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
  o 25-50% have FLG gene variant

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

Physiology
• Filaggrin is expressed in the granular layer of the skin
  o Involved in barrier functions (eg, protection from allergens, regulation of pH, and prevention of water loss)
• Absence of filaggrin protein results in ichthyosis vulgaris
  o May allow allergens to enter the body
  o 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)
  o Associated with more severe clinical presentation
• Heterozygous loss-of-function FLG variants
  o Associated with less severe clinical presentation
  o 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
  o c.1501C>T (R501X)
  o 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