Title: Heritable Thoracic Aortic Disease Overview *GeneReview* – Supplemental Information

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DeBakey Classification System

- Type I dissection originates in the ascending aorta and extends to the descending aorta
- Type II dissection originates in and is limited to the ascending aorta
- Type III dissection originates in the descending aorta and is either limited to the descending aorta above the diaphragm (type IIIa) or propagates below the diaphragm (type IIIb).

Aortic Histopathology in Heritable Thoracic Aortic Disease (HTAD)

Note: The following information is provided by the authors listed above and has not been reviewed by *GeneReviews* staff.

Pathology. A common pathologic finding in the aorta associated with TAAD is medial degeneration (previously termed Erdheim's cystic medial necrosis), which is characterized by changes in the thick medial layer of the aorta. These changes include fragmentation and loss of elastic fibers, accumulation of proteoglycans, and regions of smooth muscle cell loss [Milewicz et al 2008]. Although focal areas of smooth muscle cell loss in the aortic media with medial degeneration are observed, it is debated whether there is overall loss or gain of smooth muscle cells in the aortic media [Tang et al 2005].

Although the aortic pathology in individuals with mutation of either *ACTA2* or *MYH11* is medial degeneration, the pathology also shows localized areas of increased numbers of smooth muscle cells and smooth muscle cell disarray reminiscent of the myocyte disarray observed in hypertrophic cardiomyopathy [Guo et al 2007, Pannu et al 2007]. Mutation of these genes is also associated with medial thickening of the arteries in the vasa vasorum in the adventitial layer of the aorta, leading to stenosis or occlusion of these arteries.

Analysis of consecutive autopsies of individuals with sudden death as a result of aortic dissections showed that 84% were due to Type A dissections causing pericardial tamponade [Prakash et al 2011].

Molecular Genetics of *ACTA2*

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Syndromic HTAD. A recurrent *de novo ACTA2* pathogenic variant that disrupts the amino acid residue Arg179 causes dysfunction of smooth muscle cells throughout the body, leading to severe and highly penetrant vascular diseases and loss of smooth muscle cell contractile function in other organs called multisystem smooth muscle dysfunction syndrome (OMIM) [Guo et al 2009, Milewicz et al 2010, Munot et al 2012].

The *ACTA2* p.Lys328Asn pathogenic variant has been associated with other vascular findings (abdominal aortic aneurysm/dissection, dilatation of proximal internal carotid arteries) and systemic features (congenital mydriasis) [Ware et al 2014]. Other manifestations of Arg179 pathogenic variants such as intracranial artery straightening, pulmonary hypertension, gut malrotation/hypoperistalsis, and hypotonic bladder have not been observed with the Lys328Asn variant.

Nonsyndromic HTAD. *ACTA2* pathogenic variants, the most frequent cause of nonsyndromic familial HTAD, account for 12%-21% of cases [Guo et al 2007, Morisaki et al 2009, Disabella et al 2011, Renard et al 2013].

- Thoracic aortic aneurysms are typically fusiform aneurysms that involve the aortic root and ascending aorta, and can extend into the aortic arch; descending and abdominal aortic aneurysms are less common.
- Type A dissections are more common than type B (54% versus 21%). Type A dissections at aortic diameters <5 cm have been observed [Regalado et al 2014]. The median age of onset of type B dissections (27 years) is significantly younger than type A dissections (37 years).
- Penetrance for TAAD is reduced: the lifetime risk of an aortic event (aortic dissection or aneurysm repair) is 76% at age 85 years.

Arg179 and Arg258 pathogenic variants are associated with earlier age of onset and higher cumulative risk of aortic events compared to other *ACTA2* pathogenic variants [Regalado et al 2015].

A subset of *ACTA2* pathogenic variants cause occlusive vascular disease in addition to TAAD but are not associated with smooth muscle contractile dysfunction in other organs.

- Pathogenic variants that alter the Arg258 residue have similar but less severe cerebrovascular disease than the Arg179 alterations.
- Early onset coronary artery disease is observed with the pathogenic variants p.Arg118Gln and p.Arg149Cys.

- The pathogenic variants p.Arg212Gln and variants disrupting the Arg39 residue are also associated with early-onset stroke [Guo et al 2011].

A subset of *ACTA2* pathogenic variants is also associated with PDA [Guo et al 2009, Milewicz et al 2010].

A subset of *ACTA2* pathogenic variants cause livedo reticularis, a purplish skin discoloration in a net-like pattern caused by constriction or occlusion of deep dermal capillaries. In families in which the presence of the *ACTA2* pathogenic variant is associated with marked and persistent livedo reticularis, presence of the skin condition in an at-risk family member can be indicative of the presence of the *ACTA2* pathogenic variant [Guo et al 2007].

Iris flocculi, an ocular abnormality previously described in individuals with familial TAAD, is associated with the p.Arg149Cys *ACTA2* pathogenic variant [Lewis & Merin 1995, Guo et al 2007].

Cellular Pathways Involved in HTAD

The 13 genes grouped by the cellular pathway involved are:

- Extracellular matrix: *FBN1, MFAP5, COL3A1*
- Transforming growth factor beta (TGF-β) signaling:*TGFBR2*, *TGFBR1*, *SMAD3*, *TGFB2, TGFB3*
- Smooth muscle cell contractility: *ACTA2*, *MYH11*, *MYLK*, *PRKG1*
- Undetermined: *MAT2A*

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