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 bruised skin, atrophic scarring, joint hypermobility, and sceral 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.

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

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 |
| 2005555 | Ehlers-Danlos Syndrome, Type VI (PLOD1) Deletion/Duplication |

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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