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 (35 Genes) and Deletion/Duplication (26 Genes) 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
- Nodular 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**

- One of the most common primary immunodeficiencies
- ~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
  - Healthy controls
  - Asymptomatic first-degree relatives

Function
Encodes for TACI receptor

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

Test Interpretation

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

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

Limitations
- Not detected
  - Deep intronic or regulatory region variants
  - 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