**Introduction**

Loeys-Dietz Syndrome Type 5 (LDS Type 5) is the rarest and most recently identified subtype of Loeys-Dietz Syndrome. It arises from mutations in the *TGFB3* gene, which encodes the TGF-β3 ligand—another critical component of the TGF-β signaling pathway. LDS Type 5 manifests with connective tissue abnormalities, vascular fragility, and overlapping features with other LDS types but also displays unique clinical characteristics. Due to its recent discovery, knowledge about LDS Type 5 is still evolving.

**Genetic and Molecular Basis**

**Gene and Mutation**

* **Gene:** *TGFB3* (Transforming Growth Factor Beta 3)
* **Location:** Chromosome 14q24.3
* **Function:** *TGFB3* encodes the TGF-β3 ligand, a cytokine involved in extracellular matrix regulation, cell proliferation, and differentiation during embryonic development and tissue homeostasis.
* **Mutations:** Typically heterozygous missense or nonsense mutations resulting in altered TGF-β3 ligand function or expression.

**Molecular Pathophysiology**

* *TGFB3* mutations disrupt normal TGF-β3 ligand signaling, causing abnormal regulation of the extracellular matrix and vascular smooth muscle cell function.
* This leads to weakening of connective tissue structures, particularly in arteries, predisposing to aneurysm formation.
* Abnormalities in ECM remodeling affect skin, joints, and cardiovascular tissues.
* Like other LDS types, paradoxical upregulation of downstream TGF-β signaling pathways may occur despite ligand deficiency or dysfunction.

**Inheritance**

* Autosomal dominant.
* High penetrance but variable expressivity.
* Both inherited and de novo mutations documented.

**Epidemiology**

* LDS Type 5 is extremely rare, with only limited case reports and family studies.
* Increased genetic testing is improving recognition.
* No sex or ethnic predilection identified.

**Clinical Features**

**Cardiovascular Manifestations**

* **Aortic root aneurysm and dilation:** Common and may present in childhood or adolescence.
* **Aortic dissections:** Risk present, though clinical course may vary.
* **Arterial tortuosity:** Variable; some patients show mild to moderate tortuosity.
* **Other aneurysms:** Occasionally seen in other arteries.
* **Valvular abnormalities:** Mild mitral valve prolapse reported in some cases.
* **Hypertension:** May be present and exacerbate vascular risk.

**Skeletal and Connective Tissue Features**

* **Joint hypermobility:** Present but often mild.
* **Pectus deformities:** Pectus excavatum or carinatum can be present.
* **Scoliosis:** Mild scoliosis occasionally reported.
* **Skin:** Soft, mildly translucent skin prone to bruising.
* **Hernias:** Inguinal and umbilical hernias reported in some patients.
* **Atrophic scarring:** Less commonly reported than in other LDS types.

**Craniofacial Features**

* Generally mild or absent.
* Some patients may have subtle facial features such as mild hypertelorism.
* Bifid uvula and cleft palate are rare or not typical.

**Other Features**

* Mild developmental delay reported in rare cases.
* Mild musculoskeletal pain or joint discomfort possible.
* No clear association with early-onset osteoarthritis unlike LDS Type 3.

**Diagnosis**

**Clinical Evaluation**

* LDS Type 5 suspected in individuals with familial aortic aneurysm and mild connective tissue abnormalities without classic LDS Type 1 or 2 features.
* Careful cardiovascular and connective tissue examination is essential.

**Imaging**

* Echocardiography to monitor aortic root size and valve function.
* CT or MRI angiography for detecting aneurysms and arterial tortuosity.
* Skeletal imaging as indicated.

**Genetic Testing**

* Confirmation requires detection of pathogenic variants in *TGFB3*.
* Family screening recommended for mutation carriers.

**Differential Diagnosis**

* LDS Types 1–4: Differentiated by gene mutation and clinical phenotype.
* Marfan syndrome: Similar vascular and skeletal manifestations but different genetic cause.
* Other connective tissue disorders with vascular involvement.

**Management**

**Cardiovascular Management**

* Lifelong monitoring of the aorta and arteries with imaging.
* Blood pressure control using beta-blockers or angiotensin receptor blockers.
* Prophylactic surgical repair of aneurysms based on size and growth rate.

**Skeletal and Supportive Care**

* Orthopedic evaluation and management of chest wall deformities or scoliosis.
* Physical therapy for joint symptoms.
* Hernia repair if symptomatic.

**Surgical Interventions**

* Early elective aortic root surgery when indicated.
* Orthopedic surgery as needed.

**Supportive Care**

* Genetic counseling and psychosocial support.
* Multidisciplinary approach to address cardiovascular, orthopedic, and genetic aspects.

**Prognosis**

* Data limited due to rarity.
* Appears to have a somewhat milder clinical course than LDS Types 1 and 2.
* Risk of aortic dissection requires vigilant monitoring.
* Prognosis improves significantly with early diagnosis and appropriate management.

**Research and Future Directions**

**Molecular Research**

* Further studies on the exact role of TGF-β3 in connective tissue homeostasis and LDS pathology.
* Exploring why *TGFB3* mutations lead to a milder phenotype compared to receptor mutations.

**Therapeutic Research**

* Investigating targeted therapies modulating TGF-β signaling.
* Potential for gene therapy or molecular treatments in future.

**Biomarker and Diagnostic Advances**

* Identifying markers predictive of disease severity and progression.

**Summary**

Loeys-Dietz Syndrome Type 5 is a rare autosomal dominant connective tissue disorder caused by mutations in *TGFB3*. It shares many vascular and connective tissue features with other LDS subtypes but generally presents with milder clinical manifestations, especially regarding craniofacial features and musculoskeletal involvement. Lifelong cardiovascular surveillance and multidisciplinary care are critical to managing this condition. Research is ongoing to improve understanding and develop targeted therapies.