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

Melanie Perik1, Ilse Luyckx1, Elyssa Cannaerts1, Aline Verstraeten1 and Bart L. Loeys1
1 Cardiogenetics, Center of Medical Genetics, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium

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)

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

MH1

MH2

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).

SMAD6

MH1

MH2

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

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.