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
- 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

Penetration

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 Subset Analysis 3002216
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