# Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication

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.

## Tests to Consider

**Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication 2011156**

**Method:** Massively Parallel Sequencing/Sequencing

Determine the genetic etiology of a primary antibody deficiency in affected individuals.

**Familial Targeted Sequencing 3005867**

**Method:** Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member's test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.

See Related Tests for initial screening tests for immunodeficiency and mutation testing for a known familial pathogenic variant.

## 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 detection of large (single exon-level or larger) deletions and duplications.
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- 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]<br>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 |
|---|---|---|---|

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

| Gene | MIM Number | Disorder | Inheritance |
|---|---|---|---|
| *ADA* | 608958 | Adenosine deaminase deficiency, partial<br>Severe combined immunodeficiency due to ADA deficiency | AR |
| *ADA2* | 607575 | Sneddon syndrome<br>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<br>Isolated growth hormone deficiency, type III, with agammaglobulinemia | XL |
| *CARD11* | 607210 | Immunodeficiency 11 | AR |
| | | B-cell expansion with NFKB and T-cell energy<br>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 |
| *CTLA4* | 123890 | Immune dysregulation with autoimmunity, immunodeficiency, and lymphoproliferation | AD |
| *CXCR4* | 162643 | Whim syndrome<br>Myelokathexis, isolated | AD |
| *DCLRE1C* | 605988 | SCID, Athabascan type<br>Omenn syndrome | AR |
| *DNMT3B* | 602900 | Immunodeficiency-centromeric instability-facial anomalies syndrome 1 | AR |

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

| Gene | MIM Number | Disorder | Inheritance |
|---|---|---|---|
| *GATA2* | 137295 | Immunodeficiency 21<br>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<br>Aplastic anemia<br>Leukemia, acute lymphoblastic | AR |
| *NFKB1* | 164011 | CVID 12 | AD |
| *NFKB2* | 164012 | CVID 10 | AD |
| *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<br>SHORT syndrome | AD |
| *PLCG2* | 600220 | Autoinflammation, antibody deficiency, and immune dysregulation<br>Familial cold autoinflammatory syndrome 3 | AD |
| *PRKCD* | 176977 | Autoimmune lymphoproliferative syndrome, type III | AR |

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| Gene | MIM Number | Disorder | Inheritance |
|---|---|---|---|
| *RAC2* | 602049 | Immunodeficiency 73A and 73B with defective neutrophil chemotaxix and leukocytosis | AD |
| *RAG1* | 179615 | Combined cellular and humoral immune defects with granulomas<br>SCID, B-cell negative<br>Omenn syndrome<br>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<br>SCID, B-cell negative<br>Omenn syndrome | AR |
| *RNF168* | 612688 | RIDDLE syndrome | AR |
| *SH2D1A* | 300490 | Lymphoproliferative syndrome, X-linked, 1 | XL |
| *STAT3* | 102582 | Hyper-IgE recurrent infection syndrome<br>Autoimmune disease, multisystem, infantile-onset 1 | AD |
| *TCF3* | 147141 | Agammaglobulinemia 8A, autosomal dominant | AD |
| | | Agammaglobulinemia 8B, autosomal recessive | AR |
| *TNFRSF13B* | 604907 | CVID 2<br>Immunoglobulin A deficiency | AR, AD |
| *TRNT1* | 612907 | Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay<br>Retinitis pigmentosa and erythrocytic microcytosis | AR |
| *TTC37* | 614589 | Trichohepatoenteric syndrome 1 | AR |
| *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 |

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

## 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.


## Additional Resources

Johnson J, Filipovich AH, Zhang K. X-linked hyper IgM syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Updated: Jan 2013; Accessed: Apr 2022]

Picard C, Gaspar B, Al-Herz W, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee report on inborn errors of immunity. *J Clin Immunol.* 2018;38(1):96-128.

Smith CIE, Berglöf A. X-linked agammaglobulinemia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2020. [Updated: Aug 2016; Accessed: Apr 2022]

Winkelstein JA, Marino MC, Ochs H, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. *Medicine (Baltimore)* . 2003;82(6):373-384.

## Related Information

Common Variable Immune Deficiency Syndromes
Immunodeficiency Evaluation for Chronic Infections in Adults and Older Children Testing Algorithm
Immunodeficiency Evaluation for Chronic Infections in Infants and Children Testing Algorithm
Inherited T-Cell Deficiency Disorders
Neutropenia
Primary Immunodeficiency Diseases - Immunoglobulin Disorders
Severe Combined Immunodeficiencies - SCID

## Related Tests

Lymphocyte Subset Panel 7 - Congenital Immunodeficiencies 0095899

**Method:** Quantitative Flow Cytometry

B Cell Subset Analysis 3002216

**Method:** Flow Cytometry

Lymphocyte Antigen and Mitogen Proliferation Panel 0096056

**Method:** Cell Culture

Lymphocyte Proliferation, Antigen-Mitogen Panel by Flow Cytometry (24-Hr Critical Room Temp) 3001319

**Method:** Cell Culture/Flow Cytometry

Immunoglobulins (IgA, IgG, IgM), Quantitative 0050630

**Method:** Quantitative Immunoturbidimetry

Immunoglobulin G Subclasses (1, 2, 3, 4) 0050577

**Method:** Quantitative Immunoturbidimetry

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review May 2022 | Last Update November 2022