BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Genetic Testing Following Type A Thoracic Aortic Dissection — The Good, the Bad and the Ugly

Miriam Jassam Walker[1], Carl Simela[1,2], Paraskevi-Maria Psefteli[2], Sam Straw[1,2], Kathryn Griffin[2,3], Wazir Baig[1,*]

[1]Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[2]Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
[3]Department of Pathology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
*Correspondence: wazir.baig@nhs.net (Wazir Baig)

Abstract

Genetic testing is indicated for suspected familial thoracic aortic aneurysm or following dissection to complement targeted screening of first-degree relatives. Our data suggest that tissue storage and genetic testing in the setting of suspected heritable thoracic aortic aneurysm and dissection (HTAAD) are underutilized. In this focussed review, we outline the genetic basis of HTAAD and the current guidelines regarding genetic testing. We present a case series demonstrating both favourable and unfavourable genetic testing practices. We suggest potential improvements to current genetic testing algorithms, such as increased involvement of medical examiners and emergency department clinicians, to help identify patients and families suitable for genetic testing. Additionally, we provide a description of the pathophysiology underlying inheritable aortopathies.

Key words: thoracic aorta; thoracic aortic dissection; genetic testing; familial thoracic aortic aneurysm and dissection

Submitted: 4 December 2024 Revised: 10 February 2025 Accepted: 26 February 2025

Introduction

Acute type A aortic dissection is a medical emergency, with a reported mortality rate of 1–2% per hour if not diagnosed promptly (Mészáros et al, 2000). The incidence of acute aortic dissection is increasing, most commonly affecting males over the age of 60 who are often hypertensive (Nienaber and Clough, 2015). However, approximately one quarter of thoracic aortic aneurysms and dissections have a genetic basis (Biddinger et al, 1997). In the UK, the National Health Service Genomic Test Directory provides guidelines to identify those patients who should be considered for gene testing (NHS, 2025), which are similar to international guideline recommendations (Isselbacher et al, 2022; Mazzolai et al, 2024). These guidelines suggest that genetic testing is indicated for thoracic aortic aneurysms or dissections in people under 50 years old, people with clinical features of Loeys-Dietz syndrome or Marfan syndrome (with a systemic Ghent score of at least seven) and if there is high clinical suspicion for a relevant disease. Testing is also indicated in cases of thoracic aneurysm or dissection in patients under 60 years of age, if they have either no classical cardiovascular risk factors, clinical features of aortopathy or a first degree relative with thoracic aortic aneurysm or dissection (NHS, 2025).

How to cite this article:
Jassam Walker M, Simela C, Psefteli PM, Straw S, Griffin K, Baig W. Genetic Testing Following Type A Thoracic Aortic Dissection — The Good, the Bad and the Ugly. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2024.0984

Heritable thoracic aortic aneurysm and dissection (HTAAD) may be syndromic or non-syndromic. Syndromic HTAAD indicates involvement of multiple bodily systems and the best known of these are the Marfan, Loeys-Dietz and type 4 vascular Ehlers-Danlos syndromes. HTAAD can also be separated into familial, where several family members are affected, and non-familial (Fletcher et al, 2020). Table 1 summarises the genetic abnormalities, pathological mechanisms and described aortic syndromes. Of note, phenotypic penetrance is variable within a single family, thus adding to the complexity of patient management (Pomianowski and Elefteriades, 2013).

Non-syndromic patients possess a genetic mutation which predisposes them to aortic dissection, but other organ systems are normal. Coarctation of the aorta, Turner's syndrome and familial and non-familial bicuspid aortic valve (BCAV) disease also predispose to aortic dissection. The genetic basis of Turner's syndrome is known but the precise genetic abnormality in aortic coarctation is not. Pathogenic and likely pathogenic mutations of the notch receptor 1 gene (*NOTCH1*) (MIM: 190198) have been reported in 2% of familial BCAV cases (Debiec et al, 2022) but this gene is not routinely included in the gene panel for HTAAD.

Determining the cause of a dissection is of great importance, particularly if an inheritable aortopathy is likely (Isselbacher et al, 2022). We formed the impression that the identification of patients who had had a type A dissection and who were eligible for gene testing were not being investigated appropriately. As these results may be of central importance in the management of patients and their first-degree relatives (FDR), we analysed the use of such testing in patients referred to the thoracic aortopathy service. We present three cases which exemplify the variability in the identification and timing of gene testing following aortic dissection. The aim of this study is to increase the awareness of non-specialists of the need to consider the question of causation of aortic dissection and how practical steps can be made to improve performance.

Current Practice

We undertook a service evaluation of patients admitted to the Leeds Teaching Hospitals Trust (LTHT), a tertiary referral centre for cardiology and cardiothoracic surgery, with a confirmed diagnosis of acute type A aortic dissection between 1 January 2015 and 31 December 2022. Patients were identified using a combination of internal database searches and the Central Cardiac Audit Database (Bridgewater, 2010). In total, 121 patients were identified with a confirmed type A dissection. The mean age was 62.1 years (SD 15.0, range 20–94), and 81 (66.9%) were male. On average, women presented at a later age compared to men (67.2 $\pm$ 16.4 years vs was 59.6 $\pm$ 13.6 years, $p = 0.008$). Genetic testing practice for each patient was compared with the NHS Genomic Test Directory Criteria for gene testing for thoracic aortic disease (NHS, 2025). Of the 56 patients who had confirmed type A dissection and were under the age of 60 years, only seven patients received genetic

Table 1. The 37 genes currently implicated in both non-syndromic and syndromic familial thoracic aortic aneurysm and dissection.

Gene(s)	Key reference	Rated as green entities in the Genomics England Panel	Inheritance pattern	Syndromic or non-syndromic	Relevant syndrome
ACTA2	(Guo et al, 2007)	Y	AD	Both	Multisystemic smooth muscle dysfunction
ARIH1	(Tan et al, 2018)	N	Unknown	Mainly nonsyndromic	-
BGN	(Meester et al, 2017)	Y	X-Linked	Syndromic	Meester-Loeys syndrome
COL1A2/COL3A1/ COL5A1/COL5A2	(Schwarze et al, 2001)	Y	AD and AR	Syndromic	EDS
EFEMP2	(Huang et al, 2010)	Y	AR	Syndromic	Cutis laxa
ELN	(Callewaert et al, 2011)	Y	AD	Syndromic	Cutis laxa
EMILIN1	(Capuano et al, 2016)	N	AD	Syndromic	Connective tissue disease
FBN1	(Dietz et al, 1991)	Y	AD	Both	MFS
FBN2	(Putnam et al, 1995)	Y	AD	Syndromic	Contractual arachnodactyly
FLNA	(Chen et al, 2018)	Y	X-Linked dominant	Syndromic	Periventricular nodular heterotopia and otopalatodigital syndrome
FOXE3	(Kuang et al, 2016)	N	AD	Nonsyndromic	-
HCN4	(Vermeer et al, 2016)	N	AD	Nonsyndromic	-
LOX	(Lee et al, 2016)	Y	AD	Nonsyndromic	-
LTBP1/LTBP3	(Quiñones-Pérez et al, 2018)	N	AD/AR	Syndromic	Musculoskeletal and dental abnormalities
MAT2A	(Guo et al, 2015)	N	AD	Nonsyndromic	-
MFAP5	(Barbier et al, 2014)	Y	AD	Nonsyndromic	-
MYH11	(Pannu et al, 2007)	Y	AD	Nonsyndromic	-
MYLK	(Wang et al, 2010)	Y	AD	Nonsyndromic	-
NOTCH1	(Koenig et al, 2017)	Y	AD	Nonsyndromic	-
PRKG1	(Guo et al, 2013)	Y	AD	Nonsyndromic	-
ROBO4	(Gould et al, 2019)	N	AD	Nonsyndromic	-

Table 1. Continued.

Gene(s)	Key reference	Rated as green entities in the Genomics England Panel	Inheritance pattern	Syndromic or non-syndromic	Relevant syndrome
SKI	(Doyle et al, 2012)	Y	AR	Syndromic	Shprintzen-Goldberg syndrome
SLC2A10	(Cheng et al, 2009)	Y	AR	Syndromic	Arterial tortuosity syndrome
SMAD2/SMAD3/ SMAD4/SMAD6	(van de Laar et al, 2011)	Y	AD	Both	LDS type III/JP and HHT syndrome
TIMP3/TIMP1	(Corbitt et al, 2018)	N	X-Linked dominant	Syndromic	Aortic valve disease
TGFB2/TGFB3	(Lindsay et al, 2012)	Y	AD	Syndromic	LDS type IV/LDS type V
TGFBR1/TGFBR2	(Gallo et al, 2014)	Y	AD	Both	LDS type I/LDS type II

Legend: Table showing the genes implicated in thoracic aortic aneurysm and dissection as well as the key references. Table adapted from Faggion Vinholo et al (2019) under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).
Genes: *ACTA2*, actin alpha 2; *ARIH1*, ariadne RBR E3 ubiquitin protein ligase; *BGN*, biglycan; *COL1A2*, collagen type I alpha 2 chain; *COL3A1*, collagen type III alpha 1 chain; *COL5A1*, collagen type V alpha 1 chain; *COL5A2*, collagen type V alpha 2 chain; *EFEMP2*, EGF containing fibulin extracellular matrix protein 2; *ELN*, elastin; *EMILIN1*, elastin microfibril interfacer 1; *FBN1*, fibrillin 1; *FBN2*, fibrillin 2; *FLNA*, filamin A; *FOXE3*, forkhead box E3; *HCN4*, hyperpolarisation activated cyclic nucleotide gated potassium channel 4; *LOX*, lysyl oxidase; *LTBP1*, latent transforming growth factor beta binding protein 1; *LTBP3*, latent transforming growth factor beta binding protein 3; *MAT2A*, methionine adenosyltransferase 2A; *MFAP5*, microfibril associated protein 5; *MYH11*, myosin heavy chain 11; *MYLK*, myosin light chain kinase; *NOTCH1*, notch receptor 1; *PRKG1*, protein kinase cGMP-dependent 1; *ROBO4*, roundabout guidance receptor 4; *SKI*, SKI proto-oncogene; *SLC2A10*, solute carrier family 2 member 10; *SMAD2*, SMAD family member 2; *SMAD3*, SMAD family member 3; *SMAD4*, SMAD family member 4; *SMAD6*, SMAD family member 6; *TIMP3*, TIMP metallopeptidase inhibitor 3; *TIMP1*, TIMP metallopeptidase inhibitor 1; *TGFB2*, transforming growth factor beta 2; *TGFB3*, transforming growth factor beta 3; *TGFBR1*, transforming growth factor beta 1; *TGFBR2*, transforming growth factor beta 2; SMAD, suppressor of mothers against decapentaplegic.
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; EDS, Ehlers-Danlos syndrome; HHT, hereditary haemorrhagic telangiectasia; JP, juvenile polyposis; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome.

testing, despite 20 qualifying for gene testing based on these criteria. The mean interval from the date of aortic dissection to review in the dedicated aortopathy clinic was 13 months (range 0–29).

Case 1 — The Good

A 53-year-old female of previous good health presented to her local hospital with severe chest pain. A diagnosis of type A aortic dissection was confirmed by computerised tomography (CT) aortogram (Fig. 1). She was transferred to our centre and underwent emergency surgery. At operation, her aortic valve was intact with normal function on perioperative transoesophageal echocardiography, and she received a 28 mm interposition aortic tube graft.

Prior to discharge, the patient reported a history of aortic dissection affecting her father and paternal grandfather. After obtaining consent, a blood sample was taken for gene analysis. The patient was heterozygous for a pathogenic myosin light chain kinase (*MYLK*) gene mutation associated with familial thoracic aortic dissection. *MYLK* (MIM: 600922) encodes the myosin light chain kinase, which phosphorylates the myosin regulatory light chain to allow muscle contraction (Kamm and Stull, 2001). Most pathogenic mutations are missense *MYLK* variants that result in impaired aortic contraction and a reduced ability of the ascending aorta to withstand vascular wall forces thus culminating in dilatation (Cho et al, 2023). The patient was informed of the result, and her FDRs were advised to request referral to their local centre for screening, which included gene testing and echocardiography. The timing and investigation of the patient and her family represents optimal practice and demonstrates that such a result is realisable.

Case 2 — The Bad

A 21-year-old female presented to her local hospital with severe chest pain. A diagnosis of musculoskeletal pain was made, and she was discharged with analgesia for symptom relief but continued to have intermittent chest discomfort. Notably, she had undergone coil occlusion of a patent ductus arteriosus (PDA) as an infant and had a history of joint hyperextensibility and recurrent patellar dislocations. Because of her prior cardiac history, she self-referred to a cardiologist nine months after her original hospital attendance. An echocardiogram showed features of a chronic type A dissection (Fig. 2). She was admitted from clinic and underwent surgery with successful implantation of a 24 mm ascending hemi-arch replacement and resuspension of her native aortic valve.

Histology of the excised aortic wall showed prominent deficiency of elastin in the media raising the possibility of an underlying genetic abnormality. Postoperatively, she was referred to the aortopathy clinic and was seen four months after her operation. As she fulfilled the criteria for gene testing, a blood sample was taken at her first clinic attendance. The result became available twenty-two months after her initial presentation. Analysis showed her to be heterozygous for a pathogenic mutation in the Actin alpha 2 gene (*ACTA2*) (MIM: 102620) which is associated with an increased risk of both PDA and aortic dissection. The *ACTA2*

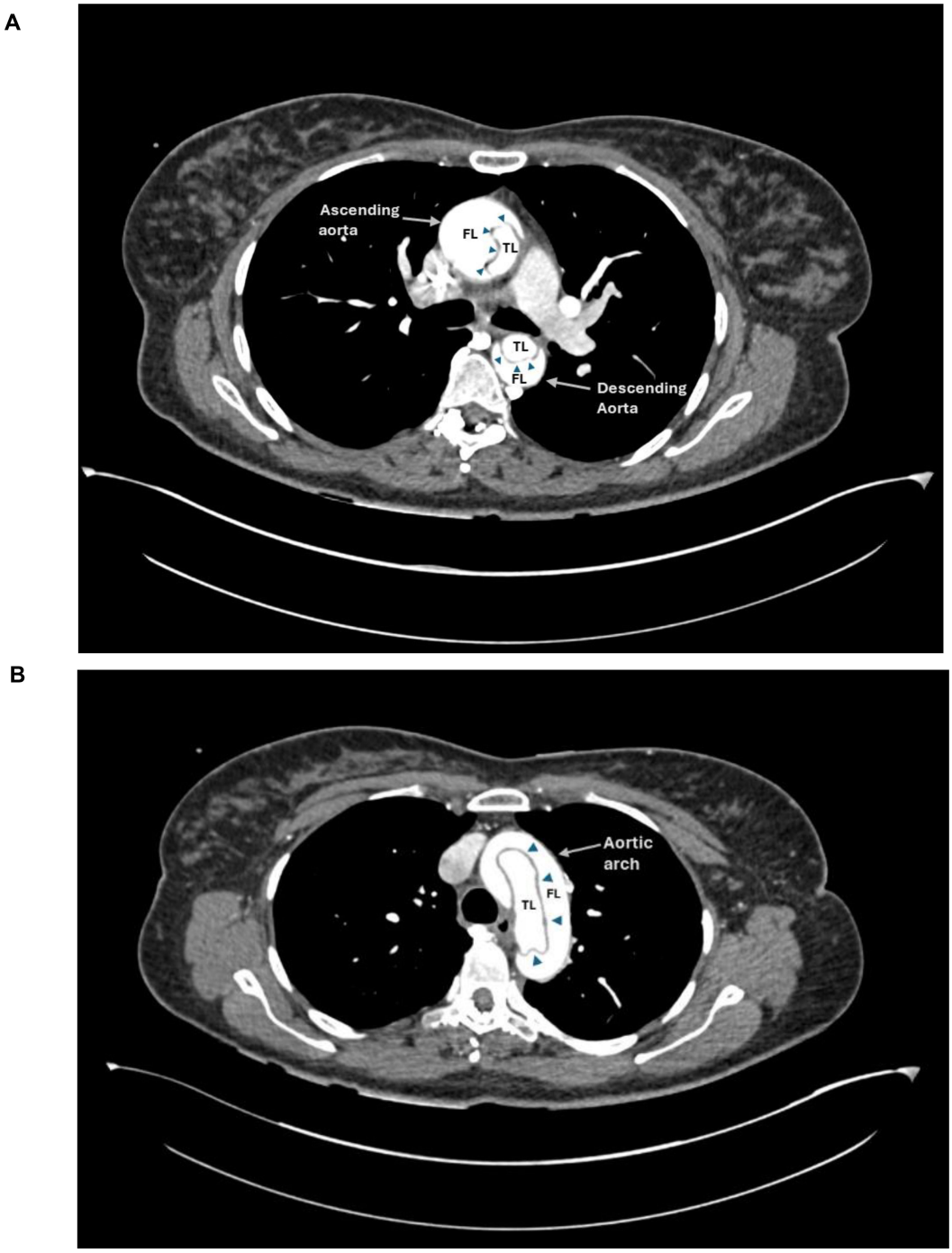

Fig. 1. Case 1 type A acute aortic dissection computed tomography aortogram images. Axial slices from computed tomography aortogram demonstrating type A acute aortic dissection at the level of the ascending and descending aorta (A) and the aortic arch (B) as described in Case 1. Blue arrowheads show the intimal flap separating the true and false lumens. Abbreviations: TL, true lumen; FL, false lumen.

gene encodes the vascular smooth muscle cell (VSMC) alpha-actin protein, which is essential for vascular contractility. *ACTA2* missense variants in the context of familial HTAAD result in VSMC disarray and deranged responses to physiological vascular wall forces resulting in aortic dilatation (Guo et al, 2007). Reduced cardiac endothelial proliferation has also been demonstrated in the setting of pathogenic

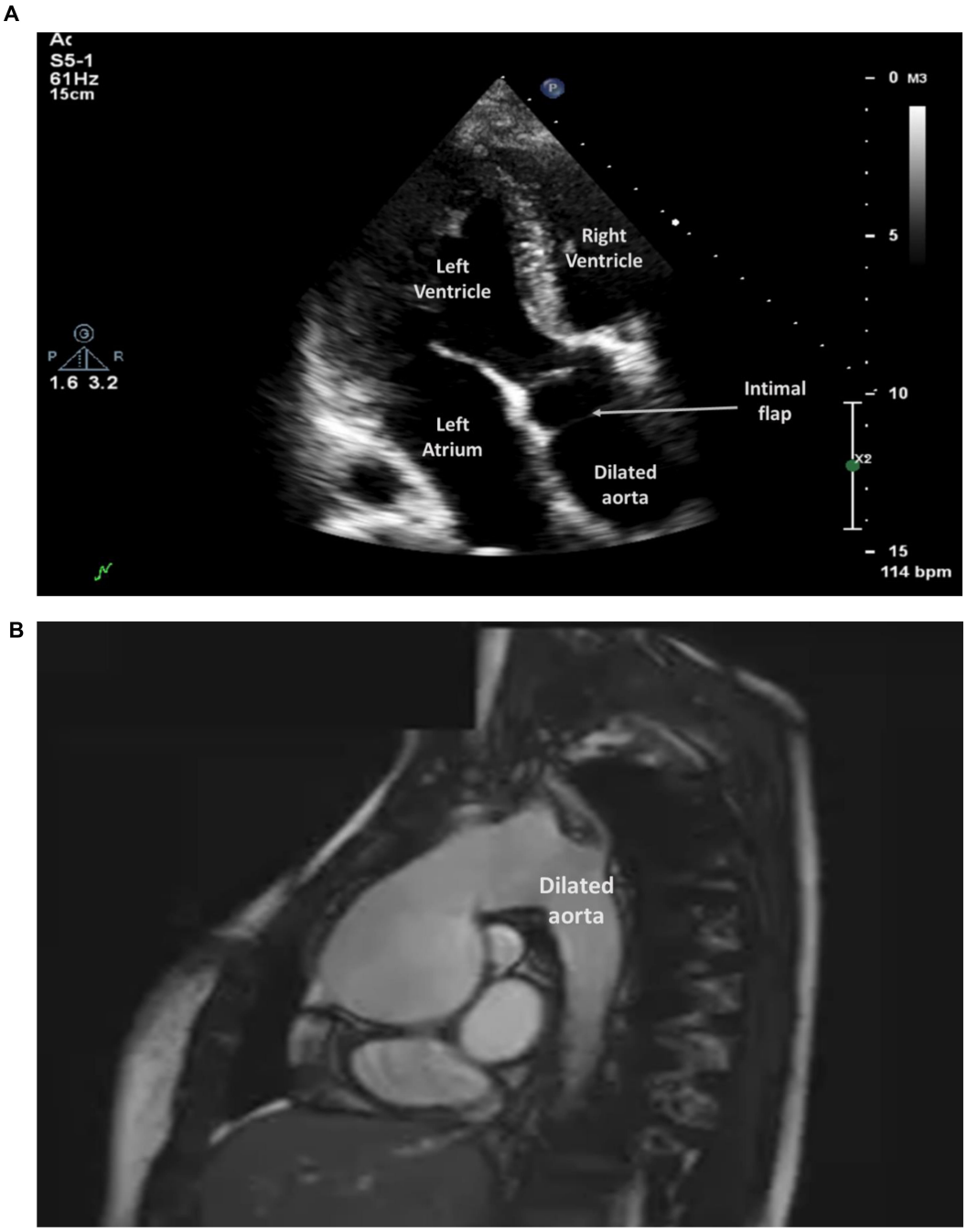

Fig. 2. Different imaging modalities of thoracic aortic pathology in Case 2. (A) Apical three chamber view of transthoracic echocardiography showing the chronic aortic dissection and dilated aorta. The white arrow signifies the intimal flap arising from the aortic dissection. (B) shows a cardiovascular magnetic resonance sagittal view of the enlarged ascending aorta.

ACTA2 mutations (Sebastian et al, 2024). Notably, missense mutations in ACTA2 are the commonest cause of non-syndromic HTAAD accounting for 14% of cases (Guo et al, 2007).

Following the availability of this result, her parents and sibling underwent gene testing and echocardiography. As none of them had the mutation it was concluded that the patient had a *de novo* mutation, thus obviating the need for ongoing imaging surveillance in them. However, in retrospect the timing of the screening of the

FDRs was delayed and could have been improved upon had the proband been gene tested shortly after the diagnosis of dissection had been made.

Case 3 — The Ugly

A 44-year-old woman was referred to the aortopathy clinic following the sudden death of her 37-year-old brother. A post-mortem examination had concluded that he had died from acute haemopericardium secondary to a type A aortic dissection. There was no other family history of aneurysmal disease. In clinic, the patient did not display any evidence of a connective tissue disorder, or a syndrome associated with an inheritable aortopathy. Her echocardiogram and electrocardiogram were normal. Further inquiries with the pathology department where the autopsy had been conducted revealed that no tissue blocks from the deceased had been saved and that no other samples from him were available. The deceased first-degree relatives comprised his mother and one brother. They attended for aortopathy screening. They had no clinical features of a syndromic HTAAD, and their echocardiograms were normal.

If gene testing in the proband had been performed and a pathogenic mutation associated with aortic dissection had been identified, then the FDRs could have been offered testing to determine if they carried the mutation. Because the index patient died at a young age, his family members have been advised that they should have long-term aortic surveillance. The lack of gene testing of the deceased's tissues has had significant implications for his at-risk family members. A normal result would have mitigated the need for ongoing surveillance, as demonstrated in Case 2. Conversely, a positive result would enable the detection of carriers of the mutation who would continue with surveillance. The lack of gene testing also impacts on resource utilisation and can result in the development of anxiety and other negative effects, for example, being perceived as unfavourable for insurance and mortgage applications (Aatre and Day, 2011).

Pathology and Mechanisms in Aortic Dissection Development

The inheritable aortopathies relate to abnormalities of connective tissues, vascular smooth muscle cell (VSMC) contraction and cell signalling. Examples of defective smooth muscle contraction causing aortic dissection are described in cases 1 and 2. However, the best known of the genetic aortopathies is Marfan syndrome which is caused by mutations of the fibrillin-1 (*FBN1*) gene located on chromosome 15 (Dietz et al, 1991). Fibrillin is a major structural component of microfibrils which are found in the extra-cellular matrix (ECM). Microfibrils are found in areas exposed to repeated stretching forces and therefore play a significant role in determining the elasticity of the aortic wall. Microfibrils also transduce mechanical forces between VSMC and the ECM, thereby enabling VSMC to respond to changing forces on the vascular wall (Humphrey et al, 2015). In Marfan syndrome, *FBN1* loss-of-function variants result in a deficiency of normal aortic microfibrils, which therefore impedes the ability of the aorta to sense and respond to mechan-

ical stress, thus predisposing to dilatation (Du et al, 2021). Other structures with a high abundance of fibrillin, such as the suspensory ligaments of the lens, bones and pleura are also affected thus explaining the multi-organ involvement observed in Marfan syndrome.

Dysregulation of the transforming growth factor β (*TGF-β)* signalling pathway has been identified as the underlying mechanism in the different types of the Loeys-Dietz syndrome (LDS). This is summarised in Fig. 3 (Deng et al, 2024). The latent *TGF-β* binding proteins (LTBPs) have structural and functional properties in the ECM and affect the availability of *TGF-β*. The binding of a *TGF-β* protein to its receptor results in the activation of suppressor of mothers against decapentaplegic (SMAD) proteins, which enter the cell nucleus to influence transcriptional activity and consequently cell division and growth (Schmierer and Hill, 2007). The wide distribution of SMAD proteins in many tissues accounts for the variable clinical manifestations of LDS. Pathogenic LDS mutations can be in the *TGF-β* receptor genes or downstream mediator genes and transducer genes, such as SMAD genes, *TGF-β* ligand genes and inhibitor genes. These LDS loss-of-function mutations cause a paradoxical increase in *TGF-β* signalling (Wang et al, 2024; Bertoli-Avella et al, 2015). This paradox may be because of paracrine and autocrine compensatory signalling activation (Lindsay et al, 2012). Irrespective of the cause, the upregulated *TGF-β* signalling predisposes to aortic aneurysm formation, likely due to extracellular signal-regulated kinase activation by the *TGF-β* non-canonical pathway (Takeda et al, 2018).

Research into the genetics of the monogenic aortopathies has resulted in clearer understanding of their underlying pathophysiology as reviewed by Ostberg et al (2020). A striking observation in genetic aortopathies is the location of the aortic root as the usual site at which structural abnormalities develop (Verstraeten et al, 2017). A study of the embryological origin of the VSMC in a murine model of LDS provides a possible explanation (MacFarlane et al, 2019). VSMC originating from the cardiac neural crest exhibited normal or increased SMAD 2/3 phosphorylation in response to *TGF-β* stimulation. Conversely, VSMC derived from the secondary heart field showed reduced activation of SMAD 2/3 in response to this stimulating agent. An imbalance in the proportion of these cell types in the aortic root might explain the phenotypic expression of aneurysmal disease in susceptible individuals.

Genetic Testing for Inheritable Aortopathies

Since fibrillin was first identified as the defective protein in the Marfan syndrome (Dietz et al, 1991), over 37 genes have been associated with HTAAD, in which inheritance occurs in a dominant Mendelian pattern (Faggion Vinholo et al, 2019) (Table 1). In non-syndromic HTAAD, heterozygous pathogenic variants in single genes are responsible for the disease (Isselbacher et al, 2022). Consequently, molecular genetic testing for inheritable aortopathies requires that a panel of genes associated with aortic disease is examined. The current Genomics England Version 3 Panel for HTAAD (R125; see https://panelapp.genomicsengland.co.uk/pan

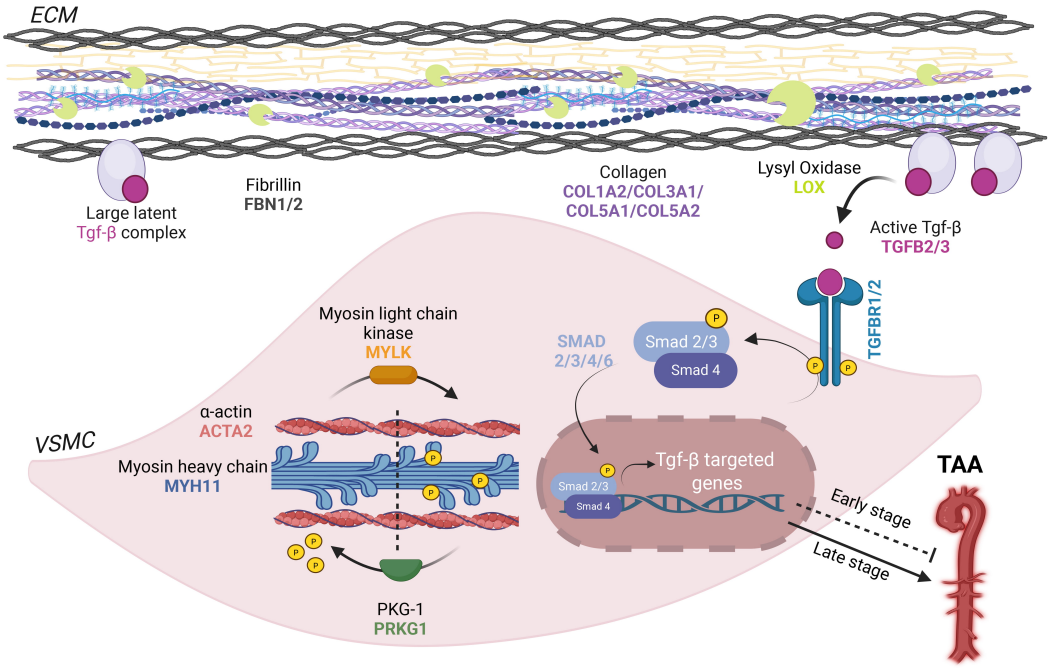

Fig. 3. The molecular mechanisms implicated in thoracic aortic aneurysm development and progression. Transforming growth factor β (TGF-β) signalling is protective in early thoracic aortic aneurysm development and deleterious in latter stages. Created in BioRender and reproduced with permission under a BioRender Academic Publication License. Abbreviations: ECM, extra-cellular matrix; PKG-1, Protein Kinase G1; PRKG1 protein kinase cGMP-dependent 1; SMAD, suppressor of mothers against decapentaplegic; TAA, thoracic aortic aneurysm; TGFβ2/3, transforming growth factor-beta 2/3; TGFBR1/2 TGFβ type 1/2 receptor; VSMC, vascular smooth muscle cell.

els/700/) includes 33 that are included on the current testing panel based on crowd-sourced expert review of the likely causative genes for a particular phenotype.

It is standard practice for multiple biopsies of the aortic wall to be taken during surgery for aortic dissection. Histological analysis can provide insights into the primary pathological abnormality. Specimen reports often describe myxoid degeneration of the medial layer of the aorta, but this is non-specific. Other histological features observed in HTAAD include elastin fragmentation, proliferation of VSMC but with little inflammation, as demonstrated in Case 2. Revised guidelines were published which aimed to improve and standardise the pathological changes observed and which could enhance the detection of more subtle abnormalities associated with specific aortic diseases (Halushka et al, 2016). The effectiveness of these guidelines await assessment.

The preferred specimen type for most types of genetic testing is whole blood. If the level of awareness and the application of the criteria for such testing became established as part of the provision of care for patients with an acute dissection, then a sample for storage could be taken pre-operatively or prior to discharge (Case 1). Detailed analysis could be performed later with either the consent of the patient, or of their family if the patient does not survive. Alternatively, if aortic or splenic tissue blocks are stored then they can be subjected to genetic analysis.

For patients who die prior to surgery then there may be no tissue specimens available for such analysis, as described in Case 3. In the UK, there has been a significant trend such that the number of invasive Coronial autopsies has declined in favour of CT-imaging based examinations (Bailey et al, 2021; Thornton, 2016). A consequence of this change is that the opportunity for storage of aortic or splenic material for later genetic analysis (under the authority of His Majesty's Coroner and with the consent of family members) may be reduced. Therefore, in cases of fatal, non-operated aortic dissection, although the diagnosis may be made or confirmed with CT scanning, this methodology is unable to contribute to the determination of aetiology if used in isolation. In such instances, we advocate that pathways for relative counselling, consent and tissue collection should be established, similar to those proposed in the investigation of sudden cardiac death (Sheppard, 2022).

Genetic testing can facilitate recognition of the underlying genetic cause for a patient's condition, which may aid directly in informing the patient's management and prognosis. It can also provide key information for relatives who may be tested for a familial mutation and discharged from cardiac screening if appropriate. Understanding the molecular cause of the condition may also allow the proband or relatives to use this information for reproductive choices and options such as prenatal testing or preimplantation genetic testing. Fig. 4 summarises the current approach based on recent European Society of Cardiology guidelines to genetic testing of a patient with suspected HTAAD with indications as to the time points along the patient's journey where we propose that samples for genetic testing could be acquired. These opportunities include in the emergency department, on the surgical ward and in the outpatient clinic.

Implications for Practice

Much of the focus in the discussion of acute aortic dissection is on rapid confirmation of the diagnosis and proceeding to emergency surgery. However, there may be less impetus to prompt clinicians to consider the aetiology of patients who have a type A dissection. The primary characteristics of patients in whom a genetic aetiology is more likely include the occurrence of aortic dissection below the age of 60 years in a non-hypertensive individual in whom there is no clear cause evident. Other important factors include the patient having clinical features of a pre-disposing condition such as the Marfan syndrome, Loeys-Dietz and vascular Ehlers-Danlos (type 4) syndromes or a family history of aortic dissection or peripheral/intracranial aneurysms in a first or second degree relative (Isselbacher et al, 2022).

In our institution, it is now standard practice that the Trust's Medical Examiners and cardiac surgical teams routinely consider establishing the aetiology of all type A dissections. These clinicians are ideally placed to systematically identify the survivors and non-survivors who might qualify for gene testing. This change confirms that such actions can be made with the collaboration of other clinicians. If similar systems are used in other hospitals, then this should lead to improving the reliability of selecting patients for gene testing more widely. Importantly, this pro-

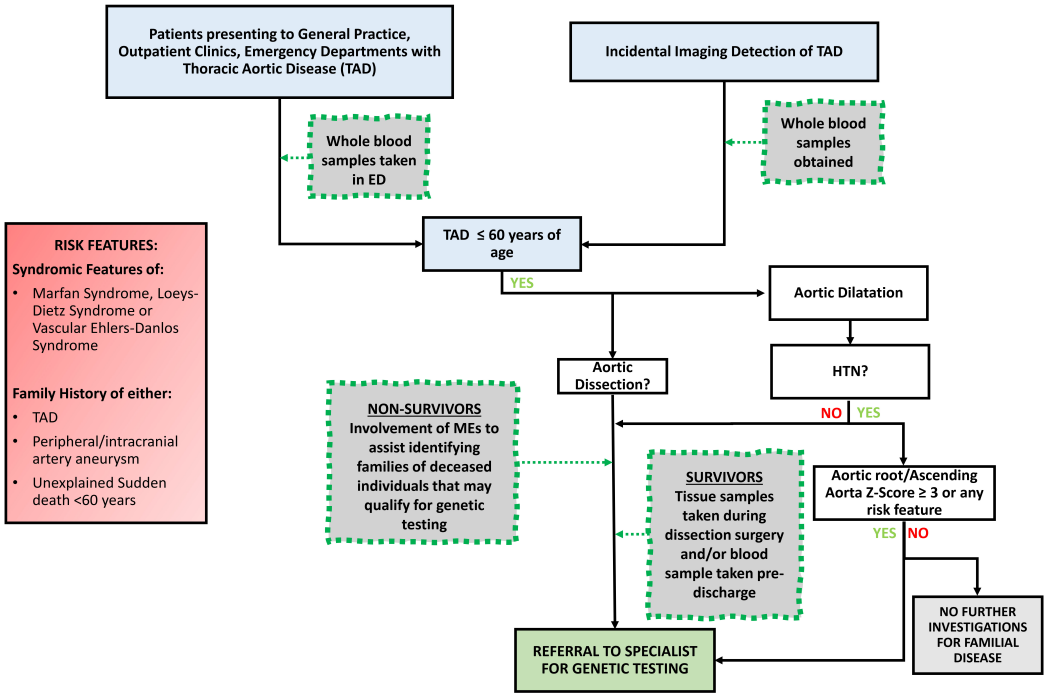

Fig. 4. Schematic summarising the current European Society of Cardiology guideline-based approach to genetic testing in patients with suspected familial thoracic aortic aneurysmal disease or dissection. Our recommendations for improvements to current practice are highlighted in grey boxes with green dashed borders. The timepoints for our suggested improvements are shown with dashed arrows. Figure based on Mazzolai et al (2024). Figure created using Microsoft PowerPoint for Microsoft 365 (Version 2501, Microsoft Corporation, Redmond, WA, USA). Abbreviations: ED, emergency department; TAD, thoracic aortic disease; MEs, medical examiners; HTN, hypertension.

cess should result in earlier patient and family referral to either the local aortopathy or clinical genetics services.

Limitations

This manuscript arises from a service evaluation conducted at a single centre, and our findings may not be generalisable to other institutions. However, the lack of awareness regarding the need for and consequences of genetic testing are likely to have broad relevance for clinicians working in secondary care throughout the UK. Our review provides a basic summary of the genetic basis of aortic aneurysms and dissections for the non-specialist.

Conclusion

Understanding where the gaps lie in relation to genetic testing is key to improving the uptake in survivors of type A aortic dissection and their relatives. Current practice may be a consequence of poor appreciation of the availability and applicability of these genetic diagnostic techniques amongst clinical teams, pathology and Coronial services. We emphasise the need for all healthcare professionals to ensure that aortic dissection cases are investigated similarly. The key is the ability to offer,

where possible, a diagnosis as to the cause of the acute dissection in an individual patient and to identify the at-risk first-degree relatives at an early stage, with the intention of improving outcomes for all.

Key Points

- Several genetic mutations, typically resulting in defective aortic wall function and structure, have been implicated in HTAAD.
- Genetic testing in the setting of HTAAD facilitates the identification and surveillance of relatives at risk of aortopathy to try and prevent the medical emergency of acute aortic dissection. However, for genetic testing to be implemented, blood and tissue samples from the proband must be appropriately collected.
- There are several opportunities for this sampling during the patient's journey, which are currently seldom used by the clinicians involved in their care.
- We propose that by raising awareness of these opportunities for sampling, performance could be significantly improved for the benefit of patients and their relatives who are at risk of HTAAD.

Availability of Data and Materials

Not applicable.

Author Contributions

MJW and CS authored the first version of the manuscript and are joint first authors. MJW and CS conducted the literature search and analysis. WB designed the work, acquired the data, was involved in analysis of data and wrote a large part of the first draft. KG was involved in the design of the work in relation to considerations of aortic pathology and contributed to the writing of the manuscript. SS designed the work and was involved in analysis and interpretation of data. PMP contributed to data acquisition and analysis. All authors provided critical revision. All authors approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All individuals discussed in this manuscript have provided written consent for their case histories and images to be published.

Acknowledgement

The authors would like to express their gratitude for the patients who consented for their cases to be discussed in this review.

Funding

This research received no external funding.

Conflict of Interest

SS is supported by the National Institute of Health and Care Research. The authors have no other conflicts of interest to declare.

References

Aatre RD, Day SM. Psychological issues in genetic testing for inherited cardiovascular diseases. Circulation. Cardiovascular Genetics. 2011; 4: 81–90. https://doi.org/10.1161/CIRCGENETICS.110.957365

Bailey D, Osborn M, Roberts I, Rutty G, Traill Z, Morgan B. Guidelines for post-mortem cross-sectional imaging in adults for non-forensic deaths. 2021. Available at: https://www.rcpath.org/static/666dbf95-de06-44ad-89c3b4e5f1ceab79/G182-Guidelines-for-post-mortem-cross-sectional-imaging.pdf (Accessed: 3 April 2025).

Barbier M, Gross MS, Aubart M, Hanna N, Kessler K, Guo DC, et al. MFAP5 loss-of-function mutations underscore the involvement of matrix alteration in the pathogenesis of familial thoracic aortic aneurysms and dissections. American Journal of Human Genetics. 2014; 95: 736–743. https://doi.org/10.1016/j.ajhg.2014.10.018

Bertoli-Avella AM, Gillis E, Morisaki H, Verhagen JMA, de Graaf BM, van de Beek G, et al. Mutations in a TGF-β ligand, TGFB3, cause syndromic aortic aneurysms and dissections. Journal of the American College of Cardiology. 2015; 65: 1324–1336. https://doi.org/10.1016/j.jacc.2015.01.040

Biddinger A, Rocklin M, Coselli J, Milewicz DM. Familial thoracic aortic dilatations and dissections: a case control study. Journal of Vascular Surgery. 1997; 25: 506–511. https://doi.org/10.1016/s0741-5214(97)70261-1

Bridgewater B, Society for Cardiothoracic Surgery in GB and Ireland. Cardiac registers: the adult cardiac surgery register. Heart (British Cardiac Society). 2010; 96: 1441–1443. https://doi.org/10.1136/hrt.2010.194019

Callewaert B, Renard M, Hucthagowder V, Albrecht B, Hausser I, Blair E, et al. New insights into the pathogenesis of autosomal-dominant cutis laxa with report of five ELN mutations. Human Mutation. 2011; 32: 445–455. https://doi.org/10.1002/humu.21462

Capuano A, Bucciotti F, Farwell KD, Tippin Davis B, Mroske C, Hulick PJ, et al. Diagnostic Exome Sequencing Identifies a Novel Gene, EMILIN1, Associated with Autosomal-Dominant Hereditary Connective Tissue Disease. Human Mutation. 2016; 37: 84–97. https://doi.org/10.1002/humu.22920

Chen MH, Choudhury S, Hirata M, Khalsa S, Chang B, Walsh CA. Thoracic aortic aneurysm in patients with loss of function Filamin A mutations: Clinical characterization, genetics, and recommendations. American Journal of Medical Genetics. Part A. 2018; 176: 337–350. https://doi.org/10.1002/ajmg.a.38580

Cheng CH, Kikuchi T, Chen YH, Sabbagha NGAAA, Lee YC, Pan HJ, et al. Mutations in the SLC2A10 gene cause arterial abnormalities in mice. Cardiovascular Research. 2009; 81: 381–388. https://doi.org/10.1093/cvr/cvn319

Cho MJ, Lee MR, Park JG. Aortic aneurysms: current pathogenesis and therapeutic targets. 2023; 55: 2519–2530. https://doi.org/10.1038/s12276-023-01130-w

Corbitt H, Morris SA, Gravholt CH, Mortensen KH, Tippner-Hedges R, Silberbach M, et al. TIMP3 and TIMP1 are risk genes for bicuspid aortic valve and aortopathy in Turner syndrome. PLoS Genetics. 2018; 14: e1007692. https://doi.org/10.1371/journal.pgen.1007692

Debiec RM, Hamby SE, Jones PD, Safwan K, Sosin M, Hetherington SL, et al. Contribution of NOTCH1 genetic variants to bicuspid aortic valve and other congenital lesions. Heart (British Cardiac Society). 2022; 108: 1114–1120. https://doi.org/10.1136/heartjnl-2021-320428

Deng Z, Fan T, Xiao C, Tian H, Zheng Y, Li C, et al. TGF-β signaling in health, disease, and therapeutics. Signal Transduction and Targeted Therapy. 2024; 9: 61. https://doi.org/10.1038/s41392-024-01764-w

Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. Nature. 1991; 352: 337–339. https://doi.org/10.1038/352337a0

Doyle AJ, Doyle JJ, Bessling SL, Maragh S, Lindsay ME, Schepers D, et al. Mutations in the TGF-β repressor SKI cause Shprintzen-Goldberg syndrome with aortic aneurysm. Nature Genetics. 2012; 44: 1249–1254. https://doi.org/10.1038/ng.2421

Du Q, Zhang D, Zhuang Y, Xia Q, Wen T, Jia H. The Molecular Genetics of Marfan Syndrome. International Journal of Medical Sciences. 2021; 18: 2752–2766. https://doi.org/10.7150/ijms.60685

Faggion Vinholo T, Brownstein AJ, Ziganshin BA, Zafar MA, Kuivaniemi H, Body SC, et al. Genes Associated with Thoracic Aortic Aneurysm and Dissection: 2019 Update and Clinical Implications. Aorta (Stamford, Conn.). 2019; 7: 99–107. https://doi.org/10.1055/s-0039-3400233

Fletcher AJ, Syed MBJ, Aitman TJ, Newby DE, Walker NL. Inherited Thoracic Aortic Disease: New Insights and Translational Targets. Circulation. 2020; 141: 1570–1587. https://doi.org/10.1161/CIRCULATIONAHA.119.043756

Gallo EM, Loch DC, Habashi JP, Calderon JF, Chen Y, Bedja D, et al. Angiotensin II-dependent TGF-β signaling contributes to Loeys-Dietz syndrome vascular pathogenesis. The Journal of Clinical Investigation. 2014; 124: 448–460. https://doi.org/10.1172/JCI69666

Gould RA, Aziz H, Woods CE, Seman-Senderos MA, Sparks E, Preuss C, et al. ROBO4 variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. Nature Genetics. 2019; 51: 42–50. https://doi.org/10.1038/s41588-018-0265-y

Guo DC, Gong L, Regalado ES, Santos-Cortez RL, Zhao R, Cai B, et al. MAT2A mutations predispose individuals to thoracic aortic aneurysms. American Journal of Human Genetics. 2015; 96: 170–177. https://doi.org/10.1016/j.ajhg.2014.11.015

Guo DC, Pannu H, Tran-Fadulu V, Papke CL, Yu RK, Avidan N, et al. Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nature Genetics. 2007; 39: 1488–1493. https://doi.org/10.1038/ng.2007.6

Guo DC, Regalado E, Casteel DE, Santos-Cortez RL, Gong L, Kim JJ, et al. Recurrent gain-of-function mutation in PRKG1 causes thoracic aortic aneurysms and acute aortic dissections. American Journal of Human Genetics. 2013; 93: 398–404. https://doi.org/10.1016/j.ajhg.2013.06.019

Halushka MK, Angelini A, Bartoloni G, Basso C, Batoroeva L, Bruneval P, et al. Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association For European Cardiovascular Pathology: II. Noninflammatory degenerative diseases - nomenclature and diagnostic criteria. Cardiovascular Pathology: the Official Journal of the Society for Cardiovascular Pathology. 2016; 25: 247–257. https://doi.org/10.1016/j.carpath.2016.03.002

Huang J, Davis EC, Chapman SL, Budatha M, Marmorstein LY, Word RA, et al. Fibulin-4 deficiency results in ascending aortic aneurysms: a potential link between abnormal smooth muscle cell phenotype and aneurysm progression. Circulation Research. 2010; 106: 583–592. https://doi.org/10.1161/CIRCRESAHA.109.207852

Humphrey JD, Schwartz MA, Tellides G, Milewicz DM. Role of mechanotransduction in vascular biology: focus on thoracic aortic aneurysms and dissections. Circulation Research. 2015; 116: 1448–1461. https://doi.org/10.1161/CIRCRESAHA.114.304936

Isselbacher EM, Preventza O, Hamilton Black J, 3rd, Augoustides JG, Beck AW, Bolen MA, et al. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 146: e334–e482. https://doi.org/10.1161/CIR.0000000000001106

Kamm KE, Stull JT. Dedicated myosin light chain kinases with diverse cellular functions. The Journal of Biological Chemistry. 2001; 276: 4527–4530. https://doi.org/10.1074/jbc.R000028200

Koenig SN, LaHaye S, Feller JD, Rowland P, Hor KN, Trask AJ, et al. Notch1 haploinsufficiency causes ascending aortic aneurysms in mice. JCI Insight. 2017; 2: e91353. https://doi.org/10.1172/jci.insight.91353

Kuang SQ, Medina-Martinez O, Guo DC, Gong L, Regalado ES, Reynolds CL, et al. FOXE3 mutations predispose to thoracic aortic aneurysms and dissections. The Journal of Clinical Investigation. 2016; 126: 948–961. https://doi.org/10.1172/JCI83778

Lee VS, Halabi CM, Hoffman EP, Carmichael N, Leshchiner I, Lian CG, et al. Loss of function mutation in LOX causes thoracic aortic aneurysm and dissection in humans. Proceedings of the National Academy of Sciences of the United States of America. 2016; 113: 8759–8764. https://doi.org/10.1073/pnas.1601442113

Lindsay ME, Schepers D, Bolar NA, Doyle JJ, Gallo E, Fert-Bober J, et al. Loss-of-function mutations in TGFB2 cause a syndromic presentation of thoracic aortic aneurysm. Nature Genetics. 2012; 44: 922–927. https://doi.org/10.1038/ng.2349

MacFarlane EG, Parker SJ, Shin JY, Kang BE, Ziegler SG, Creamer TJ, et al. Lineage-specific events underlie aortic root aneurysm pathogenesis in Loeys-Dietz syndrome. The Journal of Clinical Investigation. 2019; 129: 659–675. https://doi.org/10.1172/JCI123547

Mazzolai L, Teixido-Tura G, Lanzi S, Boc V, Bossone E, Brodmann M, et al. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases: Developed by the task force on the management of peripheral arterial and aortic diseases of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS), the European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN), and the European Society of Vascular Medicine (ESVM). European Heart Journal. 2024; 45: 3538–3700. https://doi.org/10.1093/eurheartj/ehae179

Meester JAN, Vandeweyer G, Pintelon I, Lammens M, Van Hoorick L, De Belder S, et al. Loss-of-function mutations in the X-linked biglycan gene cause a severe syndromic form of thoracic aortic aneurysms and dissections. Genetics in Medicine: Official Journal of the American College of Medical Genetics. 2017; 19: 386–395. https://doi.org/10.1038/gim.2016.126

Mészáros I, Mórocz J, Szlávi J, Schmidt J, Tornóci L, Nagy L, et al. Epidemiology and clinicopathology of aortic dissection. Chest. 2000; 117: 1271–1278. https://doi.org/10.1378/chest.117.5.1271

NHS. National Genomic Test Directory. Testing criteria for rare and inherited disease. 2025. Available at: https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-inherited-disease-eligibility-criteria-V7.1-OFFICIAL.pdf (Accessed: 3 April 2025).

Nienaber CA, Clough RE. Management of acute aortic dissection. Lancet (London, England). 2015; 385: 800–811. https://doi.org/10.1016/S0140-6736(14)61005-9

Ostberg NP, Zafar MA, Ziganshin BA, Elefteriades JA. The Genetics of Thoracic Aortic Aneurysms and Dissection: A Clinical Perspective. Biomolecules. 2020; 10: 182. https://doi.org/10.3390/biom10020182

Pannu H, Tran-Fadulu V, Papke CL, Scherer S, Liu Y, Presley C, et al. MYH11 mutations result in a distinct vascular pathology driven by insulin-like growth factor 1 and angiotensin II. Human Molecular Genetics. 2007; 16: 2453–2462. https://doi:10.1093/hmg/ddm201

Pomianowski P, Elefteriades JA. The genetics and genomics of thoracic aortic disease. Annals of Cardiothoracic Surgery. 2013; 2: 271–279. https://doi.org/10.3978/j.issn.2225-319X.2013.05.12

Putnam EA, Zhang H, Ramirez F, Milewicz DM. Fibrillin-2 (FBN2) mutations result in the Marfan-like disorder, congenital contractural arachnodactyly. Nature Genetics. 1995; 11: 456–458. https://doi.org/10.1038/ng1295-456

Quiñones-Pérez B, VanNoy GE, Towne MC, Shen Y, Singh MN, Agrawal PB, et al. Three-generation family with novel contiguous gene deletion on chromosome 2p22 associated with thoracic aortic aneurysm syndrome. American Journal of Medical Genetics. Part A. 2018; 176: 560–569. https://doi.org/10.1002/ajmg.a.38590

Schmierer B, Hill CS. TGFbeta-SMAD signal transduction: molecular specificity and functional flexibility. Nature Reviews. Molecular Cell Biology. 2007; 8: 970–982. https://doi.org/10.1038/nrm2297

Schwarze U, Schievink WI, Petty E, Jaff MR, Babovic-Vuksanovic D, Cherry KJ, et al. Haploinsufficiency for one COL3A1 allele of type III procollagen results in a phenotype similar to the vascular form of Ehlers-Danlos syndrome, Ehlers-Danlos syndrome type IV. American Journal of Human Genetics. 2001; 69: 989–1001. https://doi.org/10.1086/324123

Sebastian WA, Inoue M, Shimizu N, Sato R, Oguri S, Itonaga T, et al. Cardiac manifestations of human ACTA2 variants recapitulated in a zebrafish model. Journal of Human Genetics. 2024; 69: 133–138. https://doi.org/10.1038/s10038-024-01221-0

Sheppard MN. Sudden unexpected death: a national programme which will establish genetic testing and cardiological screening of families in the UK. Pathologie (Heidelberg, Germany). 2022; 43: 137–140.

https://doi.org/10.1007/s00292-022-01143-8

Takeda N, Hara H, Fujiwara T, Kanaya T, Maemura S, Komuro I. TGF-β Signaling-Related Genes and Thoracic Aortic Aneurysms and Dissections. International Journal of Molecular Sciences. 2018; 19: 2125. https://doi.org/10.3390/ijms19072125

Tan KL, Haelterman NA, Kwartler CS, Regalado ES, Lee PT, Nagarkar-Jaiswal S, et al. Ari-1 Regulates Myonuclear Organization Together with Parkin and Is Associated with Aortic Aneurysms. Developmental Cell. 2018; 45: 226–244.e8. https://doi.org/10.1016/j.devcel.2018.03.020

Thornton P. Chief Coroner's Guidance No.1 The use of Post-Mortem Imaging (Adults). 2016. Available at: https://www.judiciary.uk/wp-content/uploads/2022/07/guidance-no-1-use-of-port-mortem-imaging.pdf (Accessed: 3 April 2025).

van de Laar IM, Oldenburg RA, Pals G, Roos-Hesselink JW, de Graaf BM, Verhagen JM, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. Nature Genetics. 2011; 43: 121–126. https://doi.org/10.1038/ng.744

Vermeer AMC, Lodder EM, Thomas D, Duijkers FAM, Marcelis C, van Gorselen EOF, et al. Dilation of the Aorta Ascendens Forms Part of the Clinical Spectrum of HCN4 Mutations. Journal of the American College of Cardiology. 2016; 67: 2313–2315. https://doi.org/10.1016/j.jacc.2016.01.086

Verstraeten A, Luyckx I, Loeys B. Aetiology and management of hereditary aortopathy. Nature Reviews. Cardiology. 2017; 14: 197–208. https://doi.org/10.1038/nrcardio.2016.211

Wang L, Guo DC, Cao J, Gong L, Kamm KE, Regalado E, et al. Mutations in myosin light chain kinase cause familial aortic dissections. American Journal of Human Genetics. 2010; 87: 701–707. https://doi.org/10.1016/j.ajhg.2010.10.006

Wang Y, Panicker IS, Anesi J, Sargisson O, Atchison B, Habenicht AJR. Animal Models, Pathogenesis, and Potential Treatment of Thoracic Aortic Aneurysm. International Journal of Molecular Sciences. 2024; 25: 901. https://doi.org/10.3390/ijms25020901