Ichthyosis Vulgaris (*FLG*)

Indications for Ordering

- Confirm diagnosis of ichthyosis vulgaris
- Differentiate vulgaris from other forms of ichthyosis

Test Description

Multiplex polymerase chain reaction followed by fluorescence monitoring using hybridization probes to test for the c.1501C>T (R501X) and c.2282del4 variants in the *FLG* gene

Tests to Consider

Filaggrin (*FLG*) 2 Mutations 2007883

Disease Overview

Prevalence

- 1/250-400 Caucasians
- 7-10% of Caucasians have *FLG* gene variant
- 10-20% of children in industrialized countries have atopic dermatitis
  - 25-50% have *FLG* gene variant

Symptoms

- Ichthyosis vulgaris is most common form of ichthyosis
  - Frequently associated with keratosis pilaris and atopic disease
    - Atopic dermatitis (eczema), allergic rhinitis, and asthma
- Common presentations
  - Fine scaling on forearms, upper arms, lower legs, and abdomen
  - Dry, rough, thick, or flaky skin
  - Palms of the hands and soles of the feet may show hyperlinearity
  - Infection may form in cracked, dry skin
- Symptoms highly variable
  - May be asymptomatic
  - Symptoms vary with environmental conditions
  - Severe cases – scaling may interfere with sweating, resulting in heat intolerance

Physiology

- Filaggrin is expressed in the granular layer of the skin
  - Involved in barrier functions (eg, protection from allergens, regulation of pH, and prevention of water loss)
- Absence of filaggrin protein results in ichthyosis vulgaris
  - May allow allergens to enter the body
  - Allergic response may generate atopic march (eg, eczema, asthma)

Genetics

Gene – *FLG*

Inheritance

- Autosomal dominant with incomplete penetrance
- *FLG* variants on each allele (homozygous or compound heterozygous)
  - Associated with more severe clinical presentation
- Heterozygous loss-of-function *FLG* variants
  - Associated with less severe clinical presentation
  - May be clinically asymptomatic

Penetrance

- Incomplete
- Very high in individuals with two *FLG* loss-of-function variants

Variants

- Two most common loss-of-function variants in Caucasians
  - c.1501C>T (R501X)
  - c.2282del4

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – ~80% in Caucasians
- Analytical sensitivity/specificity – 99%

Results

- Positive
  - Variants tested – c.1501C>T (R501X) and c.2282del4
    - One variant detected – increased risk for ichthyosis vulgaris
    - Two variants detected (homozygous or compound heterozygous)
      - Greatly increased risk for ichthyosis vulgaris
      - Increased risk for keratosis pilaris and atopic disease
- Negative
  - No *FLG* gene variant detected

Limitations

- Only *FLG* gene variants c.1501C>T (R501X) and c.2282del4 are evaluated
- Diagnostic errors can occur due to rare sequence variations