Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication

Last Literature Review: May 2022 Last Update: October 2023

Primary antibody deficiency (PAD) syndromes are a group of rare genetic disorders affecting antibody (immunoglobulin) production. Three categories of primary antibody deficiencies include common variable immunodeficiency (CVID), agammaglobulinemia, and hyper-IgM syndrome. Symptoms may include unusual, opportunistic, or severe infections that typically affect multiple organs/organ systems. Other signs may include sepsis, failure to thrive, splenomegaly, autoimmune conditions, and neutropenia. Agammaglobulinemia and hyper-IgM syndrome usually occur within the first 2 years of life. CVID manifests at all ages, but most often in the second and third decade. Molecular testing is used to determine the genetic etiology of PAD in affected individuals.

Genetics

Genes

See Genes Tested table for genes included in the panel.

Incidence

Estimated at 1/10,000

Inheritance

X-linked, autosomal dominant, or autosomal recessive, depending on the causative gene

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for the detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

- Agammaglobulinemia, 90%[1]
- Hyper-IgM syndrome, 75-80%[2]
- CVID, 20%[3]

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a PAD syndrome.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *NFKBIA* and *TCF3*
  - Translocations
  - The following exons are not sequenced due to technical limitations of the assay:
    - *CXCR4* (NM_001348056, NM_001348059) exon(s) 2
    - *DCLRE1C* (NM_001350965) exon(s) 15
    - *DCLRE1C* (NM_001350966) exon(s) 13
    - *DCLRE1C* (NM_001350967) exon(s) 16
    - *PRKCD* (NM_001354676, NM_001354678) exon(s) 1
    - *XIAP* (NM_001167, NM_001204401, NM_001378590, NM_001378591, NM_001378592) exon(s) 4
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:
    - *ADA* (NM_000022, NM_001322051) 1; *CXCR4* (NM_001348056) 2; *CXCR4* (NM_001348059) 2; *DCLRE1C* (NM_001033855) 4-9; *DCLRE1C* (NM_001033857, NM_001289077) 6-10; *DCLRE1C* (NM_001033858, NM_001289079) 7-11; *DCLRE1C* (NM_001289076, NM_001289078) 3-7; *DCLRE1C* (NM_001350965) 4-9,15; *DCLRE1C* (NM_001350966) 3-7,13; *DCLRE1C* (NM_001350967) 6-10,16; *DCLRE1C* (NM_022487) 4-8; *HELLS*

(NM_018063, NM_001289067, NM_001289068, NM_001289069, NM_001289070, NM_001289072) 7; *HELLS* (NM_001289071) 8; *HELLS* (NM_001289073) 6; *IGLL* (NM_152855) 2; *IKZF1* (NM_001291846, NM_001291847) 4; *MOGS* (NM_001146158) 2; *PRKCD* (NM_001354676, NM_001354678) 1; *XIAP* (NM_001167, NM_001204401, NM_001378590, NM_001378592) 4; *XIAP* (NM_001378591) 5

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ADA	608958	Adenosine deaminase deficiency, partial Severe combined immunodeficiency due to ADA deficiency	AR
ADA2	607575	Sneddon syndrome Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome	AR
AICDA	605257	Immunodeficiency with hyper-IgM, type 2	AR
ATM	607585	Ataxia-telangiectasia	AR
ATP6AP1	300197	Immunodeficiency 47	XL
BLNK	604515	Agammaglobulinemia	AR
BTK	300300	Agammaglobulinemia, X-linked 1 Isolated growth hormone deficiency, type III, with agammaglobulinemia	XL
CARD11	607210	Immunodeficiency 11	AR
		B-cell expansion with NFKB and T-cell energy Immunodeficiency 11B with atopic dermatitis	AD
CD19	107265	CVID 3	AR
CD27	186711	Lymphoproliferative syndrome 2	AR
CD40	109535	Immunodeficiency with hyper-IgM, type 3	AR
CD40LG	300386	Immunodeficiency, X-linked, with hyper-IgM	XL
CD70	602840	Lymphoproliferative syndrome 3	AR
CD79A	112205	Agammaglobulinemia 3	AR
CD79B	147245	Agammaglobulinemia 6	AR
CDCA7	609937	Immunodeficiency-centromeric instability-facial anomalies syndrome 3	AR
CR2	120650	CVID 7	AR

AD, autosomal dominant; AR, autosomal recessive; SCID, severe combined immunodeficiency; XL, X-linked

Gene	MIM Number	Disorder	Inheritance
CTLA4	123890	Immune dysregulation with autoimmunity, immunodeficiency, and lymphoproliferation	AD
CXCR4	162643	Whim syndrome Myelokathexis, isolated	AD
DCLRE1C	605988	SCID, Athabascan type Omenn syndrome	AR
DNMT3B	602900	Immunodeficiency-centromeric instability-facial anomalies syndrome 1	AR
GATA2	137295	Immunodeficiency 21 Emberger syndrome	AD
HELLS	603946	Immunodeficiency-centromeric instability-facial anomalies syndrome 4	AR
ICOS	604558	CVID 1	AR
IGHM	147020	Agammaglobulinemia 1	AR
IGLL1	146770	Agammaglobulinemia 2	AR
IKZF1	603023	CVID 13	AD
IL21R	605383	IgE, elevated level of	AD
		Immunodeficiency 56	AR
KDM6A	300128	Kabuki syndrome 2	XL
KMT2D	602113	Kabuki syndrome 1	AD
LRBA	606453	CVID 8 with autoimmunity	AR
MOGS	601336	Congenital disorder of glycosylation, type IIB	AR
MS4A1	112210	CVID 5	AR
NBN	602667	Nijmegen breakage syndrome Aplastic anemia Leukemia, acute lymphoblastic	AR
NFKB1	164011	CVID 12	AD
NFKB2	164012	CVID 10	AD

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Gene	MIM Number	Disorder	Inheritance
NFKBIA	164008	Ectodermal dysplasia and immunodeficiency 2	AD
PIK3CD	602839	Immunodeficiency 14A, autosomal dominant	AD
		Immunodeficiency 14B, autosomal recessive	AR
PIK3CG	601232	Hyper-IgM	AD
PIK3R1	171833	Immunodeficiency 36 SHORT syndrome	AD
PLCG2	600220	Autoinflammation, antibody deficiency, and immune dysregulation Familial cold autoinflammatory syndrome 3	AD
PRKCD	176977	Autoimmune lymphoproliferative syndrome, type III	AR
RAC2	602049	Immunodeficiency 73A and 73B with defective neutrophil chemotaxis and leukocytosis	AD
RAG1	179615	Combined cellular and humoral immune defects with granulomas SCID, B-cell negative Omenn syndrome Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity	AR
RAG2	179616	Combined cellular and humoral immune defects with granulomas SCID, B-cell negative Omenn syndrome	AR
RNF168	612688	RIDDLE syndrome	AR
SH2D1A	300490	Lymphoproliferative syndrome, X-linked, 1	XL
STAT3	102582	Hyper-IgE recurrent infection syndrome Autoimmune disease, multisystem, infantile-onset 1	AD
TCF3	147141	Agammaglobulinemia 8A, autosomal dominant	AD
		Agammaglobulinemia 8B, autosomal recessive	AR
TNFRSF13B	604907	CVID 2 Immunoglobulin A deficiency	AR, AD
TRNT1	612907	Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay Retinitis pigmentosa and erythrocytic microcytosis	AR
TTC37	614589	Trichohepatoenteric syndrome 1	AR

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Gene	MIM Number	Disorder	Inheritance
UNG	191525	Immunodeficiency with hyper-IgM syndrome, type 5	AR
XIAP	300079	X-linked lymphoproliferative syndrome 2	XL
ZBTB24	614064	Immunodeficiency-centromeric instability-facial anomalies syndrome 2	AR

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References

1. Conley ME, Mathias D, Treadaway J, et al. Mutations in btk in patients with presumed X-linked agammaglobulinemia. *Am J Hum Genet*. 1998;62(5):1034-1043.

2. Conley ME, Dobbs AK, Farmer DM, et al. Primary B cell immunodeficiencies: comparisons and contrasts. *Annu Rev Immunol*. 2009;27:199-227.

3. de Valles-Ibáñez G, Esteve-Solé A, Piquer M, et al. Evaluating the genetics of common variable immunodeficiency: monogenetic model and beyond. *Front Immunol*. 2018;9:636.

Related Information

Common Variable Immunodeficiency
Primary Immunodeficiency Diseases - Immunoglobulin Disorders

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