

Ehlers-Danlos Syndrome Kyphoscoliotic Form, Type VI (*PLOD1*) Sequencing and Deletion/Duplication

*TO CONFIRM A SUSPECTED DIAGNOSIS OF EHLERS-DANLOS
SYNDROME VI OR DETERMINE CARRIER STATUS*

Disease Overview

- Ehlers-Danlos syndrome kyphoscoliotic form, also known as type VI (EDS VI or VIA), is a connective tissue disorder characterized by kyphoscoliosis at birth or within the first year of life, severe neonatal hypotonia, thin hyperextensible and bruisable skin, atrophic scarring, joint hypermobility, and scleral fragility leading to increased risk for rupture of the globe. There is an increased risk for rupture of medium size arteries, and individuals with severe kyphoscoliosis are at increased risk for respiratory compromise.
- EDS VI is caused by deficiency of lysyl hydroxylase, an enzyme important in the formation of collagen cross-links.
- EDS VI can be diagnosed in the following ways:
 - Increased ratio of deoxypyridinoline to pyridinoline crosslinks (Dpyr:Pyr) detected in urine.
 - Decreased lysyl hydroxylase activity; less than 25 percent of normal in fibroblasts.
 - Identification of two pathogenic procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (*PLOD1*) gene mutations.
- EDS kyphoscoliotic form is sometimes described as EDS VIA to differentiate it from EDS VIB, a rare condition with similar clinical features but normal lysyl hydroxylase activity.
- Management of individuals with EDS VI involves regular follow-up with several specialties, including orthopedic surgery, physical therapy, cardiology, and ophthalmology. Appropriate management helps prevent or minimize serious disease complications.

Epidemiology

Incidence is approximately one in 100,000; carrier frequency is estimated at one in 150.

Genetics

- Autosomal recessive inheritance with variable expressivity.
- The *PLOD1* gene is the only gene associated with lysyl hydroxylase deficiency or EDS VIA.
- A common 8.3kb gene duplication, located between introns 9 and 16 (exons 10–16), is responsible for approximately 20 percent of pathogenic mutations.

Indications for Ordering

- To confirm causative mutations in a symptomatic individual with an increased Dpyr:Pyr ratio.
- To determine carrier status of at-risk family members when the familial mutation is unknown.

Contraindications for Ordering

- Prenatal testing.
- The biochemical screen (ARUP test code [0080351](#)) should be ordered as a first-line test to determine whether an individual may be affected with EDS VI.

Additional Ordering Notes

If there is a family history of EDS VI and the specific familial mutation(s) has already been identified, testing can be performed on at-risk family members by contacting ARUP's genetic counselor and requesting targeted sequencing for the familial mutation(s).

Interpretation

- The detection of two pathogenic *PLOD1* mutations on opposite chromosomes predicts EDS VI.
- When one or no *PLOD1* mutations are detected in a clinically affected individual, the patient may have *PLOD1* mutation(s) undetectable by this assay. Thus, medical management should rely on clinical and biochemical findings.
- Sequencing may detect *PLOD1* mutations of unknown clinical significance.

Methodology

- PCR followed by bidirectional sequencing of the entire coding region and intron-exon boundaries of the *PLOD1* gene.
- Multiplex ligation-dependent probe amplification (MLPA) to detect large *PLOD1* coding region deletions/duplications, including the common 8.3kb duplication of exons 10–16.
- Clinical sensitivity is unknown.
- Analytical sensitivity and specificity are 99 percent.

Limitations

- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Regulatory region mutations and deep intronic mutations will not be detected.
- Large deletions/duplications of exon 9 will not be detected. Large deletions/duplications of exons 1, 3, 5, and 19 may or may not be detected based on the breakpoints of the rearrangement.
- The breakpoints of large deletions/duplications will not be determined.

Related Test

Ehlers-Danlos Syndrome Type VI Screen ([0080351](#))—Biochemical (HPLC) test to determine whether an individual may be affected; carrier status cannot be determined with this assay.

References

1. GeneTests: Ehlers-Danlos syndrome kyphoscoliotic form. www.genetests.org (accessed on June 1, 2011).
2. Yeowell HN, Walker LC. Mutations in the lysyl hydroxylase 1 gene that result in enzyme deficiency and the clinical phenotype of Ehlers-Danlos syndrome type VI. *Mol Genet Metab* 2000;71(1–2):212–24.
3. Walker LC, et al. Heterogeneous basis of the type VIB form of Ehlers-Danlos syndrome (EDS VIB) that is unrelated to decreased collagen lysyl hydroxylation. *Am J Med Genet* 2004;131(2):155–62.
4. Heikkinen J. Duplication of seven exons in the lysyl hydroxylase gene is associated with longer forms of a repetitive sequence within the gene and is a common cause for the type VI variant of Ehlers-Danlos syndrome. *Am J Hum Genet* 1997;60:48–56.

Test Information

2005559 **Ehlers-Danlos Syndrome, Type VI (*PLOD1*) Sequencing and Deletion/Duplication**
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For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

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