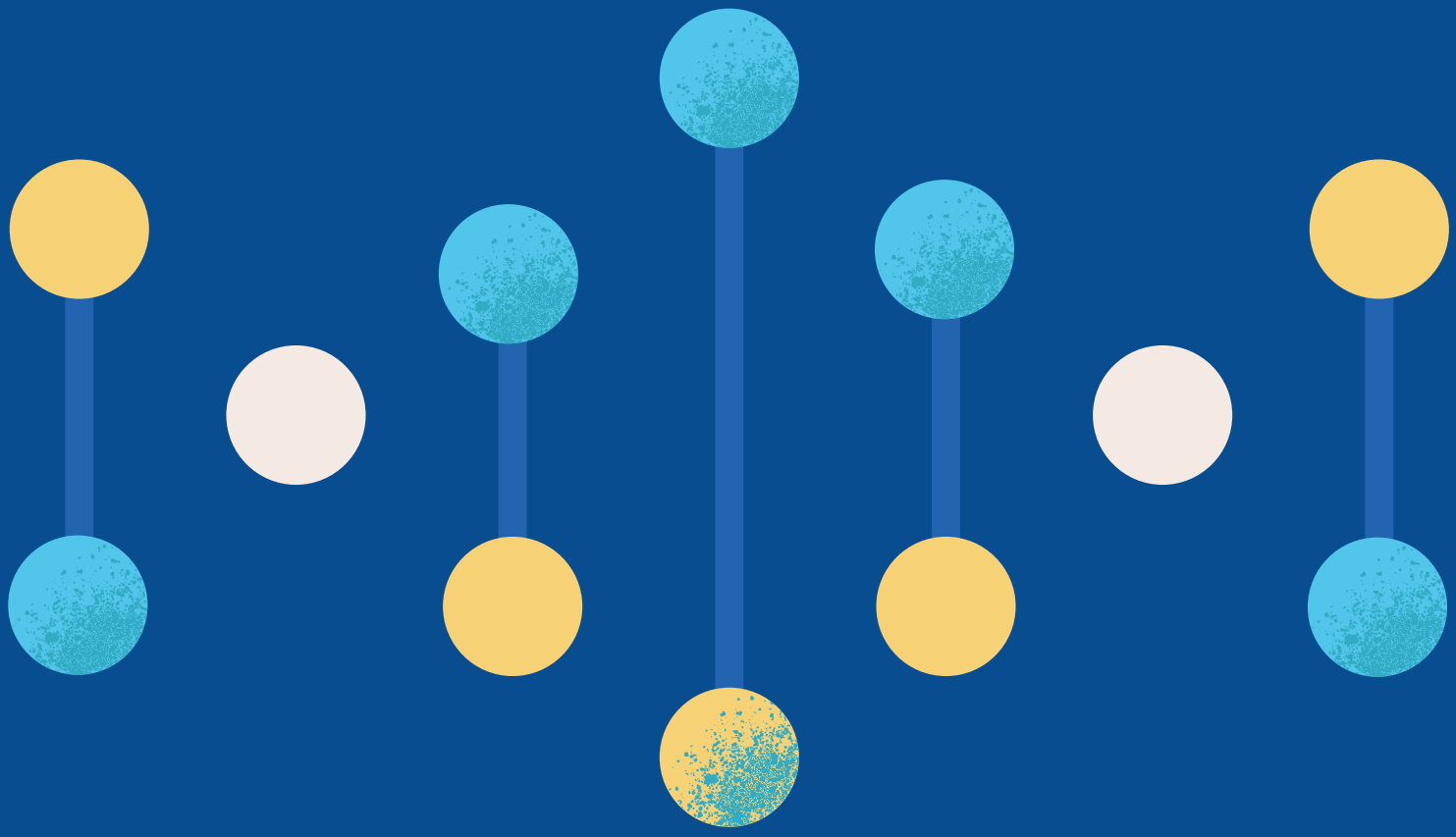
TGF-B3 GENE COMPENDIUM

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	190230
Phenotype MIM Number	615582
Orphanet code	91387
Chromosomal Position (hg19/GRCh37)	Chr14: 76,448,338–76,424,440
Chromosomal Position (hg38/GRCh38)	Chr14: 75,981,995–75,958,097
Total Number of Amino Acids	412
MANE Transcript	NM_003239.5 (412 aa)
Are there pseudogenes?	No
Other pitfalls (e.g. retrocopy insertion polymorphisms)?	No

1.2 Other phenotypes associated with FBN1 with no or lower prevalence of TAAD

In the literature, TGF-β3 has been associated with arrhythmogenic (right) ventricular cardiomyopathy (A(R)VC). However, this does not appear to be a bona fide gene for A(R)VC. There is very limited evidence for TGFB3 as an A(R)VC gene.

2. Protein Structure Overview

2.1. Scheme with important domains within the protein

Source: https://www.proteomicsdb.org/proteomicsdb/#protein/proteinDetails/52617/summary

Table: Overview of TGF-β3 protein with Amino Acid (AA) boundaries

Domain	From AA	To AA
Signal Peptide	1	23
Latency Associated Peptide (LAP)*	24	300
TGF-β3 Cytokine	331	412

*LAP domain includes:

- RGD motif (AA 261–263)
- RKKR motif (AA 297–300)

Source: www.umd.be/TGFB3

2.2 List of Exon Boundaries (at cDNA Level)

MANE- NM_003239.5	Nucleotide Range	Amino Acid Range
5'UTR - Exon 1	c.-1102 to c.352	1 to 116
Exon 2	c.353 to c.516	117 to 172
Exon 3	c.517 to c.646	173 to 215

Exon 4	c.647 to c.754	216 to 251
Exon 5	c.755 to c.926	252 to 308
Exon 6	c.927 to c.1080	309 to 360
Exon 7	c.1081 to c.1239	361 to 412
3'UTR	c.*1091	

Source: Alamut

2.3. Mutational hotspot or recurrent/founder variants

A recurrent hotspot is located at the RKKR motif, a proteolytic cleavage site between AA 297–300 (Marsili et al., 2020; Schepers et al., 2018).

cDNA annotation	**Protein annotation**	**Number of submissions in ClinVar**
c.899G>A	p.Arg300Gln	5
c.898C>T	p.Arg300Trp	7
c.787G>C	p.Asp263His	Schepers et al., 2018 and personal communication from Loeys

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

To date, all domains except the signal peptide have been implicated (Bertoli-Avella et al., 2015; Schepers et al., 2018). Missense variations in TGF-β3 cytokine domain are more likely to be pathogenic than missense variants in LAP domain. The LAP domain is cleaved off at the RKKR motif, so it is less likely that missense variants in this domain have a functional effect (Schepers et al., 2018).

Clinvar database: ClinVar - TGFB3
GnomAD database: gnomAD.v4.1 TGFB3
Mutscore: MutScore TGFB3

3. Mode of Inheritance

Loeys-Dietz syndrome (LDS) due to TGF-β3 mutations is inherited in an autosomal dominant manner.

Incomplete penetrance is very common (Bertoli-Avelli et al. 2015; Marsili et al., 2020; Schepers et al., 2018). The estimated penetrance for aneurysmal disease is 35%.

Patients with bi-allelic TGF-β3 variants have been described with more severe phenotype (Megarbane et al., 2020). For example, patient 28 from Marsili et al., 2020 (individuals with mono-allelic TGF-β3 variant have milder phenotype).

4. Constraint Matrices and Mutational Subtypes

pLI score	pLI=1; o/e=0.12 (0.06-0.25)	gnomad v.4.1
Missense constraint*	Z=2.87; o/e=0.67 (0.61- 0.73)	gnomad v.4.1
Haplo-insufficiency (nonsense or out of frame splice)	Yes	Bertoli-Avelli *et al*. 2015; Marsili *et al.*, 2020; Schepers *et al.*, 2018
Full gene deletion	Yes	Personal observation by Loeys
Multi-exon deletion	Yes**	Megarbane *et al.*, 2020
Full gene duplication	No	—
Multi-exon duplication	No	—

* missense variants in the cytokine domain are more likely to be pathogenic than missense in LAP domain
**exon 2 to 7 deletion (Megarbane et al., 2020).

5. Mode of Action of the Pathogenic Variants

Gain-of-function	No	—
Haploinsufficiency	Yes	Bertoli-Avella *et al.*, 2015; Marsili *et al.*, 2020; Schepers *et al.*, 2018
Dominant-negative	No	—
Loss-of-function (not driven by haplo-insufficiency)	Yes	Bertoli-Avella *et al.*, 2015; Marsili *et al.*, 2020; Schepers *et al.*, 2018

6. Additional Supportive Evidence for Pathogenicity

6.1. Clinical evidence

There are no phenotypic features specific to TGF-β3. A summary of clinical features observed in TGFB3 variant carriers is available in:

- Supplemental Table S4 from Schepers et al., 2018

6.2. Functional evidence

Currently, no functional tests are available that could help for missense variants interpretation. 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-β3: https://www.uniprot.org/uniprotkb/P10600/entry#structure

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

For questions about specific variants or complex TGF-β3 cases, expert consultation is available from Center for Medical Genetics, Antwerp, Belgium.

8. Phenotype Characteristics

8.1. Estimated prevalence of the disease

The prevalence of disease due to TGF-β3 mutations is currently unknown.

8.2. Youngest age of onset of aortic aneurysm

Aortic root dilatation was described as early as

- Age 6 years – Patient 2-IV:1 from Bertoli-Avelli *et al.*, 2015
- Age 14 years – Patient 12 from Marsili *et al.*, 2020

There seems to be quite a lot of early onset mitral valve disease (Bertoli-Avelli et al., 2015; Marsili et al., 2020).

Inverted Kaplan-Meier curve indicating the age-related penetrance of aortic disease, with age at first aortic event (dilatation/dissection/surgery) as the survival variable. It can be found in Figure 1 of Marsili *et al.*, 2020.

8.3. Youngest age of onset of aortic dissection

- Type A aortic dissection was reported at age 30 (patient 3-III:1 from Bertoli-Avelli *et al.*, 2015).

- Type B aortic dissection at age 52 (patient 11 from Marsili et al., 2020).

8.4. genotype-phenotype correlation validated for this gene

No specific genotype-phenotype correlations described.

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

Yes, not specific for TGF-β3, 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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