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Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication

Primary antibody deficiency (PAD) syndromes are a group of rare genetic disorders affecting antibody (immunoglobulin) production. They include common variable immunodeficiency (CVID) disorders, agammaglobulinemia, and hyper-IgM syndrome. Molecular testing is used to determine the genetic etiology of PAD in affected individuals.

DISEASE OVERVIEW

Symptoms

- Unusual, opportunistic, or severe infections
- Infections typically affect multiple organs/organ systems:
  - Lungs
    - Pneumonia/empyema
  - Gastrointestinal
    - Intermittent or chronic diarrhea
  - Skin (infections)
  - Head and neck
    - Oral ulcers/gingivitis/stomatitis
    - Conjunctivitis
    - Otitis media
    - Lymphadenopathy
  - Central nervous system
    - Meningitis
- Other signs
  - Sepsis
  - Failure to thrive
  - Splenomegaly
  - Autoimmune conditions
  - Neutropenia
  - Granulomatous disease
  - Lymphoid and nonlymphoid malignancies

Age of Onset

- 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.

Incidence

Estimated at 4.6/100,000

Inheritance

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

TEST INTERPRETATION

See Genes Tested table for genes included in the panel.

Clinical Sensitivity

- Agammaglobulinemia, 90% (Conley, 1998)
- Hyper-IgM syndrome, 75-80% (Conley, 2009)
- CVID, 20% (Guillem, 2018)

TESTS TO CONSIDER

Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication 2011156
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

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

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

Indications for Ordering

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

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 *ADA2, ATP6AP1, CARD11, CD27, CD70, CDCA7, CTLA4, CXCR4, DNMT3B, GATA2, HELLS, IKBKG, IL21, IL21R, INO80, KDM6A, KMT2D, LRBA, LRRC8A, MALT1, MAP3K14, MOGS, NFKB1, PIK3CD, PIK3CG, PIK3R1, PLCG2, PRKCD, RNF168, SH2D1A, TCF3, TNFSF12, TRNT1, TTC37, XIAP, ZBTB24*
  - Noncoding transcripts
  - Translocations
  - The following exon is not sequenced due to technical limitations of the assay:
    - *CXCR4* (NM_001348056) 2
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1 kb in the targeted genes by array
  - 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:

Gene	Exon(s)
ADA	(NM_000022) 1
AICDA	(NM_020661) 5
BTK	(NM_000061) 11; (NM_001287344) 1
CD79B	(NM_000626) 2
CR2	(NM_001006658) 1
DCLRE1C	(NM_001033855) 4, 6, 8; (NM_001289076) 3
IGLL1	(NM_020070) 2, 3; (NM_152855) 2
NFKB2	(NM_001077494) 21
RAC2	(NM_002872) 2
TNFRSF13B	(NM_012452) 2
TNFRSF13C	(NM_052945) 1

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

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

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ADA	608958	SCID, T-cell/B-cell/NK-cell negative	AR

Gene	MIM Number	Disorder	Inheritance
ADA2	607575	Polyarteritis nodosa Vasculitis Hypogammaglobulinemia	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	Xl 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	AR
CD27	186711	Lymphoproliferative syndrome 2	AR
CD40	109535	Immunodeficiency with hyper-IgM, type 3	AR
CD40LG	300386	Immunodeficiency with hyper-IgM, type 1	XL
CD70	602840	Hypogammaglobulinemia EBV susceptibility	AR
CD79A	112205	Agammaglobulinemia 3	AR
CD79B	147245	Agammaglobulinemia 6	AR
CD81	186845	CVID	AR
CDCA7	609937	Immunodeficiency-centromeric instability-facial anomalies syndrome	AR
CR2	120650	CVID	AR
CTLA4	123890	Autoimmune lymphoproliferative syndrome, type V	AD
CXCR4	162643	Whim syndrome	AD
DCLRE1C	605988	SCID with sensitivity to ionizing Omenn syndrome	AR
DNMT3B	602900	Immunodeficiency-centromeric instability-facial anomalies syndrome	AR
GATA2	137295	Immunodeficiency 21	AD
HELLS	603946	Immunodeficiency-centromeric instability-facial anomalies syndrome	AR
ICOS	604558	CVID	AR
IGHM	147020	Agammaglobulinemia	AR
IGLL1	146770	Agammaglobulinemia	AR
IKBKG	300248	Ectodermal dysplasia, hypohidrotic, with immune deficiency Ectodermal dysplasia, anhidrotic, with immunodeficiency, Immunodeficiency without anhidrotic ectodermal dysplasia Immunodeficiency 33 Invasive pneumococcal disease, recurrent isolated, 2	XL
IKZF1	603023	CVID	AD
IL21	605384	CVID	AR
IL21R	605383	IgE responsiveness, atopic	AD
		Immunodeficiency 56	AR
INO80	610169	Hyper-IgM	AR
IRF2BP2	615332	CVID	AD
KDM6A	300128	Kabuki syndrome 1	AD
		Kabuki syndrome 2	XL

Gene	MIM Number	Disorder	Inheritance
KMT2D	602113	Kabuki syndrome 1	AD
LRBA	606453	CVID with autoimmunity	AR
LRRC8A	608360	Agammaglobulinemia	AD
MALT1	604860	Immunodeficiency 12	AR
MAP3K14	604655	Hypogammaglobulinemia	AR
MOGS	601336	Congenital disorder of glycosylation, type IIB	AR
MS4A1	112210	CVID	AR
NBN	602667	Nijmegen breakage syndrome	AR
NFKB1	164011	CVID	AD
NFKB2	164012	CVID	AD
NFKBIA	164008	Ectodermal dysplasia, anhidrotic, with T-cell immunodeficiency	AD
PIK3CD	602839	Immunodeficiency 14	AD
PIK3CG	601232	Hyper-IgM	AD
PIK3R1	171833	Agammaglobulinemia	AR AD
PLCG2	600220	Autoinflammation, antibody deficiency, and immune dysregulation, *PLCG2* associated	AD
PRKCD	176977	Autoimmune lymphoproliferative syndrome, type III	AR
RAC2	602049	Neutrophil immunodeficiency syndrome	AD
RAG1	179615	Combined cellular and humoral immune defects with granulomas SCID, T-cell negative, B-cell negative, NK-cell positive Omenn syndrome Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe	AR
RAG2	179616	Combined cellular and humoral immune defects with granulomas SCID, T-cell/B-cell negative, NK-cell positive Omenn syndrome	AR
RNF168	612688	Riddle syndrome	AR
SH2D1A	300490	Lymphoproliferative syndrome, X-linked, 1	XL
STAT3	102582	Hyper-IgE recurrent infection syndrome	AD
TCF3	147141	Agammaglobulinemia 8	AD
TNFRSF13B	604907	CVID Immunoglobulin A deficiency	AR
TNFRSF13C	606269	CVID	AR
TNFSF12	602695	Hypogammaglobulinemia	AD
TRNT1	612907	Sideroblastic anemia with B-cell immunodeficiency, periodic fevers	AR
TTC37	614589	Trichohepatoenteric syndrome 1	AR
UNG	191525	Immunodeficiency with hyper-IgM syndrome	AR
VAV1	164875	CVID	AD
XIAP	300079	X-linked lymphoproliferative syndrome	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

Conley ME, Dobbs K, Farmer DM, Kilic S, Paris K, Grigoriadou S, Coustan-Smith E, Howard V, Campana D. Primary B cell immunodeficiencies: comparisons and contrasts. Annu Rev Immunol. 2009; 27: 199-227. PubMed

Conley ME, Mathias D, Treadaway J, Minegishi Y, Rohrer J. Mutations in btk in patients with presumed X-linked agammaglobulinemia. Am J Hum Genet. 1998; 62(5): 1034-43. PubMed

de Valles-Ibáñez G, Esteve-Solé A, Piquer M, González-Navarro A, Hernandez-Rodriguez J, Laayouni H, González-Roca E, Plaza-Martin AM, Deyà-Martínez A, Martín-Nalda A, Martínez-Gallo M, García-Prat M, Del Pino-Molina L, Cuscó I, Codina-Solà M, Batlle-Masó L, Solís-Moruno M, Marquès-Bonet T, Bosch E, López-Granados E, Aróstegui JI, Soler-Palacín P, Colobran R, Yagüe J, Alsina L, Juan M, Casals F. Evaluating the Genetics of Common Variable Immunodeficiency: Monogenetic Model and Beyond. Front Immunol. 2018; 9: 636. PubMed

Johnson J, Filipovich A, Zhang K. X-Linked Hyper IgM Syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews, University of Washington, 1993-2018. Seattle, WA [Last Revision: Jan 2013; Accessed: Nov 2018]

Picard C, Gaspar B, Al-Herz W, Bousfiha A, Casanova J, Chatila T, Crow YJ, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, Ochs HD, Oksenhendler E, Puck J, Tang ML, Tangye SG, Torgerson TR, Sullivan KE. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018; 38(1): 96-128. PubMed

Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012; 119(7): 1650-7. PubMed

Smith C, Berglof A. X-Linked Agammaglobulinemia. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews, University of Washington, 1993-2018. Seattle, WA [Last Update: Aug 2016; Accessed: Nov 2018]

Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm R, Conley ME. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore). 2003; 82(6): 373-84. PubMed

RELATED TESTS

CBC with Platelet Count and Automated Differential 0040003
Method: Automated Cell Count/Differential

Lymphocyte Subset Panel 7 - Congenital Immunodeficiencies 0095899
Method: Quantitative Flow Cytometry

B-Cell Memory and Naive Panel 2008901
Method: Flow Cytometry

Lymphocyte Antigen and Mitogen Proliferation Panel with Cytokine Response 2013117
Method: Cell Culture/Multiplex Bead Assay

Immunoglobulins (IgA, IgG, IgM), Quantitative 0050630
Method: Quantitative Nephelometry

Immunoglobulin G Subclasses (1, 2, 3, 4) 0050577
Method: Quantitative Nephelometry

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

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