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
  o Regulatory region mutations
  o Deep intronic mutations
  o Breakpoints of large deletions/duplications
  o Large deletions/duplications of exon 9
  o Large deletions/duplications of exons 1 and 5 may not be detected based on breakpoints of the rearrangement