SMAD2 and *SMAD6*: two novel genetic players in aortic aneurysm and dissection

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Introduction

Thoracic aortic aneurysm and dissections (TAAD) are characterised by progressive dilatation of the thoracic aorta caused by vascular wall weakness.

- Incidence: 25:200 000
- High mortality rate: 80%
- Patients with a bicuspid aortic valve (BAV, two aortic valve leaflets instead of three) have an increased risk of 7.5-79% for TAAD
- Syndromic and non-syndromic TAAD forms
- Key pathway in TAA: **Transforming growth factor-β signalling pathway (TGF-β)**

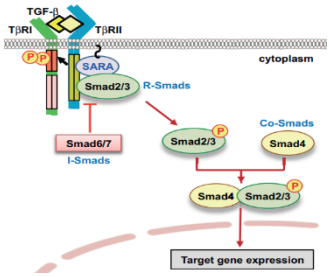

Figure 1: A schematic presentation of the TGF-β signalling pathway.
After ligand binding, complexes of heterodimeric receptors are formed for activation of SMAD2/3 (pSMAD2/3). Next, pSMAD2/3 interacts with SMAD4 and translocates to the nucleus to regulate TGF-β driven gene expression e.g. fibrilin-1. (Adapted from Choi & Kim, 2012)

Methods

Targeted next-generation sequencing was performed in syndromic and non-syndromic TAAD patients using a Haloplex-based gene panel (Agilent). Raw data were analysed with Seqpilot (JSI)/in-house developed automated Galaxy pipeline, followed by variant calling using Genome Analysis Toolkit and variant annotation via an in-house developed tool called VariantDB. We selected rare non-synonymous deleterious variants using frequencies (minor allele frequency ≤ 0,01%) and prediction programmes (CADD, MutationTaster, PolyPhen-2 and SIFT).

Results

SMAD2

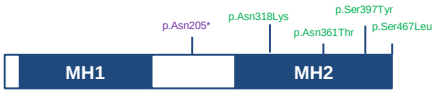

Figure 2: Mutations in *SMAD2* identified in patients with syndromic TAAD.
The 5 heterozygous *SMAD2* mutations include 1 nonsense and 4 missense mutations. The latter are all located within the functional MH2 domain of the protein. Types of mutations are shown in different colours (purple: nonsense; green: missense).

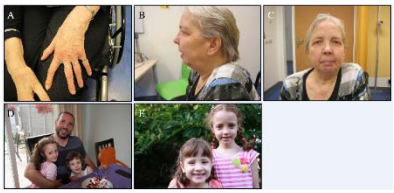

Figure 3: Clinical manifestations of patients with *SMAD2* mutations.
A: Arachnodactyly. B, C: Dysmorphic facial characteristics: dolichocephaly, downslanting palpebral fissures and retrognathia. D, E: Dysmorphic facial characteristics: hypertelorism and retrognathia.

SMAD6

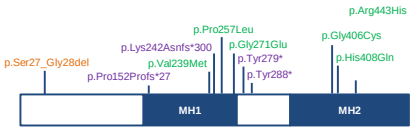

Figure 4: *SMAD6* mutations identified BAV/TAA patients.
Eleven heterozygous *SMAD6* variants were found including 2 nonsense, 2 frameshifts, 1 in-frame deletion and 6 missense variants, that are all located within a functional domain of the protein. Types of mutations are shown in different colours (purple: nonsense and frameshifts; green: missense; orange: in-frame deletion).

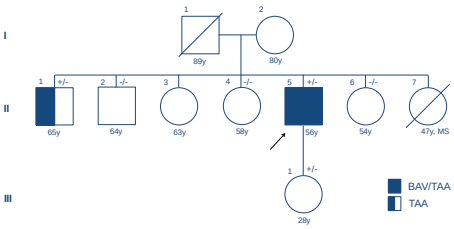

Figure 5: Segregation analysis of p.Gly271Glu *SMAD6* in BAV/TAA family.
All affected individuals (II:1, II:5) carry the SMAD6 mutation including 1 patient with TAA only. Mutation was absent in all tested unaffected individuals (II:2, II:4, II:6), except for 1 young individual (III:1). Arrow: proband. MS: multiple sclerosis. Y: years.

Conclusion

1. Loss-of-function mutations in ***SMAD2*** cause **syndromic aortic aneurysm**, with clinical features of Marfan and Loeys-Dietz syndrome.
2. ***SMAD6*** loss-of-function mutations explain 2.5% of all **bicuspid aortic valve related aortopathy** cases, and comes with variable penetrance and phenotypical expression.
3. **Loss-of-function mutations** in Smad proteins are key in the pathogenesis of aortic and arterial aneurysm and dissection, further evidenced by known genetic causes for syndromic TAAD, such as *SMAD3*.

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