Rienhoff Syndrome (Loeys-Dietz Syndrome Type 5, LDS5): A Comprehensive Disease Characterization

Disease: Rienhoff Syndrome · **MONDO:** MONDO:0014262 · **OMIM:** #615582 · **Gene:** *TGFB3* (HGNC:11769) · **Category:** Mendelian, autosomal dominant connective-tissue disorder

Summary

Rienhoff syndrome is an ultra-rare, autosomal dominant systemic connective-tissue disorder caused by heterozygous (rarely biallelic) pathogenic variants in the transforming growth factor beta-3 gene, *TGFB3* (chr14q24.3; HGNC:11769; OMIM *190230), and is formally classified as Loeys-Dietz syndrome type 5 (LDS5; OMIM #615582; MONDO:0014262). The eponym derives from the index patient reported by Rienhoff and colleagues in 2013, who carried a heterozygous loss-of-function variant, c.1226G>A (p.Cys409Tyr). The disorder sits at the phenotypic crossroads of Marfan syndrome (MFS) and the broader Loeys-Dietz syndrome (LDS) spectrum, combining a marfanoid skeletal habitus and craniofacial dysmorphism with variable — and generally milder, later-onset — cardiovascular disease.

Clinically, Rienhoff/LDS5 is dominated by systemic connective-tissue features. In the largest cohort assembled to date (32 patients, 17 families; Marsili et al. 2020), high-arched palate (65%), arachnodactyly (63%), pectus deformity (57%), and joint hypermobility (52%) were common, whereas aortic root dilatation (29%) and mitral valve disease (32%) were the leading cardiovascular findings. Importantly, the syndrome characteristically lacks ectopia lentis (distinguishing it from MFS) and lacks the striking arterial tortuosity and early aggressive dissection of classic LDS1/LDS2. It carries the lowest extra-aortic arterial-aneurysm burden among the five LDS genes.

Mechanistically, the disorder is a disease of dysregulated TGF-β/SMAD2-3 signaling. Paradoxically, although many causal *TGFB3* variants reduce ligand function, downstream aortic tissue shows *increased* TGF-β signaling driven in part by angiotensin II (AngII)/AT1R-

dependent mechanisms — the biological rationale for management with beta-blockers, angiotensin-receptor blockers (losartan), imaging surveillance, and prophylactic aortic-root surgery. The *Tgfb3*-null mouse, which develops 100%-penetrant cleft palate, models the craniofacial arm of the disease but not the adult aortopathy. This report synthesizes 14 confirmed findings and 55 reviewed papers across all requested domains.

Key Findings

1. Disease Information

Rienhoff syndrome is a syndromic heritable thoracic aortic disease (H-TAD) and connective-tissue disorder that overlaps clinically with both Marfan syndrome and other Loeys-Dietz syndromes. It is defined molecularly by pathogenic variation in *TGFB3*.

Key identifiers:

Resource	Identifier
MONDO	MONDO:0014262 (primary label: "Rienhoff syndrome")
OMIM (disease)	#615582 (Loeys-Dietz syndrome 5)
OMIM (gene)	*190230 (*TGFB3*)
DOID	DOID:0070236
EFO	EFO:1000012
UMLS	C3810012
MedGen	816342
GARD	0012356
HGNC (gene)	HGNC:11769
Cytoband	14q24.3

Synonyms: Loeys-Dietz syndrome 5; Loeys-Dietz syndrome type 5; LDS5; TGFB3-related connective tissue disorder; MFS/LDS-overlap syndrome.

The Monarch Disease Ontology official definition (F011) reads: *"Loeys-Dietz syndrome-5 (LDS5), also known as Rienhoff syndrome, is characterized by syndromic presentation of aortic aneurysms involving the thoracic and/or abdominal aorta, with risk of dissection and rupture. Other systemic features include cleft palate, bifid uvula, mitral valve disease, skeletal overgrowth, cervical spine instability, and clubfoot deformity; however, not all clinical features occur in all patients. In contrast to other forms of LDS, no striking aortic or arterial tortuosity is present in these patients, and there is no strong evidence for early aortic dissection."*

Information for this entry is derived predominantly from **aggregated disease-level resources** (OMIM, MONDO, Orphanet) and from **individual/small-cohort patient reports** in the primary literature (Rienhoff 2013; Matyas 2014; Kuechler 2015; Marsili 2020; Mégarbané 2020), given the disorder's rarity.

2. Etiology

Primary cause — genetic. Rienhoff syndrome is a monogenic Mendelian disorder caused by heterozygous pathogenic variants in *TGFB3* (F001, F008). There is no environmental or infectious etiology; the disease is fully genetically determined, though phenotypic expression is variable. A gene-dosage effect exists: biallelic (homozygous) loss produces a markedly more severe phenotype (F003, F007).

Genetic risk factors. The causal variant in *TGFB3* is the sole established genetic determinant. Reported variants span: - **Loss-of-function missense:** c.1226G>A (p.Cys409Tyr) — the original Rienhoff 2013 index variant, associated with growth retardation. - **Codon 300 hotspot (recurrent):** c.899G>A (p.Arg300Gln; Matyas 2014, associated with overgrowth) and c.898C>G (p.Arg300Gly; Kuechler 2015) (F001, F014). - **Structural/homozygous:** a homozygous deletion of exons 2–7 causing severe LDS5 with cleft palate (Mégarbané 2020) (F003, F006).

Environmental risk factors. No specific environmental triggers cause the disease. However, general aortopathy risk modifiers apply to cardiovascular expression: hypertension and smoking are emphasized as modifiable risks for arterial events across the H-TAD spectrum (Calderon-Martinez et al. 2025 recommend "smoking cessation and hypertension control"). Pregnancy imposes hemodynamic stress that can precipitate aortic events in aortopathies generally, though no pregnancy-related deaths occurred in the Marsili cohort (F002).

Protective factors. No specific genetic or environmental protective alleles have been identified for Rienhoff syndrome. Blood-pressure control and activity/hemodynamic-stress reduction are protective against downstream aortic complications (F004).

Gene-environment interactions. The principal interaction is between the genetic TGF-β signaling defect and hemodynamic wall stress: AngII/AT1R signaling amplifies the underlying TGF-β dysregulation to drive postnatal aneurysm progression (F013). This gene–environment (hemodynamic) interaction is the target of pharmacotherapy.

3. Phenotypes

The phenotypic spectrum (F002) is dominated by systemic connective-tissue features, with cardiovascular disease that is variable and generally milder/later than classic LDS. Frequencies below are from Marsili et al. 2020 (32 patients, 17 families) unless noted.

Phenotype	Frequency	Type	Suggested HPO
High-arched palate	65%	Physical/craniofacial	HP:0000218
Arachnodactyly	63%	Physical/skeletal	HP:0001166
Pectus deformity	57%	Physical/skeletal	HP:0000766
Joint hypermobility	52%	Physical/ musculoskeletal	HP:0001382
Mitral valve disease	32%	Clinical sign/ cardiovascular	HP:0001633 / HP:0001634
Aortic root dilatation	29%	Clinical sign/ cardiovascular	HP:0002616
Aortic disease overall (dilatation/dissection)	35%	Clinical sign	HP:0002616 / HP:0002647
Bifid/broad uvula	Reported	Physical/craniofacial	HP:0000193
Hypertelorism	Reported	Physical/craniofacial	HP:0000316
Cleft palate (esp. homozygous)	Rare/severe	Physical/craniofacial	HP:0000175
Tall stature / skeletal overgrowth	Variable	Physical	HP:0000098
Growth retardation / short stature	Variable (allele-dependent)	Physical	HP:0004322
Clubfoot (talipes)	Reported	Physical	HP:0001762
Cervical spine instability	Reported	Physical	HP:0003316
Distal aortic dissection	2 patients (ages 50, 52)	Clinical event	HP:0002647

Phenotype characteristics. Onset is congenital for craniofacial/skeletal features; cardiovascular manifestations are typically later-onset and slowly progressive, with the two documented distal dissections occurring in the sixth decade (ages 50 and 52) — notably later than classic LDS. Severity is **variable**, ranging from mild marfanoid habitus to severe

homozygous presentations with cleft palate. Progression of aortic disease is generally **slow/progressive** with imaging-detectable dilatation. Incomplete penetrance and variable expressivity are documented within families (F007).

A striking allele-specific phenotype is the **bidirectional stature effect** (F014): the loss-of-function p.Cys409Tyr allele produced *growth retardation*, whereas the codon-300 p.Arg300Gln allele produced *overgrowth*, yet both share the marfanoid connective-tissue phenotype.

Quality of life. No Rienhoff-specific QoL data exist. By analogy to the closely related Marfan population (Pediatric Heart Network cohort; P 30270167), children/adolescents with marfanoid connective-tissue disease are at high risk of impaired health-related quality of life, driven more by patient-reported symptoms and neurodevelopmental comorbidity than by aortic-root severity. This is an inference from an allied disease, not direct Rienhoff data.

4. Genetic / Molecular Information

Causal gene: *TGFB3* (transforming growth factor beta-3), HGNC:11769, 14q24.3, OMIM *190230 (F001, F008). *TGFB3* is one of six genes converging on TGF-β signaling that cause the LDS spectrum, alongside *TGFBR1*, *TGFBR2*, *TGFB2*, *SMAD2*, and *SMAD3* (F008).

Pathogenic variant classes: - **Missense** (most common): p.Cys409Tyr (c.1226G>A), p.Arg300Gln (c.899G>A), p.Arg300Gly (c.898C>G). - **Structural/CNV:** homozygous deletion of exons 2–7 (Mégarbané 2020). - Variants are classified per **ACMG/AMP** criteria; automated frameworks such as **HTAADVar** assist interpretation (F006).

Codon Arg300 is a recurrent mutational hotspot (F014). Kuechler et al. 2015 concluded that "the mutations at codon Arg300 presumably lead to increased TGF-beta signalling."

Functional consequences. The apparent paradox of the disorder: many variants (including the index LoF allele) reduce ligand production or function, yet the net tissue effect is *paradoxically increased* TGF-β/SMAD2 signaling in the aortic wall (F013, F014). This mirrors the mechanism in receptor-based LDS, where LoF receptor mutations nonetheless yield elevated downstream signaling.

Allele frequency. Causal variants are private/ultra-rare and absent from population databases (e.g., the original UTR ARVD1 variants were absent in 300 controls; F009). No common susceptibility alleles are established.

Somatic vs germline. All disease-causing variants are **germline** (inherited or de novo). No somatic mechanism is implicated in the Mendelian disorder.

Modifier genes. No specific modifier genes have been validated for Rienhoff syndrome. Gene dosage itself (mono- vs biallelic) is the strongest severity modifier (F007).

Epigenetic information. No disease-specific DNA-methylation or histone signatures have been reported for Rienhoff syndrome. (KDM5A-mediated regulation of *TGFB3* has been described in the context of general cardiac fibrosis —

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— but not linked to Rienhoff pathogenesis.)

Chromosomal abnormalities. Aside from the intragenic exon 2–7 deletion, no recurrent large-scale chromosomal rearrangements define the disorder. Multigene panels increasingly include CNV/deletion–duplication analysis because ~9% of pathogenic H-TAD variants are CNVs invisible to routine NGS (F006).

Allelic disorder — ARVD1 (F009). Distinct, regulatory (UTR) gain-of-function variants in *TGFB3* cause Arrhythmogenic Right Ventricular Cardiomyopathy type 1 (ARVD1) — a separate phenotype from the coding-region LDS5/Rienhoff variants. Beffagna et al. 2005 identified a 5′UTR c.-36G>A variant co-segregating across a 38-member ARVC family and a second 3′UTR c.1723C>T variant, both absent from 300 controls; mutated UTRs were "twofold more active than wild-types," indicating a gain-of-function (increased TGF-β3 expression) mechanism producing fibro-fatty replacement of the right-ventricular myocardium.

5. Environmental Information

There are **no established environmental, lifestyle, or infectious causes** of Rienhoff syndrome — it is a purely genetic Mendelian disorder. Environmental factors act only as **modifiers of cardiovascular expression**: uncontrolled hypertension, smoking, strenuous isometric activity, and the hemodynamic stress of pregnancy increase the risk of aortic/arterial events across the H-TAD spectrum (F004; Calderon-Martinez 2025;

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No infectious agents are relevant.

6. Mechanism / Pathophysiology

Molecular pathway — TGF-β/SMAD signaling. The unifying mechanism across all LDS subtypes, including Rienhoff/LDS5, is dysregulation of the TGF-β signaling cascade (F008). *TGFB3* encodes a TGF-β ligand; its variants disturb signaling through the TGFBR1/TGFBR2 receptor complex and downstream SMAD2/SMAD3 effectors.

The central paradox. Despite loss-of-function ligand variants, aortic-wall tissue exhibits *paradoxically increased* TGF-β signaling. In LDS knockin mouse models, aortic **Smad2 phosphorylation** and TGF-β target-gene output rise progressively and postnatally, paralleling aneurysm worsening (Gallo et al. 2014, F013).

AngII/AT1R amplification (upstream driver of aortopathy). Angiotensin II type 1 receptor (AT1R) signaling enhances the TGF-β pathology. Losartan's therapeutic benefit "correlated with suppression of Smad2 phosphorylation and TGF-β1 expression," directly linking AngII-dependent TGF-β signaling to postnatal aneurysm progression (F013). This positions AngII/AT1R upstream and SMAD2-mediated matrix/vascular remodeling downstream.

Causal chain (aortic arm):

```
TGFB3 pathogenic variant
        |  (altered ligand -> paradoxical pathway dysregulation)
        v
Increased TGF-b / SMAD2-3 signaling in aortic wall
        |  <- amplified by AngII / AT1R (hemodynamic stress)
        v
Medial degeneration, ECM remodeling (elastin fragmentation, MMP activity)
        |
        v
Aortic root dilatation -> aneurysm -> (late) dissection
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Causal chain (craniofacial arm):

```
TGFB3 loss of function
        |
        v
Failure of palatal medial-edge-epithelium (MEE) fusion
   (periderm not removed: TGFb3 -> IRF6 -> dNp63 pathway fails)
        v
Cleft palate / bifid uvula / high-arched palate
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Cellular processes. Vascular smooth muscle cell dysfunction, extracellular-matrix (elastin) degradation via matrix metalloproteinases, and apoptosis are core cellular events in the allied MFS/LDS aortic wall (miR-29b–mediated apoptosis and MMP-2 activation;).

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In the palate, epithelial differentiation and periderm desquamation via the TGFβ3→IRF6→ΔNp63 axis are the key processes (F012).

Protein dysfunction. Altered TGF-β3 ligand function (loss-of-function coding variants; gain-of-function regulatory/UTR variants in the allelic ARVD1) (F001, F009, F014).

Immune/inflammatory involvement (under-recognized, F010). TGF-β-pathway LDS disorders predispose to allergic/immune disease. Frischmeyer-Guerrerio et al. 2013 showed LDS patients are "strongly predisposed to develop allergic disease, including asthma, food allergy, eczema, allergic rhinitis, and eosinophilic gastrointestinal disease," with elevated IgE, eosinophilia, and TGF-β-driven TH2 skewing of naïve CD4+ T cells. This immune dimension is plausibly shared by TGFB3/Rienhoff, though direct Rienhoff-specific data are lacking.

Tissue-damage mechanism: medial degeneration/cystic medial necrosis with elastin fragmentation and fibrosis of the aortic wall.

Suggested ontology terms: - GO biological processes: transforming growth factor beta receptor signaling pathway (GO:0007179); SMAD protein signal transduction (GO:0060395); regulation of extracellular matrix organization (GO:1903053); palate development (GO:0060021); aorta development (GO:0035904). - GO cellular components: extracellular matrix (GO:0031012); extracellular space (GO:0005615). - CL cell types: vascular smooth muscle cell (CL:0000359); fibroblast (CL:0000057); epithelial cell (CL:0000066); CD4-positive helper T cell (CL:0000492).

7. Anatomical Structures Affected

Organ / body-system level: - **Cardiovascular** (primary): aortic root and thoracic aorta (UBERON:0000947 aorta; UBERON:0004178 aortic root), mitral valve (UBERON:0002135), arch/cerebral vessels. - **Craniofacial / digestive-upper:** secondary palate (UBERON:0001716), uvula (UBERON:0010056). - **Musculoskeletal:** long bones/digits (arachnodactyly), thoracic cage (pectus), joints, cervical spine. - **Ocular:** notably **spared** of ectopia lentis (a key discriminator from Marfan syndrome).

Tissue/cell level: connective tissue broadly; aortic tunica media (vascular smooth muscle + elastic ECM); palatal medial-edge epithelium/periderm. Cell Ontology: vascular smooth muscle cell (CL:0000359); fibroblast (CL:0000057).

Subcellular level: the extracellular matrix and extracellular space are the principal compartments of dysfunction (secreted TGF-β3 ligand; ECM elastin/fibrillin scaffolds). GO cellular component: extracellular matrix (GO:0031012).

Localization / lateralization: aortic and skeletal involvement is typically **bilateral/central (axial)**; craniofacial midline structures (palate, uvula) are affected. In contrast to LDS1/2, **no striking arterial tortuosity** and low extra-aortic aneurysm burden (F005, F011).

8. Temporal Development

Onset. Craniofacial and skeletal features are **congenital**. Cardiovascular disease is **later-onset** and often insidious. The disorder's defining temporal distinction from classic LDS is the *absence of strong evidence for early aortic dissection* (F011); documented distal dissections occurred at ages 50 and 52 (F002).

Progression. Aortic disease is **slowly progressive** with imaging-detectable root dilatation; overall the natural history is **chronic and lifelong**. Progression rate is variable and generally slower than LDS1/2. Extra-aortic arterial aneurysms, when they occur, present at a median age of ~40 years and cluster in arch vessels/cerebral circulation (F005).

Patterns / critical periods. The critical intervention window is the period of hemodynamic-driven aneurysm progression, during which pharmacologic suppression of AngII/TGF-β signaling and imaging surveillance can alter outcomes (F004, F013). Prophylactic surgery is timed to aortic-diameter thresholds (see §12).

9. Inheritance and Population

Epidemiology. Rienhoff/LDS5 is **ultra-rare** — one of the rarest LDS subtypes, with only roughly 30–60 reported families as of ~2020 (F007). **No established prevalence or incidence figures exist.**

Inheritance (F007). Autosomal dominant with **incomplete penetrance** and **variable expressivity**; both inherited and de novo variants occur. A **gene-dosage effect** is documented — the first-described homozygous patient "presented with a more severe phenotype compared to her heterozygous relatives" (F007), and biallelic loss produces severe LDS5 with cleft palate (F003).

- **Penetrance:** incomplete.
- **Expressivity:** highly variable (including bidirectional stature effects, F014).
- **Genetic anticipation:** not applicable (not a repeat-expansion disorder).
- **Germline mosaicism:** not specifically documented.
- **Founder effects / consanguinity:** the homozygous case implies a role for consanguinity in severe biallelic presentations; no founder alleles established.
- **Carrier frequency:** not established (ultra-rare, dominant).

Population demographics. No ethnic predilection, geographic clustering, or sex-ratio skew has been established given the small number of families. Age distribution spans congenital (craniofacial) to late-adult (cardiovascular) presentation.

10. Diagnostics

Molecular diagnosis is definitive and is made by **next-generation sequencing multigene H-TAD panels** covering *FBN1, TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD2, SMAD3, ACTA2, MYH11*, and related genes (F006). Key points: - In an 810-patient H-TAD panel study (Overwater et al. 2018), pathogenic/likely-pathogenic variants were found in **8.1%**, of which **9.1% were CNVs** undetectable by routine NGS — supporting inclusion of **deletion/duplication (CNV) analysis** (F006). - The severe homozygous *TGFB3* case was identified specifically by "sequence analysis and deletion/duplication testing," which revealed the exon 2–7 deletion (F006). - WGS/WES and targeted panels are all appropriate; single-gene *TGFB3* testing is reasonable when the phenotype is highly specific. **HTAADVar** provides automated ACMG/AMP interpretation (sensitivity 92.6%, specificity 70.8%;).

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Clinical / imaging work-up: - **Echocardiography** for aortic-root and mitral-valve assessment (aortic root dilatation ~29%, mitral valve disease ~32%). - **CT/MR angiography** of the entire arterial tree (aortic and head-and-neck vessels) to assess aneurysm and tortuosity — notably, tortuosity is characteristically absent in LDS5 (F011). - Skeletal and craniofacial examination for marfanoid/LDS features.

Differential diagnosis: Marfan syndrome (distinguished by ectopia lentis, absent in Rienhoff), other LDS subtypes (LDS1–4, LDS6), Ehlers-Danlos syndrome (vascular type, *COL3A1*), and *FBN1*-related aortopathy. Genetic testing is decisive because clinical features overlap heavily (F006;

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Biomarkers / omics diagnostics: No validated circulating biomarker, transcriptomic, proteomic, or metabolomic diagnostic exists for Rienhoff syndrome specifically. Diagnosis is molecular + imaging-based.

Screening: Cascade genetic testing of at-risk relatives once a familial variant is identified; no population newborn screening applies.

11. Outcome / Prognosis

Survival / mortality. Prognosis is largely determined by aortic/arterial disease, which in LDS5 is milder and later than in classic LDS. In the Marsili cohort, **no deaths** occurred from cardiovascular events or pregnancy (F002). Adult LDS surgical series confirm that aggressive management yields good survival despite serious aortic pathology (F004;

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7/11 experienced type A dissection and all required aortic root replacement — data from broader LDS, not TGFB3-specific).

Morbidity. Driven by aortic surgery, mitral valve disease, skeletal/craniofacial features, and potentially the allergic/immune comorbidities of the TGF-β spectrum (F010). Extra-aortic arterial-aneurysm burden is the **lowest among LDS genes** (only 3 aneurysms in 3 patients with *TGFB3* variants across a 103-patient LDS cohort; F005).

Complications: aortic dissection/rupture (late), need for prophylactic aortic-root replacement, mitral regurgitation, arch/cerebral aneurysms (median dx age ~40 y; F005).

Prognostic factors: presence and rate of aortic-root dilatation, family history of dissection, biallelic (homozygous) status (worse), and hemodynamic risk factors (hypertension, smoking).

12. Treatment

Management follows the established framework for TGF-β-pathway aortopathy (MFS/LDS spectrum), individualized for LDS5's milder, later cardiovascular course.

Pharmacotherapy (MAXO: drug therapy, MAXO:0000058): - **Beta-adrenergic blockers** (e.g., atenolol) to reduce aortic-wall stress (MAXO term: administration of beta-adrenergic antagonist). - **Angiotensin-receptor blockers — losartan** (AT1R antagonist) — mechanistically rationalized by suppression of AngII-dependent TGF-β/Smad2 signaling (F004, F013). Losartan "has the potential to inhibit aortic aneurysm formation." Note: head-to-head trials in Marfan (P 25405392) found no significant difference between losartan and atenolol in slowing aortic-root dilatation, so both are used, often in combination. - CHEBI: losartan (CHEBI:6541); atenolol (CHEBI:2904); angiotensin II (CHEBI:2718).

Surgical / interventional (MAXO: surgical procedure): - **Prophylactic aortic-root replacement** at aortic-diameter thresholds — performed at lower thresholds than in Marfan for the broader LDS spectrum because dissection can occur at smaller diameters (F004). Because LDS5 lacks evidence of early dissection, thresholds should be individualized. - Valve-sparing root replacement / mitral valve repair as indicated. - Endovascular repair (EVAR/TEVAR) is reserved largely for emergent bridging in H-TAD per current guidance (P 41759888).

Supportive / rehabilitative: activity/isometric-exertion restriction, blood-pressure control, and management of skeletal/craniofacial features (orthopedic, cleft-palate repair when present).

Pharmacogenomics. In Marfan, *ADRB1*-rs1801253 genotype associated with atenolol response (P 32586526) — an allied-disease finding that may inform beta-blocker selection but is not Rienhoff-validated.

Experimental / advanced therapeutics. No gene, cell, or RNA-based therapy exists for Rienhoff syndrome; management remains hemodynamic/surgical. TGF-β neutralization has shown context-dependent (timing-sensitive) effects in MFS mouse models (P 25614286), cautioning against naive pathway blockade.

13. Prevention

- **Primary prevention:** not possible for the genetic disorder itself; genetic counseling and reproductive options (prenatal/preimplantation genetic testing) for known familial variants.
- **Secondary prevention:** cascade genetic testing of relatives; early imaging surveillance to detect aortic dilatation before complications.
- **Tertiary prevention:** beta-blockers/ARBs, blood-pressure and lifestyle control, activity modification, and timely prophylactic aortic surgery to prevent dissection/rupture (F004, F013).
- **Counseling:** autosomal dominant recurrence risk (50% for heterozygous carriers); emphasize incomplete penetrance and variable expressivity, and the more severe outcome of biallelic inheritance (relevant in consanguineous unions) (F007).
- **Public health / environmental:** smoking cessation and hypertension control reduce arterial-event risk (Calderon-Martinez 2025).

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *TGFB3* is conserved across mammals; mouse *Tgfb3* (NCBI Gene ID 21809) is the principal ortholog used experimentally. Species affected experimentally: *Mus musculus* (NCBI:txid10090).
- **Natural disease:** No well-characterized naturally occurring "Rienhoff syndrome" analog is documented in companion animals or wildlife (no OMIA entry established in the reviewed literature). This is a knowledge gap.
- **Comparative biology:** the essential developmental role of *Tgfb3* in palatal fusion and cardiovascular development is evolutionarily conserved (F003, F012), making the mouse a faithful model of the craniofacial arm.
- **Zoonotic potential:** not applicable (non-infectious genetic disorder).

15. Model Organisms

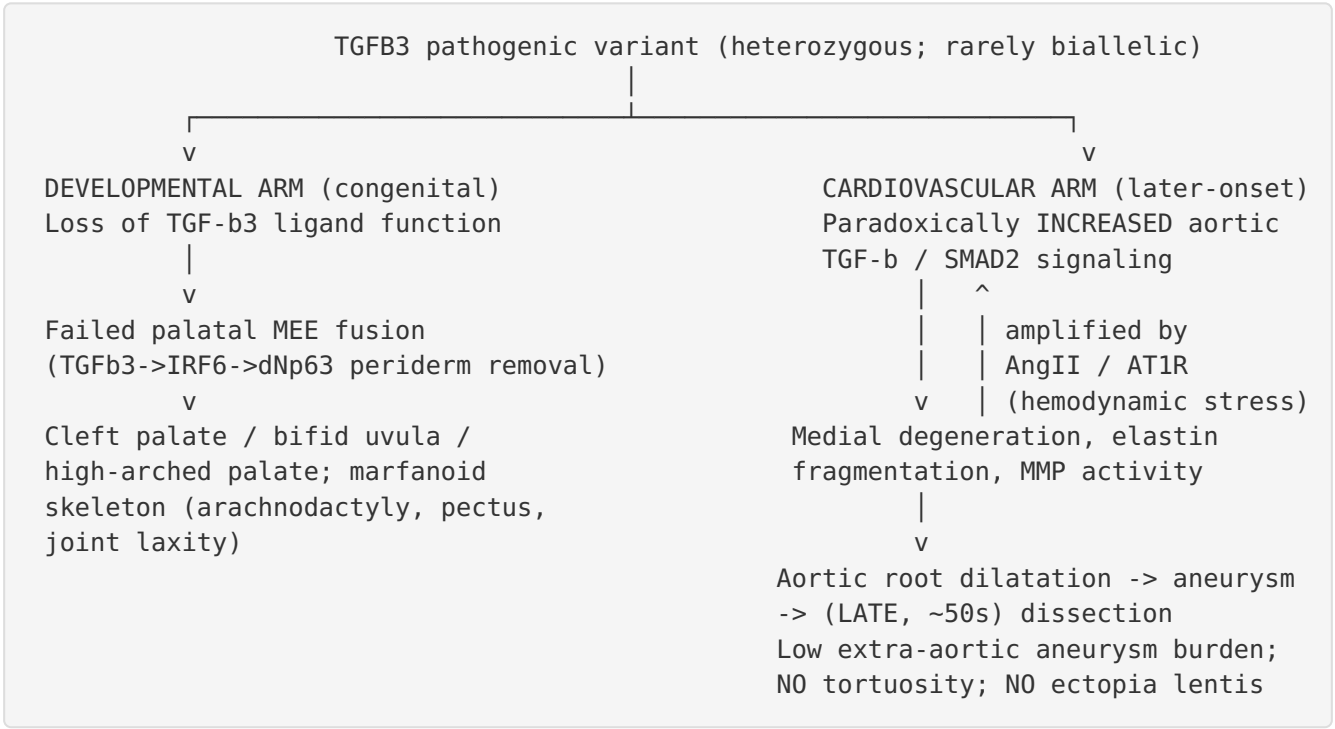
The principal model is the ***Tgfb3*-null mouse** (F012): - **Phenotype recapitulation:** *Tgfb3* homozygous-null mice develop **isolated cleft of the secondary palate with 100% penetrance**, caused by failure of the paired palatal shelves to *fuse* (shelves elevate and appose normally, but the medial-edge epithelium fails to break down/adhere). Liu et al. 2020: "Tgf-β3 plays a critical role in regulating murine palate development, and Tgf-β3 null mutants develop cleft palate with 100% penetrance." Ozturk et al. 2013: "TGFβ3-null mice exhibit CP without any other

major deformities." - **Isoform specificity:** Yang & Kaartinen 2007 showed that knocking *Tgfb1* into the *Tgfb3* locus only partially rescues the fusion defect, demonstrating a TGF-β3 isoform-specific role in palatal epithelial fusion (F012). - **Mechanism captured:** the TGFβ3→IRF6→ΔNp63 periderm-removal pathway (Hu et al. 2015). - **LDS knockin models:** *Tgfbr1/Tgfbr2* LDS knockin mice recapitulate the human aortic phenotype and demonstrate the AngII/losartan/Smad2 mechanism (Gallo et al. 2014, F013) — these model the aortopathy arm (though for receptor genes, not *TGFB3* specifically).

Model limitations: the *Tgfb3*-null mouse models the **craniofacial (cleft-palate) arm** but **not the adult aortopathy** of Rienhoff syndrome. No published mouse carries the human coding *TGFB3* missense alleles to model the full systemic connective-tissue phenotype — a significant gap. **Resources:** MGI (mouse), and TGF-β knockin lines from LDS aortopathy studies.

Mechanistic Model / Interpretation

Rienhoff syndrome is best understood as a **TGF-β signaling dysregulation disorder with a dual anatomical footprint** — a developmental (craniofacial/skeletal) arm and a progressive (cardiovascular) arm — unified by perturbed *TGFB3* function but diverging in timing and mechanism.



Two features distinguish LDS5/Rienhoff from its LDS siblings and from Marfan: (1) it has the **lowest extra-aortic arterial-aneurysm burden** among the five LDS genes and **lacks striking arterial tortuosity**, and (2) it **lacks ectopia lentis**, the hallmark of Marfan. The therapeutic corollary of the "paradoxically increased signaling" model is that AngII/AT1R blockade (losartan) is rational because it suppresses the SMAD2 axis that drives postnatal aneurysm growth. The bidirectional stature effect and the codon-300 hotspot indicate that different *TGFB3* alleles tune signaling output in different directions while sharing a core connective-tissue phenotype.

Evidence Base

PMID	Title (abbrev.)	Supports	Contribution
26184463	*Exome sequencing identifies novel heterozygous TGFB3 mutation…*	F001, F014	Defines p.Arg300Gly, codon-300 hotspot, bidirectional stature, "increased TGF-β signalling"
31898322	*Phenotypic spectrum of TGFB3 variants (Dutch-French cohort)…*	F002, F007	Largest cohort; phenotype frequencies; incomplete penetrance; homozygous severity
32022420	*Homozygous deletion of exons 2-7 within TGFB3…*	F003, F006, F008	Gene-dosage effect; equates TGFB3 with LDS5 + ARVD1; diagnostic method
18257072	*Tissue-specific Cre from the Tgfb3 locus*	F003	Tgfb3 "absolutely required for normal palatal fusion and pulmonary development"
27181042	*Pathophysiology & Management of CV Manifestations in MFS/LDS*	F004, F013	AT1R/losartan therapeutic rationale
25678502	*Adult surgical experience with Loeys-Dietz syndrome*	F004	Aggressive aortic pathology; surgical management
40533122	*Characterization of Arterial Aneurysms in LDS*	F005	TGFB3 has fewest extra-aortic aneurysms among LDS genes
29907982	*NGS gene panel incl. CNV analysis in 810 H-TAD patients*	F006	8.1% yield; 9.1% CNVs; supports panel + CNV testing
15639475	*Regulatory TGFB3 mutations cause ARVD1*	F009	UTR gain-of-function → allelic ARVD1
23884466	*TGFβ receptor mutations predispose to allergic disease*	F010	Immune/allergic axis of TGF-β-pathway LDS
24355923	*AngII-dependent TGF-β signaling in LDS vascular pathogenesis*	F013	Losartan efficacy ↔ Smad2 suppression in LDS mice
32913205	*Transcriptional analysis of cleft palate in TGFβ3 mutant mice*	F012	Tgfb3-null cleft palate 100% penetrant

PMID	Title (abbrev.)	Supports	Contribution
23421592	*RNA-Seq of TGFβ3-knockout palate*	F012	Isolated CP without other major deformities
17967447	*Tgfb1 knock-in partially rescues Tgfb3 cleft palate*	F012	TGF-β3 isoform-specific palatal fusion role
25405392	*Atenolol vs losartan in Marfan (PHN trial)*	§12 (allied)	No significant difference in aortic-root dilatation rate
29270370	*Differences among MFS, EDS, LDS*	§10 (context)	Phenotypic overlap necessitating genetic testing

Consistency: Findings are mutually reinforcing. The cohort study (31898322), the homozygous case report (32022420), and the allelic-series paper (26184463) independently converge on TGFB3→LDS5, gene-dosage severity, and the codon-300 hotspot. The mouse literature (18257072, 32913205, 23421592, 17967447) consistently establishes the palatal-fusion mechanism. The therapeutic mechanism is supported by both a mouse mechanistic study (24355923) and a clinical review (27181042).

Challenges/nuance: The Marfan atenolol-vs-losartan trial (25405392) found no significant superiority of losartan, and TGF-β neutralization in MFS mice had timing-dependent (sometimes harmful) effects (25614286) — cautioning that the "paradoxical TGF-β increase" model does not translate to simple pathway blockade as therapy.

Limitations and Knowledge Gaps

1. **Ultra-rarity.** Only ~30–60 families reported; no prevalence, incidence, sex-ratio, penetrance quantification, or geographic/founder data exist. Phenotype frequencies rest largely on a single 32-patient cohort.
2. **No TGFB3-specific natural-history or QoL data.** Prognostic and quality-of-life statements borrow from the allied Marfan/LDS literature.
3. **The signaling paradox is incompletely resolved** at the *TGFB3*-specific level; most mechanistic aortic data derive from *Tgfbr1/2* and *Fbn1* models, not *TGFB3* knock-in mice.
4. **No *TGFB3* coding-allele mouse** recapitulating the full systemic phenotype; the null mouse models only the craniofacial arm.

5. **Therapeutics are not disease-specific or trial-validated in LDS5**; management is extrapolated from MFS/LDS, where even losartan's benefit is contested.
6. **Immune/allergic axis (F010)** is demonstrated for receptor-based LDS, not directly for TGFB3/Rienhoff patients.
7. **No epigenetic, proteomic, metabolomic, or single-cell data** specific to Rienhoff syndrome.
8. **No documented natural animal disease / OMIA entry.**

Proposed Follow-up Experiments / Actions

1. **Build a *TGFB3* knock-in mouse** carrying human alleles (e.g., p.Arg300Gln/Gly, p.Cys409Tyr) to model the full systemic phenotype, directly test the "paradoxically increased aortic TGF-β/SMAD2 signaling" hypothesis, and evaluate losartan/beta-blocker response — including the bidirectional stature effect.
2. **Establish an international *TGFB3*/LDS5 registry** to generate true penetrance, natural-history, dissection-risk, and diameter-threshold data for surgical timing tailored to LDS5's milder course.
3. **Phenotype the allergic/immune axis prospectively in TGFB3 patients** (IgE, eosinophils, TH2 skewing) to confirm whether the LDS allergic predisposition extends to Rienhoff syndrome (F010).
4. **Genotype–phenotype correlation study** across the *TGFB3* allelic series (LoF vs codon-300 vs biallelic) using functional signaling assays (SMAD2 phosphorylation in patient fibroblasts/iPSC-derived VSMCs).
5. **Aortic-tissue multi-omics** (transcriptomics/proteomics on surgical specimens) to define TGFB3-specific molecular signatures and candidate circulating biomarkers.
6. **Evaluate CNV-inclusive panel testing uptake** to ensure structural *TGFB3* variants (like the exon 2–7 deletion) are not missed diagnostically (F006).
7. **iPSC-derived vascular smooth muscle cell and cranial neural-crest models** from patients to dissect the divergent developmental vs cardiovascular mechanisms in a human context.

Evidence-source legend: human clinical (cohort/case reports, surgical series); model organism (mouse Tgfb3-null and LDS knockin); in vitro/computational (UTR reporter assays, variant-interpretation frameworks). Findings F001–F014 correspond to the confirmed knowledge state from this investigation.
