TACI-Associated Common Variable Immunodeficiency, TNFRSF13B Sequencing

TACI protein is a B-cell-specific tumor necrosis factor encoded by the TNFRSF13B gene. Both biallelic and monoallelic variants in this gene have been identified in patients with common variable immunodeficiency (CVID). Clinical phenotypes associated with TNFRSF13B gene variants are highly variable and many individuals are asymptomatic. Monoallelic or biallelic pathogenic TNFRSF13B variants confer increased risk for developing hypogammaglobulinemia/CVID.

DISEASE OVERVIEW

Common Variable Immunodeficiency

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

IgA Deficiency

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

Tests to Consider

TACI-Associated Common Variable Immunodeficiency (TNFRSF13B) Sequencing 2007569
Method: Polymerase Chain Reaction/Sequencing
Identify pathogenic TNFRSF13B variants in individuals with clinical phenotype for CVID or symptomatic selective IgAD

For initial screening tests for immunodeficiency and additional genetic tests, see Related Tests.
• 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
Autosomal dominant or autosomal recessive

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
- Diagnostic errors can occur due to rare sequence variations
- Variants in CD19, CD81, ICOS, MS4A1, TNFRSF13C, or other genes implicated in CVID will not be evaluated

**REFERENCES**


**RELATED INFORMATION**

Common Variable Immune Deficiency Syndromes - CVID

**RELATED TESTS**

- **Immunoglobulins (IgA, IgG, IgM), Quantitative** 0050630
  Method: Quantitative Nephelometry
- **Immunoglobulin G Subclasses (1, 2, 3, 4) 0050577**
  Method: Quantitative Nephelometry
- **B-Cell Memory and Naive Panel 2008901**
  Method: Flow Cytometry
- **Lymphocyte Subset Panel 7 - Congenital Immunodeficiencies 0095899**
  Method: Quantitative Flow Cytometry
- **Familial Mutation, Targeted Sequencing 2001961**
  Method: Polymerase Chain Reaction/Sequencing
- **Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication 2011156**
  Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray