**Introduction**

**Loeys-Dietz Syndrome Type 4 (LDS Type 4) is one of the rarer subtypes of Loeys-Dietz Syndrome, caused by mutations in the *TGFB2* gene. This type shares the hallmark connective tissue fragility and vascular anomalies characteristic of the LDS spectrum but differs in clinical presentation and severity compared to Types 1–3. LDS Type 4 features a wide range of cardiovascular and skeletal abnormalities with somewhat milder craniofacial involvement.**

**Genetic and Molecular Basis**

**Gene and Mutation**

* **Gene: *TGFB2* (Transforming Growth Factor Beta 2)**
* **Location: Chromosome 1q41**
* **Function: *TGFB2* encodes the TGF-β2 ligand, a cytokine involved in regulating cellular proliferation, differentiation, and ECM production through TGF-β signaling.**
* **Mutations: Typically heterozygous missense, nonsense, or frameshift mutations that reduce or alter ligand function.**

**Molecular Pathophysiology**

* **Mutations in *TGFB2* reduce normal TGF-β2 ligand signaling, disturbing the delicate balance of TGF-β pathway activity.**
* **This leads to defective ECM remodeling and weakening of connective tissue structures, especially in blood vessels.**
* **Similar to other LDS types, paradoxical upregulation of TGF-β downstream signaling pathways occurs, promoting arterial aneurysms and tortuosity.**
* ***TGFB2* mutations particularly affect vascular smooth muscle and fibroblast function.**

**Inheritance**

* **Autosomal dominant inheritance.**
* **High penetrance but variable expressivity.**
* **De novo mutations reported.**

**Epidemiology**

* **LDS Type 4 is rare and less frequently diagnosed compared to Types 1 and 2.**
* **Increasing identification due to expanded genetic testing.**
* **Affects both sexes and all ethnicities equally.**

**Clinical Features**

**Cardiovascular Manifestations**

* **Aortic root dilation and aneurysm: Common but may progress more slowly.**
* **Aortic dissection: Risk present but generally lower than Types 1 and 2.**
* **Arterial tortuosity: Mild to moderate, less severe than Types 1 and 2.**
* **Other aneurysms: Possible but less frequent.**
* **Valvular abnormalities: Mitral valve prolapse occasionally observed.**
* **Hypertension: Can contribute to vascular complications.**

**Skeletal System**

* **Pectus deformities: Pectus excavatum or carinatum occur frequently.**
* **Scoliosis: Moderate scoliosis common.**
* **Joint hypermobility: Mild to moderate.**
* **Arachnodactyly: Present in some patients.**
* **Other skeletal anomalies: Mild osteopenia reported occasionally.**

**Craniofacial Features**

* **Less pronounced craniofacial abnormalities compared to LDS Types 1 and 2.**
* **Bifid uvula or cleft palate: Rare.**
* **Mild facial features such as downslanting palpebral fissures may occur.**

**Skin and Connective Tissue**

* **Translucent, soft skin with mild bruising.**
* **Hernias (inguinal, umbilical) may occur.**
* **Mild to moderate joint laxity.**
* **Atrophic scarring less common.**

**Other Features**

* **Mild developmental delays occasionally reported.**
* **Gastrointestinal complications such as diverticula possible but uncommon.**

**Diagnosis**

**Clinical Evaluation**

* **Consider LDS Type 4 in patients with familial or early-onset aortic aneurysm with mild connective tissue findings.**
* **Milder craniofacial signs can complicate clinical suspicion.**

**Imaging**

* **Echocardiography to assess aortic root and valve.**
* **CT or MRI angiography to evaluate for aneurysms and tortuosity.**
* **Skeletal imaging for deformities.**

**Genetic Testing**

* **Confirmatory diagnosis requires identification of pathogenic *TGFB2* mutation.**
* **Family screening recommended.**

**Differential Diagnosis**

* **LDS Types 1–3: More severe craniofacial and skeletal features.**
* **Marfan syndrome: Similar skeletal and vascular features.**
* **Other thoracic aortic aneurysm syndromes.**
* **Ehlers-Danlos syndrome variants.**

**Management**

**Cardiovascular Management**

* **Regular cardiovascular surveillance with imaging every 6–12 months.**
* **Blood pressure control with beta-blockers or ARBs.**
* **Early elective surgical repair of aneurysms per guidelines.**

**Skeletal and Supportive Care**

* **Orthopedic management of scoliosis and chest wall deformities.**
* **Physical therapy for joint hypermobility.**
* **Hernia repair as needed.**

**Surgical Interventions**

* **Elective aortic root replacement and repair of other aneurysms.**
* **Orthopedic surgeries for significant deformities.**

**Supportive Care**

* **Genetic counseling.**
* **Psychological support.**
* **Multidisciplinary approach for optimal care.**

**Prognosis**

* **Generally considered milder than LDS Types 1 and 2.**
* **Lifespan may be near normal with appropriate management.**
* **Risk of aortic dissection present but often lower.**
* **Progressive monitoring essential due to variable expressivity.**

**Research and Future Directions**

**Molecular Studies**

* **Understanding the role of TGF-β2 ligand deficiency in LDS pathogenesis.**
* **Exploring potential therapeutic targets to normalize TGF-β signaling.**

**Therapeutic Development**

* **Investigations into ARBs and other agents targeting the TGF-β pathway.**
* **Gene-based therapies are under experimental consideration.**

**Biomarker Identification**

* **Developing biomarkers for early vascular involvement and progression.**

**Summary**

**Loeys-Dietz Syndrome Type 4 is a rare connective tissue disorder caused by mutations in the *TGFB2* gene, resulting in milder but significant vascular and skeletal manifestations. Lifelong surveillance and multidisciplinary management are essential to mitigate risks of aneurysm and other complications. Continued research into the molecular mechanisms holds promise for improved therapies.**