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

Ehlers-Danlos syndrome type VI (EDS VI) is an autosomal recessive generalized connective tissue disease caused by variants in the *PLOD1* gene. EDS VI is characterized by hypotonia, early-onset progressive kyphoscoliosis, osteopenia, generalized joint hypermobility, skin fragility, artery rupture, and ocular abnormalities (eg, eye globe rupture). Life expectancy and quality of life may be affected by the risk of artery rupture and an increased risk for complications due to restrictive lung disease, recurrent pneumonia, and cardiac failure in adults with severe kyphoscoliosis.

Tests to Consider

Ehlers-Danlos Syndrome Type VI Screen 0080351

Method: High Performance Liquid Chromatography (HPLC)

- Initial test to diagnose or rule out EDS VIA (kyphoscoliotic type)
- Not recommended to screen for other types of EDS

Ehlers-Danlos Syndrome Kyphoscoliotic Form, Type VI (PLOD1) Sequencing and Deletion/Duplication 2005559

Method: Polymerase Chain Reaction/Sequencing

- Preferred test to confirm a diagnosis of EDS, type VI, when urine Dpyr:Pyr is elevated
- Not recommended to rule out other types of EDS

Disease Overview

Prevalence

1/100,000[1]

- Carrier frequency 1/150

Nomenclature

- Sometimes described as EDS VIA to differentiate from EDS VIB
- EDS VIB individuals have normal lysyl hydroxylase activity

Symptoms

- Kyphoscoliosis at birth or within first year of life
  - Leads to respiratory compromise
- Severe neonatal hypotonia
- Thin, hyperextensible, bruisable skin
- Atrophic scarring
- Joint hypermobility
- Scleral fragility
  - Increased risk of globe rupture

Diagnostic criteria

- Increased urinary Dpyr:Pyr
- Identification of two pathogenic *PLOD1* gene variants
- Decreased lysyl hydroxylase activity (<25% of normal in fibroblasts)

Physiology

Lysyl hydroxylase is involved in formation of collagen cross-links

Genetics

Gene

PLOD1

Inheritance

Autosomal recessive

Structure/Function

Common 8.3 kb duplication of exons 10-16 is responsible for 20% of pathogenic variants

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity
  - Sequencing: 67%
  - Deletion/duplication: 33%
- Analytical sensitivity/specificity: 99%

Results

- Detection of two pathogenic *PLOD1* pathogenic variants on opposite chromosomes predicts EDS VI
- When one or no *PLOD1* pathogenic variants are detected in a clinically affected individual, individual may have *PLOD1* variants undetectable by this test
- Variants of uncertain clinical significance may be detected

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated:
  - Regulatory region variants
  - Deep intronic variants
  - Breakpoints of large deletions/duplications
  - Large deletions/duplications of exon 9
  - Large deletions/duplications of exons 1 and 5 may not be detected based on breakpoints of the rearrangement

References

1. Kariminejad A, Bozorgmehr B, Khatami A, et al. Ehlers-Danlos syndrome type VI in a 17-year-old Iranian boy with severe muscular weakness - a diagnostic challenge? Iran J Pediatr. 2010;20(3):358-362. PubMed

Additional Resources

Brady AF, Demirdas S, Fournel-Gigleux S, et al. The Ehlers-Danlos syndromes, rare types. Am J Med Genet C Semin Med Genet. 2017;175(1):70-115. PubMed

Giunta C, Randolph A, Steinmann B. Mutation analysis of the PLOD1 gene: an efficient multistep approach to the molecular diagnosis of the kyphoscoliotic type of Ehlers-Danlos syndrome (EDS VIA). Mol Genet Metab. 2005;86(1-2):269-276. PubMed

Yeowell HN, Steinmann B. *PLOD1*-Related Kyphoscoliotic Ehlers-Danlos Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Oct 2018; Accessed: May 2020]

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review May 2020 | Last Update July 2020