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

Romberg N, Chamberlain N, et al. CVID-associated TACI mutations affect autoreactive B cell selection and activation. J Clin Invest. 2013;123:4283-4293