Primary Antibody Deficiency Panel

Indications for Ordering

Confirm suspected primary antibody deficiency in individual with clinical symptoms

Test Description

- Targeted capture of all coding exons and intron/exon boundaries followed by massively parallel sequencing
  - Reported variants are confirmed by Sanger sequencing
- Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization (CGH) array

Tests to Consider

Primary test

Primary Antibody Deficiency Panel, Sequencing (35 Genes) and Deletion/Duplication (26 Genes) 2011156

- Preferred test for individuals with clinical phenotype of
  - Primary antibody deficiency
  - Agammaglobulinemia
  - Hyper IgM syndrome
  - Common variable immunodeficiency (CVID)
  - Atypical severe combined immunodeficiency
  - Other related immunodeficiency disorder

Related tests

Initial screening for immunodeficiency

- CBC with Platelet Count and Automated Differential 0040003
- Lymphocyte Subset Panel 7 - Congenital Immunodeficiencies 0095899
- B-Cell Memory and Naive Panel 2008901
- Lymphocyte Antigen and Mitogen Proliferation Panel with Cytokine Response 2013117
- Immunoglobulins (IgA, IgG, IgM), Quantitative 0050630
- Immunoglobulin G Subclasses (1, 2, 3, 4) 0050577
- Familial Mutation, Targeted Sequencing 2001961

Disease Overview

Incidence/prevalence – see table

Age of onset

- Agammaglobulinemia and hyper IgM syndrome – usually within first two years of life
- CVID – across all ages, but mostly in the second and third decade

Symptoms

- Unusual, opportunistic, or severe infections
  - Most common organisms
    - *Histoplasma capsulatum*
    - *Candida* spp
    - *Cryptococcus neoformans*
- Common sites
  - Respiratory – pneumonia/empyema
  - Gastrointestinal
    - Diarrhea – intermittent or chronic
  - Skin
  - Head and neck
    - Oral ulcers/gingivitis/stomatitis
    - Conjunctivitis
    - Otitis media
    - Lymphadenopathy
  - CNS
    - Meningitis
- Other symptoms
  - Sepsis
  - Failure to thrive
  - Splenomegaly
  - Autoimmune conditions
  - Neutropenia
  - Granulomatous disease
  - Associated with increased risk of lymphoid and nonlymphoid malignancies

Genetics

Genes – see table

Mutations

- Mutations in multiple genes appear to cause overlapping phenotypes
- Other genetic and/or environmental factors may influence severity of clinical phenotype

Test Interpretation

Clinical sensitivity

- CVID – 20%
- Hyper IgM syndrome – 75-80%
- Agammaglobulinemia – 90%

Results

- Positive
  - Two pathogenic mutations on opposite chromosomes detected in a gene with autosomal recessive (AR) inheritance
    - Confirms diagnosis of primary antibody deficiency
  - One pathogenic mutation in an X-linked gene detected in males, or one pathogenic mutation in an autosomal dominant gene detected in males or females
    - Confirms diagnosis of primary antibody deficiency
  - One pathogenic mutation detected in an AR gene
    - Individual is a carrier
  - One pathogenic mutation detected in an X-linked gene in females
    - Individual is a carrier
- Negative – no pathogenic mutation detected
  - Reduces, but does not exclude, a diagnosis of primary antibody deficiency
- Inconclusive – variants of uncertain clinical significance may be identified

Limitations

- Not determined or evaluated
  - Mutations in genes not included on the panel
  - Deep intronic and regulatory region mutations
  - Breakpoints for large deletions/duplications
  - Translocations
- Deletions/duplications will not be detected in
  - *IKBKG, LRBA, LRRC8A, PIK3CD, PIK3R1, PLCG2, PRKCD, SH2D1A*, or *XIAP/BIRC4* gene
- Small deletions or insertions may not be detected
- Diagnostic errors can occur due to rare sequence variations
- Lack of a detectable gene mutation does not exclude a diagnosis of primary antibody deficiency

Gene Symbol	Gene Name	NM #	OMIM #	Phenotype/Disorder	Inh.*	Incidence/ Prevalence
ADA	Adenosine deaminase	NM_000022	608958	SCID T-cell/B-cell/NK-cell negative, due to ADA deficiency SCID due to ADA deficiency – delayed onset	AR	1-9/million live births Higher in populations with high degree of consanguinity
AICDA	Activation-induced cytidine deaminase	NM_020661	605257	Immunodeficiency with hyper IgM, type 2	AR	Unknown
ATM	Ataxia telangiectasia mutated (includes complementation groups A, C and D)	NM_000051	607585	Ataxia telangiectasia	AR	1/40,000 – 100,000 Varies with degree of consanguinity
BLNK	B-cell linker	NM_013314	604515	Agammaglobulinemia	AR	Unknown
BTK	Bruton agammaglobulinemia tyrosine kinase	NM_000061	300300	Agammaglobulinemia and isolated growth hormone deficiency X-linked agammaglobulinemia	XL	1-9/million
CD19	CD19 antigen	NM_001770	107265	CVID	AR	Unknown
CD40	CD40 antigen	NM_001250	109535	Immunodeficiency with hyper IgM	AR	Unknown
CD40LG	CD40 ligand (TNF superfamily, member 5, hyper IgM syndrome, TNFSF5)	NM_000074	300386	Immunodeficiency with X-linked hyper IgM	XL	2/million males
CD79A	CD79A antigen, Iga	NM_001783	112205	Agammaglobulinemia	AR	Unknown
CD79B	CD79B molecule, Igb	NM_000626	147245	Agammaglobulinemia	AR	Unknown
CD81	CD81 molecule	NM_004356	186845	CVID	AR	Unknown
CR2	Complement component (3d/Epstein Barr virus) receptor 2	NM_001006658	120650	CVID	AR	Unknown
ICOS	Inducible T-cell costimulator	NM_012092	604558	CVID	AR	Unknown
IGHM	Immunoglobulin heavy constant mu	cDNA:X17115	147020	Agammaglobulinemia	AR	Unknown
IGLL1	Immunoglobulin lambda-like polypeptide 1, l5	NM_020070	146770	Agammaglobulinemia	AR	Unknown
IKBKG	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma, NEMO	NM_001099857	300248	Hypohidrotic ectodermal dysplasia with immune deficiency Anhidrotic ectodermal, dysplasia, lymphedema, and immunodeficiency Immunodeficiency 33 syndrome Incontinentia pigmenti Recurrent isolated invasive pneumococcal disease	XL	Unknown

Gene Symbol	Gene Name	NM #	OMIM #	Phenotype/Disorder	Inh.*	Incidence/ Prevalence
LRBA	LPS-responsive vesicle trafficking, beach and anchor containing	NM_006726	606453	CVID with autoimmunity	AR	Unknown
LRRC8A	Leucine rich repeat containing 8 family, member A	NM_019594	608360	Agammaglobulinemia	AD	Unknown
MRE11A	Meiotic recombination 11 homologue A	NM_005591	600814	Ataxia-telangiectasia-like disorder	AR	Unknown
MS4A1	Membrane-spanning 4-domains, subfamily A, member 1	NM_152866	112210	CVID	AR	Unknown
NBN/NBS1	Nibrin	NM_002485	602667	Nijmegen breakage syndrome	AR	~1/100,000
NFKB2	Nuclear factor of kappa light polypeptide gene enhancer in B cells 2	NM_002502	164012	CVID	AD	Unknown
NFKBIA	Nuclear factor of kappa light polypeptide gene enhancer in B-cell inhibitors, alpha	NM_020529	164008	Anhidrotic ectodermal dysplasia with T-cell immunodeficiency	AD	Unknown
PIK3CD	Phosphoinositide-3-kinase, catalytic, delta polypeptide	NM_005026	602839	Immunodeficiency 14 syndrome	AD	Unknown
PIK3R1	Phosphoinositide-3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)	NM_181523	171833	Agammaglobulinemia	AR	Unknown
PLCG2	Phospholipase C gamma 2	NM_002661	600220	Autoinflammation, antibody deficiency, and immune dysregulation syndrome Familial cold autoinflammatory syndrome	AD	Rare
PRKCD	Protein kinase C, delta	NM_006254	176977	CVID	AR	Unknown
PTPRC	Protein tyrosine phosphatase, receptor type C	NM_002838	151460	SCID, T-cell negative, B-cell/NK-cell positive	AR	Unknown
RAG2	Recombination activating gene 2	NM_000536	179616	SCID, T-cell/B-cell negative, NK-cell positive Omenn syndrome Combined cellular and humoral immune defects with granulomas	AR	~1/100,000 live births
SH2D1A	SH2 domain protein 1A, Duncan's disease (lymphoproliferative syndrome)	NM_002351	300490	X-linked lymphoproliferative syndrome	XL	1/million males
TNFRSF13B	Tumour necrosis factor receptor superfamily, member 13b, TACI	NM_012452	604907	CVID, immunoglobulin A deficiency	AD or AR	Unknown
TNFRSF13C	Tumour necrosis factor receptor superfamily, member 13C, BAFFR	NM_052945	606269	CVID	AR or AD	Unknown
UNG	Uracil DNA glycosylase	NM_080911	191525	Immunodeficiency with hyper IgM syndrome	AR	Unknown
VAV1	Vav1 guanine nucleotide exchange factor	NM_005428	164875	CVID	AD	Unknown
XIAP/BIRC4	X-linked inhibitor of apoptosis	NM_001167	300079	X-linked lymphoproliferative syndrome	XL	1/million males
*Inh. = inheritance, AD = autosomal dominant, AR = autosomal recessive, XL = X-linked						