

CardioGeneScan

Familial Aortopathy – an Overview

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Overview Summary

Aortopathy is characterized by aortic dilation, which can lead to life threatening aneurysms and/or dissections. Early diagnosis is critical, since timely initiation of pharmacological treatment can slow dilation and prophylactic surgery can prevent aortic dissection or rupture.¹⁻⁵ Lifestyle adjustments may also help to reduce the risk of catastrophic events.¹⁻⁵ About 30% of thoracic aortic aneurysm and dissection (TAAD) are familial and typically associated with more aggressive disease progression than non-familial forms.⁶ Familial TAAD is seen in the context of several multi-system syndromes with overlapping symptoms, such as Marfan syndrome (MFS),¹ Loeys-Dietz syndrome (LDS),² and vascular-type Ehlers-Danlos syndromes (vt-EDS),³ but can also occur in isolation.^{4,6} Identifying the underlying cause of TAAD is very important, since therapy and prognosis may vary considerably. For example, prophylactic surgery is recommended for MFS,¹ LDS,² and isolated TAAD,⁴ but contraindicated for vt-EDS,³ due to the extreme tissue friability associated with vt-EDS. In cases where prophylactic surgery is recommended, timing of surgery depends on the underlying genetic cause. In particular, aortic aneurysms due to mutations in the genes *TGFBR1* and *TGFBR2* may require prophylactic surgery earlier and at

smaller degrees of aortic dilation than aortic aneurysms due to other causes.^{2,4} Similarly, pharmacological treatment may also vary with the underlying genetic cause, since promising results have been achieved in Marfan patients with the angiotensin II, type 1 receptor antagonist Losartan.⁵ Genetic testing can assist in the differential diagnosis of aortopathies, since the genes underlying MFS, LDS, vt-EDS, and about 15% of isolated familial TAADs are known.¹⁻⁴ Once a familial mutation has been identified, genetic testing can also help to identify family members who carry the mutation and are thus at high risk of TAAD, as well as family members who do not carry the familial mutation and may not need the same level of continual screening and lifestyle adjustments.⁷ Aortopathies typically show autosomal dominant inheritance; however, a family history may not always be clear, since type, severity, and age of onset of symptoms can vary even within families. In addition, 25%, 50%, and 75% of MFS, vt-EDS, and LDS, respectively, are due to *de novo* mutations.¹⁻³ Genetic causes of aortopathy tested for in the Aortopathy sequencing evaluation (see Table 2) account for about 30% of familial cases overall and about 90% of syndromic cases.^{1-4,6}

Table 1: Disease Facts (reviewed in ¹⁻⁵)				
Disease Name	Marfan Syndrome	Loeys-Dietz Syndrome	Vascular-type Ehlers-Danlos Syndrome	Thoracic Aneurysms and Dissections
MIM number	154700	609192	130050	607086
Estimated prevalence	1 in 5000	rare	1 in 250000	1 in 500
Penetrance	high (close to 100%)	high (close to 100%)	high (close to 100%)	Reduced (50% ⁸), especially in women
Average age of onset of aortic aneurysm	young adulthood	childhood	variable	adulthood
Selected Symptoms that <u>may</u> be present				
Thoracic aortic aneurysm and dissection	yes	yes	yes	yes
Non-thoracic aortic aneurysms		yes	yes	yes
Arachnodactyly	yes	yes		
Reduced arm span to height ratio of >1.05	yes			
Pectus carinatum or excavatum	yes	yes		
Scoliosis	yes	yes		
Joint hypermobility	yes	yes	yes	
Ectopia lentis	yes			
Lumbosacral dural ectasia	yes	yes		
Bifid uvula or cleft palate		yes		
Craniosynostosis		yes		
Velvety and translucent skin		yes	yes	
Easy bruising		yes	yes	
Widened, atrophic scars		yes	yes	
Therapy of aortic aneurysms				
Beta blocker	yes	yes	in trials	yes
Angiotensin II, type 1 receptor antagonist	In trials			
Prophylactic surgery	yes	yes	no	yes

Table 2: Molecular Genetics (according to ¹⁻⁴, unless otherwise noted)

Gene	Proportion of Disease Attributable to Gene				Comments
	Marfan Syndrome	Loeys-Dietz Syndrome	Vascular-type Ehlers-Danlos Syndrome	Thoracic Aneurysms and Dissections	
<i>FBN1</i>	Close to 100% ¹				
<i>TGFBR1</i>		25% ²		1% ¹	Mutations in <i>TGFBR1/2</i> tend to lead to aortic dissection and rupture at an earlier age than mutations in <i>ACTA2</i> or <i>MYH11</i> . ¹
<i>TGFBR2</i>		75% ²		2.5% ¹	
<i>COL3A1</i>			60% ²		Two-thirds of pathogenic mutations in <i>COL3A1</i> are glycine substitutions in the triple helical domain. ⁹
<i>MYH11</i>				<1% ^{1,3}	Mutations in <i>MYH11</i> have been reported in two families with TAAD and patent ductus arteriosus. ³
<i>ACTA2</i>				14% ⁴	Mutations in <i>ACTA2</i> have been reported in families with TAAD and livido reticularis, early-onset coronary artery disease, or premature ischemic stroke. ^{4,5}

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