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

Indications for Ordering

To confirm causative mutations in a symptomatic individual with an elevated urinary deoxypyridinoline-to-pyridinoline ratio (Dpyr:Pyr)

Test Description

Ehlers-Danlos Syndrome Type VI Screen
- Urine screening by high-performance liquid chromatography to determine Dpyr:Pyr

Sequencing and Deletion/Duplication Mutation Testing
- PCR followed by bidirectional sequencing of the entire coding region and intron-exon boundaries of procollagen-lysine, 2-oxoglutarate 5-dioxygenase (*PLOD1)* gene
- Multiplex ligation-dependent probe amplification (MLPA) to detect large coding region deletions/duplications
  - Includes common 8.3 kb duplication of exons 10-16

Tests to Consider

Typical testing strategy
- Urine screen for Dpyr:Pyr
- DNA testing of *PLOD1* (sequencing and deletion/duplication)
- Lysyl hydroxylase enzyme activity in cultured fibroblasts
  - Not currently offered at ARUP

Primary tests

Ehlers-Danlos Syndrome Type VI Screen 0080351
- Initial test to diagnose or rule out Ehlers-Danlos syndrome (EDS), type 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
- Preferred test for confirmation of EDS, type VI, when urine Dpyr:Pyr is elevated

Disease Overview

Incidence – 1/100,000
- Carrier frequency 1/150

Nomenclature
- Condition is also known as EDS VI
- Sometimes described as EDS VIA to differentiate from EDS VIB
  - EDS VIB individuals have normal lysyl hydroxylase activity

Symptoms
- Kyphoscoliosis at birth/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 2 pathogenic *PLOD1* gene mutations
- 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
- Responsible for 20% of pathogenic mutations

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity of sequencing and deletion/duplication unknown but expected to detect the vast majority of mutations
- Analytical sensitivity/specificity – 99%

Results

- Detection of 2 pathogenic *PLOD1* mutations on opposite chromosomes predicts EDS VI
- When one or no *PLOD1* mutations are detected in a clinically affected individual, individual may have *PLOD1* mutations 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 mutations
  - Deep intronic mutations
  - 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