TACI-Associated Common Variable Immunodeficiency, *TNFRSF13B* Sequencing

**Indications for Ordering**

Identify pathogenic *TNFRSF13B* gene variants (transmembrane activator, calcium modulator, and cyclophilin ligand interactor [TACI] defect) in individuals with
- Common variable immunodeficiency (CVID) clinical phenotype
- Symptomatic selective IgA deficiency (IgAD)

**Test Description**

Bidirectional sequencing of entire coding region and intron/exon boundaries of *TNFRSF13B* gene

**Tests to Consider**

**Primary test**

*TACI-Associated Common Variable Immunodeficiency (TNFRSF13B) Sequencing 2007569*
- Identify pathogenic *TNFRSF13B* variants in individuals with clinical phenotype for CVID or symptomatic selective IgAD

**Related tests**

Initial screening tests for immunodeficiency
- Immunoglobulins (IgA, IgG, IgM), Quantitative 0050630
- Immunoglobulin G Subclasses (1,2,3,4) 0050577
- B-Cell Memory and Naive Panel 2008901
- Lymphocyte Subset Panel 7 – Congenital Immunodeficiencies 0095899

Genetic test
- Familial Mutation, Targeted Sequencing 2001961
  - Useful when a pathogenic familial variant identifiable by sequencing is known
- Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication 2011156

**Disease Overview**

**CVID**

**Prevalence**
- 1/25,000-60,000 Caucasians
- 1/100,000 Japanese

**Age of onset** – bimodal peaks (childhood, 10-29 years)

**Symptoms**
- Hypogammaglobulinemia with impaired ability to produce antibodies after vaccination
- Recurrent respiratory tract infections
- Intermittent or chronic diarrhea
- Splenomegaly
- Lymphadenopathy
- Nodal lymphoid hyperplasia of small bowel
- Autoimmune symptoms are common
  - Autoimmune cytopenias
    - Hemolytic anemia
    - Thrombocytopenia
  - Rheumatoid arthritis
  - Vitiligo
  - Alopecia
  - Granulomatous disease
- Associated with increased risk of lymphoid and nonlymphoid malignancies

**IgAD**

**Prevalence**
- ~1/700 Caucasians

**Symptoms**
- Most individuals are asymptomatic
  - IgAD may precede CVID
  - IgAD and CVID can co-occur in first-degree relatives

**Physiology**
- TACI is involved in pathogenesis of disease
  - Found on
    - B cells
    - Plasma cells
  - Interacts with
    - B-cell activating factor (BAFF)
    - A proliferation-inducing ligand (APRIL)
  - Mediates antibody class-switch recombination
  - Prevents autoimmunity
  - Regulates
    - Survival of antibody secreting cells
    - B-cell activation
    - Proliferation
    - Differentiation
Genetics

Gene – TNFRSF13B

Inheritance – variable

Penetrance – incomplete, suggested by
- Ala181Glu and Cys104Arg identified in
  o Healthy controls
  o Asymptomatic first-degree relatives

Function
Encodes for TACI receptor

Variants
- ~30 TNFRSF13B variants identified in patients with
  o CVID
  o IgG subclass deficiency
  o IgAD
  o Good syndrome
- Variants statistically significant associated with CVID
  o p.Cys104Arg
  o p.Ala181Glu
  o p.Leu69ThrfsX12
- Patients with Smith-Magenis syndrome with chromosome 17p11.2 microdeletion
  o Haploinsufficient for TNFRSF13B
  o Impaired humoral immunity
- No genotype/phenotype correlations have been observed

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity – ≤10%
- Analytical sensitivity/specificity – 99%

Results
- Positive
  o Detection of one or two TNFRSF13B variants
  ▪ Confers disease susceptibility
  ▪ Association with CVID or related deficiencies
- Negative
  o No detection of TNFRSF13B variants
  o Does not rule out CVID or related deficiencies
- Inconclusive – although TNFRSF13B variant was detected, whether variant affects protein function is unknown

Limitations
- Not detected
  o Deep intronic or regulatory region variants
  o Large deletions and/or duplications
- May detect variants of unknown significance
- Rare diagnostic errors may occur due to primer- or probe-site variants
- Variants in CD19, CD81, ICOS, MS4A1, TNFRSF13C, or other genes implicated in CVID will not be evaluated

References