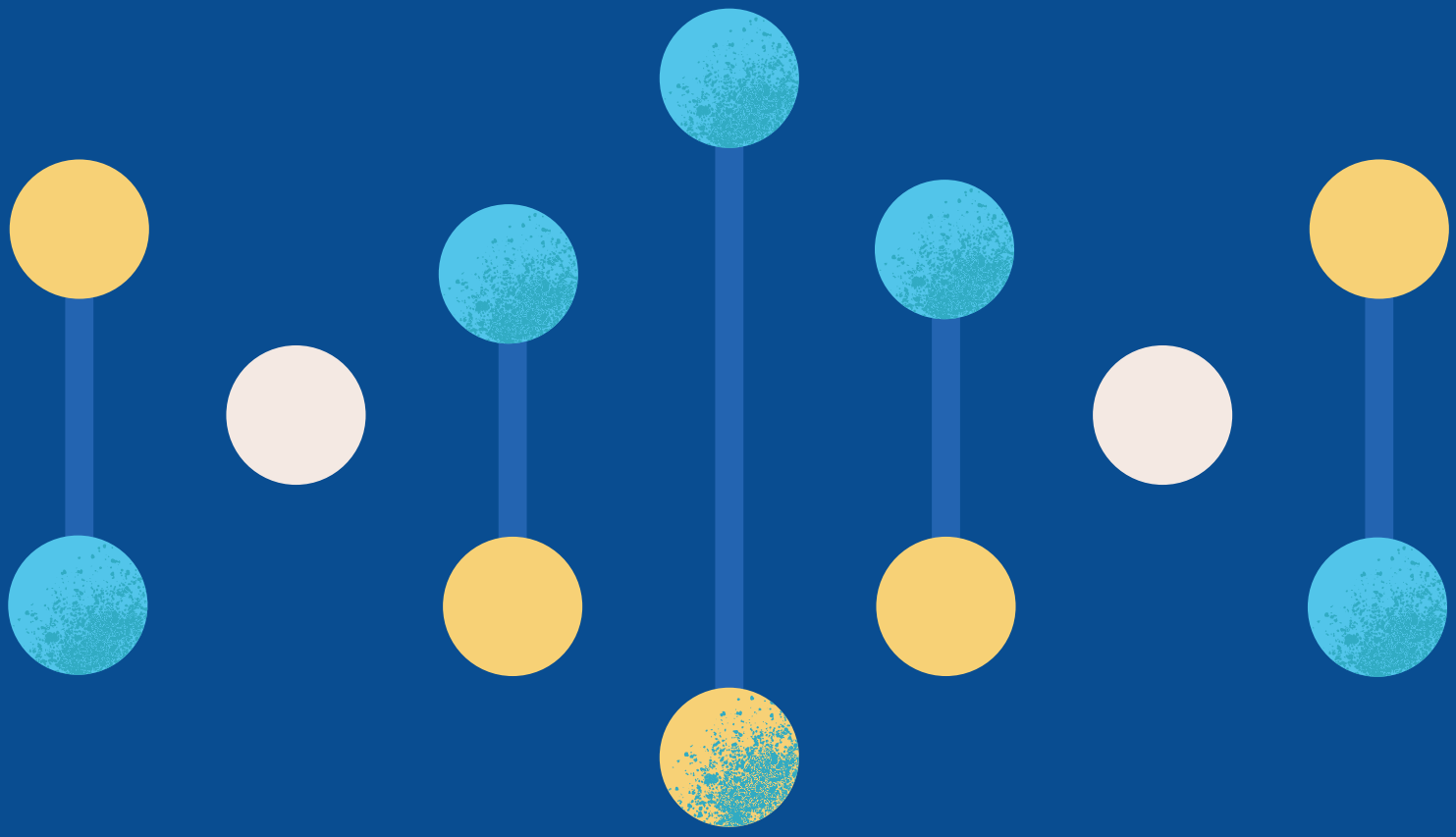
TGF-B2 GENE COMPENDIUM

A Curated Reference for Thoracic Aortic Aneurysm and Dissection (TAAD)



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Notices
This compendium is provided as an educational resource.
Medical and genetic knowledge evolves rapidly, and users are advised to consult up-to-date literature and clinical guidance when interpreting genetic variants.

Curators have made every effort to ensure accuracy but bear no liability for clinical or diagnostic outcomes based on this document. All variant classifications and recommendations should be considered in context and with professional clinical judgment.

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1. Basic Information for TAAD Gene

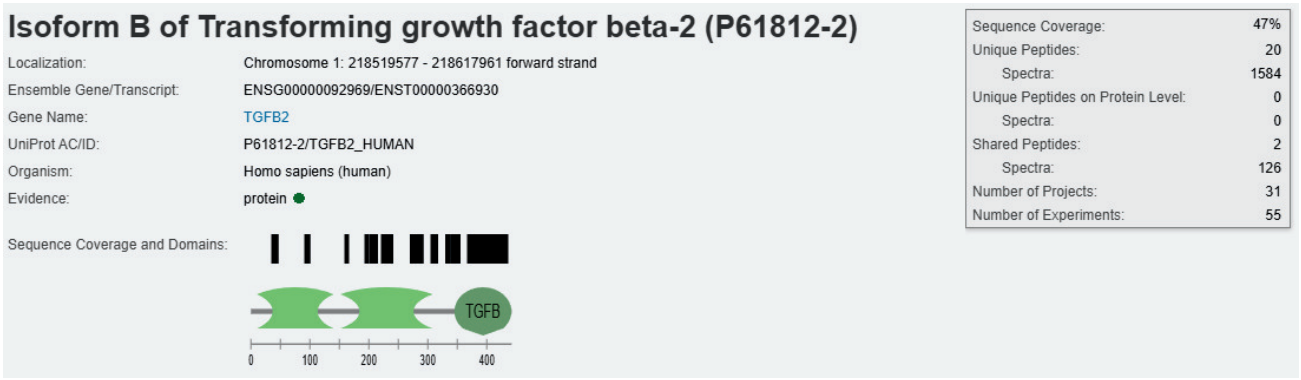
1.1 Gene Identifiers

Gene MIM Number	190220
Phenotype MIM Number	614816
Orphanet code	91387
Chromosomal Position (hg19/GRCh37)	Chr1:218,518,676-218,617,961
Chromosomal Position (hg38/GRCh38)	Chr1:218,345,336-218,444,619
Total Number of Amino Acids	442
Consensus NM transcript	NM_001135599 (442aa)
MANE Transcript	NM_003238 (414aa)
Are there pseudogenes?	No
Other pitfalls (e.g. retrocopy insertion polymorphisms)?	No

No other condition(s) associated with this gene with no or low prevalence of aneurysm.

2. Protein Structure Overview

2.1. Scheme with important domains within the protein



Source: https://www.proteomicsdb.org/proteomicsdb/#protein/proteinDetails/57336/summary

Table: Overview of TGF-β2 protein with Amino Acid (AA) boundaries

Domain	From AA	To AA
Signal Peptide	1	20
Latency Associated Peptide (LAP)*	21	330
TGF-β2 Cytokine	331	442

TGF-β2 has no RGD motif

Source: www.umd.be/TGFB2

2.2 List of Exon Boundaries (at cDNA Level)

MANE NM: 003238	Nucleotide Range	Amino Acid Range
5'UTR / Exon 1	c.-1366 to c.346	1 to 116
Exon 2	c.347 to c.430	116 to 144
Exon 3	c.431 to c.594	144 to 198
Exon 4	c.595 to c.727	199 to 243

Exon 5	c.728 to c.838	243 to 280
Exon 6	c.839 to c.1016	280 to 339
Exon 7	c.1017 to c.11-70	339 to 390
Exon 8 and 3'UTR	c.1171 to c.*3257	391 to 442

Source: Alamut

2.3. Mutational hotspot or recurrent/founder variants

RKKR motif (proteolytic cleavage site) between amino acids 327 and 330 (Schepers et al., 2018; and personal data).

2.4. Major domain(s) that involves more pathogenic variants

To date, all domains except the signal peptide have been implicated (Schepers et al., 2018; and personal data). Pathogenic variants found all along the gene, more missense variations in TGFB2 cytokine domain (Schepers et al., 2018; and personal data).

Clinvar database: ClinVar - TGFB2
GnomAD database: gnomAD.v4.1.0 TGFB2
Mutscore: MutScore TGFB2

3. Mode of Inheritance

Loeys-Dietz syndrome (LDS) due to TGF-β2 mutations is inherited in an autosomal dominant manner. Incomplete penetrance has been described without clear estimation (Boileau et al. 2012 DOI: 10.1038/ng.2348 and Schepers et al. 2018)

4. Constraint Matrices and Mutational Subtypes

pLI score	pLI=1 ; o/e= 0.29(0.18 - 0.46)	gnomad v.4.1
Missense constraint*	Z=2,36; o/e=0.72 (0.66 – 0.79)	gnomad v.4.1
Haplo-insufficiency (nonsense or out of frame splice)	Yes	Boileau et al., 2012; Lindsay et al., 2012; Schepers et al., 2018
Full gene deletion	Yes	Bichat hospital

Multi-exon deletion	No	—
Full gene duplication	No	—
Multi-exon duplication	No	—

5. Mode of Action of the Pathogenic Variants

Gain-of-function	No	—
Haploinsufficiency (as defined by allele that undergoes (or predicted to undergo NMD)) or full gene deletion	Yes	Boileau et al., 2012; Lindsay et al. 2012
Dominant negative	No	
Loss-of-function (not by haplo-insufficiency)	Yes	Boileau et al., 2012; Lindsay et al. 2012

6. Additional Supportive Evidence for Pathogenicity

6.1. Clinical evidence

There are no phenotypic features specific to TGF-β2. Details for phenotypic characteristics is available in: Supplemental Table S2 from Schepers et al., 2018

6.2. Functional evidence

Currently, no functional tests are available that could help for missense variants interpretation in TGF-β2. In the case of a nonsense mutation, efforts to examine nonsense-mediated decay (NMD) should be performed to demonstrate NMD escape before concluding on pathogenicity.

7. Mutation Database or Expert

7.1. Gene-specific mutation database

Leiden Open Variation Database (LOVD).

7.2 Uniprot 3D protein structure

The UniProt database provides access to the 3D structure and functional annotation of TGF-β2: https://www.uniprot.org/uniprotkb/P61812/feature-viewer

7.3 Lab "expert" for this gene that can be contacted for advice on specific cases

For questions about specific variants or complex TGF-β2 cases, expert consultation is available at

Center for Medical Genetics, University Hospital Antwerp, Belgium

- Bart.loeys@uza.be

Genetics Department, Bichat hospital, Paris, France

- pauline.arnaud@aphp.fr

8. Phenotype Characteristics

8.1. Estimated prevalence of the disease

The prevalence of disease due to TGF-β2 mutations is currently unknown. Less than 80 cases in the literature (Boileau et al., 2012; Fontana et al., 2014; Gago-Diaz et al., 2014; Gouda et al., 2022; Leutermann et al., 2014; Lindsay et al., 2012; Renard et al., 2013; Ritelli et al., 2014; Schepers et al., 2018; Schubert et al., 2016).

8.2. Youngest age of onset of aortic aneurysm

Only rare childhood aortic events associated with TGF-β2 pathogenic variations (Boileau et al., 2012; Regalado et al., 2022).

8.3. Youngest age of onset of aortic dissection

<25 years old (Regalado et al., 2022, Figure 1. Cumulative risks for aortic event (elective aortic aneurysm surgery, type A and type B aortic dissection) based on the type of variants in the TGF-β2 gene, doi: 10.1016).

8.4. Genotype-phenotype correlation validated for this gene

Some genotype-phenotype correlation have been described for TGF-β2 gene with no clear replication. Aortic event (elective aortic aneurysm surgery, type A and type B aortic dissection) seems to be higher for missense variants and lower for PTC-non NMD variants compared with the reference, PTC-NMD variants (Regalado et al, 2022).

8.5. Is there any consensus on management of the disease?

Yes, not specific for TGF-β2, but for LDS in general (Mac Carrick et al, 2014). Also consult general TAAD guidelines (Isselbacher et al., 2022, Mazzolai et al., 2024, Morris et al., 2024).

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