

# Thoracic aortic-aneurysm and dissection in association with significant mitral valve disease caused by mutations in *TGFB2*

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The pathophysiology of thoracic aortic aneurysms and dissections (TAAD) is complex and multifactorial. Classic cardiovascular risk factors play an important role in a majority of patients but genetic factors should always be considered, especially in younger subjects and/or in the presence of a family history of TAAD. To date, several genes have been identified in both syndromic and non-syndromic forms of TAAD, including *FBN1* (Marfan syndrome, MFS), *TGFBRI/2* (Loeys-Dietz syndrome, LDS), *SMAD3* (Aneurysm-Osteoarthritis syndrome, AOS), *ACTA2* (TAA6, TAAD with livedo reticularis and iris flocculi), *MYH11* (TAAD with patent ductus arteriosus), and *MYLK* (TAAD7) [1–7]. Although clinical features show significant overlap, these entities differ in the extent of vascular involvement and clinical course. As a consequence, molecular studies have become pivotal in the evaluation, counselling and management of the patient with TAAD. Moreover, the identification of new genes has led to new insights into the pathogenesis of aneurysm formation.

The crucial role of the transforming-growth-factor $\beta$  (TGF $\beta$ ) pathway in TAAD became evident from both studies on mouse models and the analysis of components of the TGF $\beta$  pathway on human aortic tissue of patients with these disorders [3,8–11]. We previously sequenced *TGFB2* as a candidate gene for TAAD, but did not identify mutations in 40 patients with isolated aortic root dilatation (Callewaert et al., unpublished results). The recent findings by Boileau and colleagues identifying the first *TGFB2* mutations leading to familial TAAD in association with cerebrovascular disease and mild systemic features reminiscent of Marfan syndrome [16] have urged us to screen this gene in a patient group associating TAAD with a wider phenotypic spectrum including cerebrovascular disease, arterial tortuosity, marfanoid skeletal features and mitral valve disease. In total, we assessed the prevalence of *TGFB2* mutations in 146 patients.

Using direct sequencing after amplification of all exons and flanking intronic sequences of the *TGFB2* gene on genomic DNA level (*TGFB2* NM\_001135599.2), we identified 4 heterozygous *TGFB2* mutations in 6 patients: c.475C>T (p.Arg159X), c.979C>T (p.Arg327Trp), c.980G>A (p.Arg327Gln), and c.1125delT (p.Gly376GlufsX17). We found 2 premature truncating mutations and also identified the first missense mutations

in *TGFB2*. All mutations are expected to result in a loss-of-function. An overview of the clinical findings is provided in Table 1 and of the mutations in Fig. 1 and Supplemental Table 1.

Aortic pathology was universally present at middle-age (z-scores > 2.5), but aortic dissection was the presenting feature in only one patient at the age of 69 years (patient 1). Importantly, type A dissection occurred in another patient 5 years after initial evaluation and at an aortic root diameter below the classical surgical threshold of 50 mm (patient 6). Significant mitral valve prolapse occurred in 4 patients and was the reason for initial evaluation in two patients (2 and 6) that both required surgical replacement. Patient 4 came to medical attention following a routine echocardiography showing aortic root dilatation and mitral valve prolapse without other manifestations. One patient (patient 3) was evaluated following transient ischemic attacks at the age of 18 years old with underlying tortuosity of the vertebral arteries. Finally, patient 5 was evaluated for skeletal marfanoid features.

Four out of 6 patients had skeletal and/or skin manifestations reminiscent of TGF $\beta$ -signalopathies which can be mild; 3 patients had myopia of which one had cataract. Importantly, family history was negative in 3 patients.

Our data indicate a prevalence of *TGFB2* mutations in the examined TAAD cohort of around 4% (6/146), which is significantly lower than the previously reported prevalence of *ACTA2* mutations (16%) [11]. The TGF $\beta$  superfamily includes 3 isoforms of TGF $\beta$ , TGF $\beta$ 1, –2, and –3 (for a review [12]). The TGF $\beta$ s are pleiotropic cytokines, controlling a broad range of biological processes. The 3 TGF $\beta$  isoforms exhibit both overlapping and divergent properties as illustrated by the phenotype of the respective knockout mouse models. *Tgfb2* knockout mice die perinatally and display a wide range of developmental defects, including cardiovascular, pulmonary, skeletal, ocular, inner ear and urogenital manifestations [13,14]. The limited range of phenotypic manifestations seen in human patients is in high contrast to the broad range of developmental problems seen in the *Tgfb2* knockout mouse model.

The phenotype in the patients discussed here shows some overlap with other TGF $\beta$ -signalopathies including Marfan syndrome, Loeys-Dietz syndrome and the aneurysm-osteoarthritis syndrome. In congruence, aortic dilatation may result in type A aortic dissection at diameters below classic surgical thresholds. We found significant mitral valve disease, possibly a signature feature that may direct molecular analyses, but this should be confirmed in larger series. Until then, we suggest to exclude *TGFB2* mutations in all patients with TAAD lacking a clear syndromic constellation. The genetic screening should not be restricted to familial cases, as we identified *TGFB2* mutations in patients without a positive family history for TAAD. The identification of *TGFB2* mutations further adds to the considerable genetic heterogeneity in TAAD with 8 genes documented to date in still a limited number of TAAD patients.

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**Table 1**

Overview of the clinical findings in all mutation-positive patients.

Nr	Age/ sex	Age at diagnosis presenting symptom	Cardiovascular features		Skeletal	Craniofacial	Skin	Ocular	Cerebro-vascular	Family	Mutation
			Aorta	Mitral valve							
1	69/F	60 y type A dissection	Type A dissection	Normal	Flat feet, hallux valgus	/	/	/	/	Mother died in childbirth, sister died from dissection at age 41	(p.Arg159X)
2	60/M	56 y MVP requiring MVR	TAA 43 mm z 2.7	MVP - MVR	Clubfeet, joint laxity, mild pectus carinatum	High arched palate	Varicose veins	Myopia	/	Negative	(p.Arg159X)
3	53/F	18 y recurrent TIA's	TAA (Dx at 43 y) 40 mm z 5.2	MVP, mild MR	Joint laxity as a child	High palate, retrognathia	Local translucency	Myopia, astigmatism, cataract	Recurrent strokes, corckscREW vertebral Aa	Daughter Marfanoid	(p.Arg327Trp)
4	38/M	38 y TAA	TAA 40 mm z 3.4	MVP	Joint laxity	/	/	Myopia, strabismus	/	Negative	(p.Arg327Trp)
5	60/M	41 y Marfanoid features	TAA 41 mm z 3.5	Trivial MR	Arachnodactyly, camptodactyly, kyphoscoliosis	Hypertelorism, downslanting palpebral fissures, malar hypoplasia, high palate, retrognathia	Atrophic scarring	/	/	Spontaneous pneumothorax in daughter, father sudden death at 43y	(p.Arg327Gln)
6	46/M	32 y MVP requiring MVR	Type A dissection <50 mm	MVP-MVR	Pectus carinatum, arachnodactyly, joint hypermobility	/	Striae	/	/	Negative	(p.Gly376Glu fsX17)

Abbreviations: M, male; F, female; y, years. MVP: mitral valve prolapse, MVR: mitral valve replacement, MR: mitral valve regurgitation, TIA: transient ischemic attack, TAA: thoracic aortic aneurysm, z: z-score of the aortic root, Aa: artery. Dx, diagnosed.

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