9 vs 33.5 ± 17.7 years; p=.110). Aortopathy and iliac or visceral arteriopathy were more frequent in males (74.2% vs 57.9%; p<.001), whereas females had higher rates of carotid–cavernous fistulae and spontaneous coronary artery dissections. The mean age at first aortopathy or arteriopathy diagnosis trended younger in males (34.4 vs 37.3 years; p=.057), confirmed by Kaplan–Meier analysis (p<.001). Males also had higher all-cause mortality (32.3% vs 20.4%; p=.001) and a trend toward increased aortic-related mortality (53.8% vs 38.1%; p=.063).

Conclusion: In this large genetically confirmed VEDS cohort, males demonstrated earlier and more frequent aortopathy/arteriopathy, greater aortic, visceral, and iliac involvement, and higher all-cause mortality, while females had higher rates of carotid/great vessel involvement, carotid-cavernous fistulae, and SCAD. These findings highlight clinically meaningful sex-based differences in VEDS presentation and outcomes, supporting sex-informed surveillance, risk stratification, and future studies of vascular territory-specific disease patterns.

FEMORAL ARTERY ACCESS FOR ENDOVASCULAR INTERVENTION IN VASCULAR EHLERS-DANLOS SYNDROME: OUTCOMES, COMPLICATIONS, AND TECHNICAL CONSIDERATIONS

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Introduction: Femoral artery access for endovascular intervention in individuals with vascular Ehlers-Danlos syndrome (VEDS) has been associated with severe access-related complications, yet endovascular therapy is often unavoidable.

Objective: We evaluated femoral artery access strategies and outcomes in patients with genetically confirmed VEDS to inform a selective, biology-informed approach to arterial access.

Methods: This is a cross-sectional cohort study of patients with genetically confirmed VEDS undergoing endovascular procedures requiring femoral arterial access between 1989 and 2025. The primary outcome was major access-related complications, defined as femoral artery dissection, pseudoaneurysm, or rupture requiring operative repair and percutaneous closure device failure requiring open repair. Outcomes were compared by closure method and sheath size (<6 or ≥6 French).

Results: Among a cohort of 392 patients with VEDS, 59 (15.1%) underwent endovascular procedures requiring femoral artery access (53% male; 86% White), accounting for 111 femoral access sites during 99 index procedures (mean age 41.5±11.4 years). Data were available for 94 femoral artery access sites (84% percutaneous, 16% surgical exposure). Femoral artery closure was achieved in 89 sites: 29 (32.6%) manual compression, 39 (43.8%) percutaneous closure devices, and 16 (18%) surgical closures, and 5 (5.6%) unknown closure methods. Technical success was 100%, 87.2%, and 93.8% in the manual compression, percutaneous closure, and surgical exposure and repair groups respectively (p=0.03). No major access-related complications occurred among femoral access sites using <6 Fr sheaths (n=40). In contrast, major access-related complications occurred in 6 (13.3%) access sites using ≥6 Fr sheaths (3 major bleeding, 3 dissection and acute limb ischemia), and all required open exposure and repair.

Conclusions: These findings support a biologically-informed approach to femoral access in VEDS. Percutaneous femoral artery access is generally safe when small-bore sheaths are used, with planned surgical exposure reserved for larger sheath requirements.

BEYOND DEFICIENCY: GENOTYPE-SPECIFIC EXTRACELLULAR MATRIX DISRUPTION IN VASCULAR EHLERS–DANLOS SYNDROME

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Introduction: Vascular Ehlers–Danlos syndrome (VEDS), caused by pathogenic *COL3A1* variants, is characterized by arterial fragility and life-threatening vascular complications. Although reduced type III collagen has long been implicated in disease pathogenesis, the relationship between genotype, collagen composition, and extracellular matrix (ECM) ultrastructure remains poorly defined.

Objectives: To characterize genotype-specific alterations in collagen composition and ECM ultrastructure in VEDS using integrated quantitative proteomic and transmission electron microscopy (TEM)-based analyses of human dermal tissue.

Methods: Dermal biopsies from 8 individuals with genetically confirmed VEDS carrying glycine substitutions or in-frame deletion variants underwent integrated ultrastructural and proteomic analysis. TEM with a semi-automated Fiji/ImageJ workflow quantified collagen fibril architecture across dermal layers. Stable isotope–labeled liquid chromatography–mass spectrometry (LC-MS) quantified type III collagen abundance and allele-specific variant peptide incorporation into the ECM. Control samples included individuals with aortopathy without a known pathogenic variant (n=12), individuals with Marfan syndrome or suspected Marfan syndrome (n=10), and healthy controls (n=16).

Results: LC-MS demonstrated significantly reduced type III collagen abundance in VEDS compared with controls (17.8% vs 27.1% of total fibrillar collagen, p=0.0102), although depletion varied substantially by genotype. Individuals with p.Gly789Ala variants demonstrated near-normal type III collagen levels despite established VEDS phenotypes. Allele-specific peptide analysis revealed marked genotype-dependent differences in ECM incorporation. Small side-chain substitutions demonstrated near-equimolar variant:wild-type collagen representation (~55%), whereas the large side-chain p.Gly765Val substitution demonstrated markedly reduced detectable variant collagen incorporation (16.6%). TEM identified distinct ultrastructural remodeling signatures, with large side-chain substitutions and deletion variants associated with smaller collagen fibrils and greater architectural disruption.

Conclusions: VEDS represents a genotype-dependent disorder of ECM organization rather than solely quantitative collagen deficiency. This study provides the first direct quantification of type III collagen and allele-specific variant collagen incorporation in human VEDS tissue, establishing a framework for biologically informed risk stratification in heritable aortopathy.

DERMAL EXTRACELLULAR MATRIX ABNORMALITIES REFLECT GENOTYPE-ASSOCIATED SUBSTRATE VULNERABILITY IN VASCULAR EHLERS–DANLOS SYNDROME

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Introduction: Vascular Ehlers–Danlos syndrome (VEDS), caused by pathogenic *COL3A1* variants, is characterized by arterial fragility and life-threatening vascular complications. However, the extracellular matrix (ECM) mechanisms underlying its variable clinical presentation remain poorly understood. We investigated whether genotype-specific differences in dermal collagen and elastic fiber ultrastructure reflect distinct patterns of arterial vulnerability.

Objectives: To characterize genotype-associated alterations in collagen fibril architecture and elastic fiber integrity in VEDS using transmission electron microscopy (TEM)-based analysis of human dermal tissue.

Methods: TEM was performed on dermal biopsies from 23 individuals with genetically confirmed VEDS and 19 controls. Collagen fibril diameter and heterogeneity were quantified using a validated semi-automated Fiji/ImageJ morphometric workflow. Elastic fiber architecture was graded semi-qualitatively based on fragmentation patterns. *COL3A1* variants were grouped by predicted structural mechanism: null, small side-chain substitutions, large/charged substitutions, and splice-site variants. Clinical phenotypes including arterial dissection, rupture, and multi-territory arteriopathy were extracted from longitudinal clinical records.

Results: Collagen fibril architecture differed by *COL3A1* variant class. Small glycine substitutions demonstrated significantly larger collagen fibrils than controls (median 0.092 vs 0.079 µm; p=0.008), whereas large/charged substitutions exhibited smaller fibrils (median 0.076 µm; p=0.23), producing an ordered fibril pattern (small substitutions > controls > large substitutions). Elastic fiber abnormalities demonstrated stronger discrimination by genotype and clinical phenotype than collagen metrics alone. Large/charged substitutions were associated with marked elastic fiber fragmentation, whereas null and small substitutions demonstrated milder disruption. Moderate-to-severe elastic fiber degradation was associated with arteriopathy involving ≥3 vascular territories (80.0% vs 30.8%; p=0.036). Elastic fiber fragmentation was present even in young VEDS patients, possibly resembling premature ECM aging.

Conclusions: VEDS demonstrates genotype-specific patterns of ECM failure, with distinct collagen and elastin ultrastructural phenotypes associated with differential arterial vulnerability. Dermal ultrastructure may provide a clinically relevant tissue-level window into vascular risk beyond arterial diameter alone.

BARRIERS IN VASCULAR EHLERS-DANLOS SYNDROME CARE: CHARACTERIZING THE INTERFACE BETWEEN PATIENT AND PROVIDERS THROUGH A CROSS-SECTIONAL SURVEY

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Introduction: Vascular Ehlers-Danlos Syndrome (VEDS) is a rare genetic condition characterized by arterial dissection and hollow organ rupture. The following barriers in VEDS care have been named in the literature: insufficient healthcare provider knowledge about VEDS, previous negative medical experiences related to VEDS, and the potential for trauma due to VEDS.

Objectives: As these barriers have not been explored in detail, this study aimed to characterize and quantify them to guide specific improvements in VEDS care.

Materials and Methods: We developed and distributed a cross-sectional quantitative Qualtrics survey to adults with VEDS and parent/guardians of children with VEDS. Listservs and social media platforms of patient advocacy organizations and community members were utilized for distribution. Previously published instruments were adapted for survey use when available. Responses were collected from December 2025 through February 2026, and data were analyzed using descriptive statistics.

Results: Responses were received for 165 individuals with VEDS. The provider most commonly perceived to lack knowledge was emergency department (ED) physicians (87%), followed by gastroenterologists (78%), primary care physicians (PCPs) (63%), and general surgeons (62%). The most endorsed negative medical experience specific to VEDS care was convincing a healthcare provider to order imaging (44%). Finally, 81% of adults with VEDS reported enduring a VEDS-related traumatic exposure. As a secondary finding, continued communication with genetic counselors (GCs) post-results disclosure was reported by almost half of the participants and was endorsed as helpful by 85% of those respondents.

Conclusion: We recommend VEDS education initiatives tailored to every provider identified in this study, especially ED physicians, gastroenterologists, PCPs, and general surgeons. We also recommend the novel adoption of trauma-informed care by all VEDS care team members. Finally, we recommend potentially expanding the GC role into follow-up care for VEDS in conjunction with a physician.

CIPROFLOXACIN CAUSES LETHAL ARTERIAL COMPLICATIONS IN A MOUSE MODEL OF VASCULAR EHLERS-DANLOS SYNDROME

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Introduction: While data support that fluoroquinolones exacerbate lethal sequela in the setting of some types of aortic pathology, the potential danger of these drugs has not been studied in the context of vascular Ehlers-Danlos syndrome (vEDS).

Objective: We tested the hypothesis that ciprofloxacin exposure increases the incidence of arterial dissection and rupture in vEDS mice.

Materials and Methods: Eight-week-old male and female vEDS mice (*Col3a1[G209S/WT]*) and wild-type littermates (*Col3a1[WT/WT]*) were randomly assigned to receive either ciprofloxacin (n=25) or vehicle control (n=24) through daily gavage for 2 weeks and were monitored for 4 weeks. We compared groups based on survival, aortic dissection and rupture incidence, and aortic tissue levels of collagen, lysyl oxidase (LOX), matrix metalloproteinases (MMP), macrophages, and apoptosis.

Results: All vEDS mice that received vehicle and all littermate controls survived the 4-week study period. In contrast, vEDS mice that received ciprofloxacin had a high rate of death (44% [11/25] vs 0% [0/24] in vehicle-treated vEDS mice, P=0.0003); 8 of the 11 deaths (73%) occurred within the first week of ciprofloxacin exposure. The cause of all 11 deaths was aortic or arterial rupture manifesting as hemopericardium or hemothorax. Mortality was significantly increased in both male and female vEDS mice exposed to ciprofloxacin compared to same-sex controls (P=0.02 and P=0.006, respectively). Compared to aortic tissue from vehicle-treated vEDS mice, tissue from ciprofloxacin-treated vEDS mice exhibited decreased collagen content, decreased LOX, increased MMP 2 and 9 levels, increased macrophage infiltration, and increased apoptosis (all P<0.001).

Conclusions: In a mouse model of vEDS, ciprofloxacin exposure resulted in aortic inflammation, collagen disruption, reduced LOX, and an increased incidence of fatal dissection and rupture of the thoracic aorta and branch arteries. These novel translational findings strongly support recommendations to avoid fluoroquinolones in patients with vEDS.

COL3A1 HAPLOINSUFFICIENCY: AN EVALUATION OF DISEASE COURSE SEVERITY IN A UK VASCULAR EHLERS DANLOS SYNDROME COHORT

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Background: Vascular Ehlers Danlos syndrome (vEDS) is a rare inherited connective tissue disorder characterised by severe tissue fragility and increased risk of life-threatening vascular and hollow-organ events due to pathogenic *COL3A1* variants. Importantly, disease course severity has shown clinical variability and *COL3A1* variants resulting in haploinsuffciency (HI) have been associated with a milder phenotype and a delayed onset of major complications. This study aimed to evaluate the impact of *COL3A1* HI variants on disease course severity in a large UK vEDS population.

Methods: 260 adults and children with vEDS were reviewed to identify *COL3A1* HI variants (e.g. frameshift ins/del/dup, nonsense substitutions). Data was obtained through clinical service review (National EDS Service London) and the NEEDS study research database, and collated from clinical examination, family history, and molecular reports.

Results: 44 individuals (n=24 females, n=20 males) with *COL3A1* HI variants were identified. Variants were most frequently nonsense substitutions (n=9 probands) but also included interstitial deletions encompassing *COL3A1* and *COL5A2* (n=4 probands). 12 clinical events were reported in 10 individuals, occurring at a median age of 42.29 years (IQR 34.59-55.29). First events were either vascular (n=7) or gastrointestinal (n=3) and time-to-event analysis showed individuals with HI variants had a significantly delayed time to first event compared to the dominant negative (DN) variants group (median age at first event: HI 42.29 years, DN 29.50 years).

Conclusion: This large, clinically detailed cohort of individuals with *COL3A1* HI provides unique insight into *COL3A1* genotype-phenotype relationships and variability in vEDS disease course in a UK cohort, enabling more personalised improvements in clinical management and counselling for individuals with *COL3A1* HI variants.

MANUFACTURER-SPECIFIC EFFECTS OF CELIPROLOL IN VEDS MICE: IMPLICATIONS FOR CLINICAL TRANSLATION

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Introduction/Objectives: Patients with vascular Ehlers-Danlos syndrome (vEDS) caused by heterozygous (likely) pathogenic sequence variants in the *COL3A1* gene are at increased risk of arterial events such as dissections and/or ruptures. Beyond preventive and emergency surgical interventions, antihypertensive therapy remains a key treatment approach. Clinical and long-term observational studies have demonstrated that treatment with the beta-blocker celiprolol leads to a reduction in arterial events. Previously, we have reported that celiprolol enhances reduced aortic rupture force in a murine model of vEDS. Other studies have reported conflicting findings regarding the survival of celiprolol-treated mice, potentially due to differences in mouse models, dosing regimens, and manufacturer of the drug. To assess this discrepancy, we have investigated the effects of celiprolol of different manufacturers in our established vEDS mouse model.

Materials and Methods: Four-week-old heterozygous *Col3a1*^{m1Lsmi} and wild-type mice of both sexes were treated for four weeks with the previously established equal dose of celiprolol from different manufacturers via drinking water (PMID: 31056650). Survival rates were assessed for all treatment groups. Furthermore, survival data from the Schlieren-Zurich (Switzerland) and the Budapest (Hungary) colonies receiving celiprolol from different manufacturers were retrospectively analyzed.

Results: Depending on the manufacturer, the survival of heterozygous mice receiving celiprolol ranged from improved survival (as observed in our previous study) to no effect or even reduced survival (as observed in other studies) compared with untreated mice.

Conclusion: The lack of global clinical consensus regarding medical therapy for vEDS underscores the need to investigate the divergent findings on the efficacy of celiprolol in preclinical models. Our results contribute to a better understanding of manufacturer-dependent effects of celiprolol in vEDS and may help refine the interpretation of its clinical relevance for patient management.

RUPTURE SENSITIVITY, PHARMACOGENETIC PROFILING AND CO-OCCURRENCE OF HEREDITARY AORTOPATHIES

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Introduction: Aortopathy research requires a robust readout capable of discriminating structurally intact from disease-prone aortic tissue at the individual level. To address this, we established an objective assay measuring murine aortic rupture force as a quantitative endpoint of vascular biomechanical integrity. This approach enables direct differentiation between normal and mechanically weakened aortic wall properties, even in the absence of overt vascular events. However, clinical translation additionally requires integration of (i) precise molecular diagnosis and (ii) pharmacogenetic (PGx) profiling, both of which can be facilitated by whole-genome sequencing (WGS) but are complicated by multilocus genetic variation.

Objectives: We aimed to (i) apply rupture force measurement as an individual-level functional readout of aortic disease severity, (ii) assess the utility of WGS for PGx profiling, and (iii) investigate the contribution of co-occurring pathogenic variants to the WGS-based molecular diagnosis of hereditary aortopathies.

Materials and Methods: We applied our aortic rupture force assay across multiple mouse models and pharmacological treatment conditions to assess biomechanical consequences of genetic predisposition and drug exposure. We analyzed an in-house WGS cohort (60×, PE150) comprising >550 patients for pathogenic and functional variants in established aortopathy genes and pharmacogenes.

Results: Rupture force measurements identified biomechanical weakening of the thoracic aorta prior to the onset of micro- and macroscopic abnormalities and enabled quantification of genotype- and treatment-dependent effects on aortic wall stability. In our Swiss cohort, we identified families harboring co-occurring pathogenic variants in distinct aortopathy genes, providing a molecular explanation for variable phenotypes and overlapping clinical manifestations. In addition, we detected actionable PGx variants in drug-metabolizing genes, including *CYP2C9* variants predicted to alter losartan metabolism and therapeutic response.

Conclusion: Our findings emphasize the necessity of functional biomechanical phenotyping as well as WGS-based molecular diagnostics and pharmacogenetic profiling to enable accurate diagnosis, mechanistic disease stratification, and personalized therapy in hereditary aortopathies.

LOSARTAN IN MFS MICE: REDUCTION OF AORTIC DILATATION BUT NO IMPROVEMENT IN AORTIC RUPTURE FORCE

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Introduction/Objectives: Marfan syndrome (MFS) can lead to aortic aneurysms, dissections, and ruptures. Losartan, an angiotensin-II-receptor-type-1 inhibitor, has been shown to slow down aneurysm progression in mouse models and humans with MFS. However, it remains unclear whether losartan exerts its beneficial effect by the prevention of rises in blood pressure or by improving the biomechanical integrity of the aortic wall. We have recently established an objective approach to measure the rupture force of the murine aorta, enabling to assess the effect of drug treatments on the biomechanical integrity of the aorta at individual level, even in the absence of arterial events. Here, we applied our approach to losartan-treated mice modeling MFS.

Material and Methods: 4-week-old homozygous (*Fbn1*$^{mgR/mgR}$) and wild-type mice were treated for 4 weeks with losartan and subsequently euthanized. Per mouse, three 1.5-mm rings of the thoracic aorta were prepared, mounted on a tissue puller, and uniaxially stretched until rupture.

Results: The mortality rate of losartan-treated *Fbn1*$^{mgR/mgR}$ mice was not significantly lower than that of untreated *Fbn1*$^{mgR/mgR}$ mice during the study interval. Losartan treatment reduced aneurysm formation, but had no impact on the aortic rupture force of *Fbn1*$^{mgR/mgR}$ mice. Aortic rupture force measurement revealed the weakened thoracic aorta prior to micro- and macroscopic changes.

Conclusion: In mice modeling MFS, the thoracic aorta treated with losartan remains susceptible to rupture despite the reduction in aortic diameter. Thus, aortic rupture force beyond aortic diameter may be useful for the investigation of drug therapies in mouse models of hereditary aortic diseases.

GLP-1 ANALOGUE IN HEREDITABLE AORTOPATHY: EFFECTS OF LIRAGLUTIDE ON THE AORTIC WALL IN A MURINE MODEL OF VASCULAR EHLERS–DANLOS SYNDROME

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Introduction: Vascular Ehlers–Danlos syndrome (vEDS) is a rare connective tissue disorder characterized by structural fragility of arteries and internal organs. Identification of novel pharmacological approaches aimed at improving aortic wall integrity may enhance both survival and quality of life. Previous studies have shown that the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide reduces the incidence of aortic rupture in murine models of aortic aneurysm. However, the known weight-reducing effects of GLP-1 analogues may potentially adversely affect disease outcomes in vEDS.

Objectives: This study aimed to evaluate the effects of liraglutide on aortic tensile strength in the *Col3a1*^{m1Lsmi} murine model of vEDS and to determine whether liraglutide-induced weight loss is associated with increased mortality.

Materials and Methods: A total of 41 mice (4–5 weeks of age, C57BL/6J background) were included. 10 wild-type (5 males, 5 females) and 11 *Col3a1*^{m1Lsmi} heterozygous (6 males, 5 females) mice received liraglutide (300 µg/kg/day intraperitoneally) for 4 weeks, whereas 10 wild-type (5 males, 5 females) and 10 heterozygous (5 males, 5 females) control animals received physiological saline. Body weight was monitored daily. Following euthanasia, thoracic aortic segments were harvested for biomechanical and histological measurements, and quantitative RT-PCR analyses.

Results: By day 28, liraglutide treatment significantly reduced weight gain in both male (29.3% vs. 24.4%) and female (27.5% vs. 15.1%) mice. Neither the mortality rates (3/21 vs. 1/20) nor the biomechanical analyses of tensile strength revealed any significant differences between treated and control animals. However, liraglutide treatment significantly reduced the aortic mRNA expression levels of markers for ECM remodelling (*Mmp9*, $p<0.001$), endothelial dysfunction (*Vcam1*, $p=0.0012$), and inflammation (*IL-6,* $p=0.0011$ and *IL-1β*, $p=0.0205$).

Conclusion: Liraglutide significantly reduced weight gain in both sexes without increasing mortality. Although no alterations in aortic tensile strength were observed, GLP-1 analogue treatment attenuated tissue remodeling and inflammatory activity in the aortic wall.

INTRALUMINAL PRESSURE AT AORTIC RUPTURE IN A MOUSE MODEL OF VASCULAR EHLERS-DANLOS SYNDROME

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Introduction: Vascular Ehlers-Danlos syndrome (vEDS) is a systemic genetic disorder caused by *COL3A1* sequence variants. Patients with vEDS are at increased risk of arterial dissections/ruptures, which are associated with a high mortality rate and thus require prevention. Preventive options are blood pressure control and prophylactic surgery. By better understanding the intraluminal pressure at aortic rupture, further preventive measures could be developed.

Objectives: We aimed to establish and evaluate methodologies for measuring intraluminal pressure at aortic rupture, thereby providing physiological insights into the biomechanical integrity of the thoracic aorta in a vEDS mouse model.

Materials and Methods: A vEDS mouse model (*Col3a1*^{m1Lsmi}) was used for the experiments, involving heterozygous (HT) and wild type (WT) mice. Using an in-house burst pressure assay, the maximal intraluminal pressure at aortic rupture (mmHg) was measured in euthanized mice. Subsequently, isolated aortic rings were subjected to uniaxial stretching according to a previously described rupture force procedure (PMID: 31056650), and maximum force at rupture (mN) was determined. *In vivo* measurements were performed through implantation of telemetric sensors for continuous blood pressure monitoring.

Results: Burst pressure values were lower in HT mice compared with WT animals ($p<0.001$). Likewise, rupture force measurements showed reduced rupture forces in aortic segments S1–S3 of HT mice compared with WT animals (S1: $p<0.0001$; S2: $p=0.0081$; S3: $p=0.0020$). Telemetric sensors were successfully implanted, enabling continuous blood pressure monitoring in both HT and WT mice.

Conclusions: The presented methodolgies enable the measurement of intraluminal pressure in the thoracic aorta and the detection of biomechanical alterations in the aortic wall in a vEDS mouse model, thereby providing an objective tool for evaluating therapeutic approaches at the individual level. Telemetry allowed the assessement of blood pressure effects on the aortic wall and proved feasible in this fragile aortopathy model.

KEY SIGNALING EVENTS LINKING EXTRACELLULAR MATRIX TO AORTIC DISEASE IN MARFAN SYNDROME

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Introduction: Thoracic aortic aneurysms and dissections (TAAD), as occur in Marfan syndrome (MFS), currently lack a cure, underscoring the need to identify disease-driving molecular mechanisms and actionable therapeutic targets. Our previous studies revealed that versican accumulation drives aortic disease in MFS through overactivation of the AKT-NO-sGC-PKG signaling pathway.

Objective: To identify the mechanisms linking versican to pathological AKT activation in MFS aortopathy.

Materials and Methods: High-throughput proteomic analysis of aortas from a mouse model of MFS (*Fbn1*$^{C1041G/+}$) and control mice was performed to identify novel mediators of aortopathy. Human aortic samples from MFS patients of both sexes and multiple *FBN1* genotypes, together with complementary mouse models of MFS, were analyzed using immunohistochemistry, immunofluorescence, and functional assays. Aortic structure, contractility, signaling activation, and disease progression were assessed *in vivo* and *ex vivo*. Genetic and pharmacological approaches were employed to inhibit candidate mediators.

Results: We show that versican-driven fibronectin (FN) accumulation activates an αVβ3-PI3K-PIP3-PDK1-ILK signaling cascade leading to AKT-NOS2 upregulation and aortic disease. FN accumulates in aortas from male and female MFS patients and mice. Disrupting FN assembly alters aortic extracellular matrix organization, suppresses AKT activation and NOS2 induction in vascular smooth muscle cells (VSMCs), prevents aortic contractile dysfunction, and reverses aortic dilation in MFS mice. MFS aortas from both humans and mice of both sexes exhibit upregulation of αVβ3 integrin and ILK. Pharmacological inhibition of αVβ3, PI3K, PDK1, or ILK, or interference with their PIP3-dependent recruitment to the plasma membrane, prevents FN-induced AKT activation, NOS2 upregulation in VMSCs and aortic contractile impairment. Furthermore, inhibition of ILK or PDK1, aortic silencing of *Ilk*, or smooth muscle-specific deletion of *Ilk* reverses or prevents aortic growth in MFS mice.

Conclusion: These findings identify a causative FN-αVβ3-PI3K-PIP3-PDK1-ILK-AKT-NOS2 signaling cascade in MFS aortopathy and reveal multiple translationally relevant targets for therapeutic intervention in MFS-associated TAAD.

TREM-1 AGGRAVATES MARFAN SYNDROME AORTOPATHY

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Marfan syndrome is a hereditary connective tissue disorder caused by mutations in the gene encoding fibrillin-1. One of its most severe manifestations is dilation and rupture of the ascending aorta. Recent studies suggest that this aortopathy is associated with an infiltration of monocytes/macrophages within the aortic wall.

Triggering Receptor Expressed on Myeloid Cells 1 (TREM-1) is a key regulator of monocyte trafficking and activation. We aimed to investigate its role in Marfan syndrome aortopathy.

We characterized the expression of TREM-1 in the *Fbn1*$^{mgR/mgR}$ mice model. We used complementary approaches to modulate its activity: genetic deletion, pharmacological agonist and inhibitor. Our findings were completed *in vitro* and confirmed with human samples.

We showed that TREM-1 is expressed by infiltrating monocytes and derived macrophages within the adventitial layer of the aortic wall in *Fbn1*$^{mgR/mgR}$ mice. *In vivo* stimulation of TREM-1 using agonistic monoclonal antibody aggravated the aortopathy, whereas genetic deletion and pharmacological inhibition led to a less severe phenotype. Inflammation was reduced locally, as well as MMP12 expression and collagen I and V degradation. The protective effects of TREM-1 deletion were abolished using a MMP12 inhibitor, meaning that TREM-1 aggravates aortic dilation and rupture through MMP12 matrix remodeling. Human data corroborated our findings. TREM-1 protein levels were significantly higher in the adventitia of ascending aorta of Marfan patients compared to controls and locally colocalized with MMP12. In a cohort of young Marfan patients (N=84), plasma sTREM-1 levels positively correlated with ascending aortic diameter (R= 0.33, P=0.002), indicating that higher sTREM-1 levels are associated with more advanced aortic dilation.

In conclusion, our study demonstrates that TREM-1 plays a central pathogenic role in the pathophysiology of Marfan aortopathy by regulating monocyte trafficking and macrophage activation in the vascular wall. These pro-inflammatory macrophages produce MMP12, which enhance deleterious tissue remodeling and therefore aggravate disease severity.

CHROMATIN AND TRANSCRIPTIONAL PROFILING REVEAL SENESCENCE PATHWAYS AS THERAPEUTIC TARGETS IN LOEYS-DIETZ SYNDROME

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Introduction: Loeys-Dietz syndrome (LDS) is a genetic aortopathy characterized by progressive thoracic aortic aneurysm (TAA) and dissection. Despite advances in understanding disease mechanisms, therapeutic options remain limited. We previously identified Gata4+ vascular smooth muscle cells (VSMCs) as a population exhibiting a less contractile, pro-inflammatory, senescence-like phenotype and enriched in LDS aortic roots.

Objectives: To characterize chromatin and transcriptional changes underlying VSMC dysfunction in LDS, compare adaptive versus maladaptive dedifferentiation responses across aortopathies, and evaluate senolytic therapy as a potential therapeutic strategy.

Materials and Methods: We profiled lineage-traced VSMCs from LDS and control mice using CUT&Tag for H3K27ac, and integrated findings with cross-species single-cell transcriptomic analysis, including samples from mouse Marfan syndrome (MFS), mouse LDS, human LDS, and human sporadic TAA. LDS mice were treated with dasatinib plus quercetin (D+Q) from 6 to 16 weeks of age.

Results: Most differential H3K27ac peaks showed reduced signal in LDS, consistent with downregulated genes outnumbering upregulated ones. Lost enhancers were enriched for SRF and MEF2 binding sites, regulators of VSMC contractile identity, while gained enhancers showed enrichment for NF-κB (RELA), C/EBPβ, and AP-1 family binding. Gained enhancers included one at the GATA4 locus, a potential driver of the senescence-like phenotype. Cross-species analysis revealed that in MFS and sporadic TAA, dedifferentiated VSMCs exhibit both senescence-like features and adaptive responses, including extracellular matrix (ECM) remodeling and YAP-TEAD-dependent transcriptional programs. In contrast, LDS VSMCs show senescence-like features without these compensatory benefits. D+Q treatment reduced aortic root diameters in LDS mice, with decreased Gata4 and p21 levels consistent with senescent cell clearance.

Conclusion: LDS VSMCs appear to undergo dedifferentiation without compensatory adaptation, suggesting a rationale for senolytic therapy. These findings point to senescence pathways as potential therapeutic targets.

PERIVASCULAR INFLAMMATION IS CRITICALLY INVOLVED IN THE PROGRESSION OF AORTIC ANEURYSMS FORMATION IN MARFAN SYNDROME

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Background: Perivascular inflammation is implicated in the development of vascular diseases, but its contribution to the structural abnormalities within the aorta in Marfan syndrome (MFS) remains unclear.

Methods: Periaortic tissue inflammation in patients with MFS and *Fbn1*$^{C1041G/+}$ mice was assessed through immunohistochemical staining for immune cells and qRT-PCR analysis of inflammatory cytokines. The impact of perivascular inflammation on aortic dilatation was examined using a high-fat diet (HFD) to induce metabolic stress in perivascular adipose tissue (PVAT) in *Fbn1*$^{C1041G/+}$ mice. These mice were also treated with low-dose pitavastatin (0.3 mg/kg/day) which exerts anti-inflammatory effects on adipose tissues. For clinical assessment of perivascular inflammation, we developed a machine learning-based automated analysis program to calculate the perivascular fat attenuation index of the ascending aorta (AA-FAI), correlating with periaortic fat inflammation. The AA-FAI was calculated in 159 non-hereditary connective tissue disorders (HCTDs) patients, 36 MFS patients, and 9 Loeys–Dietz syndrome (LDS) patients. The correlation between aortic diameter expansion rate measured by ultrasound imaging and the AA-FAI was examined.

Results: Both MFS patients and *Fbn1*$^{C1041G/+}$ mice showed a marked accumulation of macrophages in the periaortic tissue, along with elevated inflammatory cytokines (respectively; $p < 0.05$). In *Fbn1*$^{C1041G/+}$ mice, HFD feeding promoted periaortic inflammation and aortic dilatation resulting in elastic fiber fragmentation, fibrosis, proteoglycan accumulation, and activation of MMP and TGF-β downstream targets in the tunica media. These pathological changes were inhibited by low-dose pitavastatin without altering blood lipid parameters (respectively; $p < 0.05$). The AA-FAI was significantly higher in HCTDs patients, including MFS and LDS, compared to non-HCTDs patients (-52.90 ± 12.69 HU, -51.70 ± 7.99 HU vs -62.02 ± 8.54 HU, respectively; $p < 0.0001$). An elevated AA-FAI was associated with accelerated aortic enlargement in MFS patients ($R^2 = 0.332$, $p = 0.039$).

Conclusions: These findings underscore the contribution of perivascular inflammation to aneurysm formation in MFS and its therapeutic implications for managing MFS-associated vascular events.

INVERSE AGONIST ACTIVITY OF ANGIOTENSIN II RECEPTOR BLOCKER IS CRUCIAL FOR PREVENTION OF AORTIC ANEURYSM PROGRESSION IN MICE MODEL OF MARFAN SYNDROME

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Background: Marfan syndrome (MFS), an inherited disorder caused by *FBN1* gene mutations, causes fatal aortic aneurysm. We observed that aberrant activation of mechanosensitive signaling contributes to the progression of aortic aneurysm in MFS. The angiotensin II (Ang II) type 1 (AT1) receptor can be activated by mechanical stress independently of Ang II, and the inverse agonist activity of AT1 receptor blockers (ARBs) provide clinical advantage to inhibit both Ang II-dependent and -independent receptor activation. However, the impact of inverse agonism of ARBs on MFS aortopathy remains unknown.

Methods: Candesartan-7H (Can-7H) is a candesartan derivative, which lacks the carboxyl group critical for inverse agonist activity, works as a neutral antagonist for AT1 receptor. We previously reported that Can-7H (1 mg/kg/day) had almost no inhibitory effect on Ang II-induced blood pressure (BP) elevation in C57BL/6 male mice, but that Can-7H (20 mg/kg/day) suppressed Ang II-induced BP elevation, almost equally as candesartan cilexetil (Can) (1 mg/kg/day) did. In this study, Can (1 mg/kg/day), Can-7H (1 mg/kg/day or 20 mg/kg/day) was administered to *Fbn1*$^{C1041G/+}$ mice, and aortic progressive dilatation was analyzed.

Results: Aortic progressive dilatation in association with aortic wall thickening, degeneration of elastic fibers, deposition of collagen, and mechanosensitive signaling, and constitutive AT1 receptor activation in *Fbn1*$^{C1041G/+}$ mice was significantly suppressed by treatment with Can (1 mg/kg/day), but not by Can-7H even at 20 mg/kg/day.

Conclusions: A crucial role of inverse agonist activity of ARB for prevention of mechanical stress-induced AT1 receptor activation and aortic aneurysm progression in MFS mice.

THE LONG NONCODING RNA *MEG3* CONTRIBUTES TO MALADAPTIVE VSMC REMODELING IN MARFAN SYNDROME AORTOPATHY

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Introduction: Vascular smooth muscle cell (VSMC) phenotypic modulation is a hallmark of thoracic aortic aneurysm (TAA), but regulators determining whether this response remains adaptive or progresses toward maladaptive remodeling remain poorly defined. Long noncoding RNAs regulate cell-state transitions but remain unexplored in hereditary aortopathy.

Objectives: To test whether postnatal VSMC-specific *Meg3* deletion modifies aortic root dilation in Marfan syndrome (MFS) and to define *Meg3*-associated transcriptional programs using single-nucleus RNA sequencing.

Materials and Methods: *Meg3* was identified as upregulated in modulated VSMCs across human and mouse TAA transcriptomic datasets. To test its functional role, *Meg3*^{flox} mice were crossed with *Fbn1*^{C1041G}/+;*Myh11*-CreER^{T2} mice. Tamoxifen at 6 weeks induced VSMC-specific *Meg3* deletion. Aortic root dimensions were assessed by serial echocardiography. Single-nucleus RNA sequencing was performed on aortic tissue at 14 weeks, with analyses focused on contractile and modulated VSMC populations.

Results: MFS mice exhibited accelerated aortic root growth compared with controls ($P<0.05$). MFS-*Meg3*^{SMCKO} mice showed markedly attenuated growth versus MFS controls ($P<0.0001$), with rates similar to controls, representing near-complete rescue of the growth phenotype. *Meg3* deletion in controls had no effect ($P=0.89$), indicating disease-context specificity. Transcriptomics revealed that although *Meg3* is upregulated in modulated VSMCs, its deletion preferentially restored contractile VSMC programs, including *Tln1* (focal adhesion), and *Ltbp1* (TGF-β regulation), while suppressing *Ace* (renin-angiotensin signaling) and *Csf1* (inflammatory recruitment). Differential expression of select targets was confirmed at the protein level by immunofluorescence. Consistent with mouse findings, *MEG3* was elevated in human TAA tissue versus non-aneurysmal controls.

Conclusion: Postnatal VSMC-specific *Meg3* deletion attenuates aortic root dilation in MFS and partially restores contractile VSMC programs. These findings identify *Meg3* as a regulatory node in maladaptive remodeling. As lncRNAs are amenable to antisense oligonucleotide inhibition, *Meg3* warrants further investigation as a precision therapeutic target in hereditary thoracic aortic disease.

DYNAMIC ENDOTHELIAL PHENOTYPIC SWITCHING DURING INTIMOMEDIAL TEAR FORMATION IN FBN1$^{G234D/G234D}$ AORTA

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Introduction and Objective: Aortic dissection (AD), characterized by separation of the medial layers of the aorta, is a major cause of death in patients with connective tissue disorders. However, molecular mechanisms that trigger AD initiation remain incompletely understood. Here, we investigated the role of endothelial cells (ECs) in the initiation of intimomedial tears that progress to dissection using a recently established AD mouse model.

Materials and Methods: We used a spontaneous AD mouse model generated by introducing a missense FBN1 variant (p.G234D) identified in a non-syndromic familial AD patient. Vascular lesions were examined using histology, immunostaining, single-cell RNA-sequencing (scRNA-seq), and lineage-tracing analyses.

Results: At 5 weeks of age, ECs are observed at sites of intimomedial tears and invaginate into the medial layer through disruption of the internal elastic lamina. Subsequent loss of endothelial lining was associated with progression to overt dissection. scRNA-seq analysis of ascending aortas at postnatal week 1 and EC-enriched population at 3 and 5 weeks identified three EC subclusters: EC1, EC2 and EC3. EC1 was characterized by enrichment of ECM organization genes, and a proliferative EC1-Mki67+ subcluster transiently emerged in AD aortas at 1 week of age. In contrast, EC2 was enriched for angiogenesis-related genes and progressively expanded by 5 weeks in AD aortas. En face immunostaining with EdU labeling demonstrated focal EC proliferation in 1-week-old AD aortas. In addition, EC1 exhibited increased expression of adhesion molecule genes, including *Icam1*, *Vcam1,* and *Selp*. To determine the origin of migrating ECs, we performed lineage tracing using *Cdh5*-CreERT2;R26RtdTomato mice. Migrating AD ECs were derived from Cdh5-positive ECs and expressed α-SMA, suggesting endothelial-to-mesenchymal transition.

Conclusions: Our spontaneous AD mouse model demonstrates that ECs are activated at 1 week of age and exhibit a transient proliferative phenotype (EC1-Mki67+) prior to dissection onset. As intimomedial tears progress, angiogenic EC2 population markedly increases in AD aortas compared with wild-type controls. These findings highlight dynamic endothelial phenotypic changes as potential triggers of intimomedial tear formation and AD progression.

STRIKING PHENOTYPICAL DIFFERENCE BETWEEN *IPO8* KNOCK-OUT MOUSE MODELS ON DIFFERENT GENETIC BACKGROUNDS EXPLORED BY RNA-SEQUENCING

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Introduction: *IPO8* encodes importin-8, a ubiquitously expressed nuclear transport receptor responsible for translocating proteins and RNAs from the cytosol to the nucleus. We previously identified bi-allelic loss-of-function *IPO8* variants as a cause of a syndromic form of thoracic aortic aneurysm (TAA). C57Bl/6N *Ipo8* knock-out (*Ipo8*$^{-/-}$) males displayed aortic root and ascending aortic aneurysm from 8 weeks of age onwards. Surprisingly, in Sv129 males the identical *Ipo8*$^{-/-}$ alleles did not lead to progressive aortic enlargement.

Objectives: We aim to pinpoint the molecular processes promoting aneurysm development in *Ipo8*$^{-/-}$ C57Bl/6N mice. In the long term, these findings may contribute to the search for novel therapeutic targets.

Material and Methods: *Ipo8*$^{-/-}$ and wild-type (WT) C57Bl/6N and Sv129 mice (N=8/group) were sacrificed at 16 weeks. The aortic root and ascending aorta were isolated and RNA was extracted for bulk RNA-sequencing. Downstream analyses were restricted to genes passing an independent hypothesis weighting (ihw) filter threshold of <0.45.

Results: Principal component analysis of the RNA-seq data across the four groups revealed that genetic background accounted for the primary source of variation (421 upregulated and 250 downregulated genes), rather than the mutation itself. Within the C57BL/6N background, 136 genes were found to be upregulated and 69 downregulated, with significant dysregulation of TGF-β superfamily signalling being the strongest emerging process. Specifically, we observed a signature of altered BMP signalling in the C57Bl/6N mutants only, with *Fst, Inhba*, and *Gdf6* found to be upregulated, while *Bmpr1b, Smad9, Smad6*, and *Id1* were found to be downregulated.

Conclusions: RNA-sequencing suggests that dysregulated BMP signalling contributes to TAA development in a C57Bl/6N *Ipo8*$^{-/-}$ mouse model. The next step will be to assess BMP pathway activity at the protein level by evaluating the pSMAD1/5/9 to SMAD1/5/9 ratio. Moreover, these findings emphasize the critical influence of mouse genetic background on vascular disease modelling.

DEVELOPMENT OF AN IPSC-DERIVED VASCULAR SMOOTH MUSCLE CELL MODEL FOR TGFB3-LOEYS-DIETZ SYNDROME (TYPE V) AORTOPATHY

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Introduction: Thoracic aortic aneurysm and dissection (TAAD) is a hallmark of Loeys-Dietz syndrome (LDS) and an important cause of mortality. LDS type V (LDS-V) is caused by heterozygous pathogenic variants in the *TGFB3* gene. To date, 27 individuals harboring the pathogenic TGFB3 p.(Asp263His) founder variant have been reported, displaying variable clinical expressivity ranging from absent or mild to severe aortic disease. Although understanding of LDS-TAAD has improved, significant knowledge gaps remain, including mechanisms underlying phenotypic heterogeneity, hindering therapeutic development.

Objectives: We aimed to develop and characterize a patient- and control-derived LDS-V vascular smooth muscle cell (VSMC) model to further elucidate disease mechanisms and support therapeutic discovery.

Material and Methods: Induced pluripotent stem cell (iPSC)-derived neural crest-derived VSMCs (NC-VSMCs; 2 clones/individual) from two LDS-V patients harboring the p.(Asp263His) variant (with severe and mild TAAD phenotype, respectively) alongside two healthy controls were created. Expression analyses and functional assays were performed to assess and compare contractile and calcium properties of patients versus controls (minimum 2 differentiations/individual).

Results: We observed a trend toward reduced baseline expression of contractile markers (*MYOCD*, *TAGLN*, and *SMTNb*) as well as diminished U46619-driven contractility and calcium flux in NC-VSMCs from the most severely affected patient compared to the control lines. The mildly affected patient cells exhibited a less deteriorated phenotype for all assays. Unexpectedly, for all individuals the same clone showed differing behaviours when differentiated in different rounds.

Conclusions: We created the first iPSC-VSMC LDS-V model and demonstrated that it recapitulates disease aspects to some extent. Yet, caution is warranted due to technical batch effects. As such, our analysis highlights the importance of including different clones per line and doing multiple differentiation rounds per clone due to biological and technical variability, respectively. Potential strategies to reduce variability include the use of chemically defined media and automation of differentiation.

PAIN HYPERSENSITIVITY AND SPINAL REDOX-NEUROINFLAMMATORY SIGNALING IN *FBN1*$^{C1041G/+}$ MICE

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Introduction: Improved cardiovascular management has extended survival in Marfan syndrome (MFS), shifting attention toward other disabling manifestations such as chronic pain, fatigue, and muscle impairment. These symptoms are often attributed to skeletal deformity, yet it is unclear whether MFS involves intrinsic alterations in nociceptive and neuromuscular pathways.

Objectives: To determine whether *Fbn1*$^{C1041G/+}$ mice develop age- and sex-dependent nociceptive and motor phenotypes, and to identify molecular signatures that may sustain pain in MFS.

Materials and Methods: Male and female wild-type and *Fbn1*$^{C1041G/+}$ mice were studied at 2, 4, 6, 8, and 16 months. Brain RNA sequencing was performed at 3 and 13 months. Mechanical allodynia (von Frey filaments test), thermal hyperalgesia (plantar test), cold allodynia (cold plate test), and hind-limb grip strength were assessed behaviorally. Lumbar spinalcord qRT-PCR at 2 and 16 months evaluated excitatory/nociceptive signaling, inflammation, oxidative stress, and transforming growth factor-beta-(TGF-β) related markers.

Results: Brain transcriptomics showed sex- and age-dependent remodeling of pain-related pathways. Cold allodynia appeared by 2 months and preceded broader sensory dysfunction. By 16 months, male and female MFS mice showed mechanical and cold allodynia, heat hyperalgesia, and reduced grip strength. The aged spinal cord showed increased expression of genes encoding glutamatergic receptor subunits (*Grin1*, *Gria1*, and *Gria2*) in both sexes, with transient receptor potential vanilloid 1 (*Trpv1*) upregulation restricted to females, consistent with enhanced excitatory/nociceptive signaling. In females, hypersensitivity coincided with increased spinal expression of interleukin-6, tumor necrosis factor-α, inducible nitric oxide synthase, and NADPH oxidase 4 (*Nox4)*, indicating a neuroinflammatory/redox profile. In males, increased *Tgfb1* and *Nox1* expression suggested distinct TGF-β1-associated and NADPH oxidase 1-linked redox signatures.

Conclusion: *Fbn1*$^{C1041G/+}$ mice reproduce progressive pain hypersensitivity and muscle impairment relevant to MFS. Early cold allodynia and sex-specific spinal signaling provide tractable endpoints for studies addressing quality of life, perioperative pain, and mechanism-guided analgesic strategies in MFS.

PERIVASCULAR ADIPOSE TISSUE IMPOSES A SEX– AND REGION–SPECIFIC REDOX BRAKE ON AORTIC CONTRACTILITY IN MARFAN SYNDROME

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Introduction: Marfan syndrome (MFS) aortopathy is commonly interpreted through medial degeneration, endothelial dysfunction, and transforming growth factor-β/redox imbalance. Whether perivascular adipose tissue (PVAT), an active paracrine compartment, contributes to the functional vascular phenotype of MFS is unknown.

Objectives: To determine whether PVAT modifies thoracic aortic reactivity in *Fbn1*$^{C1041G/+}$ mice in a sex and region-dependent manner, and to identify redox mechanisms.

Materials and Methods: Ascending and descending thoracic aortas from 2-3-month-old male and female wild-type and *Fbn1*$^{C1041G/+}$ mice were studied by wire myography ±PVAT. Phenylephrine-induced α1-adrenergic contractions were assessed after endothelial removal and pharmacological modulation of nitric oxide (NO) and redox pathways: non-selective nitric oxide synthase inhibition with L-NAME, selective inducible NO synthase inhibition with 1400W, hydrogen peroxide degradation with catalase, peroxynitrite decomposition with FeTPPS, or exogenous peroxynitrite exposure. PVAT and aortic wall were analyzed by qPCR, nitrite measurement, immunofluorescence, and synchrotron radiation-based Fourier-transform infrared microspectroscopy (SR-μFTIR).

Results: PVAT regulation of aortic tone was shaped by genotype, sex, and aortic region. In male MFS ascending aorta, PVAT-dependent modulation was preserved, whereas MFS PVAT exerted an anticontractile effect in the descending thoracic aorta of both sexes. The most distinct phenotype was found in young female MFS ascending aorta, where PVAT attenuated α1-adrenergic contraction independently of the endothelium. Blocking NO synthases with L-NAME, or selectively inhibiting inducible NO synthase with 1400W, abolished this attenuation. MFS PVAT showed increased *Nox4* expression and oxidative-nitrosative stress, without detectable lipid oxidation or altered protein secondary structure by SR-μFTIR. Exogenous peroxynitrite increased *Nox4* expression in PVAT. The PVAT anticontractile effect was abolished by catalase and FeTPPS, supporting a hydrogen peroxide/peroxynitrite-sensitive mechanism.

Conclusion: PVAT is not passive tissue in MFS. It creates a sex-and segment-selective redox brake on aortic contractility, particularly in the female ascending aorta, and may help explain aortic vulnerability beyond diameter.

UNMASKING IMMUNE CELLS IN MARFAN SYNDROME: THE HIDDEN CULPRITS BEHIND AORTIC DISEASE?

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Introduction: The role of immune cells in the pathophysiology of Marfan syndrome (MFS) has not yet been elucidated. We recently found that mice lacking the first hybrid domain of fibrillin-1 (*Fbn1*$^{H1\Delta/+}$ mice) develop focal elastic lamellae breaks (microdissections) without aneurysm formation, associated with a signature of mast cell activation. We therefore investigated a potential role for mast cells and immune activation in early-stage aortic pathology.

Objective: Profiling immune cell involvement in the ascending aorta, with a focus on mast cells as potential drivers of early aortic remodeling in MFS.

Methods: Mouse and human aorta samples were analyzed using histochemical and immunohistochemical staining. Enzymatic assays and single nucleus RNA sequencing was performed on mouse aorta.

Results: Immunohistochemical analysis using CD68 and CD206 markers identified progressive, localized increases in specific macrophage subpopulations within the *Fbn1*$^{H1\Delta/+}$ ascending aorta. Mast cells were observed predominantly in the adventitial layer and displayed features consistent with a mature connective tissue subtype. *Fbn1*$^{H1\Delta/+}$ aortas showed increased chloroacetate esterase density, a key mediator in mast cell activation, alongside progressive mast cell protease-4 positive cell counts. Heparin-based staining revealed that mast cells in *Fbn1*$^{H1\Delta/+}$ aortas exhibited more frequent degranulation, which can be associated with activation. Complementary staining of human MFS aortic samples also showed adventitial localized mast cells with degranulation morphology. Single nucleus RNA sequencing of murine aortas allowed us to identify different vascular and immune cell populations.

Conclusion: Early disease stage (*Fbn1*$^{H1\Delta/+}$) aortas display increased mast cell presence and activation. Together with altered macrophage populations, these findings support a potential role for immune-related mechanisms in early aortic wall alterations in MFS.

ACTIVATION OF YAP OR RHO/ROCK IN WT SMCS TRIGGERS THE SAME PHENOTYPIC CHANGES AS OBSERVED IN *ACTA2*$^{-/-}$ SMCS

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Introduction: Pathogenic variants in genes that predispose to thoracic aortic disease (**TAD**) are predicted to disrupt the elastin-contractile unit, including pathogenic variants in *ACTA2* that impair smooth muscle cell (**SMC**) force generation. Two mechanosensing pathways contribute to TAD in mice; SMC loss of YAP/TAZ leads to aneurysm formation and FAK activation drives Rho/ROCK and mTOR, with mTOR identified as a major pathogenic pathway for TAD. The interplay of these mechanosensing pathways has not been explored.

Objectives: To characterize the phenotypic modulation of *Acta2*$^{-/-}$ SMCs and the role of YAP signaling in this modulation.

Materials & Methods: Ascending aortic SMCs were isolated from 8-week-old wild-type (WT) and *Acta2*$^{-/-}$ mice and differentiation driven *in vitro* by serum starvation and exposure to TGFβ1 (5 ng/mL, 48h). Pharmacological inhibitors of FAK, Rho/ROCK, and mTORC1 were applied. YAP1 was overexpressed (WT-YAP1, YAP5SA) or silenced via lentiviral constructs. Signaling was assessed by Western blot for FAK, Rho/ROCK (phospho-cofilin, phospho-MLC2), and mTOR (phospho-p70S6K) activation, alongside real-time PCR and immunofluorescence. Mitochondrial function was assessed by Seahorse assay.

Results: *Acta2*$^{-/-}$ SMCs exhibited elevated FAK, Rho/ROCK, and mTOR signaling, increased fibronectin deposition, and enhanced mitochondrial respiration that was rescued by a ROCK inhibitor. FAK inhibition suppressed Rho/ROCK and mTOR activation, identifying FAK as a central signaling node. Nuclear YAP and markers of YAP signaling were increased in the in *Acta2*$^{-/-}$ SMCs. YAP knockdown or treatment with IAG933, which disrupts YAP-TEAD interactions, reversed FAK and Rho/ROCK activation, fibronectin accumulation, and metabolic reprogramming. Conversely, constitutive activation YAP activation in WT SMCs recapitulated the *Acta2*$^{-/-}$ phenotype, establishing YAP as a key upstream driver of SMC phenotypic modulation.

Conclusion: YAP activation is responsible for the phenotypic modulation in *Acta2*$^{-/-}$ SMCs that is characterized by pathogenic FAK-driven Rho/ROCK and mTOR signaling. Elevated mitochondrial respiration reflects increased energetic demands downstream of Rho/ROCK signaling.

MONOCYTE/MACROPHAGE INFILTRATION PROMOTES MARFAN AORTOPATHY THROUGH MMP12 PRODUCTION

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Marfan syndrome is a genetic connective tissue disorder caused by mutations on the gene coding for fibrillin-1. One of the most life-threatening manifestations is the ascending aorta dilation and rupture. Recent studies suggest that this aortopathy is associated with local and systemic inflammation.

Our work aims to investigate the role of monocytes/macrophages in the pathophysiology of Marfan aortopathy and the underlying mechanisms leading to rupture.

Using the *Fbn1*$^{mgR/mgR}$ murine model, which closely mimics the human disease, we characterized local and systemic inflammation. We used macrophage depletion, monocyte tracers as well as pharmacological modulation strategies to investigate the role of monocytes/macrophages in the disease severity.

We observed early-stage accumulation of monocyte-derived macrophages within the adventitia of the aortic wall of *Fbn1*$^{mgR/mgR}$ mice. This infiltration was associated with local pro-inflammatory signature (Il6, Il1b, TNF, CCL2) and elevated metalloproteinase (MMP) activity. Collagen I, the most abundant in the aortic walll, was less abundant in the adventitia of *Fbn1*$^{mgR/mgR}$ mice.

Depletion of vascular macrophages using a CSF1R inhibitor, as well as blockade of monocyte recruitment via a CCR2 inhibitor, significantly reduced local inflammation and limited both aortic dilation and fatal rupture in *Fbn1*$^{mgR/mgR}$ mice. Among the MMPs, MMP12, produced mainly by macrophages, emerged as a key driver of destructive remodeling in the ascending aorta. We showed that MMP12 is produced by CCR2+ macrophages within the adventitia of *Fbn1*$^{mgR/mgR}$ mice. Pharmacological inhibition of MMP12 in vivo reduced type I and type V collagen degradation within the adventitia of *Fbn1*$^{mgR/mgR}$ mice and markedly attenuated aortic dilation and decreased rupture incidence.

In conclusion, our findings demonstrate that monocytes/macrophages contribute to the progression of Marfan-associated aortopathy through local inflammation and harmful tissue remodeling. MMP12, produced by infiltrating macrophages, plays a central pathogenic role by remodeling the extracellular matrix of the aorta.

INVOLVEMENT OF *TNXB* IN THE PATHOPHYSIOLOGY OF MFS

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Background: Marfan syndrome (MFS) is a hereditary connective tissue disorder caused by pathogenic variants in *FBN1*, encoding fibrillin-1, a key component of the extracellular matrix (ECM). It primarily affects the skeletal, ocular and cardiovascular systems. Among these, thoracic aortic aneurysm and dissection represent the main life-threatening complications and the leading cause of mortality in MFS. However, the molecular mechanisms underlying aortic dilatation and dissection in MFS remain incompletely understood, particularly the factors contributing to disease progression and variability in severity. A better understanding of these pathophysiological mechanisms is therefore essential to identify new therapeutic targets and improve patient management.

Objective: To identify new ECM components involved in MFS pathophysiology and uncover potential therapeutic targets.

Methods: RNA sequencing was performed on skin fibroblasts from 31 MFS patients carrying premature termination codon (PTC) variants in *FBN1* and 19 healthy controls. Gene ontology analysis revealed strong ECM dysregulation and identified *TNXB* among the most upregulated genes. Validation was conducted by qPCR on independent patient-derived fibroblasts and by immunohistochemistry on human aortic tissues.

Results: Transcriptomic profiling identified a robust MFS molecular signature associated with profound ECM remodeling. Among dysregulated genes, *TNXB* emerged as a key candidate. *TNXB* encodes tenascin-X, an ECM glycoprotein interacting with fibrillin-1 and collagen networks and involved in TGFβ signaling regulation. These functions place tenascin-X at the intersection of matrix integrity and aneurysm progression. Increased *TNXB* expression was consistently confirmed in patient fibroblasts and MFS aortic tissues.

Conclusion: Our findings identify tenascin-X as a novel ECM molecule involved in MFS pathophysiology and a promising therapeutic target in thoracic aortic disease.

ELASTIC FIBER REMODELING AND LIMITED STRUCTURAL RECOVERY IN THE LUNG OF FBN1$^{MG\Delta LPN/+}$ MICE

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Introduction: Marfan syndrome is caused by mutations in the FBN1, leading to alterations in elastic fibers (EFs) and dysregulation of TGF-β signaling bioavailability. Pharmacological modulation of the Renin–Angiotensin system, using agents such as losartan and ramipril, can attenuate TGF-β signaling; however, structural tissue recovery remains limited. Although the cardiovascular, skeletal, and ocular systems are most commonly affected, lung involvement is less explored. Improved clinical management has increased life expectancy in Marfan syndrome, revealing later manifestations in less-studied organs such as the lung. The Fbn1$^{mg\Delta lpn/+}$ mouse model recapitulates key features of Marfan syndrome and survives beyond 6 months.

Aim: To characterize the lung phenotype and EF-associated proteins in 6-month-old Fbn1$^{mg\Delta lpn/+}$ mice and assess the effects of losartan and ramipril.

Materials and Methods: Thirty-four male C57BL/6N mice were analyzed: WT (n=10), Fbn1$^{mg\Delta lpn/+}$ (n=10), Fbn1$^{mg\Delta lpn/+}$losartan (n=7), and Fbn1$^{mg\Delta lpn/+}$ramipril (n=7). Treatments began at 4 weeks. Lung morphology, EF ultrastructure (serial block-face SEM with 3D reconstruction), and immunofluorescence (fibrillin-1, perlecan, fibronectin) were evaluated.

Results: Fbn1$^{mg\Delta lpn/+}$ mice showed 45% survival at 24 weeks. Surviving animals exhibited significant alveolar enlargement, consistent with an emphysema-like phenotype. EF content was markedly reduced in lung parenchyma and alveolar walls. SBF-SEM analysis revealed pronounced EF fragmentation, loss of fiber continuity, and decreased EF density in alveolar wall. Immunofluorescence demonstrated a significant reduction in fibrillin-1, perlecan, and fibronectin, indicating disruption of the microfibrillar scaffold and impaired EF assembly. Losartan and Ramipril did not reverse alveolar enlargement. However, both treatments increased EF presence in lung parenchyma and alveolar walls and partially increase EF. No significant differences in collagen deposition were observed compared to untreated Fbn1$^{mg\Delta lpn/+}$ mice.

Conclusion: Fbn1$^{mg\Delta lpn/+}$ mice develop a severe lung phenotype characterized by alveolar enlargement and EF disruption. Renin–Angiotensin inhibition does not restore alveolar structure but partially improves EF, supporting a modulatory effect on extracellular matrix remodeling without full structural recovery.

IN VIVO INTERROGATION OF THE CONTRIBUTION OF *IGFBP2* UPREGULATION TO THORACIC AORTIC ANEURYSM DEVELOPMENT

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Introduction: Thoracic aortic aneurysm (TAA) occurs in isolation or as part of connective tissue disorders like Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS). Our lab identified a striking 8- to 30-fold increase of *Igfbp2* mRNA levels in the aortic wall of three independent syndromic TAA mouse models (*Fbn1*$^{C1041G/+}$ (MFS), *Ipo8*$^{-/-}$ (MFS/LDS) and *Smad3*$^{-/-}$ (LDS)). Igfbp2 regulates cell proliferation, growth, and extracellular matrix remodelling. Additionally, it has been identified as a marker enriched in modulated vascular smooth muscle cell populations that accumulate in TAA tissues. However, its precise functional role in TAA pathogenesis remains unclear.

Objectives: To investigate the contribution of *Igfbp2* upregulation to TAA development by evaluating the impact of Igfbp2 haploinsufficiency or complete deficiency in an *Fbn1*$^{C1041G/+}$ background.

Material and methods: *Igfbp2*$^{+/-}$ and *Fbn1*$^{C1041G/+}$ as well as *Igfbp2*$^{+/-}$ and *Fbn1*$^{C1041G/+}$/*Igfbp2*$^{+/-}$ mice are crossbred to obtain male pups belonging to four genotype groups per experimental set-up (N = 14/group): wild-type, *Fbn1*$^{C1041G/+}$, *Igfbp2*$^{+/-}$ or *Igfbp2*$^{-/-}$, and *Fbn1*$^{C1041G/+}$/*Igfbp2*$^{+/-}$ or *Fbn1*$^{C1041G/+}$/*Igfbp2*$^{-/-}$. Aortic root and ascending aorta diameters are determined monthly from 4 to 28 weeks of age via transthoracic echocardiography (LAZR-X/MS550D, VisualSonics). Data analysis involved linear mixed-effects models statistics, with Tukey's HSD post-hoc tests applied for pair-wise comparisons.

Results: Igfbp2 haploinsufficiency did not significantly affect aortic enlargement in either the *Fbn1*$^{C1041G/+}$ or wild-type background. Validity of the experimental approach was supported by the significant differences observed between *Fbn1*$^{C1041G/+}$ and wild-type mice at both the aortic root and ascending aorta levels though ($p < 0.001$). Echocardiographic data for the cohort with complete Igfbp2 knockout is currently being collected.

Conclusion: Preliminary data suggest that Igfbp2 upregulation represents a bystander effect rather than a driver or compensatory mechanism in TAA pathogenesis. Ongoing complete knock-out studies will determine whether this observation holds true, or whether partial reduction of *Igfbp2* expression is insufficient to modulate the TAA phenotype.

DIFFERENT *FBN1* MUTATIONS CAUSE DISTINCT PATHOMECHANISMS IN MOUSE MODELS OF MARFAN SYNDROME

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Introduction: Aortic dissection and rupture are the most life-threatening complications of Marfan syndrome (MFS). However, the mechanisms by which *FBN1* mutations drive ECM alterations and influence dissection risk remain unclear. Although elastic fiber fragmentation is a hallmark of MFS, it does not reliably predict aortic failure. This is evident in vascular Ehlers-Danlos syndrome, in which spontaneous arterial dissection occurs despite largely preserved elastic fibers. These observations point to ECM features beyond elastic fiber integrity as markers of rupture-prone aortic disease.

Objectives: To investigate mutation-specific collagen degradation in the Marfan aorta, we examined *Fbn1*$^{+/GT\text{-}8}$ and *Fbn1*$^{+/C1041G}$ mice during early aneurysm formation. We propose that early defects in the collagen network create a maladaptive ECM memory that increases susceptibility to dissection and rupture.

Materials and Methods: We analyzed both mouse models using echocardiography, confocal microscopy, second harmonic generation imaging, electron microscopy, proteomics, and genetic and pharmacological inhibition of the collagenase MMP-13.

Results: Homozygous mice in both models showed pronounced collagen and elastic fiber fragmentation by postnatal day 7 (P7). MMP-13 ablation improved matrix integrity at this stage, indicating a key role in early aneurysm development. Both genetic and pharmacological MMP-13 inhibition restored ECM integrity and prevented aortic dilation in *Fbn1*$^{+/GT\text{-}8}$ mice. In contrast, *Fbn1*$^{+/C1041G}$ mice showed transient protection until one month of age, whereas pharmacological inhibition delayed but did not prevent later aortic dilation. RNA sequencing revealed endothelial inflammatory signature in *Fbn1*$^{+/C1041G}$ at 4 months, which was absent in *Fbn1*$^{+/GT\text{-}8}$, suggesting distinct secondary drivers of progression.

Conclusion: Our findings demonstrate model-dependent ECM remodeling in early postnatal and adult *Fbn1* mutant mice. These results suggest that ECM-stabilizing strategies may help preserve aortic wall integrity in early Marfan aortopathy and delay inflammation-driven disease progression.

CONTEXT MATTERS: GENETIC BACKGROUND MODULATES CARDIOVASCULAR PHENOTYPES IN MARFAN SYNDROME MICE

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Introduction: Marfan syndrome (MFS) is a heritable thoracic aortic disease also characterized by myocardial involvement. Murine MFS models show background-dependent myocardial phenotypes. While the mgR/mgR-model on a mixed 129/BL6-background has been associated with dilated cardiomyopathy, our group previously identified reduced myocardial compaction and right ventricular (RV) pseudoaneurysms on a pure C57BL/6J (BL6) background. Direct comparative data are still lacking.

Objectives: To compare aortic and myocardial phenotypes in MFS mice across 129S2/SvPasCrl (129) and BL6 backgrounds.

Materials and Methods: One-month-old mice on 129 (WT n=14, MFS n=14) and BL6 (WT n=10, MFS n=14) backgrounds underwent echocardiography under isoflurane anesthesia and post-mortem examination. Variables were indexed to body surface area.

Results: MFS mice weighed less than WT on the 129 background ($p=0.019$), but not BL6 ($p=0.911$). RV pseudoaneurysms occurred in 50% of BL6 MFS mice but in none of the 129 MFS mice ($p=0.006$), whereas diaphragmatic herniation was present in 57% of 129 MFS mice but absent in BL6 ($p=0.002$). Cardiac mass increased in BL6 MFS versus WT (median 20.5 vs 15.0g/m^2; $p<0.001$), but not in 129 mice ($p=0.504$). Aortic root dimensions were enlarged in MFS mice of both backgrounds (129: 409 vs 243mm/m^2; BL6: 319 vs 249mm/m^2; both $p<0.001$), although the aortic root-to-ascending aorta ratio increased only in 129 mice (1.54 vs 1.25; $p<0.001$). Left ventricular end-diastolic diameter increased (129: MFS 654 vs WT 583mm/m^2; BL6: 731 vs 617mm/m^2; both $p=0.014$) and fractional shortening reduced (129: 28.9% vs 34.4%; BL6: 35.5% vs 49.2%; both $p\leq0.027$) in MFS mice across both backgrounds.

Conclusion: Genetic background substantially modifies aortic and myocardial phenotypes in MFS mice. While overall myocardial dysfunction was comparable, distinct manifestations–including RV pseudoaneurysms and increased cardiac mass in BL6 mice–and the more pronounced aortic root phenotype in 129 mice highlight the importance of background selection in experimental MFS studies.

A NOVEL DUAL ROLE OF FIBRILLIN-1 IN ADIPOSE TISSUE EARLY DEVELOPMENT AND LATE MAINTENANCE

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Introduction: Mutations in fibrillin-1 lead to Marfan syndrome, characterized by either a lipodystrophic or overweight body status, among other clinical symptoms. This study reveals a stage-specific novel dual role of fibrillin-1 in early adipogenesis and in late stages of adipose tissue maintenance.

Methods and Results: To investigate the role of fibrillin-1 during early adipogenesis, we first used adipose-derived and bone marrow-derived mesenchymal stem cells. Treatment with a recombinant fibrillin-1 fragment containing an integrin-binding RGD motif (*Fbn1*-RGD) significantly inhibited adipocyte differentiation. It also resulted in downregulation of key adipogenic markers. In contrast, a control fragment harboring a non-functional RGA motif (*Fbn1*-RGA) showed no inhibitory effect, indicating specific involvement of integrin receptors. To further study the signaling pathways involved, we used adipogenic 3T3-L1 cells. *Fbn1*-RGD treatment increased phosphorylation of Fak, Src, and Erk. Selective pharmacological inhibition of these effectors restored adipogenesis in presence of *Fbn1*-RGD, indicating that fibrillin-1 inhibits early adipogenesis via the Fak-Src-Erk axis. To identify the specific integrins involved, we performed siRNA-mediated knockdown of relevant fibrillin-1 receptors, α5β1, αvβ3, and αvβ6. Only knockdown of αvβ3 restored adipocyte differentiation in *Fbn1*-RGD-treated cells, establishing αvβ3 as key mediator of fibrillin-1's inhibitory effect on early stages of adipogenesis. To understand the role of fibrillin-1 during late stages of adipogenesis, an adipocyte-specific *Fbn1* knockout mouse (*Fbn1-AKO*) was generated. The progeny mice exhibited ~25% reduction in body weight and fat mass by 30 weeks of age. Histological analysis showed adipocyte hypotrophy in ~90% of white adipocytes. Gene expression analysis of adipose tissue revealed a ~75-80% reduction in adipogenic markers. Despite maintaining normal glucose clearance, *Fbn1-AKO* mice exhibited severe insulin resistance and dyslipidemia, with 2-fold increase in circulating triglycerides and 1.2-fold reduction in high-density lipoprotein levels. Single-nucleus RNA sequencing demonstrated decreased proportion of mature adipocytes and progenitor cells in *Fbn1-AKO* mice. The data highlighted downregulated insulin signaling genes and upregulation of integrin, beiging and mitochondrial fission genes in *Fbn1-AKO* mice. Western blot analysis showed significant reduction in phosphorylation of integrin pathway mediators Fak and Src, as well as Pi3k and Akt, key effectors in insulin signaling.

Conclusion: Fibrillin-1 plays a stage-specific dual role in adipose tissue, inhibiting early adipogenesis via αvβ3-Fak/Src-Erk signaling while maintaining metabolic function in mature adipocytes via integrin-Pi3k/Akt signaling. Targeting this axis may offer therapeutic potential for adipose dysfunction in Marfan syndrome and related disorders.

MOUSE MODELS OF MARFAN SYNDROME DEMONSTRATE HYPERACTIVATION OF THE RENIN ANGIOTENSIN SYSTEM

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Background: Mutations in *FBN1* cause Marfan syndrome (MFS), a connective tissue disorder with life-threatening manifestations related to aortic aneurysm. Angiotensin receptor blockers (ARB) have profoundly attenuated MFS-associated aortic growth in mouse studies, but only modest benefits have been observed in human clinic trials.

Objectives: This study investigated whether age of ARB administration and consistency of use affected aortic growth and survival in mice with MFS and the mechanism of action.

Methods: We administered losartan in drinking water to *Fbn1*$^{mgR/mgR}$ male and female mice and wildtype littermates at postnatal day 24 vs 50 to evaluate the impact of an ARB at different ages. We also administered losartan for four weeks starting at postnatal day 21 before withdrawing losartan from half of the *Fbn1*$^{mgR/mgR}$ mice to determine whether interruptions to ARB use cause harm. Mass spectrometry was used to compare renin angiotensin system metabolites between *Fbn1*$^{mgR/mgR}$ and wildtype mice. We also assayed angiotensin converting enzyme (ACE) activity in multiple tissues of *Fbn1*$^{1041G/+}$ mice at different developmental stages.

Results: We found that sex, age of ARB initiation, and constant inhibition of the renin angiotensin system affected therapeutic efficacy in *Fbn1*$^{mgR/mgR}$ Marfan mice. We also found that male *Fbn1*$^{mgR/mgR}$ mice at 68 days of age had higher angiotensin II concentrations than wildtype littermates ($p=0.028$), despite having similar angiotensin I concentrations ($p=0.897$). Furthermore, these male *Fbn1*$^{mgR/mgR}$ mice had a significantly higher level of angiotensin II turnover compared to female *Fbn1*$^{mgR/mgR}$ mice ($p=0.0027$), suggestive of higher ACE activity. This higher ACE activity in males correlated with the sexual dimorphism seen in *Fbn1*$^{mgR/mgR}$ mouse aortopathy. ACE assays revealed higher levels of tissue-specific and age-dependent ACE activity in mice with MFS compared to wildtype littermates.

Conclusion: These findings can help clinicians optimize therapy for Marfan patients and lead to development of more effective pharmacologic approaches in the future.

A SINGLE-CELL VIEW OF AORTIC WALL DYSFUNCTION IN AN ANGII-INFUSION *BGN*$^{-/0}$ MOUSE MODEL

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Introduction: To investigate the pathomechanisms underlying biglycan (*Bgn*)-related aortopathy, we developed an angiotensin II (AngII) infusion-based *Bgn*$^{-/0}$ mouse model. AngII-infused *Bgn*$^{-/0}$ mice exhibit marked susceptibility to aortic rupture and intramural haematoma formation in the descending thoracic aorta. Notably, this pronounced macroscopic pathology occurs despite largely preserved elastic lamellar organisation and overall collagen and proteoglycan content, indicating that aortic failure arises without widespread extracellular matrix (ECM) alterations.

Objectives: This study aimed to define cell-type-specific pathomechanisms in an AngII-infusion *Bgn*$^{-/0}$ mouse model using single-cell RNA sequencing (scRNAseq).

Materials and Methods: Eight-week-old male BALB/c wildtype and *Bgn*$^{-/0}$ mice received AngII (400 ng/kg/min) or vehicle infusion for five days, after which descending thoracic aortas were collected and analysed by scRNAseq. Data were processed using standard quality control, unsupervised clustering, differential expression analysis of genes specifically associated with the combined biglycan-deficiency and AngII-infusion, and focused subclustering of vascular smooth muscle cell (VSMC) and macrophage populations.

Results: Single-cell transcriptomic analysis revealed pronounced cellular changes unique to the AngII-infused *Bgn*$^{-/0}$ condition compared with AngII-infused wildtype and vehicle-infused controls. The aortic wall exhibited a substantial reduction in VSMCs, accompanied by expansion of endothelial cells and macrophages, while fibroblast proportions were comparable.

VSMCs showed downregulation of contractile markers such as *Myh11*, *Acta2* and *Tagln*, together with increased expression of genes associated with ECM remodelling and inflammatory signalling, including *Fn1*, *Col1a1*, *Lgals3* and *Spp1*.

Macrophages expanded markedly, with a shift in subtype composition characterised by a relative increase in anti-inflammatory M2 macrophages at the expense of tissue-resident macrophages, while pro-inflammatory M1 macrophage proportions remained similar.

Conclusion: Single-cell transcriptomic profiling identified VSMC loss and phenotypic switching, together with macrophage infiltration and subtype redistribution, as key cellular features underlying aortic wall dysfunction in AngII-infused *Bgn*$^{-/0}$ mice. These findings support a model in which maladaptive cellular remodelling, rather than widespread ECM disruption, drives aortic vulnerability.

ROLE OF MITOCHONDRIAL SUPERCOMPLEXES IN MARFAN SYNDROME´S PATHOLOGY

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Introduction: Mitochondrial dysfunction contributes to vascular smooth muscle cell impairment, aortic aneurysm formation, and systemic manifestations in Marfan syndrome (MFS). Previous work from our group suggests that defective mitochondrial activity is a central driver of the disease phenotype. Mitochondrial supercomplexes, formed by respiratory chain complexes I, III, and IV, enhance energy production and metabolic efficiency. MCJ (methylation-controlled J-protein) is a negative regulator of the respiratory chain that limits supercomplex assembly by inhibiting complex I. Because MCJ deficiency increases supercomplex formation and mitochondrial activity, we hypothesized that targeting MCJ could reverse mitochondrial dysfunction in MFS.

Objectives: To determine whether enhancing supercomplex formation through MCJ inhibition improves mitochondrial function and prevents vascular and systemic defects in MFS.

Materials and Methods: We used a double knockout MFS/MCJ mouse model with four groups: WT (Fbn1+/+ Mcj+/+), MCJ-KO (Fbn1+/+Mcj-/-), MFS (Fbn1C1041G/+Mcj+/+), and MFS/MCJ-KO (Fbn1C1041G/+ Mcj-/-). Aneurysm progression was monitored by echography, aortic structure by histological and immunofluorescence staining, mitochondrial respiration by Seahorse assays, supercomplex assembly by Blue Native electrophoresis, and molecular pathways by RNA-seq.

Results: Preliminary data showed reduced supercomplex assembly in MFS aortas and fibrillin-1-silenced aortic cells (shFBN1). In contrast, MCJ deletion increased supercomplex formation when compared to MFS mice. MFS/MCJ-KO mice were protected from aortic dilation compared with MFS mice. In a lethal aneurysm model induced by β-aminopropionitrile (BAPN) and angiotensin II (Ag-II), MCJ-KO mice showed improved survival (50% vs 0% in WT at day 15). Seahorse analyses confirmed enhanced mitochondrial respiration in MFS/MCJ-KO cells relative to MFS cells. Histological staining also suggested improved aortic architecture in MFS/MCJ-KO mice. Ongoing RNA-seq studies aim to elucidate the mechanisms involved.

Conclusion: Enhancing mitochondrial supercomplex formation through MCJ inhibition represents a promising therapeutic strategy to restore mitochondrial function and reduce vascular pathology in MFS.

LOSS OF ENDOGENOUS SEX HORMONES ALTERS ANEURYSM SEVERITY IN BOTH MALE AND FEMALE MFS MICE

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Introduction: The severity of aortic aneurysms and risks for dissection show significant sexual dimorphism among Marfan Syndrome patients. While every individual follows a unique trajectory, overall males are approximately 2-3 times more likely to experience severe aortic disease manifestations. Our and other studies have linked both testosterone and estrogen to aneurysm exacerbation and protection, respectively. Much remains to be learned regarding the underlying mechanisms driving sexual dimorphism in aneurysm severity, and uncovering specific molecular pathways downstream of broad-acting sex hormones has the potential to reveal novel therapeutic targets for both male and female patients.

Objectives: The objectives of the current study were to clarify the role of endogenous sex hormones in MFS aneurysm progression by studying the effects of gonadectomy in both male and female $Fbn1^{C1041G+/-}$ mice.

Materials and Methods: After baseline echocardiogram (Echo) to measure ascending aortic dimensions, male and female $Fbn1^{C1041G+/-}$ mice and their wild-type littermates underwent sham control surgery or orchiectomy / ovariectomy at 9-weeks of age. Echo was repeated at 2-, 4-, 6-and 8- weeks post-surgery to track natural progression of aortic root dimensions. In a second cohort, gonadectomized or sham mice were followed for 4-weeks after which infusion of 1ug/kg/min angiotensin II was added to exacerbate aneurysmal remodeling, collecting echo data weekly until spontaneous death or completion of 4-weeks of Ang II treatment.

Results: Orchiectomy significantly attenuated aneurysm growth in male mice, both under basal monitoring and in the presence of Ang II stress. Ovariectomy mildly exacerbated aortic root growth in female mice under basal conditions, but significantly increased vulnerability to Angiotensin II stress, with over 50% of Ova-female mice dying spontaneously before the study endpoint.

Conclusion: Loss of testosterone and estrogen/progesterone both effect aneurysm severity in MFS mice. Cellular phenotype analysis and molecular profiling experiments are underway to elucidate specific mechanisms underlying these observations.

LIPOTOXICITY IN MARFAN SYNDROME

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Introduction: Marfan syndrome (MFS) is an autosomal dominant disorder whose main cause of mortality is thoracic aortic aneurysm (TAA) and related complications, including rupture and dissection. Our group linked aortic degeneration in MFS to extracellular matrix (ECM)-driven metabolic reprogramming toward glycolysis and mitochondrial dysfunction, suggesting these processes converge during disease progression. Preliminary data indicate that impaired fatty acid oxidation (FAO) induces lipid accumulation and cellular toxicity. Lipotoxicity may promote mitochondrial dysfunction and premature senescence, amplifying vascular pathology. These findings identify metabolic dysfunction as a key driver of MFS-associated TAA and a potential therapeutic target.

Objective: To elucidate the metabolic and mitochondrial mechanisms underlying TAA in MFS and evaluate therapeutic strategies to reverse disease progression.

Materials & Methods: FAO gene expression will be analyzed by RNA-seq, qPCR, and western blot. Lipid accumulation in MFS mouse aortas will be assessed by lipidomics, Nile Red staining, and Cers6/BODIPY immunofluorescence. Primary vascular smooth muscle cells and MFS mice will serve as in vitro and in vivo models for molecular assays, lipidomics, transcriptomics, and pathological analyses. Both models will be treated with PPAR agonists to restore mitochondrial function and evaluate disease progression.

Results: RNA-seq analysis of MFS mouse aortas revealed major alterations in metabolic pathways, particularly those related to mitochondrial function and FAO. Lipidomics showed accumulation of long-chain fatty acids and ceramides in the MFS aortic wall. Pharmacological enhancement of mitochondrial activity reversed aortic dilation and restored structural and functional integrity. In contrast, silencing a key mitochondrial gene induced vascular dysfunction, cellular senescence, medial degeneration, and extensive ECM remodeling, closely resembling the MFS phenotype.

Conclusion: Lipotoxicity and mitochondrial dysfunction are interconnected drivers of TAA pathophysiology in MFS. Restoring mitochondrial function ameliorates the pathological phenotype, supporting metabolic modulation as a potential therapeutic strategy for MFS-associated aortopathy.

MITOCHONDRIAL FUNCTION IN BAPN-INDUCED AORTOPATHY IS TRANSIENTLY RESCUED BY NAD⁺ REPLETION

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Introduction: Thoracic aortic aneurysms leading to dissections (TAD) are associated with oxidative stress, mitochondrial and smooth muscle cell loss. Yet, the temporal relationship between mitochondrial changes and structural aortic alterations during TAD progression has not been investigated.

Objectives: We hypothesized that BAPN-induced TAD are associated with an early phase of mitochondrial hyperactivation during aneurysm formation, followed by bioenergetic collapse with dissection, and that NAD^+ repletion via nicotinamide riboside (NR) would restore mitochondrial function and attenuate structural aortic damage.

Materials and Methods: BAPN (0.5%) was administered in drinking water to postnatal day 21 (P21) C57BL/6J male and female mice, with aortic tissue collected from P24 to P44. Bulk RNA sequencing assessed transcriptomic changes over time. Mitochondrial health was evaluated by Seahorse assay of aortic tissue. Oxidative stress, apoptosis, DNA damage, and histological remodeling were assessed at each time point. NR daily supplementation (400 mg/kg/day) by intraperitoneal injection was initiated on P21.

Results: At P28, the root, ascending, and arch enlarge in BAPN mice despite no histopathologic changes. Mitochondrial activity increases but coupling efficiency reduces with elevated ROS. RNA sequencing shows early dysregulation of mitochondrial and NAD^+ metabolism genes in BAPN mice, including sustained *Nampt* expression from P28 to P32. By P32, mitochondrial respiration collapses. NR treatment raises NAD^+/NADH levels in aorta tissues of BAPN mice, increases dilatation of the ascending aorta, transiently improves coupling efficiency, reduces oxidative stress from P28 to P35, and prevents SMC apoptosis at P35. Dissection deaths start at P35 in BAPN mice, and NR treatment significantly delays SMC apoptosis and dissection deaths to P44.

Conclusion: BAPN induces sequential mitochondrial hyperactivation then bioenergetic collapse preceding structural failure. NAD^+ repletion offers transient metabolic benefit but fails to restore mitochondrial integrity or prevent aortic degeneration, highlighting temporal mitochondrial maladaptation as a key driver of disease progression.

IMPACT OF THE MATERNAL ENVIRONMENT ON CARDIOVASCULAR FEATURES OF THE OFFSPRING IN A MOUSE MODEL OF MARFAN SYNDROME

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Introduction and Objective: Marfan syndrome (MFS) is a connective tissue disorder caused by mutations in the FBN1 gene. Here, we determine the impact of the parental origin of the FBN1 mutation on the cardiovascular manifestations of the offspring using the Fbn1C1041G/+ mouse model of MFS.

Material and Methods: Four experimental groups were generated by crossing wild-type (WT) and MFS mice to obtain WT and MFS offspring from a paternal (MFS-P) or maternal (MFS-M) MFS parent. Cardiovascular phenotyping of offspring was performed from 1-to-6 months of age, including echocardiography, tail-cuff plethysmography, histopathology, and TGF-β signaling.

Results: At one month of age, WT and MFS offspring from MFS-M presented lower body weight than those from MFS-P. However, with age, MFS-M offspring became persistently overweight. MFS-P and MFS-M offspring exhibited an increased aortic root diameter compared with WT offspring. This enlargement appeared earlier in MFS-M than in MFS-P offspring. These parental and age-related differences in aortic root diameter were accompanied by increased TGF-β signaling. The cardiac ejection fraction was reduced at early ages in both WT and MFS offspring from MFS-M with the difference persisting only in MFS-M offspring at adulthood. Systolic blood pressure was initially lower in MFS-M offspring across both genotypes, but it progressively increased, resulting in elevated levels in both WT and MFS offspring from MFS-M in adulthood.

Conclusion: Results indicate the existence of gestational maternal MFS environmental factor(s) with an early impact on the aorta and heart of MFS offspring. In adulthood, this becomes normalized in the aorta but not in the heart.

PERLECAN DEFINES LUNG PHENOTYPE SEVERITY AS A MODIFIER GENE IN MARFAN SYNDROME

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Introduction: Marfan syndrome (MFS) is caused by mutations in the FBN1 gene, leading to elastic fiber (EF) disruption and multisystem involvement. In addition to classical cardiovascular, skeletal, and ocular manifestations, lung alterations are increasingly recognized. Clinical variability in MFS suggests the contribution of modifier genes, including HSPG2, although its role in lung phenotype remains poorly understood. In the lung, EF components range from fibers lacking tropoelastin to fully mature elastic fibers distributed within the parenchyma and alveolar walls. The $Fbn1^{mg\Delta lpn/+}$ mouse model reproduces key features of MFS and exhibits pulmonary alterations.

Aim: To investigate the influence of perlecan on lung phenotype and its relationship with spinal deformities in this model.

Methods: Twenty-nine 3-month-old female C57BL/6N mice were analyzed: wild-type (WT, n=10), $Fbn1^{mg\Delta lpn/+}$ (n=7), $Hspg2^{+/-}$ (n=7), and $dMut^{Fbn1mg\Delta lpn/+;Hspg2+/-}$ (n=5). Spinal deformities were assessed by digital radiography and quantified using the kyphosis index (KI), then correlated with alveolar area. Lung morphology and EF organization were evaluated histologically, and immunofluorescence was performed for fibrillin-1, perlecan, fibronectin, and collagen type III.

Results: dMut mice exhibited severe spinal deformities, with significantly reduced KI compared to all groups. $Fbn1^{mg\Delta lpn/+}$ mice showed significant decreased of KI when compared to WT and $Hspg2^{+/-}$groups. Alveolar area was significantly increased in $Fbn1^{mg\Delta lpn/+}$ mice compared to all groups, while dMut mice also showed significant enlargement compared to WT and $Hspg2^{+/-}$. A significant and negative correlation was observed between KI and alveolar area ($r=-0.82$). Notably, dMut group exhibited reduced alveolar area compared to $Fbn1^{mg\Delta lpn/+}$, accompanied by thickened alveolar walls and increased extracellular matrix deposition. Immunofluorescence revealed reduced fibrillin-1 and perlecan, along with increased fibronectin and collagen type III expression in dMut group.

Conclusion: Perlecan reduction in $Fbn1^{mg\Delta lpn/+}$ modulates lung and spinal phenotypes, promoting extracellular matrix deposition and altering alveolar structure. Moreover, spinal deformity severity correlates with lung remodeling, suggesting an integrated structural phenotype in Marfan syndrome.

SINGLE-CELL RNA SEQUENCING REVEALS ALTERED AORTIC CELLULAR COMPOSITION AND FIBROBLAST ACTIVATION WITH MALADAPTIVE REMODELLING IN A MOUSE MODEL OF *IPO8*-RELATED THORACIC AORTIC ANEURYSM

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Introduction: Bi-allelic pathogenic loss-of-function variants in *IPO8*, which encodes the cytosol-to-nucleus transport receptor Importin-8, cause syndromic thoracic aortic aneurysm (TAA). While vascular smooth muscle cells (VSMCs) have been the primary focus of TAA pathophysiology, the contribution of other aortic cell types remains underexplored.

Objectives: To investigate the contribution of distinct aortic cell populations to *IPO8*-related TAA.

Materials and Methods: Single-cell RNA sequencing was performed on thoracic aortic (root and ascending) samples from C57BL/6N *Ipo8*$^{-/-}$ mice and wildtype (WT) littermates, collected before (8 weeks) and after (20 weeks) aneurysm development. Data were analysed using Seurat with shared nearest-neighbour clustering, and differential gene expression analysis with *FindMarkers()* function. Immunostaining for Myh11 was used to validate changes in VSMC abundance, and F4/80 and Cd3 for macrophage and T-cell infiltration, respectively.

Results: Single-cell RNA sequencing data analysis revealed marked shift in cellular composition in dilated *Ipo8*$^{-/-}$ aortas (20 weeks), with increased fibroblast and immune cell abundance, alongside decrease in the VSMC proportion. Immunostaining confirmed decreased VSMC fraction, particularly in severely dilated aortas, accompanied by prominent adventitial expansion, medial thinning, and macrophage and T-cell infiltration. Given the striking adventitial thickening, further sub-clustering of fibroblasts was performed, identifying classical fibroblasts (*Pi16*$^{+}$), myofibroblasts (*Myh11*$^{+}$) and a distinct *Spp1*$^{+}$/*Thbs1*$^{+}$ fibroblast subset almost exclusive to aneurysmal *Ipo8*$^{-/-}$ aortas (~20% vs. ~1% in WT). Compared to WT aortic fibroblasts, *Spp1*$^{+}$/*Thbs1*$^{+}$ fibroblasts displayed TGF-β pathway activation (*Tgfb1*, *Serpine1*), whereas both *Spp1*$^{+}$/*Thbs1*$^{+}$ and classical fibroblasts from aneurysmal *Ipo8*$^{-/-}$ aortas shared a pro-inflammatory signature (*Ccl2, Il6, Cx3cl1*), and aberrant ECM remodelling programme characterized by collagens involved in regulatory and organizational roles (*Col8a1, Col5a2, Col4a2*).

Conclusion: Aneurysmal *Ipo8*$^{-/-}$ aortas display pronounced fibroblast and immune cell expansion, associated with fibroblast activation and maladaptive ECM remodelling. As these changes are absent prior to disease onset (8 weeks), they likely represent secondary responses rather than initiating events.

FIBRILLIN-1 ACTIVITY IN THE BONE MARROW OF LONG BONES

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Introduction: Bone marrow (BM) is a soft and fatty tissue located within the trabecular area of long and flat bones. BM is the primary site of hematopoiesis, characterized by hematopoietic stem cells and bone marrow stromal stem cells, which give rise to myeloid lineage cells and BM stromal cells, such as adipocytes and osteoblasts. Mesenchymal stem cells and existing osteoblasts predominantly assemble the fibrillin-1 network that permeates the bone marrow.

Objectives: The objective of this pilot study was to evaluate if and how fibrillin-1 deficiency in developing adipocytes affects bone marrow fat and bone density in long bones.

Materials and Methods: We used a unique adipocyte-specific fibrillin-1 conditional knockout mouse (*Fbn1-AKO*) generated by the Cre-LoxP system with Adipoq-Cre mice. Bone density and marrow adiposity were assessed using microCT imaging coupled with osmium tetroxide contrast labeling. Indirect immunofluorescence and H&E staining were performed to assess fibrillin-1 expression and overall BM cellularity.

Results: Baseline characterization of *Fbn1-AKO* mice at 30 weeks of age showed that adipocyte-specific loss of fibrillin-1 resulted in metabolically inefficient adipocytes. A pilot assessment of long bones and bone marrow showed a phenotype in *Fbn1-AKO* mice of both sexes. Compared to wild-type mice, shorter long bones and reduced bone mineral density occurred exclusively in female *Fbn1-AKO* mice. Tibial marrow adipose tissue was high in both female *Fbn1-AKO* and wild-type mice, with no difference between the two groups. However, male *Fbn1-AKO* mice exhibited a significant 8-fold reduction in marrow adipose tissue compared to wild-type controls. Bone marrow cellularity was altered exclusively in female *Fbn1-AKO* mice, including a decrease in megakaryocyte density.

Conclusion: The data show that fibrillin-1 deficiency in BM adipocytes causes low bone mineral density and shorter long bones in female, and decreased bone marrow fat in male *Fbn1-AKO* mice. This suggests that fibrillin-1 plays a sex-dependent role in determining the cell fate of mesenchymal stem cells in the BM.

TARGETING FIBRONECTIN ACCUMULATION REVERSES MARFAN SYNDROME-RELATED AORTIC DISEASE IN MICE

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Introduction: Marfan syndrome (MFS) presents with thoracic aortic aneurysm and dissection (TAADs), a life-threatening condition for which no curative treatment currently exists. This highlights the need to better understand the molecular drivers of disease progression and to identify novel therapeutic targets. Our previous studies demonstrated that activation of the nitric oxide (NO) pathway in vascular smooth muscle cells (VSMCs) contributes to aortic pathology in MFS.

Objective: To characterize extracellular matrix alterations and to determine their role as drivers and therapeutic targets in MFS aortopathy.

Materials and Methods: High-throughput proteomic analysis of aortas from a mouse model of MFS (*Fbn1*$^{C1041G/+}$) and *wild-type* controls was performed to identify novel mediators of aortopathy. Findings were validated by immunofluorescence in aortic tissue from male and female MFS patients and mice. Aortic structure, contractility, signaling activation, and disease progression were assessed *in vivo* and *ex vivo*. Fibronectin function was targeted using a peptide that disrupts fibronectin multimerization and an inhibitor of the fibronectin-αVβ3 integrin interaction.

Results: Fibronectin accumulation was identified as a prominent and consistent feature of MFS aortas in both humans and mice of both sexes Functional studies demonstrated that fibronectin induces activation of the NO pathway in VSMCs through αVβ3 integrin. Targeting fibronectin multimerization or its interaction with αVβ3 reduced NO pathway activation, improved vascular function, and normalized mechanical properties. Specifically, these interventions reduced aortic stiffness *ex vivo* and aortic diameter and pulse wave velocity *in vivo*, indicating reversal of key pathological features.

Conclusion: Fibronectin accumulation constitutes a central pathogenic extracellular matrix alteration in MFS aortopathy, promoting aortic stiffness and aortic disease progression through αVβ3-dependent activation of the NO pathway. Targeting fibronectin assembly or fibronectin-αVβ3 signaling reverses aortopathy in MFS mice and identifies a promising, actionable therapeutic strategy for MFS-associated TAAD.

MULTI-TARGETED OXIDATIVE STRESS PATHWAYS AS A COMPLEMENTARY STRATEGY TO CURRENT MEDICAL TREATMENT AGAINST AORTOPATHY PROGRESSION IN MARFAN SYNDROME

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Introduction and objective. Marfan syndrome is the result of multiple dysregulated molecular pathways, some of which act hierarchically and others independently. Therefore, an efficient pharmacological therapeutic strategy must be multi-targeted and based on rigorous and highly standardized pre-clinical studies applying doses that are translatable to their clinical use in patients. To explore a potential future combined pharmacological inhibition of aortic aneurysm formation/progression with angiotensin II receptor blockers (ARB; losartan), we first assay a variety of antioxidants as monotherapy (allopurinol, resveratrol, and bendavia/SS31 mitochondrial peptide) in the MFS mouse model *Fbn1*$^{C1041G/+}$ at doses compatible with clinical administration to MFS patients. This first step assesses the effect of each drug compared to no treatment.

Material and Methods. Males and females Marfan mice of 8 weeks-age were administered with resveratrol (10 and 100 mg/L), allopurinol (45 and 75 mg/L), SS31 peptide (15 mg/L) or received no treatment for a period of 16 weeks. These compounds were diluted in drinking water. They affected neither the amount of drunk water nor the body weight of animals. The aortic root diameter was evaluated by ultrasonography and aortic wall by histopathology.

Results. Preliminary results compare to untreated mice show that (i) resveratrol reduced aortic dilatation, being equally effective at both testing doses; (ii) the SS31 peptide also reduced aortic aneurysm but takes longer compared to allopurinol and resveratrol; (iii) allopurinol at 45 mg/L reduces the progression of the aneurysm only in females while allopurinol administered at 75 mg/L was equally effective in both sexes.

Conclusion. Different antioxidants contribute to reduce the progression of aortic aneurysm, with variations in the effective dose to be administered (compatible with their clinical range), the time in which the effect is observed and the sex of mice. These observations open the avenue to combine them with current medical treatment. Research supported by Marfans35.

OPPOSING CARDIOVASCULAR PHENOTYPES IN FIBRILLINOPATHIES: A PLATFORM FOR DRUG TARGET DISCOVERY IN MARFAN SYNDROME

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Thoracic aortic aneurysm and dissection (TAAD) is the most life-threatening manifestation of Marfan syndrome (MFS), yet no therapy fully prevents its development. To gain mechanistic insight into TAAD pathogenesis and identify potential therapeutic targets, a spectrum of fibrillinopathies caused by mutations in the *FBN1* gene were investigated. In addition to MFS, we studied Stiff Skin Syndrome (SSKS) and acromelic dysplasias (AD), which display phenotypes opposing those of MFS, with absence of TAAD as most remarkable.

The objective of this study is to identify TAAD-causative and/or protective mechanisms through comparative analysis of these opposing fibrillinopathies, with a specific focus on transcriptional regulatory networks. Aortic tissue was harvested from mouse models of MFS (*Fbn1*$^{C1041G/+}$), SSKS (*Fbn1*$^{W1572C/+}$), and AD (*Fbn1*$^{S1724C/+}$), all on a C57BL/6 background. Single-cell RNA sequencing was performed at 4 and 16 weeks of age, enabling assessment of both early and more advanced disease-associated transcriptional changes. Dimensionality reduction and clustering of the data was conducted using the Seurat package in R, and transcriptional regulatory network inference is being performed using pySCENIC.

As in humans, AD and SSKS mice do not develop thoracic aortic aneurysm nor dissection (with current follow-up till 56 and 24 weeks respectively). Single-cell transcriptomic analysis of the MFS and AD mouse models revealed the presence of all major aortic cell types, including vascular smooth muscle cells (VSMCs), endothelial cells, fibroblasts, and immune cells. Further subclustering of VSMCs identified four distinct subpopulations. Of particular interest, a modulated VSMC subtype was observed in all models, characterized by reduced expression of contractile phenotype-associated genes. More importantly, a putative protective VSMC subtype was identified, marked by elevated expression of *Tnnt2*, *Lum*, and *Dcn*. Enrichment of this VSMC population in AD mice compared to MFS suggests a possible protective mechanism. Preliminary pySCENIC analysis suggests Gata4 and Gata5 as potential regulons underlying this protective cell type, though further validation is required.

In conclusion, comparative analysis of fibrillinopathies identified a putative protective VSMC subpopulation that may contribute to resistance against TAAD. Additional integration of the SSKS model and transcriptional regulatory network inference will further elucidate the molecular mechanisms underlying this phenotype.

TARGETING OXIDATIVE STRESS WITH ALLOPURINOL ATTENUATES CARDIOVASCULAR REMODELING IN MARFAN SYNDROME

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Introduction: Marfan syndrome(MFS) is caused by mutations in the *FBN1* gene, leading to elastic fiber disruption and increased TGF-β signaling, both associated with aneurysm progression. The progression of aneurysms involves oxidative stress mediated by reactive oxygen species (ROS), including pathways involving NOX4 and xanthine oxidoreductase (XOR), which have also been implicated in aneurysm development. Although XOR inhibition using allopurinol has emerged as a potential therapeutic strategy for aneurysm, its effects in Marfan syndrome remain poorly explored. The Fbn1$^{mg\Delta lpn/+}$ mouse model reproduces cardinal MFS phenotypes (cardiovascular, skeletal, and ocular manifestations), and can be used as a model to investigate therapeutic strategies for the disease.

Aim: To evaluate the effects of allopurinol treatment on cardiovascular phenotype in Fbn1$^{mg\Delta lpn/+}$.

Methods: Forty-five C57BL/6N mice of each sex were analyzed: WT(n=10), Fbn1$^{mg\Delta lpn/+}$(n=15), WTallopurinol(n=10), and Fbn1$^{mg\Delta lpn/+}$allopurinol(n=10). Treatment began at 12 weeks of age (presence of aorta dilatation). Echocardiography, thoracic aortic blood flow analysis, spectral curve evaluation, and analysis of aortic morphology were performed.

Results: Fbn1$^{mg\Delta lpn/+}$ mice developed aortic dilation from 4weeks of age and showed reduced survival, reaching 45% in males and 60% in females at 24weeks. Allopurinol treatment increased survival to 77.8% in males and 82% in females. At 12 weeks, Fbn1$^{mg\Delta lpn/+}$ mice of both sexes exhibited significant enlargement of the aortic root and ascending aorta, while increased left ventricular mass was observed only in males. At 24weeks, allopurinol stabilized aortic root diameter and attenuated early diastolic dysfunction in Fbn1$^{mg\Delta lpn/+}$ males, but showed limited effects in females. Spectral curve analysis revealed arrhythmic patterns, and diastolic alterations in untreated mutant mice, whereas allopurinol partially restored normal flow patterns. Histological analysis demonstrated marked elastic fiber fragmentation in Fbn1$^{mg\Delta lpn/+}$mice, while allopurinol partially preserved elastic fiber integrity.

Conclusion: Cardiovascular severity differs between sexes in Fbn1$^{mg\Delta lpn/+}$mice. Allopurinol attenuates cardiovascular alterations and improves survival, supporting a potential role of ROS reduction in limiting MFS-associated cardiovascular progression.

RAMIPRIL OUTPERFORMS LOSARTAN IN LONG-TERM RESCUE OF AORTIC AND SKELETAL PHENOTYPES IN MARFAN SYNDROME

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Introduction: Marfan syndrome (MFS) is caused by mutations in the *FBN1* gene, leading to elastic fiber (EF) disruption and dysregulation of TGF-β signaling bioavailability. Pharmacological modulation of the renin–angiotensin–aldosterone system (RAAS), using losartan (Angiotensin II receptor blockers) or ramipril (Angiotensin-converting enzyme inhibitors), can attenuate TGF-β signaling; however, their long-term effects on aortic and skeletal phenotypes remain poorly explored. The Fbn1$^{mgΔlpn/+}$ mouse model reproduces classical manifestations of MFS (skeletal, cardiovascular and ocular manifestations) and survives beyond 30 weeks.

Aim: To evaluate the long-term effects of losartan and ramipril on skeletal and aortic phenotypes in 6-month-old Fbn1$^{mgΔlpn/+}$ mice.

Methods: Forty male C57BL/6N mice were analyzed: wild-type (WT, n=10), Fbn1$^{mgΔlpn/+}$(n=10), Fbn1$^{mgΔlpn/+}$Losartan (n=10), and Fbn1$^{mgΔlpn/+}$Ramipril(n=10). Treatments began at 4 weeks of age, corresponding to the onset of aortic dilatation. Spinal deformities were evaluated by digital radiography using the kyphosis index (KI). Aortic morphology and thoracic aortic blood flow were assessed, including spectral curve analysis.

Results: Fbn1$^{mgΔlpn/+}$ group began to die at 6 weeks and showed 45% survival at 24 weeks. In contrast, survival reached 95% in losartan-treated and 93% in ramipril-treated mice. Untreated Fbn1$^{mgΔlpn/+}$ and Fbn1$^{mgΔlpn/+}$Losartan mice exhibited severe skeletal deformities, whereas ramipril therapy significantly improved the phenotype, showing no significant differences compared to WT. Aortic analysis revealed significant EF fragmentation in Fbn1$^{mgΔlpn/+}$ mice. Both therapies significantly improved EF organization; however, only ramipril-treated mice showed EF morphology comparable to WT. Thoracic aortic blood flow was reduced in all mutant groups compared to WT. Spectral curve analysis demonstrated arrhythmic patterns, extrasystolic peaks, and diastolic alterations in untreated Fbn1$^{mgΔlpn/+}$ mice. Although both therapies improved spectral patterns, ramipril more effectively restored systolic and diastolic profiles.

Conclusion: RAAS blockade improves survival and aortic phenotype in Fbn1$^{mgΔlpn/+}$ mice. However, Ramipril demonstrates superior structural and functional recovery, as well as skeletal abnormalities, compared to losartan, suggesting enhanced long-term therapeutic efficacy in Marfan syndrome.

A NOVEL TRANSFORMING GROWTH FACTOR-β VACCINE FOR AORTIC ANEURYSM FORMATION IN A MOUSE MODEL OF MARFAN SYNDROME

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Introduction: Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder caused by variants in *FBN1*. Thoracic aortic aneurysm is the major cause of premature death in MFS. Previous studies showed that transforming growth factor (TGF)-β neutralizing antibodies attenuated aortic aneurysm formation in MFS mice, although clinical application remains limited.

Objectives: This study aimed to develop a therapeutic TGF-β vaccine for preventing aortic aneurysm formation in a mouse model of MFS.

Materials and Methods: Two TGF-β peptide vaccines (vaccine A and B), targeting amino acid sequences common to human and mouse TGF-β1, were generated using a carrier protein and an adjuvant. Following subcutaneous injection into *Fbn1*$^{+/+}$ mice, antibody titers were evaluated by ELISA. Vaccine A, which showed higher reactivity against recombinant TGF-β1, was administered to 4-week-old male *Fbn1*$^{C1041G/+}$ mice, while control mice received a control vaccine three times over 5 weeks.

Results: Both vaccines increased antibody titers in *Fbn1*$^{+/+}$ mice, whereas only vaccine A showed significant reactivity against recombinant TGF-β1. In 16-week-old *Fbn1*$^{C1041G/+}$ mice, vaccine A significantly suppressed ascending aortic enlargement compared with controls. Histological analyses demonstrated attenuation of aortic wall thickening, elastic fiber degeneration, proteoglycan deposition, and downstream signaling of the TGF-β pathway. No inflammatory cell infiltration was observed in the heart, kidney, or liver.

Conclusion: These findings suggest that therapeutic vaccination against TGF-β may represent a novel strategy for suppressing aortic aneurysm progression in MFS.

A NOVEL ZEBRAFISH MODEL OF MARFAN SYNDROME REVEALS IMMUNE INVOLVEMENT AND ENABLES IN *VIVO* DRUG SCREENING

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Introduction: Currently, no medical treatment effectively reduces the risk of lethal aortic dissection in patients with Marfan syndrome (MFS). To address this unmet need, we targeted fibrillin genes in zebrafish and found that fibrillin-3-deficient (*fbn3*$^{-/-}$) zebrafish recapitulate key cardiovascular manifestations of MFS. Complementing existing mammalian models, this system offers a novel platform to investigate disease mechanisms and facilitate the discovery of therapeutic targets.

Objective: To leverage the zebrafish model to identify new treatment strategies for MFS.

Methods: Fluorescent transgenic reporter lines enabled *in vivo* microscopy in *fbn3*$^{-/-}$larvae, which was complemented by transcriptomic analysis. A novel natriuretic peptide B (*nppb*) promoter-driven luciferase reporter was developed for *in vivo* high-throughput screening of cardiovascular stress.

Results: Approximately half of *fbn3*$^{-/-}$ larvae develop atrial endocardial detachment, resulting in loss of blood flow and early death. Surviving mutants exhibit dilation of the bulbus arteriosus, a structure analogous to the mammalian aortic root. Transcriptomic analysis revealed early enrichment of the complement signaling pathway in *fbn3*$^{-/-}$ larvae. *In vivo* imaging demonstrated increased abundance and patrolling behavior of neutrophils and macrophages. The *nppb*-driven luciferase reporter showed significantly elevated activity in *fbn3*$^{-/-}$ larvae. β-adrenergic and angiotensin receptor inhibition had limited effects on cardiovascular phenotype and reporter activity. Interestingly, *fbn3*$^{-/-}$ larvae displayed an exaggerated negative chronotropic response to β-adrenergic blockade, suggesting elevated baseline sympathetic tone. Unbiased high-throughput screening of >1500 compounds identified several preliminary hits, but none achieved robust phenotypic rescue in follow-up validation experiments.

Conclusions: The *fbn3*$^{-/-}$ zebrafish model recapitulates key cardiovascular features of MFS and implicates immune involvement. *In vivo* drug screening has not yet identified definitive therapeutic candidates, likely reflecting both disease complexity and the limited chemical space explored to date.

TARGETING MITOCHONDRIAL AND ER STRESS AS NEW THERAPEUTIC STRATEGIES TO HALT AORTIC DILATION IN A MURINE MODEL OF MARFAN DISEASE

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Background and purpose: Aortic dissection or rupture is the most devastating complication of aneurysms in the thoracic ascending aorta (TAA) of patients diagnosed with Marfan/Loeys-Dietz syndromes. Reparative surgery is the only effective strategy whereas new therapeutic strategies are expected. Therefore, we aim to determine the potential therapeutic effect of reducing mitochondrial and endoplasmic reticulum (ER) stress to limit the progression of aneurysms in *Fbn1*$^{C1041G/+}$ mice.

Methods: A transcriptomic analysis was performed by RNA sequencing using RNA isolated from TAA aneurysms of patients and from ascending aorta of multi-organ healthy donors. Differentially expressed genes (DEGs) related to mitochondrial dysfunction were identified with the DESeq2 package. The mitochondria-targeted tetrapeptide SS31, the peptide SS20 (3 mg/kg/day) or the ER stress inhibitor, TUDCA (150 mg/kg/day), were administered to 4-months-old mice in the water intake for 3 months. The dilation of ascending aorta and aortic root and the cardiac function were monitored by ultrasonography using the VEVO 3100. Moreover, the oxygen consumption rate (OCR) was measured in 2 mm-punches of freshly isolated ascending aortas and hearts. Orcein stain and gene expression studies were performed in murine aortas.

Results: alterations in the expression of the electron respiratory chain components and ATP synthase were detected in patients. In the murine Marfan model, the administration of SS31 and TUDCA reduced the dilation of aorta that was associated with a reduction in elastin fibers breaks. No differences in body weight or water intake were reported. Additionally, a decrease in exacerbated gene expression of Col1A1, Mmp2, Mmp9 and ER stress markers was observed in mice treated with SS31, which significantly improved OCR in explants when compared to untreated Marfan mice. Interestingly, cardiac function parameters were improved in Marfan males treated with SS31.

Conclusions: Targeting mitochondrial and ER stress is a promising therapeutic strategy to halt aneurysm progression in Marfan syndrome.

MECHANISM-BASED APPROACH IN DESIGNING PATIENT-SPECIFIC COMBINATION THERAPIES FOR NONSENSE MUTATION DISEASES

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Premature termination codon (PTC) diseases account for ~10% - 15% of all human pathological mutations including Marfan syndrome. Although there are no US FDA- approved treatments for increasing PTC readthrough, ataluren (Ata), a translational readthrough inducing drug (TRID), has conditional approval for treatment of Duchenne muscular dystrophy elsewhere. Ata displays low toxicity in clinical trials for treatment of PTC diseases, but its therapeutic effects are inconsistent. Our group described the mechanism of Ata's PTC readthrough activity https://doi.org/10.1038/s41467-022- 30080-6, which is suppression of peptide termination solely by competitive inhibition of the readthrough complex, RFC (RF1·RF3·GTP). Low toxicity of Ata is due to little or no effect at native stop codons. Ata does not block near-cognate tRNAs nor anticodon engineered tRNAs (ACE-tRNAs) that are directly complementary to the PTC enabling readthrough. tRNAs and RFC both bind to the ribosomal A-site, so it was puzzling that Ata didn't inhibit tRNA binding. This led to the hypothesis that some special locations in or near the A-site bind RFC, but not tRNAs. Two such sites were located by studying cryo-EM maps of pre-termination complexes containing RFC bound with a PRE- translocation ribosome having tRNA ternary complexes bound. These sites are prime targets for discovering novel TRIDs that are more effective than Ata while retaining its mechanism and low toxicity. We have identified several promising lead compounds.

GEMS-APP: A WEB-BASED DYNAMIC CONSENT PLATFORM ENABLING GENOME-WIDE EPISTASIS RESEARCH IN MARFAN SYNDROME

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Introduction: Rare disease genomics requires scalable, inclusive recruitment strategies that respect participant autonomy while complying with stringent data protection regulations. In Marfan syndrome (MFS), marked inter- and intrafamilial variability in cardiovascular severity highlights the need for large, deeply phenotyped cohorts to study genome-wide epistasis. Traditional static granular consent models remain a major barrier to participation.

Objective: We developed a consent model enabling broader participation.

Materials and Methods: We developed GEMS-App (Genome-wide Epistasis for cardiovascular severity in Marfan Study Application), a secure, GDPR-compliant platform enabling informed dynamic consent, global remote onboarding, and continuous engagement. The application was co-designed with patients, clinicians, researchers, ethicists, and legal experts. Key features include granular consent, identity verification, electronic signatures, accessibility adaptations, and bidirectional communication. The platform supports consent for adults, minors, and legally represented participants. Following consent, saliva kits are distributed globally for whole-genome sequencing, with integrated tracking and follow-up workflows.

Results: Since deployment, 182 participants completed dynamic electronic consent, including 31 minors (17.2%). One-third of participants completed consent in under 30 minutes, while asynchronous participation allowed others to consent over extended periods without attrition (mean GEMS sample journey is 93 days). Global saliva kit logistics and sample return were successfully coordinated, with DNA quality meeting sequencing requirements in the majority of cases (98%). The cohort displays broad geographic, age, and genetic diversity, including recurrent and rare FBN1 variants, supporting future genome-wide epistasis analyses.

Conclusions: GEMS-App demonstrates that legally robust, participant-controlled dynamic consent is feasible, scalable, and inclusive in rare disease genomics. By lowering participation barriers while maintaining ethical and regulatory rigor, this framework enables the identification of atypical and informative cases that may otherwise remain unstudied. The GEMS-App model is adaptable to other rare genetic disorders. 101 Genomes Foundation is the first Genomic Data Altruism Organisation recognised under the EU Data Governance Act.

INTRODUCING ALLOPURINOL TO THE MEDICAL TREATMENT OF MARFAN SYNDROME: ADVANTAGES, LIMITATIONS AND POTENTIAL EXTENSION TO OTHER AORTOPATHIES

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Marfan syndrome (MFS), a multisystemic connective tissue disorder, shows intra-and interfamilial aortopathy variability. More than 3,000 mutations have been reported in the *FBN1* gene, which encodes for fibrillin-1, a glycoprotein component of microfibrils and elastic fibres. Living with MFS affects the quality of life of patients. The aortic dilation mainly affects the aortic root and the ascending aorta, but dissection of the aortic wall can occur either before or after the aortic arch (type A and type B dissections, respectively). There is no doubt that progress in aortic surgery has significantly improved the life span of patients, but on the contrary, the current medical treatment based on beta-blockers (BB) and angiotensin receptor blockers (ARB) only slightly slows the aortic growth. The aortopathy is the result of a multiple defects in cellular and subcellular processes affecting aortic wall cells and the homeostasis and organization of the extracellular matrix. Pathomechanisms include dysregulated cell signalling (TGF-β, BMPs and nitric oxide), altered mechano-transduction and oxidative stress. Therefore, it is reasonable to consider a multi-target strategy for the medical treatment. Here, we suggest the incorporation of allopurinol as a complementary drug to the current medical (BB/ARB) treatment. Its mode of action is based on its strong antioxidant effects demonstrated in preclinical assays in different mouse models of MFS. Importantly, allopurinol is a widely used compound in medical practice for gout, and it has been demonstrated to be safe, economical and efficient in a variety of other cardiovascular diseases. We here indicate its pros and cons for its administration in MFS aortopathy and extrapolate its potential use to other aortopathies where oxidative stress was shown to be determinant in disease development. The recent approval of allopurinol as orphan drug for MFS by the European Medicines Agency (EMA) is indicative of its therapeutic potential.

ALLOPURINOL-MEDIATED REDUCTION OF OXIDATIVE STRESS AND INFLAMMASOME IMPROVES CARDIOVASCULAR PHENOTYPE IN A WILLIAMS-BEUREN SYNDROME MOUSE MODEL

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Introduction: Cardiovascular disease is the major cause of morbidity in Williams–Beuren syndrome (WBS), a neurodevelopmental disorder caused by a hemizygous 7q11.23 deletion. The condition features systemic hypertension, cardiac dysfunction, and progressive vascular remodeling driven by *ELN* haploinsufficiency and oxidative stress. Because these abnormalities emerge at pediatric age and worsen across life, patients require long-term treatment, raising concerns about cumulative drug exposure and safety.

Objectives: Evaluate whether pediatric-equivalent doses of Allopurinol (Alo) a highly specific xanthine oxidoreductase inhibitor, and Losartan (Los) an angiotensin II type 1 receptor antagonist, exert beneficial effects on the cardiovascular phenotype.

Materials and Methods: Complete deletion mouse model (CD) and wild-type (WT) littermates treated with Alo (20mg/kg) and Los (2 mg/kg). Cardiac function was assessed by echocardiography and hypertension monitoring by non-invasive blood pressure measurement. Hearts and aortas were collected for histological analysis and molecular profiling of disease- and treatment-related biomarkers.

Results: In CD, both therapeutic interventions produced significant reductions in systemic blood pressure, enhanced cardiac function, and attenuated stenosis. Notably, only Alo achieved complete normalization of left-ventricular dimensions. The cardioprotective effects of ALO appear to be mediated through reductions in oxidative stress and NLRP3 expression.

Conclusion: These findings support a therapeutic model in WBS by which Allopurinol offers broader cardiovascular protection in comparison to Losartan.

IMPACTS OF PHARMACOLOGICAL INTERVENTIONS ON AORTA CHANGE IN PATIENTS WITH MARFAN SYNDROME: A NETWORK SYNTHESIS

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Background: Drug options for treating Marfan syndrome (MFS) still warrant further investigation. This study aimed to comprehensively investigate the effectiveness and safety of medication strategies in managing MFS.

Methods: Studies of randomized controlled trials (RCT) evaluating medical outcomes in MFS published in the Cochrane Library, Cochrane CENTRAL, EMBASE, and PubMed were selected. The outcomes included changes of aortic growth rate, cardiovascular events and adverse events.

Results: Sixteen RCTs involving 1682 patients were enrolled and contributed to a seven-node network analysis model. As compared with no treatment, RI+BB significantly reduced aortic root growth (standardized mean difference [SMD] - 1.90, 95% confidence interval [CI]: -2.91–-0.89), followed by ARB+BB (SMD - 1.75, 95%CI: -2.40–-1.10). RI+BB did not significantly increase the risk of adverse events (risk ratio [RR] 0.41; 95% CI: 0.01–17.90), cardiovascular mortality (RR 1.08; 95% CI: 0.01–114.78), and all-cause mortality (RR 0.43; 95% CI: <0.01–38.02) as compared with no treatment. There was no data available regarding the risk of aortic surgery with RI+BB.

Conclusion: For cardiovascular protection in MFS, RI+BB and ARB+BB seem to be the priority medical strategies if patients can tolerate treatment without contraindications, especially for those with rapid aortic growth or aortic aneurysm. Larger RCTs with extended follow-up are warranted to provide stronger evidence for clinical practices.

FIBRILLIN-1 DEFICIENCY IN MARFAN SYNDROME DISRUPTS ENDOTHELIAL CELL QUIESCENCE

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Introduction: Marfan syndrome (MFS) is caused by mutations in the ECM protein fibrillin-1 (Fbn1) and is associated with cardiovascular, ocular and skeletal abnormalities. Fbn assembles into microfibrils that function as stretchable anchoring ligaments or serve as a scaffold for elastin deposition in the formation of elastic fibers. In the aorta of MFS patients, defects in the microfibrils and elastic fibers compromise the integrity of the aortic wall, leading to aneurysms and dissections, which are the leading cause of death. While the effects on medial smooth muscle cells have been extensively documented, little is known about the endothelium during the pathological remodeling of the aorta.

Objective: To explore the consequences of a Fbn1 deficiency on the integrity of the aortic intima in a mouse model of MFS.

Methods and Results: We used the $Fbn1^{C1041G/+}$ mouse model that leads to Fbn1 haploinsufficiency and thereby reproduces the main features of the human disease. We will present some of the alterations observed in the aortic endothelium and basement membrane of these mice, particularly those related to phenotype, signaling, and biomechanics. We will show how Losartan treatment, that prevents aortic enlargement in this model, rescues major intimal defects. The causes of these defects are explored *in vitro* in aortic endothelial cells silenced for Fbn1. These experiments reveal endothelial defects that phenocopy those observed in the endothelium of $Fbn1^{C1041G/+}$ mice.

Conclusions: In the aorta of this MFS mouse model, we demonstrate that, in addition to the defected observed in the media, the intima is significantly affected by the mutation. Given that endothelial cells play a major role in maintaining vascular wall homeostasis, intimal lesions help explain the decline in vascular function and raise questions regarding the respective contributions of the media and intima to pathological aortic remodeling, as well as regarding the mechanism of action of losartan.

THE AMP-KINASE ACTIVATOR AICAR DOES NOT RESCUE AORTIC PATHOLOGY IN TWO ANEURYSM MODELS

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Introduction and objectives: Aortic aneurysm progression may result in aortic dissection/rupture, with high morbidity and mortality rates. Apart from aortic surgery there is no pharmacological treatment to prevent aneurysm progression. Recently mitochondrial dysfunction was identified as pathological process and thus as novel target. We previously showed in *Fbn1*$^{C1041G/+}$ Marfan mice that nutraceutical resveratrol could reduce aortic root dilatation. Since resveratrol can activate sirtuin1 or the energy stress sensitive AMP-Kinase (AMPK) pathway to enhance mitochondrial biogenesis, we here used AICAR as AMPK activator to study rescue of mitochondrial dysfunction in the Marfan mice and in the angiotensin-II (AngII)-induced aneurysm/dissection model.

Materials and Methods: Male *Fbn1*$^{C1041G/+}$ mice or apolipoprotein-E deficient (ApoE-/-) mice infused with AngII (1 µg/kg/min) were treated with AICAR. The Marfan mice were 8 weeks old and received AICAR (100 mg/kg/day) in drinking water for 16 weeks. The hearts and aortae were harvested for histology, aortic measurements and RNA sequencing. Twelve weeks old ApoE-/- mice were infused with AngII via osmotic minipumps and were intraperitoneally injected with AICAR (200 mg/kg/day) for 28 days. The abdominal aorta was measured by ultrasonography and harvested for histology, RNA isolation and qPCR.

Results: AICAR treatment of Marfan mice and AngII-induced ApoE-/- mice did not rescue aortic pathology. Comparing RNA-sequencing analysis of the ascending aorta/ aortic arch of wild-type and Marfan mice showed mitochondrial dysfunction, inflammation, muscle regeneration and apoptosis as main pathological pathways in Marfan, which were exacerbated by AICAR treatment. Similarly, gene expression in the aortic tissues from AngII-infused mice revealed enhanced mitochondrial and endoplasmic reticulum stress upon AICAR administration, providing a clue that additional energy stress on top of the already existing mitochondrial dysfunction may harm the diseased aortic cells even further.

Conclusion: In targeting aortic mitochondrial dysfunction, the pharmacological agent should have immediate benefit rather than induce more metabolic stress.

LONGITUDINAL CHANGES IN AORTIC ROOT DILATION DURING GNRH AGONIST THERAPY IN PEDIATRIC MARFAN SYNDROME

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Introduction: Marfan syndrome is associated with progressive aortic root dilation beginning in childhood. Pubertal growth and sex hormone changes may influence vascular remodeling, but the potential impact of gonadotropin-releasing hormone agonist therapy on aortic root progression has not been well described.

Objectives: This study aimed to investigate whether GnRH agonist therapy is associated with changes in the progression of aortic root dilation in pediatric patients with Marfan syndrome.

Materials and Methods: We conducted a single-center retrospective cohort study of pediatric patients diagnosed with Marfan syndrome at our institution. Medical records of 158 patients were reviewed from November 1994 to July 2025. Clinical data, GnRH agonist exposure, serial echocardiographic measurements, aortic root diameter, aortic root z-scores, medication use, and follow-up duration were collected. The annual rate of change in aortic root z-score was compared according to GnRH agonist exposure and, when applicable, before and after initiation of therapy.

Results: Among 158 pediatric patients with Marfan syndrome, 46 received GnRH agonist therapy. The median age at treatment initiation was 9.9 years (range 6.6–12.9 years), and the median follow-up duration was 10.4 years (range 1.3–29.7 years). Compared with change of aortic root Z-score in patients who did not receive GnRH agonist therapy, treated patients showed no significant difference in progression of aortic root dilation. After adjustment for age, sex, baseline aortic root z-score, and use of beta-blockers or angiotensin receptor blockers, GnRH agonist therapy was not associated with aortic root z-score progression.

Conclusion: In this single-center pediatric Marfan cohort, GnRH agonist therapy was not associated with altered progression of aortic root dilation. These findings suggest that modulation of pubertal hormonal exposure may have potential relevance to aortic growth in Marfan syndrome, although further prospective studies are needed.

KLF15, A PROTECTIVE FACTOR FOR THORACIC AORTIC ANEURYSM IN MARFAN SYNDROME

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Introduction. Marfan syndrome (MFS) is a connective tissue disorder caused by pathogenic *FBN1* variants and characterized by life-threatening thoracic aortic aneurysm and dissection (TAAD). Even when MFS patients harbor the same causal *FBN1* variant, substantial variability in aortic disease severity can be observed, suggesting the presence of genetic and/or environmental factors.

Objective. To identify genetic factors modifying cardiovascular severity in Marfan syndrome patients.

Methods. We selected 13 patients at the extreme end of the phenotypical spectrum harboring the identical *FBN1* c.7754T>C p.(Ile2585Thr) variant. Patients were stratified into Affected Mutation Carriers (AMCs; n=8) and Unaffected Mutation Carriers (UMCs; n=5) based on aortic measurements and surgical history. RNA-sequencing, whole-genome sequencing, and DNA methylation analyses were performed using peripheral blood mononuclear cells (PBMCs), complemented by functional validation in *Fbn1*$^{C1041G/+}$ Marfan mice and *Klf15* knockout lines.

Results. RNA-seq of PBMCs identified seven differentially expressed genes between UMCs and AMCs, enriched for extracellular matrix–related pathways. *KLF15* emerged as the most compelling candidate, showing significantly higher expression in UMCs (adj p-*value* = 0.02), a finding confirmed by qPCR. No identified coding or regulatory variants, nor differential methylation at the *FBN1* or *KLF15* loci, explained this expression difference. Moreover, *Klf15* deficiency exacerbated aortic growth in MFS mice. Single-cell RNA-seq demonstrated reduced *Klf15* expression in vascular smooth muscle cells from Marfan mice, supporting a cell-intrinsic role.

Conclusion. These results identify *KLF15* as a potential protective factor of aortic disease in MFS, detectable in PBMCs and functionally relevant *in vivo.* This work highlights *KLF15*-dependent pathways as candidates for improved risk stratification and therapeutic targeting.

DECODING MARFAN SYNDROME CARDIOMYOPATHY USING ADVANCED STEM CELL-DERIVED HEART MODELS

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Marfan syndrome (MFS) is caused by pathogenic variants in the *FBN1* gene, encoding the fibrillin-1 protein, a major structural component in the extracellular matrix (ECM). As a result, patients may present primary cardiomyopathy of which the precise pathogenesis is still unknown to this day. To date, more than thousands of distinct *FBN1* variants have been identified, contributing to substantial variation in clinical expression among patients. Moreover, the interpretation of disease mechanisms is complicated by patient-specific genetic background effects that may act as confounding factors.

Cardiomyocytes (CM) and cardiac fibroblasts (CF) can both be derived from human induced pluripotent stem cells (hiPSCs) enabling the generation of patient specific cardiac models. CFs are increasingly recognized as crucial contributors to myocardial development, structure and mechanobiology particularly through their role in ECM production and remodeling.

Previously published data showed that MFS CMs and CFs (c.3725G>A, p.Cys1242Tyr) were stiffer than their CRISPR-Cas corrected isogenic counterparts, as measured by atomic force microscopy. MFS CMs displayed structural changes as observed by increased sarcomere length when co-cultured with CFs. In addition, the multi electrode array (MEA) revealed that MFS CMs showed decreased contraction amplitude and beat-to-beat variability compared to corrected isogenic CMs.

To better understand the substantial variation in clinical expression caused by variants across the *FBN1* gene, various hiPSCs and their CRISPR-Cas corrected isogenic counterparts are currently being generated from material of different MFS patients collected at the Ghent University Hospital. In parallel, preliminary results within these MFS CMs reveal patient-specific electrophysiological differences, based on MEA and calcium transient essays. Additionally, differences in the mitochondrial respiration were observed based on Seahorse metabolic assays. Lastly, advanced MFS cardiac organoid models exhibit early morphological inconsistencies during early development within a 3D physiologically relevant context.

By combining these cardiac cell types and their produced ECM, advanced in vitro heart tissue models can be generated from multiple patient-derived iPSCs that will be used to study the structural, electrophysiological and molecular contributions of heart muscle and matrix in Marfan-related cardiomyopathy.

MARFAN IPSC- VASCULAR SMOOTH MUSCLE CELLS (VSMCS) MODEL AORTIC ANEURYSM BY RECAPITULATING THEIR PATHOGENIC PHENOTYPIC SWITCHING EVENTS ENABLING TARGET IDENTIFICATION TO CURB CHONDROGENESIS IN MARFAN AORTAS

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Introduction: Marfan syndrome is caused by mutation(s) in *FBN1* leading to life-threatening ascending aortic aneurysms. Aortic pathology is typified by degradation of extracellular matrix(ECM) and loss of contractile vSMCs. The mechanisms by which FBN1 mutations lead to aneurysm are poorly-characterised. Increased aortic stiffness is an early feature of disease, accompanied by calcification and proteoglycan accumulation confirmed in mouse and humans. We propose that cellular source of these changes is phenotypic-switching of vSMCs. *FBN1*-mutants have altered ECM-cell surface receptor interactions likely driving signalling events favouring osteo-chondrogenic switch, explaining vascular stiffening that precedes pathogenic ECM remodelling and aneurysm.

Objectives: 1) To recapitulate aortic phenotype of Marfan patients using iPSC-derived vSMCs.

2) To manipulate disease-mechanisms using small-molecules to control phenotype-switching towards osteo-chondrogenic lineages.

Methods: Marfan-iPSC derived vSMCs were cultured on hydrogels of physiological stiffness-(12kPa). Bulk transcriptomic comparison of two Marfan lines against two WT controls was performed. We re-analysed mouse single-cell transcriptomic dataset GSE186845 (Pedroza et al, ATVB, 2020). Immunostaining of aortic sections of Marfan$^{(Mgr/Mgr)}$ mice.

Results: Phenotypic switching was detected in both Marfan lines, characterised by upregulation of chondrogenesis related-markers 1) transcription factors, 2) cell-signalling, 3) matrix proteins and 4) mineralisation. Co-upregulation at all four levels confirms a functional transition reshaping the ECM towards cartilage-like with mineralization. Upregulation of stiffness-compensatory ECM-remodellers (ADAMTSL1, ADAMTS9), and proteoglycans (MGP, SDC4, SRGN, HAS2), represent maladaptive attempts to soften matrix. This stiffness response is cell-autonomous, since, on physiologically soft hydrogels, Marfan-vSMCs showed nuclear-YAP1 whilst WT cells showed cytoplasmic YAP1 localization, demonstrating that Marfan vSMCs sense their own aberrant matrix as stiffer. We validated upregulation of chondrogenic markers in aortas of Marfan$^{(Mgr/Mgr)}$ mice and GSE186845. We previously showed that Wnt-signaling (regulator of chondrogenesis) is repressed in Marfans and GSK3β inhibitors could ameliorate proteolysis across 4 Marfan-iPSC-vSMC lines (Daavapil *et al*, SCR-2023). We currently are testing GSK3β inhibitors to control chondrogenic phenotype-switch.

Conclusion: Our findings establish aberrant chondrogenic switching as a potential disease-mechanism and therapeutic target for early intervention in Marfan syndrome.

IMPLICATION OF ASPROSIN (FIBRILLIN-1-DERIVED PEPTIDE) IN CONNECTIVE TISSUE DISORDERS

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Introduction: Proteolytic processing of fibrillin-1 (FBN1) gives rise to the C-terminal peptide hormone asprosin, which acts as a glucogenic hormone and may act as a mediator of interorgan communication.

Objectives: This study aimed to investigate the mechanisms that control the bioavailability of asprosin and to evaluate its potential as a circulating biomarker for Marfan syndrome.

Methods: Specific asprosin antibodies were generated and affinity purified, and a sensitive asprosin ELISA was established. Asprosin levels in saliva and blood from Marfan patients and controls were quantified and correlated with clinical parameters. Patient-derived fibroblasts and tissues were analyzed for fibrillin-1/asprosin expression, ECM organization, secretion dynamics, and their relationship to circulating asprosin.

Results: Asprosin was detected as long extracellular fibers within connective tissues. Asprosin fiber formation required an intact fibrillin-1 network, the interaction with the fibrillin-1 N-terminus, and transglutaminase-2 (TG2)-mediated crosslinking. Muscle-specific deletion of asprosin markedly reduced circulating levels, identifying skeletal muscle as a major reservoir and supporting a role for monomeric asprosin in interorgan communication. Adenoviral overexpression of asprosin in FBN1-low tissues led to fiber formation only in FBN1-rich organs, suggesting that firbillin-1 fibers are required for local tissue storage of asprosin. In Marfan patients, blood and saliva asprosin levels were significantly elevated and correlated with fibrillin integrity and cardiovascular complications.

Discussion: Our findings identify a new TG2-dependent mechanism of asprosin storage and bioavailability. Altered asprosin regulation in Marfan syndrome suggests that impaired fibrillin-1 integrity disrupts its tissue storage. Together, our results suggest asprosin as a potential new biomarker for Marfan syndrome.

DEVELOPMENT OF A CRISPRI-BASED FUNCTIONAL GENOMICS PLATFORM TO IDENTIFY MOLECULAR MODIFIERS OF MARFAN-RELATED CARDIOMYOPATHY IN HIPSC-DERIVED CARDIOMYOCYTES

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Marfan syndrome is a heritable connective tissue disorder caused primarily by pathogenic variants in *FBN1,* encoding for fibrillin-1, affecting multiple organ systems including the cardiovascular system. Emerging evidence is suggesting that in a subset of patients there is a intrinsic cardiomyopathy, that cannot be fully explained by altered loading conditions, valve dysfunction, or prior cardiovascular surgery. Although Marfan syndrome is primarily caused by pathogenic variants in *FBN1*, the development of Marfan-related cardiomyopathy is likely influenced by multiple interacting mechanisms, including extracellular matrix remodelling, altered mechanotransduction, dysregulated TGF-β signalling and cardiomyocyte–fibroblast crosstalk. This is why in this project, we aim to develop, optimize and validate an **arrayed CRISPR interference (CRISPRi) genetic screening approach in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs)** to identify novel causal and mainly disease-modifying genes for cardiomyopathy. The platform is built around a hiPSC line stably expressing a dCas9-KRAB transcriptional repressor, enabling efficient and reversible gene silencing.

We have compiled a curated list of 250 cardiomyopathy-related candidate genes for which sgRNA library design and delivery will be optimized using photoporation or lipofection. Following successful gene knockdown, functional phenotyping will be performed in an arrayed format, using multi-electrode array (MEA) recordings to assess electrical activity, conduction, and arrhythmic behaviour alongside live calcium imaging to quantify calcium handling abnormalities. Knockdown efficiency and downstream transcriptional effects will be validated using RNA sequencing and RT-qPCR.

Overall, this work will provide a robust methodological framework for CRISPRi-based functional genomics in hiPSC-CM. The platform provides a powerful strategy to systematically investigate disease-modifying pathways and identify genes that contribute to or modulate the Marfan-related cardiac phenotype, thereby advancing our understanding of the underlying molecular mechanisms and potentially revealing novel therapeutic targets.

SKIN AS A WINDOW TO THE ARTERY: A NOVEL PILOT STUDY OF EXTRACELLULAR MATRIX CONCORDANCE

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INTRODUCTION: While vascular tissue quality is central to pathology development and intervention outcomes, pre-operative evaluation of arterial tissue quality is not feasible.

OBJECTIVES: We hypothesize that skin extracellular matrix (ECM) analysis can be used as a surrogate for arterial tissue ECM architecture. We aim to characterize distributional similarity of collagen fibrils between dermal and arterial tissue.

METHODS: Paired dermal and arterial samples were obtained from six patients with arteriopathy and one control and analyzed via transmission electron microscopy (TEM). Collagen fibril diameter and heterogeneity were quantified using validated macros in ImageJ/FIJI. Distributional similarity was assessed with overlapping coefficient (OVL) via kernel density estimation, and effect size was evaluated using Cohen's d.

RESULTS: Papillary dermis fibril distributions showed greater similarity to arterial tissue than reticular dermis (mean OVL: 44% vs. 19%). The control sample exhibited the highest papillary-to-arterial overlap (OVL = 83.2%, d = -0.26). Except for one case with vascular Ehlers-Danlos Syndrome, effect sizes between papillary dermis and arterial tissue were smaller than in reticular dermis. Median fibril diameter in papillary dermis more closely approximated arterial tissue, whereas reticular dermis medians were on average 5-6x more distant (range: 2.8x-12.6x).

CONCLUSION: Dermal collagen fibril distributions in TEM demonstrate measurable similarity to arterial tissue, particularly the papillary dermis. Although this work is exploratory and requires further validation, the findings indicate that skin may serve as a surrogate for arterial ECM organization and provide a foundation for biologically informed assessment of vascular tissue quality.

THE ROLE OF FIBRILLIN FRAGMENTS IN MARFAN AORTOPATHY

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Introduction: Marfan syndrome (MFS) is a heritable connective tissue disorder with highly variable disease severity and clinical presentation, even among affected individuals within the same family. Reliable circulating biomarkers reflecting disease severity and underlying pathophysiology remain lacking.

Objectives: To assess circulating fibrillin-1 fragments in patients with MFS versus healthy controls and evaluate their potential as biomarkers.

Materials and Methods: Plasma samples from 85 patients with MFS (43.5% male; median age 36.0 years [IQR 22.4-47.3]) and 39 age- and sex-matched controls were analyzed. Three fibrillin-1 fragments (B15-HRP78, B15-HRP201, B15-HRP26) were quantified. The highest fragment concentration per individual was used. Associations with *FBN1* variant type, age and cardiovascular disease severity were evaluated. Aortic root and ascending aorta diameters were measured by echocardiography and expressed as z-scores (Campens nomograms).

Results: Fibrillin-1 fragment levels were significantly lower in patients with MFS compared to controls (median 0.03µg/mL [IQR 0.02-0.05] vs 0.04µg/mL [IQR 0.03-0.05]; p=0.012). Levels remained consistent across sexes and did not vary by *FBN1* variant type (haploinsufficient vs dominant-negative). A significant inverse correlation was observed between fragment levels and age (ϱ = -0.247; p=0.006), independent of MFS diagnosis. Within the MFS cohort, lower fragment levels were associated with larger aortic dimensions, reaching significance for the ascending aorta z-score (ϱ = - 0.41; p=0.005) but not for the aortic sinus (ϱ = -0.10; p=0.441). Fragment levels were not associated with the occurrence of aortic events.

Conclusion: Circulating fibrillin-1 fragment levels were inversely correlated with age and ascending aortic dimensions, but not with aortic events. Although their utility as a clinical biomarker appears limited, reduced levels in MFS may reflect diminished systemic fibrillin-1 availability rather than increased matrix degradation. These findings provide insight into disease pathophysiology and may help inform and inspire future targeted therapeutic strategies, including molecular or gene-based approaches.

DISCRIMINATIVE VALUE OF CARDIOVASCULAR MAGNETIC RESONANCE-DERIVED PULSE WAVE VELOCITY FOR AORTIC DISSECTION IN MARFAN SYNDROME

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Introduction: Aortic root dilatation is a key cardiovascular feature of Marfan syndrome (MFS), and aortic dissection (AoD) remains a leading cause of mortality. Prophylactic aortic root replacement (AoRR) prevents AoD, with surgical timing currently guided by aortic diameters, growth rate, and family history. Nevertheless, some patients experience AoD before reaching surgical thresholds.

Objectives: To evaluate whether aortic pulse wave velocity (PWV) improves prediction of AoD in patients with MFS.

Materials and Methods: We conducted a prospective study including 45 patients with MFS (55.6% women, age 34.5±11.6years). All underwent magnetic resonance angiography with measurement of total aortic PWV and were followed for 7.6±1.7years. Patients were divided according to occurrence of AoD after PWV assessment (n=8). Multivariate Firth's logistic regression identified independent predictors of AoD, and ROC-curve analysis determined the optimal PWV cutoff.

Results: As previously described, higher total aortic PWV was associated with older age ($p<0.001$), larger aortic root diameter ($p=0.002$), and hypertension ($p=0.016$). During follow-up, eight patients (17.8%) developed AoD (1 type A, 7 type B). Patients with AoD had significantly higher baseline PWV than those without AoD (median 7.5m/s [IQR 6.2-8.1] vs 4.8m/s [4.3-5.5]; $p<0.001$). In multivariate analysis, total aortic PWV independently predicted AoD (OR 3.5 per m/s increase, 95% CI 1.7-15.2; $p<0.001$), whereas baseline aortic diameter was not independently associated with risk. ROC-analysis identified a PWV cutoff of 5.84m/s as the best discriminator for AoD (sensitivity 87.5%, specificity 85.7%, AUC 0.907).

Conclusion: Higher baseline total aortic PWV may indicate increased dissection risk during long-term follow-up in MFS. Although increased PWV and vascular stiffness have previously been described in MFS, their direct association with subsequent aortic dissection has not been clearly established. These results therefore suggest that PWV may complement existing criteria for prophylactic aortic surgery. Larger studies are needed to validate these results and refine PWV cutoffs.

INVESTIGATION OF IGFBP2 SERUM LEVELS AS A BIOMARKER FOR THORACIC AORTIC ANEURYSM AND DISSECTION

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Background: TAAD is a condition that is often detected only in its advanced and life-threatening stages, impeding efficient intervention. Reliable circulating biomarkers could improve early detection and monitoring. IGFBP2, involved in vascular remodelling and smooth muscle cell dysfunction, is upregulated in TAAD aortas and is therefore an interesting candidate biomarker for TAAD.

Objectives: This study investigated the biomarker potential of serum IGFBP2 levels for thoracic aortic aneurysm and dissection (TAAD).

Methods: Serum IGFBP2 levels were cross-sectionally measured in 34 controls, 184 patients with thoracic aortic aneurysm (TAA), and 20 patients with thoracic aortic dissection (TAD). Longitudinal Igfbp2 levels were also analysed in mouse models of Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS) aortopathy.

Results: Serum IGFBP2 levels were significantly higher in patients with TAD (497.2 ± 365.4 ng/mL) compared with both controls (315.3 ± 123.6 ng/mL, p = 0.016) and TAA patients (351.7 ± 228.9 ng/mL, p = 0.023). Discriminative ability was modest (AUCTADvsCONTROL = 0.669 & and AUCTADvsTAA = 0.642), and no significant correlation was observed between IGFBP2 levels and aortic z-scores in TAA patients. Sex-stratified analyses suggested an improved discrimination ability in females (AUC TADvsCONTROL= 0.782, AUCTADvsTAA=0.742). In both mouse models, serum Igfbp2 levels did not correlate with aortic diameter and were not significantly different between mutant and wild-type (WT) animals across age.

Conclusions: Overall, serum IGFBP2 levels are elevated in patients with TAD but show limited performance as a standalone biomarker. IGFBP2 may nevertheless contribute to multi-marker biomarker panels for TAD.

GENERATION AND FUNCTIONAL CHARACTERIZATION OF AN IPSC-DERIVED ENDOTHELIAL CELL MODEL FOR *IPO8*-RELATED SYNDROMIC THORACIC AORTIC ANEURYSM AND DISSECTION

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Introduction: Thoracic aortic aneurysm and dissection (TAAD) is a life-threatening condition often developing in the context of hereditary connective tissue disorders. Endothelial cells (ECs) regulate vascular homeostasis through barrier integrity maintenance, inflammation control, and nitric oxide (NO) production, with EC dysfunction contributing to TAAD. However, most TAAD research focuses on characterization of vascular smooth muscle cell abnormalities, leaving EC involvement insufficiently explored.

Objectives: This study aims to investigate EC dysfunction in *IPO8*-related TAAD by generating and characterizing a mutant induced pluripotent stem cell–derived EC (iPSC-EC) model.

Materials and Methods: Two iPSC clones with a bi-allelic *IPO8* c.819delT ((p.F273Lfs*22) variant and its isogenic control clone were each differentiated twice into iPSC-ECs following the protocol of de Graaf et al. (2019). Functional assays assessing proliferation (CyQUANT, Invitrogen, #C35011), NO production (DAF-FM DA, Sigma-Aldrich, #D1946), and oxidative stress (CellROX, Invitrogen, #C10444) were used along with immunocytochemistry targeting the standard EC markers PECAM1 and VE-Cadherin as well as the EC activation markers ZO-1, caveolin-1, eNOS, and ICAM.

Results: All iPSC-ECs showed expected morphology, formed confluent monolayers, and expressed PECAM1 and VE-Cadherin. Mutant iPSC-ECs displayed reduced proliferation ($p < 0.0001$), matching observations during routine culture. Oxidative stress assay showed elevated reactive oxygen species in mutants compared to control ($p = 0.0347$). ICC revealed no differences in ZO-1, caveolin-1, eNOS, and ICAM expression. NO production was also comparable between groups ($p = 0.4646$). All assays were consistent across differentiation rounds and between the two IPO8 mutant clones.

Conclusion: Findings suggest that EC dysfunction in *IPO8*-related TAAD is driven primarily by impaired proliferation and oxidative stress rather than NO dysregulation. However, further studies should address additional EC functions, such as barrier integrity, and confirm results in an independent *IPO8* mutant line.

QUANTITATIVE 3D AORTIC SHAPE ANALYSIS DETECTS HERITABLE THORACIC AORTIC DISEASE IN NON-DILATED AORTAS

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Introduction: Heritable thoracic aortic disease (HTAD)—including Marfan, Loeys-Dietz, vascular Ehlers-Danlos, and related syndromes—can dissect catastrophically before the aorta meets diameter criteria for dilation. In gene-positive individuals with normal-sized aortas and in those with uninformative genetic testing, no established imaging biomarker positively identifies aortic involvement, and management defaults to indefinite serial imaging.

Objectives: To develop a high-resolution geometric framework for vertex-wise shape comparison across patients and evaluate whether quantitative 3D shape descriptors detect HTAD in non-dilated aortas independent of diameter.

Materials and Methods: Thoracic CT angiograms were segmented and parameterized into a 3D polynomial representation of the ascending aorta, arch, and descending aorta (root and arch vessels excluded), enabling vertex-wise correspondence across patients. Six purely geometric wall-surface descriptors were specified a priori: focal bulging, surface tangential skew, wall bending, ascending and descending cross-sectional asymmetry, and descending longitudinal proportion. The primary cohort comprised non-dilated aortas (mid-ascending ≤38 mm, sinus of Valsalva ≤40 mm); HTAD cases were matched 1:3 to controls on age, sex, and body surface area. Diameter-adjusted shape descriptors and sinus diameter were combined in a cross-validated multivariable logistic model. Performance was also evaluated in expanded cohorts including mildly dilated (≤42 mm) and unrestricted-diameter aortas.

Results: The non-dilated cohort comprised 41 HTAD cases (12 Marfan syndrome, 29 non-Marfan gene-confirmed HTAD) and 123 matched controls. The combined model achieved AUC 0.87 [95% CI 0.79–0.94], sensitivity 83%, specificity 85%, NPV 94%. Shape alone (AUC 0.83) outperformed sinus diameter alone (0.69); mid-ascending diameter added no signal beyond sinus. In expanded cohorts including mildly dilated (n=168) and unrestricted-diameter aortas (n=214), combined-model AUC rose to 0.89 and 0.93, respectively.

Conclusion: Quantitative 3D shape analysis detects HTAD in patients with normal-sized aortas with high NPV, providing diagnostic information where diameter is silent and complementing it where diameter contributes. This supports earlier and more confident risk stratification of gene-positive individuals before dilation occurs.

DEVELOPMENT OF AN AI-POWERED MOBILE APPLICATION FOR POINT-OF-CARE FACIAL PHENOTYPING IN HERITABLE THORACIC AORTIC DISEASE

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Introduction: Heritable thoracic aortic diseases (HTAD) are frequently underdiagnosed despite the availability of effective surveillance and preventive surgical strategies. Recognition remains challenging because syndromic features are often subtle, variable, and overlooked outside specialized genetics clinics. Existing facial analysis tools are not optimized for HTAD, have limited gene-level resolution, and are often proprietary. An accessible point-of-care facial phenotyping application could improve early detection and referral for genetic evaluation across diverse clinical settings, including pediatrics, emergency care, and regions without access to genetic specialists or testing.

Objectives: To develop and evaluate a mobile facial phenotyping application for point-of-care identification of syndromic HTAD.

Materials and Methods: We developed an iOS mobile application integrating deep learning-based facial phenotyping models trained on facial photographs from individuals with molecularly confirmed HTAD enrolled through the Montalcino Aortic Consortium (MAC). The application performs real-time image capture and classification for HTAD-associated conditions, including Marfan syndrome (*FBN1*), vascular Ehlers-Danlos syndrome (*COL3A1*), and Loeys-Dietz syndrome associated with *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2* genes. Explainable AI methods were incorporated to identify facial regions contributing to classification predictions. Model performance was evaluated using receiver operating characteristic analyses.

Results: The application accurately identified multiple syndromic forms of HTAD with high overall diagnostic performance, with AUC values ranging 0.82 to 0.98 across gene-specific models. The platform distinguished affected individuals from controls and differentiated clinically overlapping HTAD conditions. Explainable AI heatmaps identified discriminative facial regions involving the eyes, nose, lips, and midface. The application enabled real-time image capture and generated gene-level probability scores and visual classification outputs directly at the point of care.

Conclusion: This mobile facial phenotyping application demonstrates the feasibility of point-of-care AI screening for syndromic HTAD. This approach could improve early diagnosis, reduce delays in referral for genetic testing, and extend specialized aortic disease expertise beyond genetics clinics.

NANOPARTICLE CONTRAST-ENHANCED COMPUTED TOMOGRAPHY OF AORTOPATHY AND CARDIAC ABNORMALITIES IN A MOUSE MODEL OF MARFAN SYNDROME

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Introduction: Thoracic aortic aneurysm and dissection (TAAD) remain a leading cause of mortality in individuals with Marfan syndrome (MFS). Although aortic diameter is widely used for clinical risk stratification, dissections often occur in the absence of significant dilation, highlighting the need for biomarkers that directly assess aortic wall health.

Objective: To evaluate nanoparticle contrast–enhanced computed tomography (nCECT) for *in vivo* phenotyping of thoracic aortopathy and cardiac abnormalities in the fibrillin-1 hypomorphic *Fbn1*$^{mgR/mgR}$ mouse (mgR), a well-established model of MFS.

Methods: Longitudinal nCECT was performed in mgR (n = 25) and wild-type (n = 8) mice starting at ~6 weeks of age and repeated every 2–3 weeks for 6 months. A liposomal iodine nanoparticle contrast agent was used for nCECT. Acute and delayed nCECT scans were acquired at each time point to evaluate aortic enlargement and wall barrier integrity. Images were also analyzed for cardiothoracic abnormalities. Imaging findings were correlated with gross pathology, histological analyses and synchrotron phase-contrast imaging of excised aortas.

Results: nCECT enabled *in vivo* visualization of MFS-like cardiovascular abnormalities in mgR mice, including ascending aortic aneurysm (84%), aortic root enlargement (76%), and aortic tortuosity (80%). Intramural CT signal consistent with compromised aortic wall barrier integrity was detected in the ascending aorta (76%) and aortic root (56%) and correlated with aortic dissection on gross examination. Additional findings included cardiomegaly (76%), diaphragmatic hernia (32%), valvular enhancement (28%), and myocardial enhancement (44%). These abnormalities were absent in wild-type mice. Overall, 68% of mgR mice died prematurely, with 29% showing evidence of ascending aortic rupture.

Conclusion: nCECT enabled *in vivo* detection and imaging of aortic wall barrier failure in thoracic aortopathy and revealed multiple MFS-like phenotypes that may contribute to the high mortality observed in mgR mice.

DO ECHOCARDIOGRAPHIC THRESHOLDS UNDERESTIMATE TRUE AORTIC SIZE? A MULTIMODALITY ANALYSIS

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Introduction: Accurate assessment of aortic root diameters is essential in aortic disease. While transthoracic echocardiography (TTE) in the parasternal long-axis (PLAX) view is the clinical reference, cross-sectional imaging (CCT/CMR) enables multiple measurement approaches, leading to absolute discrepancies. TTE single-plane approach may not capture the true maximal aortic size, particularly in asymmetric phenotypes, and may therefore underestimate the risk of aortic events.

Objectives: To determine whether conventional PLAX measurements underestimate the largest aortic root diameter, defined as the MAX cusp-to-cusp measurement in any direction.

Materials and Methods: A total of 106 subjects were included (BAV n=32, HTAD n=39, controls n=35). Aortic root diameters were measured using TTE and CCT/CMR. Differences between modalities were assessed using t-test. The impact on clinical classification (≥45 mm) was evaluated using McNemar's test, and agreement with Cohen's kappa coefficient. The relationship between measurement approaches was assessed using linear regression analysis.

Results: Maximal aortic root diameter by CCT/CMR was larger than TTE (40.0 ± 5.5 mm vs 38.6 ± 5.4 mm), with a mean difference of 1.5 ± 2.2 mm (95% CI: 1.0 to 1.9; $p<0.001$). Using a threshold of ≥45 mm, 9 of 106 patients (8.5%) were reclassified between methods, with similar rates of up-classification (5 patients) and down-classification (4 patients). No significant difference in classification was observed (McNemar $p=0.74$), with overall agreement of 91.5% ($\kappa = 0.71$; $p<0.001$). Linear regression demonstrated a strong association between PLAX and maximal diameters ($R^2=0.84$; $p<0.001$). However, a slope <1 ($\beta=0.94$) and a positive intercept (3.9 mm) indicate that PLAX measurements systematically underestimate aortic root size.

Conclusion: Maximal aortic root diameter derived from cross-sectional imaging is consistently larger than TTE measurements, demonstrating that echocardiography systematically underestimates true aortic size. Despite high classification agreement, this bias may lead to suboptimal assessment of aortic risk, whereas incorporation of maximal diameters may enhance clinical evaluation and decision-making.

IMPACT OF CUSP-TO-CUSP MEASUREMENT CONVENTION ACROSS MULTIMODALITY IMAGING ON Z-SCORE–BASED CLASSIFICATION OF AORTIC ROOT DILATION

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Introduction: Accurate assessment of aortic root diameter is critical in patients with aortic disease. While transthoracic echocardiography (TTE) using the parasternal long-axis (PLAX) view is the clinical reference, cross-sectional imaging (CCT/CMR) allows multiple measurement conventions. However, variability in measurement approaches may lead to inconsistent classification across modalities, particularly in heterogeneous populations including bicuspid aortic valve (BAV) and heritable thoracic aortic disease (HTAD).

Objectives: To compare Z-score–based classification agreement of aortic root dilation between TTE and CCT/CMR-derived measurements using mid cusp-to-cusp (MID) and maximum cusp-to-cusp (MAX) conventions.

Materials and Methods: A total of 106 subjects were included (three sinus BAV n=32, HTAD n=39, controls n=35). Aortic root diameters were measured using TTE and CCT/CMR. Z-scores were calculated using the Campens model, and dilation was defined as $Z \geq 3.0$. Paired comparisons of classification were evaluated using McNemar's test. Agreement was assessed using Cohen's kappa. Differences in agreement between conventions were assessed using bootstrap resampling (1,000 iterations).

Results: Dilatation based on MID measurements in the right-to-noncoronary (RCC–NCC) sinus direction significantly differed from TTE (7.5% vs 25.5% dilated, respectively; McNemar $p<0.001$), indicating systematic underestimation with this convention. In contrast, the MAX diameter in the same direction showed no significant difference compared to TTE (20.8% vs 25.5%; $p=0.18$). Agreement was higher for MAX (91.5%, $\kappa=0.76$) than MID (82.1%, $\kappa=0.39$), with a difference in classification agreement of +9.4% (bootstrap 95% CI 2.8–16.0; $p=0.005$). In a secondary analysis, maximum cusp-to-cusp measurements in any direction identified a higher proportion of dilated patients (37.7%), which may reflect geometric differences not fully captured by TTE.

Conclusion: MAX measurements in the RCC–NCC direction closely reproduce TTE-based Z-score classification of aortic dilation, whereas MID significantly underestimates disease burden. These findings support the MAX convention as a robust approach for multimodality assessment, aligning with established echocardiographic standards for risk stratification.

CARDIAC MAGNETIC RESONANCE ASSESSMENT OF MARFAN PATIENTS UNDERGOING A SUPERVISED EXERCISE PROGRAM: INSIGHTS INTO MYOCARDIAL STRAIN AND INTRAVENTRICULAR FLOW DYNAMICS

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Background: Exercise prescription in Marfan syndrome (MFS) remains controversial, with limited evidence. Myocardial deformation and intraventricular flow dynamics by cardiac magnetic resonance (CMR) may help to evaluate the impact of exercise.

Objectives: To assess the effects of supervised exercise on myocardial strain and hemodynamic forces (HDFs) in MFS.

Methods: Adult MFS patients (age>18years, aortic root≤45mm, no prior acute aortic syndrome) were prospectively enrolled. Participants underwent a 6-month supervised exercise program (3 sessions/week) combining aerobics, resistance, and respiratory training. CMR was performed before (T0) and after the intervention (T1), and ventricular volumes, ejection fraction (EF), left (LV) and right ventricular (RV) global longitudinal strain (GLS), and HDFs in their two main directions [apex-to-base (AB) and lateral-septal (LS)] were computed (QStrain, Medis).

Results: Nineteen patients (47±10years,74%female) were included. Ventricular volumes were stable, with preserved LV and RVEF (T0 vs T1: 56.9±6.0 vs 56.2±7.4%,p=0.341;56.2±7.1 vs 55.7±8.2%,p=0.704). LV-GLS remained stable (T0 vs T1: −23.1±3.6 vs −22.9±2.5%,p=0.747), while RV-GLS improved (−25.7±4.5 vs −27.0±4.9%,p=0.039). Peak VO_2 remained stable (20.4±3.8 vs 20.6±4.1mL/kg/min, p=0.638). HDFs were largely within published reference ranges, with 3(16%) patients showing AB forces<14% (estimated 25th percentile of published reference values). HDF components remained stable (AB 19.1[15.6–24.0] vs 20.9[15.1–25.7]%,p=0.841; LS 3.0[2.7–4.2] vs 3.1[2.5–3.7]%,p=0.243), with a trend toward improved alignment after exercise (LS/AB ratio 17.0[13.4–21.3] vs 15.9[10.4–19.7]%,p=0.059). Comparing pre-and post-exercise, changes in peak VO_2 correlated with changes in longitudinal HDFs (rho=0.618,p=0.019), but not with changes in EF (rho=0.157,p=0.593) or LV-GLS (rho=0.253,p=0.383). Six patients(32%) showed an increase in peak VO_2>1mL/kg/min; in this subgroup, AB HDFs increased significantly (15.7[14.8–19.8] vs 22.4[17.2–24.0]%,p=0.046).

Conclusion: Supervised exercise was associated with stable ventricular function and improved RV-GLS, while longitudinal HDFs were associated with changes in exercise capacity, suggesting a potential role in detecting subtle physiological adaptations beyond conventional systolic indices.

3D FACIAL IMAGE-BASED MORPHOMETRIC PHENOTYPING FOR DIAGNOSIS AND RISK STRATIFICATION IN HERITABLE THORACIC AORTOPATHIES

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Introduction: Robust phenotyping is essential for precision medicine in heritable thoracic aortopathies (HTAD), including Marfan, Loeys–Dietz, and vascular Ehlers–Danlos syndromes. The analysis of facial morphology from 3D facial images presents a promising opportunity for deep phenotyping. However, differences in image-processing across clinical sites has historically limited its scalability.

Objectives: To develop a quantitative 3D imaging framework for facial phenotyping, evaluating its utility for diagnosis, phenotypic characterization, and risk stratification in HTAD.

Materials and Methods: High-resolution 3D facial images were acquired across multi-site networks using multi-camera systems. The dataset comprises over 12,000 individuals (>4,000 syndromic, >8,000 non-syndromic) spanning 400 conditions, including HTAD. Raw scans were processed via a semi-automated pipeline to fit an atlas of 5,629 landmarks to each scan. Manual guide-points were placed to facilitate initial rigid alignment, followed by a non-rigid registration step where the dense surface mesh was warped to capture each facial surface**.** Geometric morphometric analyses identified syndrome-specific facial patterns and quantified variation across age, sex, and disease severity.

Results: Standardized processing yielded a large, harmonized dataset across sites. Distinct, reproducible syndromic facial signatures were identified. Comparing patterns of variation between affected and unaffected individuals revealed that syndromic facial signatures are not unique and instead, follow normal patterns of human facial variation. This supports a model for shared polygenic architecture underlying monogenic syndromes. Subtle phenotypic deviations detected in unaffected relatives suggested underlying genetic liability. In HTAD cohorts, early analyses demonstrate that quantitative facial phenotyping may effectively inform disease classification, track developmental variance, and assist severity assessment.

Conclusion: This standardized multi-site 3D morphometric framework allows for scalable, non-invasive deep phenotyping across diverse populations. By obtaining high-dimensional phenotypic data of facial shape, this approach improves diagnostic accuracy and refines risk stratification in HTAD while directly addressing challenges of variable expressivity to advance precision medicine.

AORTA: A DIGITAL HEALTH TOOL TO IMPROVE EQUITABLE ACCESS TO GUIDELINE-BASED AORTIC CARE

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Introduction: Aortic diseases encompass a broad spectrum of conditions requiring complex, multidisciplinary management. Contemporary guidelines have refined diagnostic and therapeutic pathways, introducing genotype-specific thresholds, individualized surveillance strategies, and expanded indications for intervention. However, variability in clinician familiarity with evolving recommendations, referral delays, and limited patient health literacy contribute to persistent care disparities. Translating complex guideline recommendations into real-time clinical decision-making and accessible patient education remains a critical barrier.

Objectives: To describe the development and implementation of AORTA, a digital health platform designed to operationalize guideline-based aortic care, and to evaluate its potential to improve equitable access across diverse health systems.

Materials and Methods: AORTA was developed through a collaboration between the Montreal Heart Institute and the Loeys-Dietz Syndrome Foundation Canada, with design support from ProductShop. Contemporary guidelines (AHA 2022; EACTS/STS 2024) were systematically reviewed and translated into scenario-based algorithms covering the spectrum of aortic pathology. A user-centered co-design approach involving aortic specialists, referring clinicians, and patient representatives guided iterative development, with usability testing to optimize workflow integration.

Results: AORTA provides a dual-interface digital platform. The patient-facing module delivers accessible educational content, clinic navigation tools, and curated resources supporting informed engagement. The clinician-facing module centralizes guideline recommendations and features algorithm-driven decision-support tools incorporating patient-specific inputs (aortic dimensions, growth rates, genetic context, body surface area, family history, and clinical presentation) to generate individualized risk assessments, surveillance intervals, and intervention thresholds across degenerative, genetic, and acute aortic conditions.

Conclusion: AORTA bridges the gap between complex guideline recommendations and frontline clinical practice by providing actionable decision-support tools for clinicians and accessible information for patients, promoting more consistent, coordinated, and equitable aortic care. Future evaluation will assess clinical adoption and patient outcomes.

DECREASED MASS TO VOLUME RATIO ON CARDIAC MRI IN MARFAN SYNDROME

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Introduction: Ventricular dysfunction is an increasingly recognized feature of Marfan Syndrome (MFS), though early markers and optimal treatments are not well established. Cardiac magnetic resonance (CMR) is commonly used in assessment of aortic dimensions in MFS and may identify early cardiomyopathic changes. Prior studies have shown abnormal ventricular strain and systolic function in Marfan Syndrome hearts.

Objectives: We aim to characterize ventricular mass and volume in young patients with MFS. Secondary objective is to characterize CMR and genetic parameters in MFS which predict development of cardiomyopathy.

Materials and Methods: This is a single-institution retrospective study. Children and young adults up to 25 years old with a genetic or clinical diagnosis of MFS were included. Individuals with concomitant congenital heart disease, or CMR not completed prior to cardiac surgery were excluded.

Results: A genetic diagnosis was confirmed in 41/53 (77%) of individuals, 19/53 (36%) were female. Average age at CMR was 16.65 (range 8.2-24.7). When indexed for body surface area, there was no difference in males vs. females for maximal aortic root or ascending aortic diameter or left ventricular (LV) ejection fraction ($p>0.05$). Average LV mass index (males: 58.9 +- 9.6 gm/m^2, females: 46.9 +- 6 gm/m^2) and mass:volume ratio (males: 0.588±0.10 gm/mL, females: 0.528±0.07 gm/mL) was decreased to low-normal range. Decreased M:V ratio was associated with greater LV volume and lower ejection fraction ($p<0.05$) but not severity of mitral regurgitation ($p>0.1$). No significant changes in left ventricle mass or function ($p>0.1$) were associated with either cysteine-altering or nonsense/frameshift variants.

Conclusions: Left ventricle mass:volume ratio is decreased in young people with Marfan Syndrome. Decreased left ventricular function is more strongly correlated to changes in left ventricular mass:volume ratio in MFS than mitral regurgitation. There is a need for further evaluation of markers of primary cardiomyopathy in MFS.

RETHINKING PENETRANCE AND EXPRESSIVITY FOR GENETIC DISEASE: LEVERAGING FACIAL SHAPE ANALYSES TO PREDICT SEVERITY OF GENETIC DISEASE

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Introduction: Many Mendelian diseases exhibit variable expressivity and penetrance. For heritable thoracic aortopathies, variation in underlying disease severity may influence the probability of adverse outcomes such as aortic dissection. Facial shape is affected in genetic disorders, and morphometric analysis of facial shape variation allows quantification of phenotypic severity along specific, disease-defining axes of variation. Such facial shape severity axes hold tremendous potential for exploring the polygenic basis of disease and predicting severity in individuals with genetic disease.

Objectives: Proposing a novel framework for analyzing variable penetrance and expressivity heritable thoracic aortopathies to improve precision diagnostics and therapy.

Materials and Methods: We synthesize evidence from human genetics, developmental biology, advanced imaging and morphometric analyses to evaluate how genetics, environment, and nonlinear developmental processes influence disease expression.

Results: Facial shape variations in genetic diseases often align with background population axes, which are enriched for developmental genomic variants, as seen in achondroplasia and heritable thoracic aortopathies. Multivariate-genotype phenotype mapping in mice models confirmed that syndrome-informed GWAS recovered homologous, human genetic disease-associated facial shape effects, suggesting that facial shape variation may reveal underlying disease severity. This framework integrates Mendelian and polygenic effects, providing a tool for evaluating phenotypic severity in conditions like thoracic aortopathies.

Conclusion: Many genetic diseases can be understood as extreme positions along continuous axes of variation, representing latent variables for severity. Deep phenotyping, specifically via facial imaging and morphometrics, can characterize these multivariate axes. Characterizing these axes and exploring their genetics is likely to yield significant insights into the genetics of variable expressivity and penetrance that may offer insights into the genetics of variable expressivity and penetrance, improving predictive, personalized outcomes for patients.

THINK RARE-AORTAFIND: USING ARTIFICIAL INTELLIGENCE TO IDENTIFY PATIENTS WITH UNDIAGNOSED HEREDITARY AORTOPATHIES

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Introduction: ThinkRare is an AI-enabled clinical decision support tool designed to support earlier identification of rare diseases using electronic medical record data. Developed at the Children's Hospital of Eastern Ontario (CHEO), ThinkRare analyzes patterns of clinical features, healthcare utilization, and diagnostic history to identify patients who may benefit from genetics evaluation. The platform has demonstrated strong retrospective and prospective performance and is expanding nationally and internationally. We are now beginning to explore disease-specific algorithms to support more targeted identification of individual rare genetic conditions.

Objectives: We will build upon the success of ThinkRare to develop and validate a disease-specific AI-driven screening tool capable of identifying pediatric patients at risk for previously unrecognized hereditary aortopathies who may benefit from genetic evaluation and cardiovascular surveillance.

Materials and Methods: This study will use structured and unstructured EMR data from the CHEO Epic Data Warehouse. Patients seen after Epic implementation at CHEO will be screened by the algorithm developed through clinician–data scientist collaboration. Variables incorporated into the model will include mainly cardiovascular, skeletal and ophthalmologic features in addition to family history and imaging data. Algorithm performance will be optimized iteratively through chart review, feature refinement, and validation against known genetically evaluated patients.

Results: We anticipate identifying approximately 20 patients with previously undiagnosed hereditary aortopathies across the retrospective application of the algorithm, and 5-10 potentially undiagnosed cases annually following prospective implementation. The final model is expected to demonstrate high sensitivity for known hereditary aortopathy cases while improving specificity through iterative refinement. Patients identified by the algorithm may subsequently be referred to Genetics for clinical evaluation, consideration of genetic testing, and ongoing cardiovascular surveillance where appropriate.

Conclusion: ThinkRare-AortaFind aims to improve early recognition of hereditary aortopathies through AI-enabled EMR screening. Earlier identification may facilitate timely genetic evaluation, cardiovascular surveillance, preventative intervention, and family screening, ultimately reducing morbidity and mortality associated with aortic disease.

BUILDING A HERITABLE CONNECTIVE TISSUE PROGRAM: THE CHEO GENETICS EXPERIENCE

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Introduction: Rapidly growing referrals to our heritable connective tissue clinic, serving adults and children, led to increasing wait-times.

Objective: Optimize care for these patients.

Material and Methods: We collaborated with stakeholders to develop a multi-pillar approach.

Results: The following elements were developed.

1. Virtual Pan-Canadian aortic rounds launched in September 2021 to promote learning, discussion and sharing. Thirty-four multidisciplinary sessions hosted a community of clinicians from across the country and beyond.
2. Epic tools were created to improving efficiency and serve as learning and data collection tool for potential future research uses. With the CHEO EPIC team, we built clinician (physical exam) and patient facing (review of systems and family history) tools which can be clinician-edited during the appointment and feed into the clinical note. This process optimizes clinician time by empowering patients to gather pertinent family history prior to the clinical encounter.
3. Triage to e-consults allows us to provide patient-specific guidance for patients not eligible for a full genetic consultation.
4. Website has nearly 3000 unique visits (Canadian and international). It hosts developed patient education materials/information pamphlets (including a genetic testing counselling aid for heritable thoracic aortopathy used for mainstreaming). The website also lists accepted referral criteria and includes links to tools from outside clinics.
5. Mainstreaming with the Aortic Clinic at the Heart Institute was initiated in 2023 and led to prompt actionable diagnosis. Testing is ordered by the aortic clinic team at the time of referral while results are disclosed by the genetic team.

Conclusion: Our clinic now has capacity to see over 500 new patients per year bridging the care of pediatric and adult family members in close collaboration with the Ottawa Heart Institute Aortic clinic and with pediatric cardiology at CHEO. The developed tools and workflow frameworks could be adapted for other clinics.

FROM VARIANT TO VESSEL: PATIENT-SPECIFIC VSMC DYSFUNCTION MIRRORS AORTOPATHY SEVERITY

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Background: Thoracic aortic disease (TAD) encompasses genetic diverse conditions such as Marfan syndrome, Loeys–Dietz syndrome, and ACTA2-related vasculopathies. Aortic diameter, the primary clinical decision metric, poorly predicts type-A aortic dissection (TAAD) risk, and existing preclinical models fail to capture human aortic pathophysiology. Patient-specific platforms are therefore needed to clarify variant-driven mechanisms and guide therapeutic development.

Objective: To develop a translational platform that identifies high-risk aortic remodelling patterns and enables personalized functional testing of therapeutic strategies in the form of an *in-vitro* vascular biopsy.

Methods: Aortic tissue samples from a 250 TAD patient biobank were assessed for remodelling phenotypes and kinase-activity profiling characterised molecular signatures driving different phenotypes. Furthermore, induced pluripotent stem cells (iPSCs) from healthy controls and patients with Marfan, Loeys–Dietz, and contractile-cell-disorder variants (n = 3 per condition) were differentiated into neural-crest–derived vascular smooth muscle cells (VSMCs) and functionally phenotyped. Marfan VSMCs were subsequently incorporated into 3D engineered vascular tissues (EVTs) to assess contractile function and therapeutic response.

Results: Proteomic profiling of aortic tissue identified two distinct medial remodelling clusters: a hypotrophic subgroup co-clustering with Marfan and TAAD samples, characterised by downregulation of contractility-related kinase pathways. Kinase-activity profiling within this cluster highlighted NUAK1 as a candidate therapeutic target, with metformin emerging as a pharmacological modulator of this pathway. At the cellular level, iPSC-derived VSMCs from Marfan, Loeys–Dietz, and contractile-gene-disorder patients exhibited variant-specific dysfunction, including altered stiffness, impaired mitochondrial function, and aberrant proliferation, that correlated with clinical disease severity. In 3D engineered vascular tissues, Marfan-derived VSMCs displayed significant inter-variant heterogeneity in contractile force generation, while contractile-gene variants produced the most severe dysfunctional phenotype.

Conclusion: Integrating tissue-level remodelling with patient-specific VSMC and EVT phenotyping reveals distinct high-risk molecular signatures and supports a functional vascular biopsy approach for individualized risk assessment and therapeutic testing in heritable aortopathies.

GENE AND SEX-SPECIFIC RISK FOR FIRST AORTIC EVENTS IN HERITABLE THORACIC AORTIC DISEASE: INSIGHTS FROM THE MONTALCINO AORTIC CONSORTIUM (MAC)

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Abstract Background: Heritable thoracic aortic disease (HTAD) has gene-specific variability in the type and timing of first aortic events, defined as proximal aneurysm repair or a type A or B dissection.

Objectives: We sought to update previous MAC data to include additional genes and cases.

Methods: Cases in the MAC registry with pathogenic variants in HTAD genes (*ACTA2, COL3A1, FBN1, MYH11, MYLK, PRKG1, SMAD3, TGFB2, TGFBR1,* and *TGFBR2*) were analyzed. The primary outcome was time to first aortic event. Kaplan-Meier analyses were performed and stratified by sex and proband status.

Results: Among 1,398 cases, first aortic events varied by gene. Aortic repair was the predominant first event for *TGFBR2* (60-year cumulative incidence, 60.5%), *TGFBR1* (42.5%), *TGFB2* (44.0%), *FBN1* (41.4%), and *SMAD3* (29.8%). Type A dissection was the predominant first event in *ACTA2* (41.3% at 60 years), *MYH11* (15.2% at 40 years), and *PRKG1* (22.0% at 40 years). *COL3A1* was the only gene in which Type B dissection was the most common first aortic event (22.3% at 60 years). Sex-stratified analyses showed that for *TGFB2* cases, aortic repair was the leading first event overall and among males (28.1% at 40 years), whereas females had markedly fewer repairs (2.4% at 40 years), making Type A dissection the most frequent observed first event in females (8.6% at 40 years). Proband/relative stratification showed higher cumulative incidences among probands across genes, Gene-specific first-event patterns were generally preserved, except in *SMAD3*, where probands had predominantly aortic repair (41.2% at 60 years), whereas relatives showed Type A dissection predominance (34.8% at 60 years).

Conclusions: The aortic events in HTAD are gene-dependent. For genes lacking overt syndromic features, type A dissections continue to be predominant first event. *TGFB2* females had significantly fewer aortic repairs, and dissections as the predominant event. *COL3A1* had type B dissections as the first event.

HIGH-THROUGHPUT FUNCTIONAL PROFILING OF ARTERIAL FRAGILITY GENES REVEALS SHARED MECHANISMS OF EXTRACELLULAR MATRIX DYSFUNCTION AND VASCULAR INSTABILITY

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Introduction: Heritable thoracic aortic disease (HTAD) arises from disruption of extracellular matrix integrity and abnormal vascular signaling, including mechanotransduction and Transforming Growth Factor Beta signaling. However, the cellular effects of disease-associated gene disruption in human vascular cells remain difficult to model systematically, limiting scalable functional characterization.

Objectives: To establish a scalable human vascular cell platform for functional profiling of arterial fragility genes and identify shared and gene-specific mechanisms contributing to vascular instability.

Materials and Methods: CRISPR/Cas9-mediated perturbations were introduced into primary human vascular smooth muscle cells and fibroblasts targeting COL3A1, FBN1, SMAD3, and ITGA1. Cells were profiled using Cell Painting, multiplexed dyes staining different cellular compartments, to quantify high-dimensional morphological phenotypes and a decellularized ECM assay to assess extracellular matrix deposition. Experiments were performed under serum starvation and following TGF-β stimulation, with feature extraction and unsupervised analysis across ~1,200 cells per replicate and 6 biological replicates per condition.

Results: Distinct phenotypic differences were observed across perturbations, including altered actin organization, cell spreading, and architecture. Across all knockout conditions, Cell Painting identified increased phalloidin intensity following TGF-β stimulation, consistent with enhanced F-actin formation. COL3A1 and ITGA1 perturbations reduced cell and nuclear eccentricity, while FBN1 and SMAD3 showed divergent effects on cell size; FBN1 additionally reduced Hoechst intensity and proliferation. Under serum starvation, knockout conditions clustered together, consistent with a shared stress-associated state. Following TGF-β stimulation, perturbations segregated into biologically coherent groups, with COL3A1/ITGA1 and FBN1/SMAD3 clustering separately. In the ECM assay, COL3A1, FBN1, and ITGA1 perturbations reduced ECM-covered area by ~50%.

Conclusion: CRISPR perturbation combined with high-content imaging enables scalable functional interrogation of arterial fragility genes in human vascular cells. These data support high-content phenotyping as an approach to define shared cellular mechanisms underlying HTAD and prioritize pathways for therapeutic screening.

SMAD4 GAIN-OF-FUNCTION DISRUPTS TGF-β AND FLOW SENSING PATHWAYS IN AORTIC HYPOPLASIA

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Introduction: Loss-of-function mutations in canonical TGF-β signaling genes are well established drivers of aortic enlargement and aneurysm formation. In contrast, the mechanisms underlying the opposite phenotype, diffuse or segmental aortic hypoplasia, remain poorly defined. Here, we investigate vascular dysfunction in Myhre syndrome, a disorder caused by SMAD4 gain-of-function variants and characterized by multisystem fibrosis, vascular stiffness, and aortic hypoplasia, to define mechanisms of impaired arterial growth.

Objectives: To define how pathogenic SMAD4 variants alter vascular cell signaling and endothelial responses relevant to aortic remodeling.

Materials and Methods: Primary patient-derived fibroblasts and engineered human aortic endothelial and vascular smooth muscle cells expressing pathogenic SMAD4 variants were evaluated using biochemical signaling assays, immunofluorescence imaging, and laminar shear stress exposure assessing endothelial alignment and flow-responsive gene expression.

Results: SMAD4 mutant cells demonstrated constitutive activation of canonical TGF-β signaling and Rho GTPase pathways, with increased actin cytoskeletal remodeling and altered cellular morphology. In vascular cell models, pathogenic variants induced stress fiber formation and phenotypic changes consistent with enhanced profibrotic signaling. Under laminar shear stress, endothelial cells carrying SMAD4 variants failed to align appropriately to flow and showed impaired induction of the flow-responsive transcription factors KLF2 and KLF4, suggesting defective mechanosensitive signaling.

Conclusion: SMAD4 gain-of-function disrupts vascular cell signaling and endothelial mechanotransduction, linking aberrant TGF-β/Rho activation to aortic hypoplasia in Myhre syndrome and identifying altered flow-responsive signaling as a candidate mechanism for arterial remodeling.

FURTHER DELINEATION OF THE VASCULAR AND CONNECTIVE TISSUE PHENOTYPE OF THE *LOX* GENE AND SCREENING RECOMMENDATIONS

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Introduction: Heterozygous pathogenic variants in *LOX*, encoding lysyl oxidase, an enzyme implicated in connective tissue integrity, have been implicated in familial thoracic aortic aneurysms and dissections (FTAAD) in a limited number of families.

Objectives: To further delineate the clinical and genetic spectrum of *LOX*-related vascular disease.

Materials and Methods: We collected clinical and genetic data from 76 individuals with pathogenic or likely pathogenic P/LP *LOX* variants from 11 families. Findings were compared with previously reported individuals with P/LP LOX variants.

Results: Nine distinct P/LP *LOX* variants were identified, most located in the catalytic domain, and all were novel. Thoracic aortic disease was the primary manifestation: 32/76 individuals (42%) had thoracic aortic dilatation or dissection, including early-onset thoracic aortic aneurysm as young as two years, and thoracic aortic dissection at the age of 21 years. Surgical intervention was required in 11 individuals, and sudden death was reported in seven. Extra-aortic vascular lesions were documented in 9/76 individuals (12%) and included carotid and vertebral artery dissections, renal artery aneurysm, cranial aneurysm, and cerebrovascular events. Connective tissue abnormalities were variably present and mainly included visceral hernias, scoliosis, pectus deformities, tall stature, and skin striae, although none fulfilled the systemic score for Marfan syndrome. Ectopia lentis was not observed. Compared with previous reports, bicuspid aortic valve and classical connective tissue manifestations were less frequent. Overall, the vascular and connective tissue phenotype showed marked inter- and intrafamilial variability, consistent with reduced penetrance.

Conclusion: This case series further delineates the phenotypic spectrum of *LOX*-related vascular disease by describing the largest cohort to date. Based on previous literature and our findings, including early childhood thoracic aortic dilatation, young adult dissections, and extra-aortic vascular findings, we recommend initiating thoracic aortic screening in the first year of life and considering expanded imaging of the entire vascular tree.

THE CLINICAL IMPACT AND GENOMIC PROFILE OF PATIENTS WITH NONSYNDROMIC *FBN1*-RELATED THORACIC AORTIC ANEURYSM AND DISSECTION

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Background: Marfan syndrome (MFS) is characterized by annulo-aortic ectasia (AAE) and multisystem disorders of the skeleton, eyes, and lungs (syndromic). With the widespread use of gene panel testing, *FBN1* pathogenic or likely pathogenic (P/LP) variants have also been identified in some patients with non-syndromic thoracic aortic aneurysm and dissection (*FBN1*-related TAAD).

Methods: We retrospectively analyzed 319 cases that underwent panel analysis of candidate genes for hereditary TAAD at our center between January 2018 and September 2025. Cases diagnosed with MFS were those that met the revised Ghent criteria. *FBN1*-related TAAD was defined as cases without the typical physical features of MFS (systemic score of 4 or less, no ectopia lentis, and no family history of MFS) in which *FBN1* P/LP variants were identified through genetic testing. Severe aortic events (SAEs) were defined as type A or B aortic dissection (AD), prophylactic surgery for AAE or aneurysm of the descending to abdominal aorta.

Results: *FBN1* P/LP variants were identified in 126 out of 319 cases. 104 cases (82.5%) were diagnosed with MFS and 29 cases (27.9%) involved concomitant SAEs at the time of diagnosis. Meanwhile, 22 cases (17.5%) classified as *FBN1*-related TAAD, with numerous patients (77.3%) already exhibiting SAEs at the time of diagnosis. We found a similar family history of AD or AAE in both groups, but a higher number of dominant-negative variants in the *FBN1*-related TAAD group and a significantly later age at start of follow-up (33.9 ± 11.3 vs 16.2 ± 14.7 years), which was associated with a lower systemic score (1.9 ± 1.5 vs 6.9 ± 4.3 points) (respectively, $p<0.05$). In contrast, the majority of *FBN1*-related TAAD group (81.8%) began outpatient care following AD, and there were no significant differences in the timing of SAEs [*FBN1*-related TAAD vs. MFS: Adjusted HR 0.73 (0.4-1.4); $p=0.370$].

Conclusion: *FBN1*-related TAAD represents a silent spectrum of MFS that is challenging to diagnose and manage early.

WHOLE-GENE SEQUENCING OF FBN1: IDENTIFYING NEW SPLICING AND DEEP-INTRONIC VARIANTS

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Introduction: Advances in molecular diagnostics have enabled the identification of causative variants in approximately 80-90% of individuals with a clinical diagnosis of Marfan syndrome (MFS), while still genetic studies are negative in 10%. The standard approaches of exon-based diagnosis via exome sequencing or NGS gene-panels allow the detection of most pathogenic variants in coding regions or canonical splice sites, but are unable to detect most non-coding alterations including deep intronic variants.

Objective: To study the entire FBN1 gene using capture NGS in a cohort of MFS patients at our hospital, in order to identify new splicing and deep-intronic causative variants.

Materials and Methods: In a cohort of 244 MFS patients with negative genetic results between 2021 and 2025, we sequenced the entire FBN1 gene using a custom NGS capture-panel. The potential impact of candidate variants on splicing was evaluated in silico using three independent splicing prediction tools. For the candidate variants, mRNA was obtained from fibroblasts and/or aortic tissue, and RT-PCR plus sanger and NGS sequencing where performed to identify their effects.

Results: We identified splicing-altering variants in 4 patients: two were variants in the splicing region: c.247+5G>A and c.7819+4A>G , and two were deep-intronic: c.5296+590C>T and c.5422+498T>G. The c.247+5G>A causes the skipping of exon 2. The c.7819+4A>G variant caused the exonization of 4 nucleotides altering the normal reading frame. Both deep-intronic variants caused pseudoexons of 142 and 121 base pairs respectively, introducing premature termination codons within the FBN1 mRNA

Conclusions: We identified and characterized four new intronic FBN1 variants in our cohort, increasing the diagnostic yield in MFS. Although the overall proportion is modest, our results highlight a critical limitation of exon-based sequencing approaches of FBN1, supporting the implementation of strategies that will study the entire gene. RNAseq and other techniques may assist in further studies in these patients.

STATIC PANELS IN A DYNAMIC FIELD: GLOBAL VARIATION IN HTAD GENE TESTING

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Introduction: Gene panels are widely used in the evaluation of heritable thoracic aortic disease (HTAD), yet the associated gene landscape continues to expand. In 2018, ClinGen defined a core set of 11 definitive HTAD-associated genes, while Renard et al. independently reviewed 53 proposed HTAD genes and identified additional genes with moderate or limited evidence.

Objectives: To compare the composition of HTAD gene panels across international laboratories, evaluate alignment with ClinGen-defined core genes, and assess whether panel expansion impacts diagnostic sensitivity relative to broader sequencing approaches.

Materials and Methods: We compared gene content across commercial and regional HTAD panels from 5 U.S. and 7 international laboratories. Panel genes were evaluated relative to the ClinGen HTAD core gene set. In parallel, 43 published cohort studies since 2015 were reviewed to assess diagnostic yield across panel-based and exome/genome sequencing approaches.

Results: All reviewed U.S. and European panels included the ClinGen-defined core HTAD genes, while greater variability was observed among select international panels. Substantial divergence emerged beyond the core set, with European/international panels incorporating a broader range of emerging, syndromic, and mechanistically plausible genes (44–61 genes vs. 26–41 genes in U.S. panels). Panel-based diagnostic yield remained inconsistent in the literature reviewed due to cohort size and characteristics more so than panel composition. Exome/genome approaches generally demonstrated similar yield yet broader variant detection.

Conclusion: HTAD panels consistently capture established core genes but vary significantly in inclusion of emerging and mechanistically plausible genes. These findings highlight limitations of static panel design in a rapidly evolving field and support broader sequencing approaches that allow iterative reinterpretation as gene–disease relationships continue to evolve.

ASSOCIATION OF OCULAR FEATURES WITH MUTATION TYPE AND CARDIOVASCULAR SEVERITY IN MARFAN SYNDROME

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Introduction: In addition to those serving as classical diagnostic criteria (ectopia lentis, myopia), several other ocular manifestations of Marfan syndrome were discovered recently. However, it is still not clear whether ocular parameters could contribute to the assessment of cardiovascular risk.

Objectives: We aimed to unravel associations of ophthalmological manifestations with the genotype and cardiovascular severity by launching a comprehensive ophthalmological screening programme for Hungarian Marfan syndrome patients.

Materials and Methods: Out of 106 Marfan syndrome patients enrolled into this cross-sectional study, *FBN1* mutation was confirmed in 65 subjects. Anterior segment features and optical coherence tomography angiography (OCTA) parameters were assessed in groups of 42 and 39 genetically confirmed cases, respectively. *FBN1* mutations were categorized into haploinsufficient (HI) and dominant negative (DN) types. Subjects were also assigned into subgroups based on previous aortic surgery.

Results: In HI patients, central corneal thickness, thinnest point of the cornea, anterior chamber depth and intraocular pressure were lower, while lens thickness was larger compared to the DN patients ($p \leq 0.042$). In the total, foveal, parafoveal and perifoveal areas, retina of HI patients was thinner in comparison to the whole DN group ($p \leq 0.047$) and to the subgroup of DN subjects in which the *FBN1* mutation involved cysteine elimination ($p \leq 0.032$). When compared to the non-operated individuals, superficial and deep vessel density was significantly lower in multiple regions of the retina of patients who underwent aortic surgery ($p \leq 0.043$).

Conclusion: Based on a comprehensive analysis of ocular genotype-phenotype correlations, we first demonstrated several relationships of anterior segment and OCTA parameters with the genotype of Marfan syndrome patients. Furthermore, here we also found associations between OCTA parameters and aortic involvement. Serving as a proxy for the genotype, the identified ocular parameters may form the basis of novel, easily accessible predictors of severe cardiovascular manifestations.

IMPACT OF ATTENTION DEFICIT DISORDER (ADHD) AMONG CHILDREN WITH MARFAN SYNDROME: A MULTICENTER STUDY FROM CLARITY

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Introduction: Several studies suggest a link between Marfan syndrome (MFS) and Attention-Deficit/Hyperactivity disorder (ADHD). The coexistence of ADHD and MFS presents a therapeutic dilemma, with hesitancy initiating stimulant medication in children with MFS.

Objectives: This study investigates whether phenotypic severity, aortic root dilation, or Marfan-related sequelae differ between MFS patients with and without ADHD, and whether treatment strategies differ between these groups.

Materials and Methods: MFS patients aged 18 and younger from the Collaborative for Longitudinal Aortic Research in the Young (CLARITY), a multi-site database, were included. Patients were categorized into ADHD and non-ADHD groups. Chi-square or Fisher's exact tests were used to compare categorical variables, and student t-tests were used for continuous variables.

Results: 325 patients met inclusion criteria for analysis. Mean age was 11.2 (SD 5.3), with 42.2% reported female. Prevalence of ADHD was 12.6% compared to 11.4% in US children. Gender and age distributions were similar between ADHD and non-ADHD groups. Compared to the non-ADHD group, the ADHD group had a significantly higher prevalence of autism (5% non-ADHD and 32% ADHD, $p < 0.001$), developmental delay (9% non-ADHD and 30% ADHD, $p < 0.001$), and anxiety (8% non-ADHD and 29% ADHD, $p < 0.001$). There was no significant difference between groups in Ghent scoring, history of aortic dissection, rupture, or need for surgery. In a subset of 133 patients with echocardiographic and detailed medication data, there was no significant difference in baseline aortic root z-scores between ADHD and non-ADHD groups, including 8 patients on stimulant medications. Anti-hypertensive medication use was similar between groups, regardless of stimulant use.

Conclusion: ADHD is associated with higher rates of other neurodevelopmental disorders and anxiety in patients with MFS. However, ADHD was not associated with greater phenotypic severity or aortic root dilation. Preliminary data does not suggest an association between stimulant use and aortic root dilation in patients with MFS and ADHD.

EMPLOYMENT STATUS AND SOCIOECONOMIC DEPRIVATION AMONG ADULTS WITH MARFAN SYNDROME IS RELATED TO AORTIC DISSECTION BUT NOT WITH PREVENTIVE AORTIC SURGERY

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Introduction: Marfan syndrome (MFS) is a rare genetic connective tissue disorder affecting multiple organ systems. The impact of MFS on employment and socioeconomic outcomes remains insufficiently studied.

Objectives: To assess associations between clinical factors, employment status, and socioeconomic deprivation (i.e., lack of social and/or economic resources important to living quality) in a French MFS cohort.

Materials and Methods: we performed a cross-sectional study using data from the French ComPaRe Marfan Syndrome e-cohort. Participants self-reported their employment status and socioeconomic deprivation was assessed by using the EPICES score. Relationships with clinical and sociodemographic variables were assessed using multivariable regression models.

Results: we analyzed the data from 292 adults with Marfan syndrome (mean age of 40±11 years, Female 65.4%). 74% were employed or in training. 30.5% of the patients had prophylactic aortic surgery and 19.7% had a history of aortic surgery for dissection. Unemployment was associated with aortic dissection and scoliosis surgery, but not with preventive aortic surgery. Socioeconomic deprivation was linked to aortic dissection, scoliosis surgery and single status, but not preventive aortic surgery.

Conclusion: Adults with Marfan syndrome who had suffered an aortic dissection had a less favorable socioeconomic status and were less likely to be employed. In contrast, preventive aortic surgery was not associated with unemployment or social precariousness. These findings highlight the need for early specialized care and particular attention to social determinants in order to reduce long-term socioeconomic vulnerability.

"NONE OF OUR DOCTORS KNOW ABOUT THIS": STAKEHOLDER PERSPECTIVES ON THE GAPS BETWEEN CLINICAL RECOMMENDATIONS AND REAL-WORLD CARE IN HERITABLE CONNECTIVE TISSUE DISORDERS

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Objective: To explore the extent to which existing clinical recommendations for diagnosis and management in HCTDs reflect the realities of real-world care.

Methods: We conducted a pan-Canadian consultation to contextualize clinical recommendations for HCTDs through lived and clinical experience. Before the consultation, participants explored a database of recommendations identified through a systematic literature review and completed a survey. The one-day virtual consultation included an information session on existing recommendations, followed by small-group discussions aimed at contextualizing these recommendations through their experiences and identifying priorities for care and research. In the days following the consultation, participants completed a post-consultation survey to rate priorities and share reflections and appreciation of the event. Stakeholders were recruited through research team contacts, clinicians, patient organizations, and online support groups. Discussion notes and transcripts were analyzed using qualitative reflexive thematic analysis.

Results: A total of 90 participants contributed to at least one phase of the consultation, including the pre-consultation survey, the consultation, and the post-consultation survey. Participants included individuals with one or multiple roles, including people living with HCTDs (n = 72), caregivers (n = 29), clinicians (n = 11), healthcare managers (n = 3), and patient organization representatives (n = 10). Findings highlight gaps between published recommendations and care, including limited provider awareness and unmet psychosocial and interdisciplinary care needs. Across consultation phases, care models for chronic pain, fatigue, and rehabilitation emerged as a central priority. Participants also emphasized the need for a better coverage and access to allied health professionals, as well as the need for more training among healthcare providers regarding these conditions.

Conclusion: Our findings underscore the need for more coordinated, interdisciplinary, and accessible care models that can better translate clinical recommendations into meaningful support for people living with HCTDs, including better access to allied health professionals to support quality of life.

ACCOMMODATIONS OR RESTRICTIONS? PARENTAL IMPRESSIONS OF SCHOOL EXPERIENCE IN CHILDREN WITH MARFAN SYNDROME

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Introduction: Children with Marfan Syndrome (MFS) report challenges within the school setting including reduced scores in psychological well-being, physical health, and social/school functioning compared to their peers.

Objectives: In parents of children with Marfan syndrome, we examined parental perceptions of physical and emotional challenges within the school environment.

Materials and Methods: Parents of school-aged children with MFS completed a web-based survey with mixed multiple-choice and free-response questions. Free-response questions were evaluated using thematic analysis by a 6-person medical team.

Results:157 of 355 participants met inclusion criteria: (age>18, completed>50% of survey, included school grade). 73% (116/157) attended public schools, 45% reported having a formal individualized education program. More than 35% reported missing >7 days in a school year for medical reasons. Three themes were identified: 1) Medically imposed and/or inherent limitations of physical capabilities in MFS; 2) Social and emotional experiences in MFS; 3) Impact of school's understanding of MFS. Parents overwhelmingly reported that imposed physical activity restrictions and self-perceived physical limitations led their children to feel excluded and frustrated. Parents reported that their children felt an overarching sense of being different and a desire for social interaction. The physical differences in children with MFS influenced their social interactions and perceptions from peers and teachers. Additionally, parents expressed stress and frustration over the burden of educating schools about MFS, emphasizing the importance of schools receiving accessible information on MFS.

Conclusions: The study highlights perceived feelings of exclusion and frustration among parents' school-aged children with MFS, with additional frustration due to lacking school knowledge of this condition. It is prudent for the medical community to support educational institutions so that children feel they can more easily participate in physical activities at school, as regular, safe play and exercise are essential for fostering social connections, building confidence, and improving overall quality of life.

RATES OF GUIDELINE-RECOMMENDED AORTIC IMAGING IN PATIENTS WITH MARFAN AND LOEYS-DIETZ SYNDROME FOLLOWING INCORPORATION OF AN ADULT AORTOPATHY SPECIALIST WITHIN A PEDIATRIC HOSPITAL

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Introduction: Individuals with Marfan (MFS) and Loeys-Dietz (LDS) syndromes require lifelong aortic surveillance, yet pediatric to adult care transition leads to gaps in monitoring. We hypothesized that guideline-recommended aortic imaging rates would improve after integration of an adult congenital cardiologist specializing in aortopathy at a tertiary pediatric institution as an internal option compared to previously referring patients externally.

Objectives: To determine whether guideline-recommended aortic imaging improved in adults with MFS and LDS after incorporating an adult aortopathy specialist within a pediatric hospital.

Materials and Methods: Adults who turned 18 years after 1/1/2016 with MFS or LDS treated or enrolled in research at our institution were included. Guideline-recommended imaging was defined using the 2022 American Heart Association Guideline for the Diagnosis and Management of Aortic Disease, which included echocardiography, computed tomography, and/or magnetic resonance imaging of the thoracic aorta performed at our institution or through linked electronic medical records. Era 1 included individuals age 18 years before 1/1/2022; Era 2 included those turning 18 years on or after 1/1/2022. The primary outcome was the proportion of patient-years with completed guideline-recommended imaging. Multivariable logistic regression examined the association between era and adherence among all patient-years; subanalysis focused on healthcare transition years (18-21 years).

Results: Among 143 patients, (MFS N=104, 72.7%; LDS N=39, 27.3%), 75 (52.4%) were in Era 1 and 68 (47.6%) were in Era 2. Era 2 had higher odds of imaging adherence than Era 1 both overall (65.6% of patient-years vs 51.7%; OR 1.79, 95% CI 1.18- 2.76, p=0.007) and during healthcare transition years (65.6% of patient-years vs 53.4%; OR 1.81, 95% CI 1.14-2.89, p=0.01).

Conclusion: Guideline-recommended surveillance rate increased in Era 2 (after incorporating an adult aortopathy specialist within our pediatric system) compared to Era 1, suggesting an internal option may facilitate transition to adult care, regardless of whether patients were transferred internally or externally.

COMPARING PARENTAL PERSPECTIVES ON RAISING CHILDREN AFFECTED WITH INHERITED VS. *DE NOVO* MARFAN SYNDROME

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To document the perspectives of parents of children with inherited or *de novo* Marfan Syndrome (MFS) and outline any discovered differences, parental perspectives were collected using a REDCap survey which included self-reported demographics, validated scales, and targeted closed and open-ended questions. Follow-up qualitative interviews were conducted with parents who indicated interest in further participation which were then transcribed and analyzed using thematic analysis. Three hundred and twelve (312) total surveys were collected from October to November 2023 and follow-up interviews were conducted with 18 parents between August and December 2024. Parents report worrying about physical health, quality of life, and adult life for their children with MFS. Concerns relevant to raising children with MFS include balancing MFS and other life responsibilities, fear of MFS and the unknown, MFS understanding and knowledge, family impact, MFS awareness, advocacy, and access to healthcare. Parents of children with *de novo* MFS have lower pre-diagnosis familiarity with MFS as well as increased self-reported worry and concern. Perspectives on parenting children with MFS differ when MFS is inherited or *de novo*. Study results could be utilized by medical professionals to improve care for children with MFS.

OPTIMIZING DIAGNOSTIC REFERRALS FOR MARFAN SYNDROME: PHENOTYPIC RISK STRATIFICATION IN THE PEDIATRIC POPULATION

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Introduction: Marfan syndrome (MFS) is a multisystem disorder affecting the skeletal, ocular, and cardiovascular systems. Due to the risk of complications such as aortic dissection, patients with suspected MFS are often referred for genetic evaluation. Referrals are commonly made based on skeletal features ("Marfanoid habitus"), but limited guidance contributes to potential over-referral.

Objectives: This retrospective study aimed to identify clinical features associated with higher likelihood of MFS to improve referral accuracy.

Methods: We conducted a review of patients evaluated in a single pediatric Connective Tissue Disorders clinic. Referrals were based on skeletal manifestations alone, and patients were assessed by the same medical geneticist to ensure consistency. Collected data included demographics, referral indications, family history, interventions for Marfan-related features, age at evaluation, growth parameters, mid-parental height (MPH), and examination findings specific to MFS. Detailed phenotypical assessments and systemic features were recorded, along with genetic testing recommendations, testing types, and outcomes.

Results: 292 patients were evaluated with a mean age of 14.45 (SD=3.09); 81.5% were male. Genetic testing was recommended for 46.2%, while the remainder were either clinically determined not to have MFS or genetic testing for alternative diagnoses was recommended. Among those recommended for testing, 82.2% underwent *FBN1* single gene testing. Of patients who completed testing, only 5 (4.1%) were diagnosed with MFS (4 by genetic testing and 1 based on clinical criteria alone). Features associated with greater likelihood of genetic testing included pes planus, height exceeding predicted MPH by more than 10th percentile, arm span to height >1.05, facial features consistent with MFS, and positive thumb and/or wrist signs.

Conclusions: Phenotypic comparison of patients with higher versus lower suspicion for MFS highlights opportunities to refine referral practices. Improved guidance for referring providers may enhance identification of patients at higher risk, facilitating timely evaluation while reducing unnecessary genetic referrals.

ELECTRONIC MEDICAL RECORD-BASED TOOLS TO IMPROVE CARE FOR INDIVIDUALS WITH HEREDITARY THORACIC AORTIC DISEASE

• Rigelsky

Introduction: Patients with Loeys-Dietz syndrome (LDS) and vascular Ehlers-Danlos syndrome (VEDS) require lifelong surveillance imaging and coordinated care. Appropriate interval imaging is critical but may be inconsistently followed because of fragmented care and limited provider familiarity with recommended surveillance guidelines. Electronic medical record (EMR)-based genomic tools may improve adherence to imaging schedules, increase provider awareness, and facilitate timely specialty referrals and emergency management.

Objectives: To implement an EMR tool and practice advisories to support interval imaging follow-up, specialty referrals, provider education, and emergency care coordination for patients with hereditary thoracic aortic disease (HTAD).

Materials and Methods: A tool known as “Genomic Indicators” was developed within the EMR for patients with genetically confirmed LDS and VEDS to track patients with these conditions and provide education to patients and providers. Clinical decision support alerts notify providers when surveillance imaging or specialty referrals are overdue, support referral pathways to specialists and provide additional information in high-risk situations such as in the emergency department or when colonoscopy is ordered. Lastly, an ICD-10-based practice advisory was developed for thoracic aortic dissection to identify patients who may benefit from genetics evaluation and referral to genetics and specialized aortic care.

Results: Implementation of EMR-based genomic indicators enabled standardized monitoring of patients requiring surveillance imaging and facilitates timely education of providers and suggested referrals to specialty services. Use of ICD-based practice advisories increased recognition of patients with thoracic aortic dissection who have not previously been referred for genetic evaluation or who have not been getting ongoing cardiology care.

Conclusion: EMR genomic indicator tools and practice advisories can enhance longitudinal management of HTAD by improving surveillance adherence, provider education, emergency care awareness, and referral pathways to genetics and multidisciplinary aortic care. Future directions include automated identification of thoracic aortic enlargement and expansion to other HTAD.

SYMPTOMS, QUALITY OF LIFE AND PHENOTYPIC SPECTRUM OF AORTIC DISEASE IN PEDIATRIC HERITABLE AORTOPATHY IN CANADA: PRELIMINARY ANALYSIS FROM THE CAN-ACT REGISTRY

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Introduction: The CANadian Aortopathy and Connective Tissue Disorders (CAN-ACT) Registry is a pan-Canadian cohort currently focused on pediatric heritable thoracic aortic disease (HTAD) irrespective of aortic phenotype, enabling characterization across the full disease spectrum.

Objectives: To define the epidemiologic, genetic, and clinical spectrum of pediatric HTAD in Canada, evaluate aortic dilation, and compare characteristics of index vs. cascade diagnosed patients.

Material and Methods: Observational cohort of pediatric patients enrolled in CAN-ACT with genetically confirmed HTAD. Variables collected include age at diagnosis, gene and variant type, index vs. cascade diagnosis. Imaging data, comorbidities, medications, quality of life (QoL) and symptom questionnaires have been recorded.

Results: To date, 218 participants have been enrolled, with data available for analysis in 183 (median age 13.9 years). Common variants were *FBN1* (64%) and *TGFBR1/2* (12%), with 38% index cases and 62% identified through cascade screening. At diagnosis (median age 5.8 years), 49% had aortic root dilation. On follow-up (median duration 5 years), mean aortic root Z-scores had not changed significantly. Medication use increased to 50% by 18 years of age. At diagnosis, index cases were older (7.5 vs. 4.6 years), with higher prevalence of aortic root dilation (78 vs. 37%) and more systemic features. Of 124 parents and patients completing the QoL and symptoms questionnaires, anxiety, fatigue, sadness, headaches and myalgia were reported by 40% of parents, with 20-40% reporting these symptoms to impact their child moderately or intensely. Patients themselves reported similar data. Mean scores for QoL and satisfaction with life were mostly normal.

Conclusion: Preliminary analysis from the CAN-ACT registry for pediatric HTAD showed many children do not have aortic root dilation at diagnosis, particularly those identified on cascade screening. On follow-up, medication use had increased and aortic root Z-scores had remained unchanged. Despite multiple symptoms, QoL scores appeared normal in this cohort.

FROM LIVED EXPERIENCES TO SYSTEMIC CHANGE: PATIENT PERSPECTIVES ON THE DIAGNOSTIC JOURNEY OF LOEYS-DIETZ SYNDROME

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Introduction: Loeys-Dietz syndrome (LDS) is a rare heritable connective tissue disorder associated with life-threatening aortic aneurysms and dissections. Early diagnosis is critical to reduce morbidity and mortality; however, diagnosis is often delayed because of phenotypic variability, overlap with other connective tissue disorders, and limited clinician awareness. This study explored the diagnostic experiences of Canadians living with LDS to identify barriers, supports, and patient-informed priorities for improving diagnosis and care.

Objectives: To examine the lived diagnostic experiences of individuals with LDS in Canada and identify patient-perceived gaps and opportunities to improve recognition, care coordination, and support.

Materials and Methods: A qualitative phenomenological study was conducted using in-depth semi-structured interviews with nine adults across Canada who were the first in their family to receive a molecular diagnosis of LDS within the past five years. Participants were recruited through the Loeys-Dietz Syndrome Foundation Canada and tertiary care clinics. Interviews were conducted virtually, transcribed, de-identified, and analyzed thematically using an inductive approach with iterative coding and consensus-driven theme development.

Results: Five interrelated themes emerged: (1) patients acted as persistent self-advocates throughout prolonged diagnostic journeys; (2) clinicians functioned as either catalysts or barriers to diagnosis depending on awareness and responsiveness; (3) the healthcare system was perceived as reactive, fragmented, and inequitable, particularly across geographic regions; (4) diagnosis provided validation and clarity but also introduced psychosocial and identity-related challenges; and (5) participants identified unmet needs in clinician education, diagnostic pathways, psychosocial support, and multidisciplinary care coordination.

Conclusion: Timely LDS diagnosis is shaped by the interaction of patient persistence, clinician recognition, and healthcare system coordination. Findings highlight the need for improved clinician awareness, integrated cardiology-genetics care pathways, and centralized multidisciplinary support models to enhance diagnosis and management of rare genetic cardiovascular diseases.

EXPLORING THE INTERRELATIONSHIP BETWEEN PAIN, EXERCISE, MIGRAINES, SLEEP, FATIGUE, AND ANXIETY IN INDIVIDUALS WITH LOEYS-DIETZ SYNDROME

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Introduction: Exercise and physical fitness are known to help mitigate fatigue, pain, anxiety and migraines while pain, fatigue, migraines, sleep disturbances and anxiety are described by individuals with Loeys-Dietz syndrome (LDS). Moreover, these domains are highly interconnected and may substantially impair daily functioning and overall well-being. They are also clinically significant, as sleep disturbance and obstructive sleep apnea have been associated with increased risk of aortic complications, including aortic dissection, while chronic pain, fatigue, anxiety, and physical deconditioning may contribute to worsening morbidity over time. Although several symptom domains have been individually described in small LDS cohorts, no study has comprehensively examined how they interrelate and collectively contribute to symptom burden in LDS.

Objectives: To evaluate exercise participation and to assess the prevalence and severity of key symptom domains in individuals with LDS. To perform exploratory partial correlations between these domains. Impact of subtype of LDS and severity of aortic disease on these domains will also be explored.

Materials and Methods: Adults with a molecularly confirmed diagnosis of LDS are being recruited through patient support organizations (including the Loeys-Dietz Syndrome Foundation Canada) and clinical recruitment pathways. Participants will be asked to complete sequential online survey waves administered through REDCap at approximately two-week intervals. Demographic and molecular information, pain, fatigue, sleep quality, diagnosed sleep apnea, anxiety, headaches/migraines, exercise participation will be gathered using validated patient-reported outcome measures alongside study-specific questions relevant to LDS. Descriptive and exploratory analyses will evaluate symptom prevalence, severity, and interplay between these variables.

Results: Results are pending, but we hope to have some preliminary data to discuss by October 2026.

Conclusion: This study will 1) provide prevalence data, 2) explore the interplay between diverse symptoms impacting the quality of life of individuals with LDS and 3) assess the effects of exercise on these domains.

FATIGUE AND REDUCED DAILY PHYSICAL ACTIVITY IN HERITABLE THORACIC AORTIC DISEASE: IMPLICATIONS FOR HEALTH-RELATED QUALITY OF LIFE

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Introduction: Heritable thoracic aortic diseases (HTAD) increase the risk of aortic aneurysm and dissection, often leading to exercise restrictions. Fatigue is common, but underlying mechanisms remain poorly understood. Better understanding of fatigue and exercise in HTAD is important to support daily functioning, well-being, and quality of life.

Objectives: To describe fatigue, Health Related Quality of Life (HRQoL), mental health and exercise in individuals with HTAD, compared to healthy controls.

Materials and Methods: Patients with HTAD were recruited during routine clinic visits, and age- and sex-matched controls were included; all participants completed self-assessment questionnaires.

Results: This study included 34 patients (median age: 42 years, IQR 21); 26 with Marfan Syndrome, five with Loey-Dietz, two with vascular Ehler Danlos Syndrome and one with Beals Syndrome, and 27 healthy controls (median age: 45 years, IQR 25). Severe general and physical fatigue were more common in patients (71% and 68%) than controls (16% and 5%; $p < 0.001$), while engagement in structured exercise and daily physical activity was substantially lower (44% and 18% vs 89% and 71%; $p < 0.001$). Patients reported bigger kinesiophobia (median: 33, IQR: 12) than controls (median: 24, IQR: 4) while belief in exercise benefits was similar between groups (patients median: 28, IQR: 20, control median: 31, IQR: 19; $p<0.001$). Symptoms of anxiety and depression were reported at similar rates in patients (27% and 18%, respectively) and in healthy controls (11% and 0%). HRQoL was significantly lower in patients than controls (mean score 71 vs. 81, $p < 0.001$). An association was found between severe physical fatigue and lower HRQoL in patients ($p=0.003$).

Conclusion: Findings indicate that fatigue is more prevalent, and daily movement is lacking in patients, compared to healthy controls. Severe physical fatigue seems to affect HRQoL negatively in patients.

TRANSFORMING CLINICAL RESEARCH AND CARE QUALITY IN RARE CONNECTIVE TISSUE DISORDERS: A MIXED-METHODS, CROSS-COMMUNITY CLUSTERING STUDY INTEGRATING PATIENT PERSPECTIVE

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Background: Rare heritable connective tissue disorders (hCTDs) with aortopathies, including Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, and arterial tortuosity syndrome, are associated with significant morbidity and mortality but remain underrepresented in patient-centered research. This study aimed to identify shared clinical and research gaps across rare hCTDs by integrating patient and clinician perspectives.

Methods: A mixed-methods study (n=127) was conducted through the CONECT initiative, incorporating IRB-reviewed surveys, patient-led panels, clinician workshops, and educational webinars across eight rare disease communities. Quantitative and qualitative analyses were performed to identify patterns in disease burden, care delivery, and outcomes.

Results: Genetic confirmation was reported in 83% of participants, highlighting the importance of molecular diagnosis in differentiating clinically overlapping disorders and guiding management. Diagnostic delays were common (median 3.2 years), particularly in patients without a known family history. Across diseases, patients reported high prevalence of gastrointestinal symptoms (46%), fatigue, chronic pain, and mental health burden—manifestations often underrepresented in clinical guidelines. Emergency care analysis revealed a 28% rate of delayed or missed diagnosis in cardiovascular presentations, with prolonged time to appropriate intervention. Quality-of-life impacts were substantial, including delays in educational attainment (30.6%) and significant caregiver burden (27.1%).

Conclusions: Clustering rare hCTDs reveals shared challenges across conditions traditionally studied in isolation. Findings support the need for standardized emergency care protocols, improved integration of patient-reported outcomes, and broader implementation of genetic testing to enable precision medicine. Cross-disease collaboration offers a scalable framework to improve clinical care, accelerate research, and address unmet needs in rare aortopathy-associated disorders.

SUSPECTED MARFAN SYNDROME PRESENTING WITH CHEST PAINS IN A 39 YEAR OLD NIGERIAN; A CASE REPORT

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Introduction: Marfan syndrome(MFS) is a rare genetic disorder affecting the body's connective tissue due to mutation in FBN 1 gene. Presentation may be diverse or overlap mimicking other disease condition. A high index of suspicion and detailed syndromic clinical evaluation remains valuable in suspected cases even where genetic screening is not accessible.

Objective: To report a case of a 39-year-old man who presented to the cardiology clinic with two weeks history of worsening palpitations and retrosternal chest pains. An echocardiography was done.

Methods: Patient presented to the clinic with 2 weeks history of worsening palpitation and retrosternal chest pain, described as dull and radiating to the back. Has associated difficulty with breathing but no orthopnea or Paroxysmal nocturnal dyspnea. General examination revealed some dysmorphic body features: High arched palate,arm length >height,pectus excavatum. Cardiovascular examination reveals pulse of 64bpm, blood pressure of 120/60mmHg and apex beat displaced with apical systolic trill. Heart sounds-S1S2 with grade 4 mitral regurgitation murmur. Review of other systems was not contributory.

Results: Echocardiography revealed a valvular heart disease(mitral valve) with predominant mitral regurgitation. Patient had surgical intervention with resolution of symptoms and improve quality of life. He is on follow up at the cardiology clinic.

Conclusion: there is variable expressivity in MFS with patients presenting with different signs and symptoms. Clinical evaluation is key in the absence of molecular genetic screening to ensure early intervention and improved quality of life.

Key words: chest pain, marfan syndrome

FROM CHEST PAINS TO DEATH, CATASTROPHIC ACUTE AORTIC DISSECTION IN A 65 YEAR OLD WOMAN; A CASE REPORT

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Introduction: Chest pain is the commonest cardiac complaint seen at the Medical Emergency Department and acute coronary syndrome is the most suspected and evaluated condition in this setting. An uncommon but catastrophic cause of chest pain which is frequently missed is acute aortic dissection (AAD). The diagnosis of AAD following chest pain is said to be missed in about 15% to 43% of cases at initial presentation by physician.

Objective: To report a case of a 65-year-old woman who presented to the Accident and Emergency Department with three weeks history of persistent chest discomfort which worsen in the last 6 hours before presentation. Chest pains is severe and of sudden onset, an eventual diagnosis of AAD was made following echocardiography.

Methods: Patient presented to the A&E department with 6 hours history of worsening central chest pain, described as severe, tearing and radiating to the back and neck. Urgent echocardiography done showed features in keeping with a diagnosis of AAD. She was immediately given emergency medical care. Emergency consult was sent for cardiothoracic team intervention. However about 100 minutes into admission while patient was seated up in bed, she dramatically stopped breathing and had a cardiac arrest.

Results: Echocardiography revealed dissecting flap in the dilated aortic root extending to the ascending aorta. Aortic regurgitation and pericardial effusion also found.

Conclusion: Although AAD is an infrequent cause of acute chest pain in our environment, high index of suspicion is needed in diagnosis. In our setting, less than ¼ of persons with chest pains present early at the emergency unit. Late presentation in AAD worsens prognosis and its associated with high mortality. Therefore, an early presentation is needed in evaluating and ensuring timely emergency intervention in AAD.

Key words: chest pain, acute aortic dissection

THE IMPACT OF TIME SPENT NORMOTENSIVE ON SURGICALLY MANAGED AORTIC DISSECTION OUTCOMES

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Introduction: Impulse control after aortic dissection is standard of care. There is a paucity of long term, granular data exploring the impact of quality blood pressure control on long term outcomes for aortic dissection.

Objectives: Using outpatient electronic medical record data, evaluate the quality of long term blood pressure management and surgically managed aortic dissections.

Materials and Methods: All patients with Type A or Type B aortic dissection who underwent surgical management at the University of Michigan from 7/2014 to 1/2026 were identified. All postoperative outpatient systolic blood pressure (SBP) measurements were collected. We calculated the percentage of time below a SBP of 140 mmHg. Our primary endpoints were death or dissection related reintervention. Statistical analyses were performed with Python 3.13.5.

Results: 1130 patients underwent intervention, with mean follow-up of 3.2 years and 14,153 SBP measurements (median per patient 6.0, IQR 1-181). Average age at index procedure was 60.4 years. Death occurred in 13.5% of patients; 21.3% underwent reintervention.

In our multivariate Cox model, every 10% increase in percentage time spent under a SBP of 140 demonstrated a 3% decrease in mortality and reintervention (0.94-1.00 OR, *p=0.037*). Significant covariates were: age at index operation (OR 1.00=1.02, p=*0.024*) and the vascular connective tissue disease diagnosis (OR 1.17-2.39, *p=0.005*). On Kaplan-Meier analysis, patients with SBP <140 for >80% of the follow up duration were at lower risk for reintervention (p=0.017-0.019) and composite endpoint (p=0.005 against patients <40% time below 140). The <40% control cohort demonstrated higher mortality (p=0.003-0.049, Figure 2), that persisted after Cox adjustment for age and connective tissue disease versus the 40-80% cohort (p=0.029-0.047).

Conclusion: Consistent, long term systolic blood pressure control plays a significant role in combined mortality and reintervention following dissection surgical repair.

AI RISK STRATIFICATION AND BIOMARKER DISCOVERY FOR THORACIC AORTIC DISSECTION USING A LARGE CLINIC COHORT

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Introduction: Thoracic aortic dissection (TAD) has a high mortality rate, yet early risk stratification remains challenging due to the acute presentation of dissection in most cases. Large-scale electronic health record (EHR) datasets provide an opportunity to identify patient-level risk patterns and derive predictive biomarkers using machine learning (ML) approaches.

Objectives: We aimed to develop and evaluate ML models for assessing risk of TAD in a large cohort with long-term EHR data and to identify model-derived biomarkers associated with disease presence, progression, or adverse clinical outcomes.

Materials and Methods: We identified individuals with TAD from Geisinger's EHR. Combining Type A and Type B, we considered one TAD diagnosis as a case. We collected longitudinal clinical, anthropometric, and lab values from EHR. Inclusion criteria were age 20-85 and at least 80% complete clinical record. ML models were trained to predict the diagnosis of TAD. Model performance was assessed using a 90/10 train/test split, evaluating AUROC on the held-out set. Shapley Additive explanations (SHAP) values were used to identify impactful biomarkers.

Results: The cohort included 946,110 patients, of whom 1,548 (0.16%) had TAD. The cohort was 53% female and 91% white (self-reported). The best-performing prediction model was XGBoost, achieving an AUROC of 0.922, positive predictive value of 0.702, with low false negative and positive rates of 0.13% and 0.015% respectively. Model-derived biomarkers most strongly associated with risk include hypertension, RDW, and low platelet count.

Conclusion: ML models can accurately identify patients at elevated risk for TAD using routinely collected EHR data. In addition to strong predictive performance, model explanations identified clinically relevant risk factors and biomarkers, including hypertension, RDW, and low platelet count. These results support the use of explainable EHR-based ML models to advance precision risk assessment and inform targeted surveillance and prophylactic care for TAD.

AORTAGPT: AN AI-ENABLED CLINICAL DECISION SUPPORT PLATFORM FOR HERITABLE THORACIC AORTIC DISEASES

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Introduction: Heritable thoracic aortic diseases (HTAD) are characterized by substantial clinical and genetic heterogeneity. The probability of aortic dissection or surgical intervention varies according to the mutated gene and specific variant, aortic disease presentation, and clinical risk factors such as smoking or hypertension. However, translating gene-based risk estimates and clinical care guidelines into individualized patient guidance remains challenging.

Objective: To develop AortaGPT, an AI-enabled clinical decision support platform that generates updated individualized risk estimates and evidence-based clinical guidance for patients with HTAD.

Materials and Methods: Development proceeded in three integrated phases: (1) construction of a backend risk engine using survival data from the Montalcino Aortic Consortium and CLARITY registries to generate time-to-event estimates for aortic surgery, dissection, and peripheral arterial events; (2) creation of a continuously updated knowledge base with AI-assisted curation; and (3) iterative refinement of the clinician-facing interface through a co-design process in which physicians engaged with representative HTAD case scenarios and provided structured feedback to optimize the application's usability, functionality, and clinical utility.

Results: AortaGPT generated individualized survival curves using age-, sex-, and gene-matched registry data and delivered gene-specific clinical recommendations embedded within patient-centered narrative clinical context. Risk estimates were further personalized through integration of hypertension, smoking history, prior aortic events, and continuously updated clinical registry data. The knowledge base was developed using a semi-automated retrieval-augmented generation pipeline coupled with structured expert review. Iterative co-design sessions with both specialist and generalist clinicians produced a functional interface prototype aligned with real-world HTAD clinical workflows and end-user priorities.

Conclusion: AortaGPT integrates personalized risk modeling with continuously updated evidence and clinician-centered design to support individualized HTAD care guidance. Future plans include prospective clinical validation, integration with electronic health records, and a patient-facing module for informed shared decision-making.

GENE-SPECIFIC ENRICHMENT OF BICUSPID AORTIC VALVE IN HERITABLE THORACIC AORTIC DISEASE: INSIGHTS FROM THE MONTALCINO AORTIC CONSORTIUM

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Introduction: Bicuspid aortic valve (BAV), the most common congenital heart malformation, predisposes to thoracic aortic aneurysms and dissections (TAD). We hypothesized that BAV may accelerate clinical progression or increase dissection risk in individuals with pathogenic HTAD genetic variants.

Objectives: We evaluated associations between BAV, gene variants, and aortic outcomes in the Montalcino Aortic Consortium (MAC) registry.

Materials and Methods: We performed a multicenter study of MAC participants with curated genotype and phenotypic data. Primary outcomes included aortic dilation (Z-score >3), aortic dissection, proximal aortic repair, and aortic valve surgery. Modified Poisson regression with adjustment for age, sex, and the mutated gene.

Results: Among 816 participants, BAV was present in 48 (6%) and enriched in carriers of *TGFBR1* (6/72, 8%) and *TGFBR2* (10/96, 10%) variants. Compared with participants without BAV, those with BAV more frequently exhibited aortic regurgitation (38% vs. 11%, P<0.001), sinus of Valsalva dilation (52% vs. 17%, P<0.0001), ascending aortic dilation (25% vs. 3%, P<0.0001), and proximal aortic repair (56% vs. 30%, P<0.001). Individuals with BAV presented at a younger age at first aortic event (24 vs. 40 years, P<0.001), but dissection rates were similar (13% vs. 18%, P=0.44). Among carriers of TGF-β pathway variants, coexisting BAV was associated with greater aortic valve surgery (57% vs. 28%; PR 1.99 [1.40–2.83], P<0.01) and sinus of Valsalva dilation (69% vs. 35%; PR 1.96 [1.40–2.63], P<0.001).

Conclusions: In HTAD, BAV is selectively enriched among carriers of Loeys-Dietz syndrome genes and identifies a distinct valvulo-aortic phenotype characterized by early proximal aortic dilation, aortic regurgitation, and increased elective aortic interventions but not excess dissection risk. These findings support incorporation of valve phenotype into genotype-informed risk models while arguing against lower surgical thresholds based solely on BAV status.

THE IMPACT OF SEX HORMONES ON HERITABLE THORACIC AORTIC DISEASES: A MONTALCINO AORTIC CONSORTIUM STUDY

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Introduction: Heritable Thoracic Aortic Diseases (HTAD) cause life-threatening cardiovascular complications. Differences in hormone exposure may influence HTAD progression.

Objectives: To characterize lifetime sex hormone exposure among participants with HTAD in the Montalcino Aortic Consortium (MAC) registry.

Materials and Methods: We developed a survey to assess contraception, hormone supplementation, pregnancy, and assisted reproductive technologies. The survey incorporated validated questions from the PhenX Toolkit and was refined through stakeholder and expert feedback. The finalized survey was implemented in Research Electronic Data Capture (REDCap) and distributed to adult MAC participants at US sites.

Results: We received completed surveys from 123 participants: 92 (75%) were female, the median age was 47 (IQR 39-56) years, and 71% had pathogenic variants, primarily in ACTA2 (29%), COL3A1 (15%), or MYLK (11%). Forty-one participants (33%) reported at least one aortic event (72% dissections) at a median age of 36 years (IQR, 27–49). Only 5 of the 31 male respondents (16%) took testosterone supplements or androgen inhibitors. Among female respondents, 83 (90%) reported hormonal contraceptive use, including pills (85%), hormonal intrauterine devices (29%), vaginal rings (14%), and/or implants/injectables (16%). Nineteen of 41 (46%) postmenopausal women used hormone replacement therapies. Fourteen women (15%) had used fertility enhancing medications (12%) and/or assisted reproductive technologies (6%). Fifty-nine women (64%) reported 160 pregnancies, and 48 (81%) reported multiple pregnancies. The rate of peripartum aortic interventions was 9%, and there were 13 peripartum dissections (8%). Median age at menarche was 12.5 (11-13) years and was comparable to the general population, but menopause occurred earlier than the reported US mean (43 (38-50) vs 52 years).

Conclusion: Sex hormone exposures are prevalent in the MAC cohort. We plan to investigate the impact of calculated cumulative and episodic hormone exposures on aortic outcomes.

CUTTING THROUGH THE GENETIC COUNSELING WAITLIST-QUEUE: A GUIDELINE BASED APPROACH

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Introduction: Guidelines recommend genetic counseling and testing in individuals under 60, with positive family history, or with a dissection at any age. Financial constraints limit hiring of genetic counselors, necessitating innovative approaches to counseling and testing.

Objectives: To evaluate genotype positive rate in our clinic and determine low-yield cases appropriate for initial evaluation by a trained Advanced Practice Provider rather than a genetic counselor.

Method: Deidentified clinical data (2016-2024) was analyzed to determine the incidence of actionable genetic variants based on (1) age and (2) positive family history in our clinical cohort.

Results: Among 1061 patients with aneurysms or dissections, 778 were < 60 at time of the event and 283 were ≥60y. Of those < 60, 504 (64.78%) had a positive family history and 274 (35.21%) did not. Genetic testing conducted in 423 with a family history revealed 43 (10.17%) pathogenic/likely pathogenic variants (P/LP), 127 (30.02%) variants of uncertain significance (VUS) and 250 (59.1%) were negative. Of the 274 without a family history 223 underwent genetic testing with 23 P/LP (10.31%), 64 VUS (28.7%) and 136 negative (60.99%). Of those ≥60y, 197 (69.61%) had a positive family history and 86 (30.39%) did not. Genetic testing was pursued in 169 of the former with 8 P/LP (4.73%), 39 VUS (23.08%) and 122 (72.19%) negative. For those without a family history, genetic testing in 69 revealed 3 P/LP (4.35%), 19 VUS (27.54%) and 47 negative results (68.12%). Overall, the P/LP (and VUS) identification rate in the group below and above age 60y was 10.22%. The VUS identification rare was 29.57% and 24.37% respectively.

Conclusion: In the setting of limited resources, aortic programs should leverage guideline-based risk stratification to streamline genetic counseling referrals and utilize other trained team members, when appropriate.

GENETIC CONTRIBUTION TO NON-SYNDROMIC AORTIC DISSECTION: THE EXPERIENCE OF THE FRENCH REFERENCE CENTER

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Introduction: Aortic dissection is an uncommon but life-threatening condition associated with high morbidity and mortality. Although a significant number of disease-causing genes are described, the contribution of each gene in patients presenting with non-syndromic aortic dissection remains poorly defined.

Objectives: To assess the prevalence of (likely) pathogenic (LP/P) variants in individuals with non-syndromic aortic dissection and better characterize the genetic contribution in this specific population.

Materials and methods: Consecutive individuals with aortic dissection underwent comprehensive clinical evaluation to assess for Marfan syndrome or related heritable connective tissue disorders and were offered genetic testing. Patients with non-syndromic aortic dissection were included.

Results: A total of 198 individuals were included in this analysis. This cohort consisted mainly of men (147/198; 74.2%) with a mean age of 53.8±12.3 yo (range 23 to 92 yo). A positive family history of thoracic aortic disease was reported in 27% of patients. Type A aortic dissection was observed in 78% of cases. LP/P variants were identified in 25/198 patients (12.6%). The presence of a LP/P variant was associated with gender (25.4% among women, vs 8.2%, among men; p = 0.003) and younger age (46.4 years in LP/P variant group vs 55.4 years in negative results), but not with the type of dissection. *ACTA2* was the most frequently affected gene (8/25; 32%); however, a substantial proportion of variants were also identified in other genes classically associated with syndromic aortopathies. On average, more than one relative per family was identified afterwards as carrier of the familial LP/P variant.

Conclusion: Genetic testing should be considered in patients with aortic dissection at any age in the absence of cardiovascular risk factor. The genetic diagnostic yield is higher in women, in younger patients and in those with a positive family history, supporting a broader use of genetic evaluation in these subgroups.

THORACIC AORTIC DISEASE WITH BICUSPID AORTIC VALVE: LIMITED CONTRIBUTION OF GENETIC TESTING

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Introduction: Bicuspid aortic valve (BAV) affects approximately 1% of the general population. It is associated with dilation of the ascending aorta in half of cases. Aortic events related to BAV are rare. Some familial cases of BAV exist. The question of whether genetic testing should be performed in patients with BAV associated with a non-syndromic form of thoracic aortic disease remains to be determined.

Objectives: To assess the prevalence of (likely) pathogenic (LP/P) variants in individuals with BAV and thoracic aortic disease (TAD), namely dissection or dilation of the ascending aorta, and without extra-aortic signs suggestive of Marfan syndrome (Marfan syndrome).

Materials and methods: Consecutive individuals with BAV and TAD (ascending aortic dissection, surgery for ascending aortic dilation, or ascending aortic enlargement with a Z-score > 2) underwent clinically evaluation for the diagnosis of MFS or a related disorder and were offered genetic testing. Individuals without clinical suspicion of MFS or related disorders, presenting with BAV and TAD and who underwent genetic testing were included in this study.

Results: 198 individuals were included in this analysis. This cohort consisted mainly of men (155/198; 78%) with a median age of 48.5 ± 14.9 years. The predominant morphology of the BAV was a fused BAV with 3 sinuses and a right-left cup fusion (118/198; 59.6%). Nine patients had a personal history of aortic dissection and 31 had preventive surgery for ascending aortic dilation. LP/P variants were present in only 3/198 patients (1.5%). In 1 of the 3 patients with LP/P variants, positive family history would have led to genetic testing anyway. Variants of unknown significance were found in 12/198 (6.0%).

Conclusion: (Likely) pathogenic variants are rare in individuals with BAV and TAD who have no extra-aortic signs or family history of thoracic aortic disease. In this context, systematic genetic screening seems inappropriate.

LOSS-OF-FUNCTION VARIANTS IN ADAMTS6: A NOVEL SYNDROME WITH HEART DEFECT, THORACIC AORTIC ANEURYSM AND NEURODEVELOPMENTAL FEATURES

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Introduction: Marfan syndrome, Loeys-Dietz syndrome and hereditary thoracic aortic aneurysms/dissections (hTAAD) are autosomal dominant connective tissue disorders with overlapping clinical manifestations and marked molecular heterogeneity. A substantial proportion of hTAAD cases remain genetically unexplained.

Objectives: This study aimed to describe a novel genetic cause of syndromic aortic disease and to characterize its molecular and clinical consequences.

Materials and Methods: Whole-exome and whole-genome sequencing were performed in a French cohort of patients with syndromic or isolated hTAAD, revealing rare deleterious variants in *ADAMTS6* gene in four unrelated individuals presenting with either syndromic or isolated vascular disease. Functional studies assessed protein expression, secretion, and extracellular matrix (ECM) incorporation in cellular systems. Patient-derived fibroblasts and *Adamts6*-deficient mice were used to evaluate the *in vivo* effects of candidate variants. Downstream signaling pathways were investigated using targeted functional assays.

Results: Functional analyses showed that these *ADAMTS6* variants impaired protein secretion or enzymatic activity, disrupting the processing of fibrillin-1 and fibrillin-2. This resulted in abnormal ECM accumulation and disorganized microfibrils. The missense variant p.(Leu814Arg) additionally disrupted Hippo and TGFβ signaling pathways and impaired cell adhesion. Patient-derived fibroblasts and *Adamts6*-deficient mice exhibited parallel pathological defects, supporting *ADAMTS6* loss-of-function as disease-causing. The clinical spectrum ranged from early-onset multisystem disease involving cardiovascular, skeletal, craniofacial, and neurodevelopmental abnormalities to isolated adult forms of hTAAD.

Conclusion: These findings demonstrate that ADAMTS6 deficiency causes a previously unrecognized connective tissue disorder, with heart defect, thoracic aortic aneurysm and neurodevelopmental features. This discovery expands the spectrum of ADAMTS-related diseases and highlights the essential role of ADAMTS6 in ECM integrity and vascular homeostasis.

HEALTH-RELATED QUALITY OF LIFE IN GENETIC VERSUS NON-GENETIC AORTIC DISEASE: PRELIMINARY EVIDENCE FROM THE AORTIC-CHILE PROSPECTIVE COHORT

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Introduction: Heritable thoracic aortic disease (HTAD) including Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and non-syndromic bicuspid aortic valve (BAV) — imposes a chronic, multisystemic burden across lifespan. Health-related quality of life (HR-QoL) data from Latin American HTAD populations are absent from the literature.

Objectives: To characterize HR-QoL in patients with HTAD compared to non-genetic aortic disease within the AORTIC-Chile registry, the first prospective multidimensional aortic cohort in Latin America.

Materials and Methods: Cross-sectional HR-QoL analysis was performed within recently established AORTIC-Chile registry, a prospective cohort of patients with aortic disease in Santiago, Chile. HR-QoL was assessed using the EQ-5D-5L (five dimensions plus visual analogue scale [VAS]) and SF-36 (eight domains). Descriptive between-group comparisons were performed.

Results: Of 40 enrolled patients, 23 had complete HR-QoL data. Distribution according to etiology was n=17 with HTAD (MFS 71%, LDS 18%, BAV 6%) and n=6 with non-genetic aortic disease. HTAD patients were markedly younger than non-genetic patients (mean 37.0 ± 14.9 vs. 65.2 ± 4.0 years). Despite being younger, HTAD patients demonstrated substantially lower EQ-5D-5L VAS scores (61.8 vs. 93.3). The most impaired EQ-5D-5L dimension was “Usual Activities”, with only 64.7% of HTAD patients reporting no limitation versus 91.7% in the non-genetic group. Across SF-36 domains, HTAD patients scored lower in Physical Function (59.1 vs. 80.0), Physical Role (45.3 vs. 66.7), Vitality (47.8 vs. 63.3), and Social Functioning (49.2 vs. 62.5). Mental Health scores appeared relatively preserved in the HTAD group (60.3 vs. 51.7), suggesting a dissociation between physical and psychological burden in these patients.

Conclusion: Patients with HTAD presented impaired HR-QoL across physical and functional domains compared to non-genetic counterparts, while mental health appears comparatively preserved. These findings from the first Latin American HTAD registry underscore the need for multidimensional care models and provide a foundation for future genotype-specific QoL analyses as enrollment continues.

ELUCIDATING THE GENOTYPE-PHENOTYPE ASSOCIATIONS IN SMAD6-DISORDERS: FAMILIAL CONGENITAL CRANIOSYNOSTOSIS AND DILATED ASCENDING AORTA, AND A VARIANT OF UNCERTAIN SIGNIFICANCE IN SMAD6

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Introduction: *SMAD6* encodes an intracellular inhibitor of the bone morphogenetic protein signalling pathway and is associated with bicuspid aortic valve (BAV) and dilation of the ascending aorta, and susceptibility to craniosynostosis and radioulnar synostosis. Identical heterozygous loss-of-function variants have been reported to cause all three phenotypes, displaying a lack of genotype–phenotype correlation.

Objectives: To identify a genetic cause of familial congenital craniosynostosis and dilatation of the ascending aorta.

Materials and methods: We obtained clinical information on proband and family members. Whole-genome sequencing was performed in DNA extracted from whole blood from the proband, and 37 genes associated with thoracic aortic aneurysm and -dissection was analyzed.

Results: The proband was born with craniosynostosis and bilateral forefoot adduction, both requiring surgical correction. At age 30, he experienced chest pain and was diagnosed with a dilated ascending aorta, remaining stable at 50 mm for 2 years, and a tricuspid aortic valve with a small insufficiency. His brother was also born with craniosynostosis and was diagnosed with dilated ascending aorta at age 24 years. They have healthy, unrelated parents and a healthy sister. In the proband, we identified a heterozygous frameshift variant in *SMAD6*: c.204_213del, p.(Arg69Trp*53) (NM_005585.5), introducing a premature stop codon and thus loss of protein product. The identified variant has not previously been reported in patients, but in one healthy individual in the gnomAD database. Loss-of-function variants have been reported in individuals with craniosynostosis and in some individuals with aortic disease, but also in many healthy individuals in the gnomAD database. The variant was interpreted to be of uncertain clinical significance.

Conclusion: We identified a VUS in *SMAD6* in two brothers with congenital craniosynostosis and early-onset dilated ascending aorta. Further evaluation is ongoing, in order to elucidate the potential pathogenicity of the variant.

TELOMERE LENGTH IN PATIENTS WITH MARFAN SYNDROME

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Introduction Chronic inflammation and oxidative stress are increasingly recognized in the pathophysiology of Marfan syndrome (MFS). These processes have also been linked to accelerated biological aging. Telomeres, the protective end caps of chromosomes, progressively shorten with cellular replication and exposure to inflammatory stress. Telomere length (TL) is an established marker of aging.

Objectives To test the hypothesis that adults with MFS have shorter TL than healthy controls, indicating accelerated biological aging.

Materials and Methods Relative average leukocyte TL was measured in 59 patients with a diagnosis of MFS (mean age 39.5±11.1 years, 29 females) based on the revised Ghent criteria and a confirmed (likely) pathogenic variant in the FBN1 gene and 59 age- and sex-matched healthy controls. TL was quantified using a singleplex quantitative PCR adapted from Cawthon's method in which separate reactions targeted telomeric repeats and a single copy gene.

Results Patients with MFS had significantly shorter TL compared to healthy controls (0.99±0.19 vs. 1.07±0.21, p=0.033). In univariable analysis, a history of major adverse cardiovascular events (defined as aortic dissection, arrhythmia or heart failure) was associated with shorter TL (β=-0.168, 95%CI -0.291; -0.013, p=0.008). No other clinical or genetic variables showed significantly associated with TL.

Conclusion Adults with MFS exhibit shorter leukocyte TL compared to matched control. These findings suggest the presence of systemic biological stress in MFS beyond connective tissue involvement and support a role for accelerated aging mechanisms in the disease pathophysiology. The observed association between a history of severe cardiovascular events and shorter TL warrants further investigation.

MAINSTREAMING GENETIC TESTING FOR SUSPECTED INHERITED AORTIC DISEASE: A QUALITY IMPROVEMENT INITIATIVE

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Introduction: Increasing demand for genetic testing among patients referred from Cardiology to Medical Genetics for suspected inherited aortic disease has contributed to prolonged wait times and delayed access to care. Mainstreaming genetic testing—defined as the integration of genetic testing prior to the initial assessment by Medical Genetics—has been used as a strategy to improve efficiency in select patient populations.

Objective: To develop a mainstreamed genetic testing approach for patients referred by Cardiology to Medical Genetics for suspected inherited aortic disease.

Methods: A quality improvement initiative compared timelines across pre-mainstreaming and mainstreamed cohorts for patients referred for general genetic assessments, which included suspected inherited aortic disease.

Across the entire Medical Genetics practice at our centre, time from referral to sample collection and time from referral to result disclosure was calculated for all referrals, including suspected inherited aortic disease.

Results: Genetic testing was organized in advance of the consultation by Medical Genetics. Data was collected for these and all other mainstream eligible referrals over a period of one year. Aggregate data shows significantly reduced time to care with time from referral to genetic test result disclosure reduced by 69 days and time to sample collection reduced by 70 days.

From this, two specific pathways for mainstreaming genetic testing in suspected inherited aortic disease were developed: one for Medical Genetics initiated genetic testing and one for Cardiology initiated genetic testing.

Conclusion: Mainstreaming genetic testing for inherited aortic disease referrals improves access to genetic testing and reduces time to results. Implementation involved collaboration with Cardiology colleagues, educational resources, and streamlined workflows for Medical Genetics assessment. This model addresses the growing demand for timely genetic testing for suspected inherited aortic disease.

GENOTYPE–PHENOTYPE DECISION MAKING IN INHERITED AORTOPATHY: A LONGITUDINAL CASE

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Introduction: Risk stratification is central to clinical decision making in inherited aortopathy. However, uncertainty in variant interpretation can complicate management, particularly in high-risk contexts such as pregnancy.

Objective: To illustrate the challenges of genotype–phenotype correlation in suspected inherited aortopathy, highlighting how early variant suspicion, evolving variant interpretation, and multi-centre family assessments influence longitudinal risk stratification and clinical decision making.

Materials and Methods: A 32-year-old pregnant woman (G3P2) was referred for genetic assessment because of a family history of clinically diagnosed Marfan syndrome. Clinical findings, imaging, family history, and serial genetic testing results were reviewed longitudinally. Variant interpretation evolved through incorporation of external data and information obtained from relatives assessed at multiple centres.

Results: The proband had a strong paternal history of aneurysmal disease, including a father clinically diagnosed with Marfan syndrome at age 42 who died at 57 following a second aneurysm, as well as several relatives with aneurysms. Genetics assessment of the father, including skin biopsy collagen studies, was non-diagnostic. Initial testing in the proband identified a variant of uncertain significance in *FBN1* (c.1036T>C; p.Ser346Pro). Despite uncertainty regarding pathogenicity, the family history and phenotype prompted enhanced surveillance and pregnancy management as a presumed inherited aortopathy. Mild aortic root dilation identified during pregnancy (3.4 cm, Z score 1.08) progressed over five years to 4.0 cm (Z score 3.39). Updated testing later identified an additional uncertain *COL5A1* variant (c.2002G>A; p.Glu668Lys), further complicating interpretation.

The family phenotype was highly variable, including type A and B dissections, infrarenal, iliac, and femoral aneurysms, and asymptomatic individuals. Subsequent identification of the same *FBN1* variant in multiple affected relatives at another centre increased suspicion for pathogenicity.

Conclusion: This case highlights how phenotype-driven management may appropriately precede definitive variant classification. Variant evolution and multi-site family assessments assisted with interpretation, reinforcing the importance of integrating genotype, phenotype, and longitudinal family data in clinical decision making.

PREVIOUSLY UNRECOGNIZED SYNDROMIC CONNECTIVE TISSUE DISORDERS IDENTIFIED BY POSTMORTEM WHOLE GENOME SEQUENCING IN FATAL AORTIC DISSECTION

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Introduction: Acute aortic dissection carries high mortality, with an estimated 20–50% of deaths occurring prior to reaching medical care. Heritable factors contribute substantially to aortic dissection risk, with pathogenic variants identified in 11 validated genes and additional genes awaiting validation.

Objectives: We sought to characterize the diagnostic yield of postmortem whole genome sequencing (WGS) in a racially diverse cohort of sequential decedents from a single county whose cause of death was established as aortic dissection at autopsy.

Materials and Methods: Included cases were decedents who underwent autopsy at the Cuyahoga County Medical Examiner Office between 2019-2024, whose cause of death was determined to be aortic dissection, and for whom blood samples were available. Age at death ranged from 28-95 years (median 55). The cohort was 65% male, 66% White, 31% Black or African American, and 3% Asian. WGS data were analyzed and correlated with findings from the medical death investigation.

Results: WGS data from 68 decedents were available for analysis. Likely pathogenic or pathogenic variants were identified in 6 (8.8%) decedents aged 28–70 years, including two White females, three White males, and one Black male. Detected variants were *SMAD3* c.546dupT (p.G183Wfs*5), *SMAD3* c.715G>A (p.Glu239Lys), *COL3A1* c.1609-1G>T, *FBN1* c.2735A>G (p.Asp912Gly), *FBN1* c.7754T>C (p.Ile2585Thr), and *COL5A2* c.2419G>A (p.Gly807Ser).

Conclusion: Postmortem genetic testing in this autopsy cohort identified pathogenic or likely pathogenic variants in heritable thoracic aortic disease genes in 8.8% of decedents, despite no recognized genetic aortopathy diagnosis during life. Notably, all identified variants were in genes associated with syndromic connective tissue disorders, suggesting these conditions may be substantially underrecognized in patients with fatal aortic dissection. These findings support postmortem genomic testing as a mechanism to identify previously unrecognized genetic aortopathies and create opportunities for cascade testing and potentially life-saving intervention in surviving relatives.

MULTIDISCIPLINARY APPROACH TO PREGNANCY IN WOMEN WITH MARFAN SYNDROME: A CASE SERIES

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Background: Pregnancy in women with Marfan syndrome (MFS) carries a high risk of cardiovascular complications, particularly aortic dissection, due to hemodynamic and hormonal changes. Multidisciplinary management is essential to minimize maternal and fetal complications.

Case Series: We report three cases of women with MFS managed at our cardio-obstetric clinic during pregnancy.

A 27-year-old woman with familial MFS (pathogenic FBN1 mutation) was referred at 12w during her second pregnancy. She was in mWHO class 11-111 and started on low-dose beta-blocker for heart rate and blood pressure control. Echocardiography showed stable aortic root dimensions throughout pregnancy, and regular fetal growth. Cesarean delivery was successfully performed at 38w with general anaesthesia due to dural ectasia.

A 34-yo woman with MFS (double mutation of FBN1 and connexin 26) had a planned pregnancy with pre-implant genetic testing. Angiotensin-11receptor-blocker was discontinued upon pregnancy confirmation. Echocardiography revealed a stable aortic root dilatation associated with mitral annular disjunction. Cesarean section was performed at 37w due to mWHO Class III.

The third case, a 23-yo woman, was referred at 12w due to suspected MFS (aortic root 49 mm, severe aortic regurgitation). She was started on beta-blocker and continued pregnancy under close follow-up. Due to mWHO Class IV and worsening chest pain, caesarean section was performed at 32w with cardiac surgery back-up, without maternal or fetal complications.

Conclusion: Pregnancy in MFS requires individualized, multidisciplinary care. Early risk assessment, close monitoring with serial echocardiograms, and coordination among cardiologists, obstetricians, anaesthesiologists, and cardiac surgeons are crucial to optimize both maternal and fetal outcomes.

	Case 1	Case 2	Case 3
Age	27 yo	34 yo	23 yo
Ethnicity	Caucasian	Caucasian	Hispanic
Family history of Marfan syndrome	Yes, mother	Yes, father	No
Family history of aortic dissection	Yes, mother	No	No
Genetic mutation	FBN1	FBN1 and connexin 26	NA
Aortic dimensions – I trimester	38 mm (z score 3.0)	44 mm (z score 2.3)	49 mm
Aortic dimensions – II trimester	38 mm (z score 2.2)	44 mm (z score 2.2)	49 mm
Aortic dimensions – III trimester	38 mm (z score 2.1)	44 mm (z score 2.2)	50 mm
Aortic regurgitation	Mild	Mild	Severe
Type of conception	Spontaneous	In vitro fertilization + pre-implantation genetic testing	Spontaneous
Parity	G2P1	G1P0	G3P1
mWHO 2.0	II-III	III	IV
Delivery mode	Cesarian section	Cesarian section	Cesarian section
Week of delivery	38	37	32
Fetal outcome	Favorable	Favorable	Favorable

Table 1: Patients characteristics. yo: years-old, FBN1: fibrillin-1, ART: assisted reproductive technology, NA: not available.

HPO-GUIDED EXOME SEQUENCING IDENTIFIES SYNDROMIC AND ATYPICAL DIAGNOSES IN HEREDITARY CONNECTIVE TISSUE DISORDERS

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Introduction: Heritable thoracic aortic disease (HTAD) and related connective tissue disorders exhibit substantial phenotypic and genetic heterogeneity, frequently overlapping with syndromic and non-syndromic presentations. Whole exome sequencing (WES) has emerged as an important diagnostic tool in clinically complex cases.

Objectives: To evaluate the contribution of WES in patients with suspected HTAD and related connective tissue disorders, and to identify phenotypic features associated with molecular diagnosis.

Materials and Methods: A cross-sectional analysis of 31 patients undergoing WES since 2023 at Dr. Balmis University General Hospital in Alicante for suspected HTAD or connective tissue disorders was performed. Clinical and molecular variables included age, sex, prior NGS testing, cardiovascular manifestations, Human Phenotype Ontology (HPO)-guided indication, CNV and secondary findings, and molecular results. WES findings were classified as definitive diagnosis, clinically compatible variant of uncertain significance (VUS), or non-diagnostic.

Results: Mean age was 47±15 years and 71% were male. Cardiovascular manifestations included aortic dilatation (45%), prior aortic dissection or surgery (16%), and mitral valve prolapse (16%). A definitive molecular diagnosis was achieved in 6/31 patients (19%), while 5/31 (16%) harbored clinically compatible VUS. Diagnosed patients were significantly younger than VUS-compatible and unresolved patients (38±16 vs 63±10 vs 46±14 years; p=0.029). HPO-guided WES accounted for 83% of solved cases. Among all the HPOs used, “HP:0001519 Disproportionate tall stature” was significantly enriched among solved cases (67% vs 20%; p=0.024). One CNV and two secondary findings were identified. Molecular diagnoses included pathogenic variants in FBN1 and SMAD3, as well as atypical syndromic diagnoses involving ERF, FGF10, ATP1A3, and ADAMTSL4, illustrating the broad phenotypic and molecular overlap within HTAD-related disorders.

Conclusion: In a clinically heterogeneous HTAD cohort, WES identified clinically relevant and atypical molecular diagnoses. Syndromic phenotypic enrichment and HPO-guided evaluation may improve molecular diagnostic resolution and support precision medicine approaches in genetic aortopathies.

MITRAL ANNULAR DISJUNCTION AND AORTIC PHENOTYPE IN ADULTS WITH MARFAN SYNDROME

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Background: Mitral annular disjunction (MAD) is increasingly recognised in connective tissue disorders, yet its relationship with aortic phenotype in Marfan syndrome remains incompletely defined.

Methods: We conducted a retrospective study of adult patients with Marfan syndrome evaluated at Sant'Orsola-Malpighi Hospital and St Bartholomew's Hospital. MAD was assessed on echocardiography and/or cine cardiovascular magnetic resonance. Aortic dimensions were obtained from cross-sectional imaging (CT or CMR) using the first and last available examinations. Aortic growth rate was calculated as the difference between last and first measurements divided by time (years). Multivariable linear regression was used to assess the association between MAD and aortic diameters, and logistic regression to evaluate the association with elective aortic surgery, adjusting for age, sex, and body surface area. Major arrhythmic events and sudden cardiac death were also recorded.

Results: A total of 329 patients were included (mean age 42.2±6.5 years; 51% male), of whom 79 (24%) had MAD. Mean SoV diameter was larger in MAD vs non-MAD patients (40.6±6.7 mm vs 37.9±6.9 mm, p=0.0039). MAD was independently associated with greater SoV diameter (β +3.7 mm, 95% CI 2.0–5.4; p<0.001). Overall, 139 patients underwent elective aortic surgery at a mean age of 31.6±14 years. Patients with MAD had a higher likelihood of elective surgery (OR 3.2, 95% CI 2.2–4.6; p<0.001) and underwent surgery at a younger age (β −9.3 years, 95% CI −15.6 to −3.1; p=0.004). In the cohort 3 SCD deaths and 3 major arrhythmic events were observed during follow-up. MAD was not associated with differences in aortic growth rate over time (β +0.02 mm/year, 95% CI −0.67 to 0.70; p=0.97).

Conclusions: In adults with Marfan syndrome, MAD identifies a subgroup with larger aortic dimensions at presentation, a higher likelihood of requiring elective aortic surgery, and need for surgical intervention at a younger age, without evidence of accelerated aortic growth over time.

BEYOND THE AORTA: EXTRACARDIAC MORBIDITY IN A PEDIATRIC LOEYS-DIETZ SYNDROME COHORT

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Introduction: Loeys-Dietz syndrome (LDS) is a very rare connective tissue disorder caused by pathogenic variants affecting the TGF-β signaling pathway. Although cardiovascular manifestations, particularly arterial involvement, are well characterized, extracardiac morbidity remains less defined, especially in pediatric populations.

Objectives: To describe extracardiac morbidity and clinical severity in pediatric LDS patients followed at a tertiary referral center.

Materials and Methods: Retrospective unicentric study including all patients diagnosed with LDS during childhood over a 12-year period. Demographic, genetic, cardiovascular and extracardiac clinical data were collected from medical records.

Results: Twenty-nine patients were included, with balanced sex distribution (52% females). Median age at diagnosis was 10.6 years (IQR 4.2–14.7). Pathogenic variants were mainly identified in *TGFBR2* (45%), followed by *TGFBR1* (31%), *SMAD3* (17%) and *TGFB3* (7%); 45% of variants were de novo. *TGFBR2* variants were associated with the most severe phenotype, including greater skeletal and craniofacial involvement and increased need for surgery.

Aortic dilation was present in 76% of patients, 55% of them requiring aortic surgery (median age 13.3). Vertebrobasilar tortuosity was identified in 95%, with 4 patients presenting intracranial aneurysms or vascular malformations.

Extracardiac manifestations were highly prevalent. Pectus deformity was observed in 20/27 (74%) of patients, with surgery required in 4/20 (20%). Scoliosis was present in 65%, and 35% required orthopedic surgery. Cleft palate was identified in 8/29 (28%) and cervical spine instability occurred in 8/21 (38%), requiring surgical stabilization in 3/8 affected patients. Asthma was documented in 41%, and two patients developed ulcerative colitis. Two patients required home mechanical ventilatory support due to severe respiratory complications. During follow-up, 35% transitioned to adult care and 21% died due to vascular complications.

Conclusion: Pediatric LDS is associated with substantial multisystem morbidity extending beyond cardiovascular disease. *TGFBR2* variants appear to confer greater clinical severity, supporting early multidisciplinary assessment and systematic screening for extracardiac complications.

LONGITUDINAL AORTIC GROWTH IN INDIVIDUALS WITH FILAMIN A DEFICIENCY

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Introduction: Filamin A (FLNA) deficiency is associated with periventricular nodular heterotopia (PVNH), cardiopulmonary disease, and other complications. Prior aortic disease descriptions have been limited.

Objectives: Describe the degree and progression of aortic root (AoR) and ascending aorta (AAo) dilation in FLNA deficiency, assess factors associated with aortic dilation, and describe other cardiac and extra-cardiac associations.

Materials and Methods: Retrospective cohort study of individuals with pathogenic, likely pathogenic or clinically suspicious *FLNA* variants in the CLARITY and MAC registries.

Results: Of 49 individuals (82% female), median follow-up age was 13.8 years (IQR 8.8,20.2; 39% adult). Variants were: 63% predicted to cause nonsense-mediated decay (NMD, frameshift n=19, nonsense n=8, splicing n=4), 16% missense, 10% other splicing, 8% CNV, 2% synonymous. Aortic dilation (AoR or AAo z ≥+2) was noted in 72%, patent ductus arteriosus (PDA) in 42%, aortic insufficiency in 83%, and atrioventricular valve (AVV) prolapse in 16%. PVNH was seen in 79%, seizures in 24%, lung disease in 48%, pulmonary hypertension in 39%, and joint hypermobility in 38%. Baseline median AoR z-scores were normal (+1.0, IQR 0.1,2.6) but progressive dilation occurred (+0.20 z/year, $p<0.001$). AoR growth was faster in individuals with NMD (+0.17 z/year) and missense (+0.26 z/year) versus splicing variants (-0.04 z/year, $p<0.05$ for both), and with PVNH (z +0.17/year vs. - 0.02/year, $p=0.039$). Baseline median AAo z-scores were dilated (+2.2, IQR 0.6,3.9) but remained stable (-0.02 z/year, $p=0.739$). No features were associated with faster AAo growth or larger size at follow-up. Twenty-three individuals underwent cardiothoracic interventions: 14 PDA closures, 7 AoR/AAo replacements, 2 AVV repairs, and 7 lung transplants (BLT). Two individuals had repeat BLT, one of which was heart-lung. There were no aortic dissections but 6 deaths (5 from pulmonary complications).

Conclusion: FLNA deficiency is associated with aortic dilation, especially in individuals with variants causing NMD. Pulmonary disease is a primary driver of morbidity and mortality.

CARDIOVASCULAR OUTCOMES AND SURVIVAL IN PATIENTS WITH NEONATAL MARFAN SYNDROME

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Introduction: Neonatal Marfan Syndrome (nMFS) is the most severe presentation of MFS with significant morbidity and mortality. Cardiovascular manifestations, notably atrioventricular valve prolapse and aortic root (AoR) dilation, are early and severe.

Objectives: Describe the baseline characteristics and outcomes of patients with nMFS and analyze factors associated with survival.

Materials and Methods: Retrospective cohort study using the Collaborative for Longitudinal Aortic Research In The Young (CLARITY) and Montalcino Aortic Consortium (MAC) registries.

Results: Of 46 patients (61% male), median age at diagnosis was 6.4 months (IQR 1.4,13.9) and median age at last follow-up was 6.0 years (IQR 1.8,15.3). Features present <5 years included arachnodactyly (98%), facial characteristics (95%), ectopia lentis (56%), joint contractures (44%), scoliosis (59%), pectus deformity (33%), and lung disease (19%). *FBN1* variants (available in 43) were predominantly exonic single nucleotide variants (n=34, 79%), although 5 were intronic splice variants and 4 were intragenic multiexonic deletions; 39/43 were in the neonatal "hotspot". Fifty-two percent underwent mitral valve (MV) operation at a median age of 2 years (IQR 1.16,7.7). Median AoR Boston z-score was +5.7 (IQR +4.8,+8.4). AoR replacement was performed in 26% at median age of 3.4 years (2.2–8.4 years). Thirteen deaths were observed, 10 by age 3 years. Kaplan-Meier (KM) survival at 6, 12, and 18 years was 77%, 69%, and 69%, respectively. Among those surviving beyond the age of 3 years, 18-year survival was 89%. At 18 years, KM survival was 77% for patients with ≥ moderate MV regurgitation (MR) with surgery, 48% for patients with ≥ moderate MR without surgery, compared to 100% for patients with < moderate MR.

Conclusion: Mortality in nMFS is associated with MV disease, but MV surgery is associated with improved survival. Overall and post-surgical survival is higher than previously reported. As a very rare disease, collaborative expertise in diagnosis, genetics, and multidisciplinary management is crucial.

SEVERE OCULAR MANIFESTATIONS IN NEONATAL MARFAN SYNDROME: CASE SERIES AND LITERATURE REVIEW

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Introduction: Though rare, neonatal Marfan Syndrome (nMFS) is the most severe presentation of Marfan Syndrome with cardiac and systemic manifestations present from birth. Cardiovascular manifestations are the primary contributors to the high rates of morbidity and mortality. With improved survival beyond the neonatal period, addressing extra-cardiac manifestations, such as ocular disease, becomes increasingly important. Severe myopia, megalocornea, astigmatism, glaucoma, retinal detachment, microspherophakia, cataracts, and coloboma have been reported previously.

Objectives: To present two cases of nMFS with aniridia, coloboma, and congenital aphakia, not previously described.

Material and Methods: Retrospective chart review, case series and literature review.

Results:
1) 3-year-old female with nMFS with severe mitral valve prolapse (MVP) and regurgitation (MR), and aortic root dilation. Severe ocular disease was present from birth, including glaucoma. Ultrasound biomicroscopy (UBM) demonstrated minute iris stumps in keeping with aniridia. Crystalline lenses were never demonstrated on physical exam, ultrasound or MRI orbits confirming congenital aphakia. Initial genetic panel sequencing was negative, but later whole genome sequencing confirmed a multi-exon intragenic deletion within the *FBN1* gene (exons 33-38).

2) 1-month-old female with nMFS and severe MVP, MR, aortic root dilation, and tricuspid valve prolapse. Eye disease was noted in the neonatal period, including anterior segment dysgenesis with elevated IOP and corneal haziness. There was also right eye corneal edema, optic nerve coloboma, aniridia, and complete luxation of the lens into the mid-vitreous. Genetic testing revealed a mosaic multi-exon intragenic deletion within the *FBN1* gene (exons 33-43).

Conclusions: As survival of patients with nMFS extends beyond the first few years of life, the recognition and management of the associated ocular conditions become paramount. Screening of all ocular segments and components should be carefully and regularly performed with consideration of early intervention to optimize vision and quality of life and minimize morbidity.

LOEYS-DIETZ SYNDROME IN AN INDIVIDUAL OF INUIT ANCESTRY: EXPANDING CLINICAL RECOGNITION OF A HERITABLE THORACIC AORTIC DISEASE IN INDIGENOUS POPULATIONS

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Introduction: Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder caused by pathogenic variants in genes of the transforming growth factor-beta (TGF-beta) signaling pathway. It is associated with a multi-systemic presentation affecting primarily the vascular, skeletal, and cutaneous systems. The penetrance and expressivity of recognizable craniofacial features (such as hypertelorim, bifid uvula, and craniosynostosis) are variable. Published data predominantly reflect individuals of European ancestry, with limited representation of Indigenous populations in genomic cohorts.

Objective: To describe the clinical presentation of *TGFB3*-related LDS in an Inuit male and to highlight implications for recognition in an underrepresented population.

Materials and Methods: We report the clinical, including photographs, and molecular findings of a 43-year-old Inuit male referred for assessment of thoracic aortic disease.

Results: This 43 year male presented with multiple and recurrent hernias, joint hypermobility (Beighton 8/9), marked hypertelorism, upslanted palpebral fissures, and attached earlobes. He was 174 cm tall, had a history of a previous repaired bifid uvula and family history of aortic aneurysm. Echocardiography demonstrated an aortic root aneurysm measuring 5.2-cm. Molecular analysis identified a recurrent heterozygous pathogenic variant in *TGFB3* (c.898C>T; p.(Arg300Trp)), establishing the diagnosis of LDS. Multidisciplinary management was initiated, including surgical repair of his thoracic aortic aneurysm, recommendations for broader imaging and ophthalmological assessment.

Conclusion: This is the first case report of LDS in an individual of Inuit ancestry and highlights features of this condition in the context of his ancestry.

BEYOND AORTIC DISEASE: PRELIMINARY EVIDENCE OF MYOCARDIAL DYSFUNCTION AND ARRHYTHMIAS IN PEDIATRIC HTAD

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Introduction: Marfan syndrome (MFS) and related heritable thoracic aortic diseases (HTAD) are increasingly recognized as systemic cardiovascular disorders with potential myocardial involvement beyond aortic pathology. However, the prevalence and clinical significance of ventricular dysfunction and arrhythmias in children remain insufficiently characterized.

Objectives: To determine the prevalence of myocardial dysfunction and arrhythmias in a multicenter pediatric HTAD cohort.

Materials and Methods: Children with genetically confirmed HTAD carrying pathogenic variants in *FBN1*, *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, *TGFBR2* or *LOX* were enrolled prospectively from four European and one UK referral centers. Clinical records, echocardiography, and Holter monitoring were reviewed. Patients were classified into extracellular matrix (ECM) or TGFβ-signaling pathway (TGFB) groups.

Results: Seventy-nine patients were included: 61 ECM (60.7% male; median age 13.6years) and 18 TGFB (55.6% male; median age 12.7years). Aortic root replacement was more frequent in TGFB patients (27.8% vs 6.6%). Prior myocardial dysfunction or heart failure was reported in 6.6% of ECM and 16.7% of TGFB patients. Prior non-sustained ventricular tachycardia (NSVT) occurred in 4.9% of ECM patients, while atrial arrhythmias occurred in 5.6% of TGFB patients. Median LVEF and LVEDD z-scores remained preserved and comparable between groups (LVEF 61% vs 60.3%; p=0.122; LVEDD z-score -0.10 vs 0.20; p=0.344). Nevertheless, reduced LVEF (≤55%) was present in 11.5% and 22.2%, and increased LVEDD in 6.9% and 11.1%, respectively. Right ventricular dysfunction (TAPSE <17mm) was present in 15.8% of ECM and 27.8% of TGFB patients. Holter monitoring identified arrhythmic events exclusively in ECM patients, including atrial tachyarrhythmias (10.5%), ventricular ectopy (11.1%), and NSVT (2.6%).

Conclusion: Myocardial dysfunction and arrhythmias are frequent in pediatric HTAD. Although differences between ECM and TGFB groups did not reach statistical significance, ventricular arrhythmias occurred exclusively in ECM patients. These findings underscore the importance for systematic cardiac surveillance and early risk stratification in this vulnerable population.

MYOCARDIAL RECOVERY AFTER MITRAL VALVE SURGERY IN CHILDREN WITH MARFAN SYNDROME: A MULTICENTRE EUROPEAN STUDY

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Introduction: Children with Marfan syndrome (MFS) are at increased risk of ventricular dysfunction and arrhythmias, and volume overload may accelerate heart failure (HF). Despite this, surgical timing for mitral valve (MV) insuffciency generally follows standard pediatric recommendations.

Objectives: To assess surgical characteristics, postoperative outcomes, and long-term cardiac function in children with MFS undergoing MV-surgery.

Materials and Methods: We conducted a retrospective multicentre study across six centres in Belgium, Spain, Norway, and the United Kingdom. Thirty-one children with MFS (61.3% female; median age 11.8years, 16.1% early-onset MFS) who underwent MV-surgery between 2002–2024 were included. Data on clinical history, surgical procedures, and echocardiographic parameters were collected preoperatively and at 6months, 1year, 5years, and 10years postoperatively.

Results: MV repair with annuloplasty was performed in 77.4% of patients, repair without annuloplasty in 12.9%, and mechanical MV replacement in 9.7%. Concomitant procedures were performed in 61.3%. Early postoperative complications included urgent reintervention (12.9%), arrhythmias (16.1%), and infections (12.9%). Median ICU and hospital stays were 3 and 10 days, respectively.

During follow-up (107 patient-years), 9.7% required MV-reintervention, 29% developed HF (of which 22.2% needed heart transplantation), and 6.4% developed arrhythmias. Overall mortality was 19.4%, with one-third of deaths occurring within 3 months postoperatively. Early-onset MFS accounted for 50% of deaths despite representing only 16% of the cohort ($p=0.04$). Patients who developed HF had significantly greater preoperative LVEDD z-scores (median z-score 6.5 vs 3.3; $p=0.001$) and a trend toward lower LVEF (58.5% vs 62.9%; $p=0.08$). An LVEDD z-score >4.0 predicted HF during follow-up with 100% sensitivity and 70% specificity (AUC 0.861). Postoperatively, LVEDD decreased significantly within 6months ($p<0.001$), while LVEF remained stable.

Conclusion: MV-surgery in children with MFS reduces ventricular dilation and stabilizes ventricular function, but postoperative HF remains common. Marked preoperative ventricular dilation identifies patients at high risk, supporting earlier intervention and tailored long-term follow-up.

INTRAFAMILIAL VARIABILITY OF CARDIAC ABNORMALITIES IN LOEYS- DIETZ SYNDROME PATIENTS WITH TGFB2 MUTATIONS

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Background: Loeys-Dietz syndrome (LDS) is a rare autosomal dominant aortopathy, characterized by arterial tortuosity, early-onset aggressive aneurysm formation, and arterial dissections even at smaller aortic root diameters. Mutations in genes encoding the transforming growth factor-beta (TGF-β) signaling pathway, specifically TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3, and SMAD2, are considered the genetic basis of the syndrome. Mitral valve abnormalities are frequently observed[1]. Extra-aortic cardiac features include atrial septal defects and patent ductus arteriosus. Here, we report intrafamilial variability of mitral valve and intraventricular abnormalities associated with the TGFB2 mutation.

Methods: Routine echocardiograms for pediatric patients diagnosed with the TGFB2 mutation, conducted biannually at the Children's Heart Center in Winnipeg, MB, Canada, were reviewed over a nine-year period following diagnosis.

Results: Four patients (2 male and 2 female, aged between years, median age years) with a definitive diagnosis of LDS4 based on genetic testing are included in this study. The two pairs, consisting of two boys and two girls, are first cousins sharing the same TGFB2 mutation. The two female patients have been diagnosed with abnormal and prolapsing mitral valves. Additionally, a sigmoidal septum, representing a late finding, was identified in both. No cardiac abnormalities were detected in the two boys.

Conclusion: Intrafamilial clinical variability, although not fully understood, has been documented in patients with LDS. In our study, we observed intrafamilial variability in mitral valve disease among our patients. Notably, among the four related patients carrying the same mutation, only the two female siblings were affected. Furthermore, and unexpectedly, a sigmoid septum was identified in both during their most recent echocardiogram. Typically, this condition occurs in normal adult hearts, with its incidence increasing with age. We do not attribute this to their mutation. However, we are cautious not to promptly conclude that it is purely coincidental.

1. Gouda, P., et al., Clinical features and complications of Loeys-Dietz syndrome: A systematic review. Int J Cardiol, 2022. 362: p. 158-167.

DESCENDING AORTIC DISTENSIBILITY IS NOT ASSOCIATED WITH DEVELOPMENT OF TYPE B DISSECTION IN MARFAN SYNDROME

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Background: Type B aortic dissection (TBAD) is a life-threatening complication in patients with Marfan syndrome (MFS), yet current surveillance strategies rely primarily on aortic diameter, which incompletely reflects biomechanical instability. Vascular Deformation Mapping (VDM) is an image analysis method that allows quantification of aortic distensibility from multiphasic CTA studies and may improve risk stratification.

Objectives: To evaluate whether distensibility of the descending thoracic aorta can predict TBAD in MFS patients.

Materials and Methods: We conducted a single-center retrospective study (2004–2024) evaluating adults with MFS using multiphasic CT angiography (CTA). Pre-dissection distensibility of the descending thoracic aorta was assessed by VDM through quantification of the cyclic (systole to diastole) change in wall surface area divided by pulse pressure. The descending aorta was divided into 3 segments (proximal, middle, distal). The association between descending aortic distensibility and incident type B aortic dissection was evaluated using multivariable logistic regression adjusted for baseline diameter and age.

Results: Out of 374 potential MFS patients, 131 met inclusion criteria with 58.8% being male with a median age of 41 years. Over a median follow-up of 5.3 years, 14 patients (11%) of the cohort developed acute TBAD. Baseline characteristics and aortic diameters were similar between groups, but TBAD patients had higher prevalence of dural ectasia (75.0% vs. 32.5%, $p < 0.001$) and coronary artery disease (31.3% vs 3.4%, $p < 0.001$). Distensibility decreased significantly with age across all segments ($p < 0.001$) but was not associated with development of TBAD in any segment ($p>0.7$).

Conclusion: Descending aortic distensibility by VDM was not independently associated with development of TBAD in MFS. The relationship between aortic biomechanics and dissection risk is likely complex and may involve non-linear effects not captured by the present analysis, underscoring the need for further work to identify sensitive biomechanical markers of dissection risk.

PERSONALIZED 3D AORTIC Z-SCORES IDENTIFY HERITABLE AORTOPATHY FROM SINGLE CTA

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Introduction: Latent aortic growth (LAG) in the non-dilated descending thoracic aorta, measured by Vascular Deformation Mapping (VDM), is a marker of heritable thoracic aortic disease (HTAD). However, LAG requires two CT angiograms (CTAs) ≥2 years apart, which is not always available; identifying HTAD risk at baseline would be clinically advantageous.

Objectives: To evaluate whether z-scores from a baseline CTA using Virtual Normal, a 3D statistical technique adjusted for age, sex, and BSA, identify patients at risk for LAG on follow-up imaging.

Material and Methods: We included 213 adults with non-dilated descending thoracic aortas (diameter <30 mm) and serial CTAs ≥2 years apart: 99 with HTAD-associated pathogenic variants and 114 with negative genetic assessment. Descending aortic growth rate was quantified between baseline and most recent CTA using VDM, a validated 3D growth mapping technique; LAG was defined as growth >0.3 mm/year. Point-wise z-scores were computed at every surface point on the baseline CTA using Virtual Normal, built from ~500 patients with ECG-gated CTAs and no aortic disease or cardiovascular risk factors. The 95th-percentile descending z-score was used for analysis.

Results: HTAD patients were younger than negative-assessment patients (41.1 vs 54.1 years, $p<0.001$). LAG occurred in 22.5% patients, more frequently in HTAD patients (35.4% vs 11.4%, $p<0.001$). Absolute descending diameter predicted LAG after age adjustment (OR 1.19, $p=0.002$); z-score predicted LAG independently (OR 1.49 per z-unit, $p=0.037$). For HTAD diagnosis, absolute diameter was not significant after age adjustment (OR 1.08, $p=0.16$); while z-score was (OR 1.95, $p=0.002$). In a combined model, 3D z-score and LAG were independently associated with HTAD (z-score OR 1.84, $p=0.008$; LAG OR 3.90, $p<0.001$).

Conclusion: Personalized aortic z-scores from a single baseline CTA independently predict latent aortic growth and HTAD diagnosis, capturing genetic-aortopathy risk in apparently normal-caliber aortas. Virtual Normal may enable earlier detection and targeted surveillance from a single CTA.

ROLE OF [18F]FDG PET/CT IN EARLY DETECTION AND THERAPEUTIC MANAGEMENT OF AORTIC GRAFT INFECTIONS IN PATIENTS WITH HEREDITARY THORACIC AORTIC DISEASE

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Background: Aortic graft infections are associated with significant mortality, and their clinical management presents a substantial challenge, particularly due to the need for early diagnosis. This study aimed to assess the diagnostic performance and potential therapeutic impact of 18F-fluorodeoxyglucose positron emission/computed tomography (18 FDG PET/CT) in comparison with contrast-enhanced CT (CE-CT) in outpatients with Marfan syndrome (MFS) and other hereditary aortic diseases (HTAD) presenting with suspected aortic graft infection.

Methods: HTAD/MFS outpatients with suspected aortic graft infection. All patients were non-surgical candidates and received oral antibiotic therapy as clinically indicated. Final diagnosis by a multimodal reference standard integrating clinical, laboratory, microbiological and conventional imaging findings. FDG PET/CT and CE-CT examinations were retrospectively evaluated in 38 outpatients with MFS and HTADs who mostly presented with mild or nonspecific clinical symptoms, such as malaise, pains, fever, shivers, unableness to work, sweatiness, multiple mild upper airway or bladder infections, etc. All outpatients were non-surgical candidates and therefore received oral antibiotic therapy as needed throughout follow-up. For FDG PET/CT, diagnostic performance was analyzed based on maximum standardized uptake value (SUVmax) in the periprosthetic region and quantified metabolic active infection volume (MAIV) . A multimodal reference standard incorporating clinical presentation, laboratory and microbiological results, and findings of conventional imaging was used to confirm the final diagnosis.

Results: Diagnostic performance, NPV, and A of FDG PET/CT and CE-CT were 100%, and 24.1%, respectively (NPV 100 % vs. 4.3%, and Accuracy of 100% vs. 26.7%). In 36 of 38 patients FDG PET CT was found to be positive, Median SUVmax was 5.8 (IQR 4.6-8.5), and Median MAIV was 29.4cm³ (IQR 15.0-43.4).

Additional Findings were positive blood cultures in 28,9%. SUVmax and MAIV decreased in 41.7% during antibiotics. Follow-up time compriosed of 12 to 52 months. Concordant therapy completion was achieved in 7 patients. Two patents died of multiorgan failure due to chronic sepsis.

Conclusions: FDG PET/CT accurately detected aortic graft infection in HTAD outpatients and clearly outperformed CE-CT. PET/CT had substantial therapeutic impact even when CRP, WBC and clinical symptoms were not indicative of active infection. PET/CT may be reasonable for outpatient monitoring during oral antibiotic therapy.

REPRODUCTIVE DECISION-MAKING IN MARFAN SYNDROME: OUR CENTER'S EXPERIENCE

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Introduction: Marfan syndrome (MFS, OMIM #154700) is an autosomal dominant connective tissue disorder. Reproductive counseling includes discussion of options such as accepting the recurrence risk, adoption, unassisted pregnancy with prenatal diagnosis (PND), *in vitro* fertilization with preimplantation genetic testing (IVF-PGT), gamete donation, or reproductive limitation. Although there are studies on reproductive experiences in patients with aortic or cardiac disease, specific evidence for MFS is limited.

Objective: To analyze reproductive preferences and trajectories of patients with MFS followed at our hospital.

Materials and Methods: Retrospective descriptive study including patients with a clinical and molecular diagnosis of MFS visited between 2007–2026. Patients aged 20–45 years at their first visit were selected.

Results: A total of 181 patients with MFS were included, with a balanced sex distribution. Thirty-five percent (65/181) had offspring (a total of 97 children), of whom 32% (31/97) had MFS. Molecular diagnosis was established prior to having children in 72% (131/181); however, in familial cases, 42% (13/31) of affected children were born before molecular diagnosis was available. Genetic counseling was offered to 58% of patients (105/181), and a preferred reproductive option was documented in 46% of those counseled (48/105); the most common was IVF-PGT as the only option (30/48; 63%), followed by IVF-PGT and PND as equally acceptable options (9/48; 19%). Among those patients with children, 48% (31/65) were referred to IVF-PGT, 25% (16/65) had an unassisted pregnancy without PND, 25% (16/65) underwent PND, and 3% opted for gamete donation or adoption (1/65 each); among those with PND, 44% (7/16) underwent termination of pregnancy.

Conclusions: Genetic counseling and early molecular diagnosis are key elements in reproductive planning in MFS. Although IVF-PGT is the most frequently prioritized and used option, reproductive decisions follow diverse trajectories depending on clinical, familial, and personal context. This diversity of choices highlights the importance of comprehensive and non-directive reproductive counseling.

ORTHOTOPIC HEART TRANSPLANT IN A PATIENT WITH ARTERIAL TORTUOSITY SYNDROME

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Introduction: Arterial tortuosity syndrome (ATS) is a rare autosomal recessive connective tissue disorder with severe vascular involvement. While pulmonary artery stenosis, aneurysm formation, and systemic vasculopathy are well described, orthotopic heart transplantation (OHT) has not been reported in these patients.

Objectives: To describe long-term outcomes following OHT in a patient with ATS, expanding understanding of its cardiovascular manifestations.

Materials and Methods: Single-patient case review including genetic confirmation, surgical history, imaging studies, transplant course, and 17-year longitudinal follow-up.

Results: A 9-year-old male with progressive cardiac disease was transferred for heart transplant evaluation. His course was marked by previous aortic valve repair with reduction aortoplasty for a dilated aortic root, followed by bioprosthetic aortic valve replacement. He had complicating progressive left ventricular dilation post-op with severe systolic dysfunction (ejection fraction 20%), worsening mitral regurgitation, and intermittent complete heart block requiring pacemaker placement. Despite maximal medical therapy, he developed refractory heart failure requiring OHT which was successful. Post-transplant course demonstrated preserved graft function with long-term survival into adulthood. Subsequent genetic testing revealed homozygous *SLC2A10* mutations confirming ATS. Ongoing surveillance imaging showed persistent arterial tortuosity without significant graft-related complications after 17 years.

Conclusion: This case expands the cardiovascular spectrum of ATS by documenting the first reported successful OHT in a patient with ATS. It highlights the diagnostic complexity of ATS, which can mimic other connective tissue disorders, and underscores the importance of molecular confirmation. The trajectory also suggests valvular degeneration and myocardial remodeling as underrecognized features of ATS. Heart transplantation may be lifesaving in select severe ATS phenotypes. Early genetic confirmation is critical for accurate diagnosis and care planning.

PERI-ANESTHETIC CONSIDERATIONS FOR ARTERIAL TORTUOSITY SYNDROME

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Introduction: Arterial tortuosity syndrome is a rare autosomal recessive connective tissue disorder, characterized by generalized elongation and tortuosity of the medium and large sized arteries, predisposing affected individuals to aneurysm formation, narrowing, and impaired blood flow at sites of arterial stenosis or vessel kinking. Notable malformations of the mandible and maxilla, thoracic cage, limbs, and great vessels are sometimes present as are pulmonary hypertension, right and left heart hypertension, left heart dilation and mitral valve prolapse, peripheral arterial stenoses and tortuosities, esophageal and other hernias, elbow/knee contractures, and cutis laxa.

Objective: Outline an approach to peri-anesthetic care

Recommendations: Anesthetic management requires familiarity with the condition, consultation as needed for affected organ systems, and meticulous planning and preparation. Airway management may include maintaining spontaneous ventilation under regional or neuraxial anesthesia or fiberoptic-assisted securement of airways for general anesthesia. Baseline blood pressure targeting may help maintain flow to areas with arterial restriction (including brain, kidneys, and coronary arteries) while avoiding excessive myocardial strain from hypertension or tachycardia. Invasive peripheral blood pressure monitoring may be difficult to establish. Precautions are taken for gastroesophageal reflux associated with a sliding esophageal hernia. Non-steroidal anti-inflammatory agents and angiotensin receptor blockers are used cautiously or avoided if renal blood flow may be compromised by impaired renal artery patency. Positioning requires support of contracted limbs and even distribution of weight of the torso to accommodate for scoliosis and pectus deformities. For cutis laxa, increased depth of cannulation into the lumens of arteries and veins may help prevent dislodgement of the intravascular portion of the catheter fixed to hypermobile skin. Post-anesthetic care requires attention to hemodynamic normalcy with adequate pain control, intravascular volume, blood pressure management, as well as nausea and vomiting prophylaxis.

Conclusion: Phenotypic expression of ATS is highly variable affecting multiple organ systems requiring individualized anesthetic care.

FIRST REPORT OF RAPIDLY PROGRESSIVE MULTISEGMENT AORTIC DISSECTION IN COMBINED *FBN1* AND *MYH11* MUTATIONS: A STAGED SURGICAL STRATEGY

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Background: *FBN1* mutations confer connective tissue fragility typical of Marfan syndrome, while *MYH11* variants impair vascular smooth muscle contractility. Their coexistence is rare and may drive an aggressive aortic phenotype characterized by rapid progression despite prior proximal repair. This is the first reported case of aortic dissection in a patient with coexisting *FBN1* and *MYH11* mutations.

Objective: To describe a staged surgical management of retrograde Stanford type A dissection and subsequent thoracoabdominal repair in an individual with rapidly progressive aortic disease due to combined *FBN1* and *MYH11* mutations.

Materials and Methods: The patient, with a history of type B dissection, presented with a new type A dissection extending into the root and left carotid artery. Emergent total arch replacement using a branch-first technique with deployment of a conventional elephant trunk into the distal true lumen as a planned component of a staged distal repair, along with Bio-Bentall root and ascending aorta replacement, was performed. This approach maintained continuous cerebral perfusion while minimizing myocardial ischemic time. At 3-month surveillance, the descending aorta measured 5.0 cm and expanded to 6.6 cm over the subsequent 3 months. She then underwent left carotid–subclavian bypass followed by open extent II thoracoabdominal repair. Partial left heart bypass with selective visceral perfusion was used. Reconstruction was completed from the elephant trunk with visceral debranching and distal anastomosis. Spinal cord protection included mild hypothermia, elevated mean arterial pressure, hemoglobin optimization (>10 g/dL), and cerebrospinal fluid drainage.

Results: Both procedures proceeded without neurologic deficit, spinal cord ischemia, or end-organ dysfunction. The patient recovered uneventfully and remains clinically stable at 18 months post procedure.

Conclusion: This case highlights the aggressive phenotype associated with digenic *FBN1* and *MYH11* mutations, in which rapid progression despite proximal repair supports a proactive, staged surgical strategy to achieve durable repair while preserving end-organ function.

PROPHYLACTIC IRBESARTAN THERAPY IN YOUNG PATIENTS WITH BICUSPID AORTOPATHY: AORTIC GROWTH RATES FROM A NEW ENGLAND COLLABORATIVE REGISTRY

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Introduction: Bicuspid aortic valve (BAV) is associated with risk of aortic dilation and dissection. Data on medical treatment (Rx) for BAV aortopathy are limited our pilot study (American Journal of Cardiology 2021) demonstrated that losartan and atenolol each attenuated aortic growth.

Objective: To assess the effect of irbesartan Rx on aortic root (ARo) and ascending aorta (AA) growth in a pediatric BAV aortopathy regional cohort.

Methods: Retrospective study of BAV patients at 7 New England centers with ARo and/or AA dilation [z score (Z) >4 or dimension >4 cm] treated with irbesartan (no prior Rx) using a prospectively designed standardized Rx plan. Maximal dimensions from 2D echocardiograms and BSA-adjusted Zs were modeled using mixed effects regression. The primary outcomes were the annual rate of change in Z and dimension of the ARo and AA; rates pre- and on Rx were compared.

Results: Patients (n=79) were followed for a median of 4.9 y (IQR, 2.1-7.9) prior to Rx and 2.4 y on Rx (maximum 5.4 y) with 411 total pre-treatment and 291 post-treatment echocardiograms. Mean age at start of Rx was 11.8±5.5 y. Mean ARo and AA Zs at start of Rx were 2.2±1.5 and 4.8±1.4, respectively. ARo Z increased over time prior to Rx and decreased on Rx. AA Z increased prior to Rx and had zero change on Rx. ARo and AA dimensions had slower growth rates on Rx (Table) compared to pre-treatment. **Conclusion:** Irbesartan monotherapy attenuates short-term aortic root and ascending aorta growth in young patients with BAV aortopathy. Longer-term studies are needed to determine if the effect of early prophylactic irbesartan is sustained and reduces aortic events in adults with BAV aortopathy.

Table. Annual Rate of Change: Pre & Post-Treatment (95% CI)

	Pre-Treatment	Post-Treatment	*p value*
Aortic root z score	**+0.08*** (+0.04, +0.12)	**-0.10*** (-0.16, -0.04)	***<0.001***
Aortic root (cm)	**+0.12*** (+0.11, +0.13)	**+0.05*** (+0.04, +0.07)	***<0.001***
Ascending aorta z score	**+0.16*** (+0.12, +0.21)	**-0.07** (-0.16, +0.02)	***<0.001***
Ascending aorta (cm)	**+0.14*** (+0.13, +0.15)	**+0.07*** (+0.05, +0.09)	***<0.001***

**Slope differs from zero, p < 0.05*

NEUROVASCULAR RISK STRATIFICATION IN PAEDIATRIC LOEYS-DIETZ SYNDROME: TOWARDS A TAILORED SURVEILLANCE

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Introduction and Objectives: Loeys-Dietz syndrome (LDS) is an autosomal connective tissue disorder characterized by hypertelorism, bifid uvula, aortic aneurysms and arterial tortuosity. Currently, there are no guidelines for neurovascular surveillance. Hence, our aim was to assess arterial tortuosity index (ATI) and its progression over time in order to propose the frequency of neuroimaging to lessen avoidable screening in order to decrease the exposure to anesthesia, contrast and radiation of these patients.

Materials and Methods: A multicentric observational retrospective study of genetically confirmed paediatric LDS patients (November 2012 - December 2025) was conducted. ATI was measured at first and last available head and neck magnetic resonance angiography (MRA).

Results: Over a total of 59 patients with LDS, 31 patients had at least one head-and -neck MRA. From them, 24 patients had a minimum of one follow-up head-and-neck MRA, available for analysis in 17. All patients had AT which tended to stabilize or decrease over time. One patient presented with microaneurysms in the middle cerebral arteries and small cerebellum haemorrhages, which remained stable through follow-up. No other neurovascular abnormalities were observed. Patients with *TGFBR2* variants had higher values of ATI compared to patients with *TGFB2* variants (p=0.037). A significant correlation was found between SV z-score and the ATI (rs=0.547). There was one death throughout follow-up.

Conclusion: This is the first study that has analysed ATI in an exclusively LDS paediatric cohort. Our results demonstrate absence of neurovascular pathology progression over time allowing for extended neuroimaging intervals. Nevertheless, patients with *TGFBR2* variants and larger SV z-score may warrant closer neurovascular surveillance. We propose a follow-up algorithm based on initial neurovascular MRA findings. However, studies with larger sample size and longer follow-up are needed to better define risk stratification and surveillance.

AORTIC EVENTS AFTER PROXIMAL THORACIC AORTIC REPAIR IN HERITABLE THORACIC AORTIC DISEASE: INSIGHTS FROM THE MONTALCINO AORTIC CONSORTIUM

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Introduction: Despite elective proximal aortic repair, individuals with heritable thoracic aortic (HTAD) remain at risk for subsequent aortic events, but genotype-specific risks remain poorly defined.

Objectives: Determine the risk of subsequent thoracic aortic events following elective proximal thoracic aortic aneurysm repair in cases with pathogenic variants (PVs) in HTAD genes.

Methods: A retrospective cohort of individuals in the MAC registry with PVs in *ACTA2, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2*, and *FBN1* who underwent elective repair of the aortic root and/or ascending thoracic aorta was reviewed. Affected genes and covariates were investigated for association with the primary outcome of a second aortic event (aortic dissection or aortic repair) using Kaplan-Meier (KM) analysis.

Results: Among 229 individuals, median age at last follow-up 46 years (IQR 34, 58), second aortic events occurred in 46 (20.1%). Event incidence differed according to gene (p=0.022), with the most in *TGFBR2* cases (17/43, 40%), followed by *FBN1* (14/68, 21%), *TGFBR1* (6/31, 19%), *TGFB2* (3/24, 13%), *SMAD3* (3/24, 13%), and *ACTA2* (3/26, 12%); no second aortic events occurred in *COL3A1* cases. Type B dissections were the most frequent second event (23/229, 10%) and were observed in all genes except for *TGFB2* and *COL3A1*. KM analyses demonstrated gene-specific differences in time to second events (log rank p = 0.02), with the lowest 5-and 10-year freedom from events in *TGFBR2* and *TGFBR1* cases. Time to second thoracic aortic repair differed by gene (p=0.02), whereas no differences were observed in time to type B dissections. Individuals with second events were younger at first repair (p=0.008) and more frequently reported smoking (33% vs 18%, p=0.006) and hypertension (46% vs 30%, p=0.046).

Conclusion: Although type B dissection rates are similar among *FBN1*, *TGFBR1,* and *TGFBR2* cases, *TGFBR2* cases demonstrated the highest need for second aortic repairs, supporting genotype-specific postoperative surveillance strategies.

WHAT WE'VE LEARNED FROM 20 YEARS OF TREATING COMPLEX SPINAL DEFORMITY IN MARFAN SYNDROME: A REPORT ON CARDIOVASCULAR AND ORTHOPEDIC OUTCOMES

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Introduction: Scoliosis in Marfan Syndrome (MFS) presents a unique clinical challenge as deformity correction may alter intrathoracic volume. While orthopedic success has been documented, the secondary impact on cardiovascular hemodynamics remains poorly characterized.

Objectives: This study discusses orthopedic and cardiovascular outcomes in MFS patients following spinal surgery utilizing a 20-year institutional experience.

Materials and Methods: Of 17 genetically confirmed MFS patients undergoing spinal surgery, 12 had pre/post echocardiographic assessment, and 10 had complete orthopedic and cardiac datasets. Cardiac measures of systolic, diastolic, chamber size, and aortic root dimension were assessed. Of the 12 included, 4 had additional pectus carinatum, and 3 had excavatum. Paired t-tests were used to compare pre-post cardiac parameters; Pearson's for orthopedic-cardiac interaction.

Results: There were 6 patients with planned spinal fusion and 6 with growth-friendly constructs. Mean age at surgery was 13.2 years (SD 2.6). Mean time between echocardiograms was 2.8 years (SD 5.7). Surgical correction resulted in height (mean **+2.9 cm**, $p<0.01$), Cobb angle (mean **-45.9°**, $p<0.01$), anterior-posterior chest diameter (mean +1.5 mm, $p=0.358$), and BSA change (mean +0.18, $p=0.018$). Planned fusion yielded higher correction magnitudes than growth-friendly constructs, though inter-group differences were non-significant. Pre-operative mean aortic root Z-score (3), aortic strain (10.47%), left ventricular ejection fraction (LVEF) (69.1%), left atrium diameter Z-score (-0.03). No clinically significant changes in cardiac parameters were noted post-op. While there was a statistically significant decrease in LVEF ($p< 0.01$), this was not clinically significant (69.1% to 61.4%). Change in Cobb angle and anterior-posterior chest diameter did not demonstrate a significant association with cardiac variables.

Conclusion: To our knowledge, this study provides the first characterization of cardiac outcomes following scoliosis surgery in the pediatric MFS population. We report no deleterious cardiac impact of spinal correction surgery. A larger sample may indicate further benefit to cardiopulmonary mechanics for this complex phenotype.

ANATOMIC DISTRIBUTION AND TEMPORAL PROGRESSION OF AORTOPATHY IN GENETICALLY CONFIRMED MARFAN SYNDROME

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Objectives: To evaluate the distribution and temporal progression of aortopathy in Marfan syndrome (MFS) using age at diagnosis and zone-based phenotyping.

Methods: We performed a retrospective single-center study of 203 patients with pathogenic or likely pathogenic *FBN1* variants. Data included demographics, systemic features, imaging findings, and operative history. Aortopathy, defined as dilation, aneurysm, dissection, or rupture, was classified anatomically by aortic zone (Zones 0–11). Comparisons were made by age at diagnosis, pediatric versus adult, and by aortic phenotype: Limited Zone 0 versus Extended Aortic Phenotype, defined as involvement of Zones 1–11 with or without root pathology.

Results: Mean age was 28 ± 17 years and 48% were male. Aortopathy was present in 135 individuals (67%), most commonly involving Zone 0A-C. Individuals diagnosed in adulthood (n=84) had higher rates of dissection (23% vs. 1%) and aneurysm (61% vs. 10%) than those diagnosed in childhood (n=119; all $p<.05$). Aneurysms were identified in 64 patients (47%) and demonstrated a cranio-caudal progression pattern. Extended disease was identified in 27 patients (13.3%), compared with 108 patients (53.2%) with root-limited involvement. Patients with extended involvement were older (50 vs. 24 years, $p<.01$), diagnosed later (44 vs. 16 years, $p<.01$), and had more hypertension (79% vs. 18%, $p<.05$) and sleep apnea (43% vs. 10%, $p<.05$). Tarlov cysts, osteoarthritis, and dural ectasia were also enriched. Aortic operations were more frequent in this group, with 45 operations in 27 patients versus 31 operations in 108 patients with root-limited disease ($p<.01$). Survival was lower among patients with extended involvement (93% vs. 100%, $p<.01$).

Conclusions: Aortopathy in MFS progresses in a cranio-caudal pattern and is more severe among those diagnosed in adulthood. The MFS Extended Aortic Phenotype is associated with older age, later diagnosis, hypertension, systemic features, greater surgical burden, and increased mortality.

TITLE: EXAMINING THE CLINICAL FEATURES AND DIAGNOSTIC YIELD AMONG PEDIATRIC PATIENTS ASSESSED FOR MARFAN SYNDROME AND OTHER AORTOPATHIES

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Introduction: Recognition of aortic disease is important as interventions are available to reduce the risk of life-threatening sequelae. At least 20% of aortopathies are caused by monogenic disorders. Identifying a genetic etiology is important to guide treatment and surveillance. Evidence-based guidelines for diagnosis and management among pediatric patients are limited and were primarily extrapolated from adults. Recent publications report wide variability in diagnosis and management of children.

Marfan syndrome is a well-described monogenic aortopathy syndrome. The Marfan syndrome diagnostic criteria (Ghent-2 criteria) were developed for adults. Its utility in children is limited as many criteria are age-dependent. Documentation of the Ghent-2 score in children <15 is limited to small cohorts. The Hospital for Sick Children has a large pediatric aortopathy cohort who receive care through cardiology, genetics and other specialties. We created a pediatric aortopathy research registry to help reduce evidence gaps in this population.

Objectives: To assess the application of Ghent-2 nosology in pediatric Marfan syndrome patients, including how many patients with a genetic diagnosis meet diagnostic criteria.

Methods: The Pediatric Aortopathy Registry is an observational study. Clinical data will be abstracted retrospectively from medical records. Current patients will be enrolled to enable prospective collection of clinical data including imaging, genetic testing, family history, and results from clinical assessments including the Ghent-2 criteria.

Results: There are >125 Marfan syndrome patients receiving care through our clinic. Pending analyses, we will report how many patients we assessed, how many of these patients met diagnostic criteria for Marfan syndrome, how many underwent genetic testing, and how many received a molecular diagnosis. We will assess how the Ghent-2 criteria changes over time among Marfan syndrome patients.

Conclusions: Findings may clarify diagnostic yield of genetic testing among pediatric patients assessed for Marfan syndrome and how the Ghent-2 criteria changes with age Marfan syndrome patients.

SYSTEMATIC REVIEW OF LOEYS-DIETZ SYNDROME: TWO DECADES OF RESEARCH PROGRESSION

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Background: Loeys-Dietz syndrome (LDS) was first described in 2005, marking the recognition of a distinct autosomal dominant connective tissue disorder characterized by arterial aneurysms, craniofacial abnormalities, and systemic involvement driven by pathogenic variants in the transforming growth factor beta (TGF-β) signaling pathway. In the 20 years since its identification, research has expanded rapidly, moving from initial gene discovery and clinical characterization to surgical management, imaging guidelines, and more recently, translational advances in gene therapy and genetic screening.

Methods: We systematically reviewed all publications on LDS between 2005 and 2025. From 1,358 identified articles, 1,275 met inclusion criteria. Publications were thematically coded into six domains: *clinical manifestations, diagnostics and measurements, genetic and syndrome mechanisms, prognosis and patient outcomes, scientific and technological advancements, and treatment and management.* Codes were applied at primary, secondary, and tertiary levels to capture depth and diversity in the literature.

Results: The largest body of work addressed genetic and syndrome mechanisms (n=352, with 245 focused on genetic mutations) and treatment and management (n=323, including 296 surgical intervention studies). Clinical manifestations were well-characterized (n=406), dominated by cardiovascular involvement (n=194). Diagnostics and measurement studies (n=139) highlighted the growing importance of imaging guidelines (n=94). Fewer studies addressed prognosis and patient outcomes (n=16), particularly quality of life (n=7) and mental health (n=4). Emerging work on gene therapy, genetic screening, and bioengineering suggests a translational shift toward preventive and molecular interventions.

Conclusion: Over two decades, LDS research has evolved thematically: from genetic discovery and diagnostic clarification (2005–2010) to diagnostic imaging and phenotype expansion (2010–2015), to surgical optimization and improved survival (2015–2020), and now toward genetic screening and translational therapies (2020–2025). While advances have transformed LDS into a manageable chronic condition, gaps remain in patient-centered outcomes. Future research must integrate psychosocial domains with molecular and surgical progress.

LONGITUDINAL AORTIC ROOT GROWTH AND OUTCOMES IN PEDIATRIC MARFAN SYNDROME COMPARED BY BASELINE DILATION STATUS: A MULTICENTER STUDY FROM CLARITY

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Introduction: Approximately 20-30% of children with Marfan syndrome (MFS) have non-dilated aortic roots (AoRs). AoR growth and outcomes in pediatric MFS stratified by dilation status remain undefined.

Objectives: Compare pediatric MFS AoR growth and outcomes by dilation status.

Materials & Methods: MFS patients meeting revised Ghent criteria from the Collaborative for Longitudinal Aortic Research In The Young (CLARITY) registry with ≥2 echocardiograms were included. Exclusion criteria included first echocardiogram >18 years, neonatal MFS, or critical congenital heart disease. Z-scores were calculated using Boston nomograms; z-scores associated with BMI ≥95%tile and echocardiograms after AoR replacement were excluded. Patients were stratified by baseline z-score into dilated (≥2.0) and non-dilated (<2.0); non-dilated patients were stratified by final z-score into developed dilation and never dilated. Continuous variables were compared with Wilcoxon rank-sum tests and categorical variables with Fisher's exact tests. Longitudinal z-score changes were assessed with mixed-effects linear regression.

Results: Among 260 subjects (54% male), 70% had dilated and 30% had non-dilated baseline AoRs. Median first echocardiogram age and follow-up time were 6.0 (IQR 3.3,10.6) and 5.5 (IQR 2.4,10.1) years. Z-scores progressively increased in both dilated (+0.018/year, p<0.001) and non-dilated (+0.029/year, p<0.001) patients. Baseline dilated male z-scores grew faster than dilated females (+0.047/year vs. -0.011/year, p<0.001). Of non-dilated patients, 32% developed dilation. Developed dilation group exhibited higher median baseline z-scores (+1.5, IQR +1.2,+1.9) vs. never dilated (+1.0, IQR +0.4,+1.6, p=0.002), and faster z-score change (+0.058/year vs. -0.004/year; p<0.001). Baseline dilated patients had higher odds of surgery vs. non-dilated (21% vs 4%, OR 6.56, p<0.001). Of non-dilated patients, surgery was only performed in those who developed dilation (n=3). Aortic dissections (n=3, type B) and deaths (n=2) were only observed in patients with baseline dilation.

Conclusion: Pediatric MFS AoR growth is progressive regardless of baseline dilation status. Dilated males exhibit faster AoR growth. Non-dilated individuals remain at risk for AoR dilation and surgery.

VERTEBRAL ARTERY TORTUOSITY AND ACUTE TYPE A AORTIC DISSECTION IN MARFAN SYNDROME

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Introduction: Aortic root (AoR) dimension is a suboptimal predictor of acute type A aortic dissection (ATAAD) in Marfan syndrome (MFS).

Objectives: To determine the association between clinical characteristics, including vertebral artery tortuosity is associated with earlier ATAAD and ATAAD at AoR <5cm in MFS.

Methods: Patients with MFS and 1) an *FBN1* variant or ectopia lentis and 2) magnetic resonance/computed tomography angiography <40y in the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions or our institution were included. The primary exposure and outcome were height-adjusted vertebral tortuosity index (VTI-h, dichotomized using receiver operator curve [ROC] analysis) and ATAAD before age 40y, respectively. We employed multivariable Cox regression with time-varying covariates, exploring surgical history and clinical features as covariates. Clinical profiles of patients with ATAAD by risk status were described.

Results: Of 132 patients (53.0% male, median age at last follow-up 23.6y), median VTI-h was 48.2 (IQR 22.9-85.2). Twenty had ATAAD (15.2%), 60.0% (12/20) of whom were high-risk. VTI-h cutoff of 131 was identified on ROC analyses as the cutpoint that optimized sensitivity and specificity (75% and 94% respectively). VTI-h ≥131 (HR 2.8, 95% CI 1.1-7.3, p=0.04), pregnancy (HR 90.0, 95% CI 7.7-1059.8, p=0.0003), and type B aortic dissection without AoR replacement (HR 7.4, 95% CI 1.9-28.9, p=0.004) were associated with higher ATAAD risk. Of the 6 high-risk patients with ATAAD and confirmed aortic dimensions, 3/6 (50.0%) dissected at >5cm, while of the remaining 3 (all females), 1 dissected between 4-5cm, 1 was peripartum, and 1 had a VTI-h of 94. Of the 2 low-risk patients with ATAAD and aortic dimensions, both dissected at ≥4cm.

Conclusion: Elevated VTI-h, prior type B aortic dissection without AoR replacement, and pregnancy were associated with higher likelihood of ATAAD in MFS. Further research is warranted.

WHEN OVERGROWTH MIMICS MARFAN SYNDROME: AORTIC COMPLICATIONS IN TATTON-BROWN-RAHMAN SYNDROME

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Introduction: Tatton-Brown-Rahman syndrome (TBRS) is a rare overgrowth disorder caused by pathogenic variants in the *DNMT3A* gene, characterized by intellectual disability, distinctive dysmorphic features and variable systemic involvement. Cardiac manifestations have also been reported, mainly congenital malformations such as atrial septal defect, ventricular septal defect and cardiac valvular disease. Aortic dilatation had been described, but dissection or rupture had not, and it remained to be established whether aortic dilatation is static or progressive.

Objectives: To describe the prevalence, clinical characteristics and outcomes of aortic dilation in patients with TBRS followed at a tertiary hospital.

Materials and Methods: Retrospective unicentric study including patients with molecularly confirmed TBRS. Clinical, genetic and cardiovascular data were collected from medical records, including echocardiographic measurements and longitudinal follow-up of aortic dimensions.

Results: A total of 12 patients with TBRS were included, all harboring pathogenic or likely pathogenic variants in *DNMT3A*. Aortic dilation was identified in 33% (4/12) of patients, predominantly involving the aortic root and/or ascending aorta; notably, one patient presented with a ruptured bilateral aortoiliac aneurysm. Three patients presented with aortic dissection at diagnosis, all occurring around the age of 40 years. The aortic dilation in the fourth patient was detected at the age of 17 years and has shown a progressive course.

Interestingly, three patients were initially referred for evaluation with suspected Marfan syndrome due to marfanoid habitus and the presence of aortic dilation or dissection.

Conclusion: Aortic dilation may represent an underrecognized feature of TBRS, with can be progressive and lead to dissection and rupture, beyond the aortic root, in more peripheral aortic territory. These findings support the inclusion of regular cardiac and arterial surveillance in clinical management protocols for TBRS. Importantly, TBRS should be considered in the differential diagnosis of Marfan syndrome, particularly in individuals presenting with marfanoid features, in addition to cognitive impairment, and overgrowth. Continued follow-up of affected patients is warranted to better define the true prevalence of vascular involvement and to optimize management strategies, including potential therapeutic approaches.

NOTES

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