MAYO CLINIC

1-800-533-1710

Combined Immunodeficiency GenePanel

COMID

PATIENT NAME				ORDER NUMBER
COMID, ABNORMAL				**P409000294**
PATIENT ID X100498730	DATE OF BIRTH 10/30/1990	AGE 34 Y	SEX Male	REQUESTED BY PROVIDER UNKNOWN
COLLECTED 5/9/2025, 9:00 AM	RECEIVED 5/12/2025, 3:09 PM	REPORTED 5/13/2025, 12:21 PM		

The collected, received, and reported dates and times on the report are in the time zone of the performing location.

7028846
MCL RochesterCampus
Rochester MN 55901

CLIENT ORDER NUMBER
X100498730

CLIENT MRN
C7028846-0006415

TEST DESCRIPTION

Evaluation of 117 genes associated with combined immunodeficiency.

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variants Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
RAG1 (NM_000448.2)	c.519del p.Glu174Serfs*27 (p.E174Sfs*27) Chr11(GRCh37):g.36595373del	homozygous	PATHOGENIC

The following PATHOGENIC variant was detected:
RAG1 (NM_000448.2), chr11(GRCh37):g.36595373del, c.519del, p.Glu174Serfs*27 (p.E174Sfs*27), homozygous

No additional reportable variants were detected within all other tested genes. See the Genes Analyzed section for a complete list of genes evaluated by this assay.

INTERPRETATION

RAG1 c.519del (p.Glu174Serfs*27), PATHOGENIC
The homozygous c.519del (p.Glu174Serfs*27) deletion in the RAG1 gene (MIM:179615) is classified as pathogenic. The RAG1 gene encodes the recombination activating gene 1 protein, a key component of VDJ recombination. Pathogenic variants in this gene are associated with autosomal recessive T cell-negative (T-), B cell-negative (B-), natural killer cell-positive (NK+) severe combined immunodeficiency (SCID), autosomal recessive Omenn syndrome, and autosomal recessive combined cellular and humoral immune defects with granulomas. Patients with null variants manifest with a SCID phenotype, while hypomorphic variants in this gene are associated with leaky SCID or Omenn syndrome. RAG deficiency with higher residual recombination activity is associated more with immune dysregulation, including autoimmunity and granulomas, rather than a typical immunodeficient-phenotype. In typical SCID manifestations, there is severe B and T cell lymphopenia, with low serum immunoglobulins, and abnormal T cell function.

The c.519del (p.Glu174Serfs*27) variant has been reported in multiple individuals, primarily in the homozygous state, in

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association with Omenn syndrome, SCID, or combined immunodeficiencies (1-8). Functional studies indicate that this variant is a hypomorphic variant with residual enzyme activity; this variant results in an N-terminally truncated RAG1 protein due to the use of an alternate start site (1,3,4). The overall minor allele frequency for this variant (rs1241698978) is approximately 0.0004% with a frequency up to 0.001% in Non-Finnish European sub-populations (9,10). This result is supportive of a diagnosis of autosomal recessive T cell-negative (T-), B cell-negative (B-), natural killer cell-positive (NK+) severe combined immunodeficiency (SCID), autosomal recessive Omenn syndrome, or autosomal recessive combined cellular and humoral immune defects with granulomas for this individual. Clinical correlation is recommended.

Please note, this test is not designed to differentiate between somatic and germline variants. Thus, individuals with a clonal hematologic proliferation may have somatic variants detected by the methodology used for this testing. In addition, the presence of a clonal population comprising a high percentage of the peripheral white blood cell population may obscure germline findings, resulting in a false negative. Also, if an individual has had an allogeneic hematopoietic stem cell transplant or a recent non-leukocyte reduced blood transfusion, results may be inaccurate due to the presence of donor DNA. If the individual tested here has a clonal hematologic disorder, submission of an alternate specimen type (e.g. skin biopsy or fibroblast culture) for repeat genetic testing may be useful to assess for germline variants. Clinical correlation is recommended.

Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family.

FOLLOW-UP OPTION(S)
Familial Testing:
If relevant, genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:
1) Noordzij JG, Verkaik NS, Hartwig NG, de Groot R, van Gent DC, van Dongen JJ. N-terminal truncated human RAG1 proteins can direct T-cell receptor but not immunoglobulin gene rearrangements. Blood. 2000;96(1):203-209. (PMID 10891452)
2) de Villartay JP, Lim A, Al-Mousa H, et al. A novel immunodeficiency associated with hypomorphic RAG1 mutations and CMV infection. J Clin Invest. 2005;115(11):3291-3299. doi:10.1172/JCI25178 (PMID 16276422)
3) Lee YN, Frugoni F, Dobbs K, et al. A systematic analysis of recombination activity and genotype-phenotype correlation in human recombination-activating gene 1 deficiency. J Allergy Clin Immunol. 2014;133(4):1099-1108. doi:10.1016/j.jaci.2013.10.007 (PMID 24290284)
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5) Cifaldi C, Brigida I, Barzaghi F, et al. Targeted NGS Platforms for Genetic Screening and Gene Discovery in Primary Immunodeficiencies [published correction appears in Front Immunol. 2019 May 31;10:1184. doi:

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10.3389/fimmu.2019.01184.]. Front Immunol. 2019;10:316. Published 2019 Apr 11. doi:10.3389/fimmu.2019.00316 (PMID 31031743)
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7) Valeri L, Lugli L, Iughetti L, et al. Omenn Syndrome due to RAG1 Mutation Presenting With Nonimmune Hydrops Fetalis in Two Siblings. Pediatrics. 2022;149(1):e2021052411. doi:10.1542/peds.2021-052411 (PMID 34889447)
8) Sorel N, Díaz-Pascual F, Bessot B, et al. Restoration of T and B Cell Differentiation after RAG1 Gene Transfer in Human RAG1 Defective Hematopoietic Stem Cells. Biomedicines. 2024;12(7):1495. Published 2024 Jul 5. doi:10.3390/biomedicines12071495 (PMID 39062069)
9) dbSNP: www.ncbi.nlm.nih.gov/snp/
10) gnomAD Browser: gnomad.broadinstitute.org/

METHOD

Next generation sequencing (NGS) and/or Sanger sequencing was performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. NGS and/or a polymerase chain reaction (PCR)-based quantitative method was performed to test for the presence of deletions and duplications in the genes analyzed. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. See the Genes Analyzed field for a list of genes tested. A supplemental PCR-based method was used to test for the presence of a large deletion in IKBKG.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com (TEST ID COMID) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ADA, AK2, ARPC1B, ATM, BCL10, BCL11B, BLM, CARD11, CD247, CD28, CD3D, CD3E, CD3G, CD40, CD40LG, CD70, CD8A, CDCA7, CHD7, CIITA, CORO1A, CTLA4, DCLRE1C, DNMT3B, DOCK2, DOCK8, EPG5, ERCC6L2, EXTL3, FCHO1, FOXN1, GINS1, HELLS, ICOS, ICOSLG, IKBKB, IKBKG, IKZF1, IL21, IL21R, IL2RA, IL2RB, IL2RG, IL7R, ITK, ITPKB, JAK3, KDM6A, KMT2A, KMT2D, LAT, LCK, LCP2, LIG1, LIG4, LRBA, MAGT1, MALT1, MAP3K14, MCM10, MSN, MTHFD1, MYSM1, NBN, NFKBIA, NHEJ1, NSMCE3, ORAI1, PAX1, PGM3, PNP, POLD1, POLE, POLE2, PRKDC, PSMB9, PTPRC, RAC2, RAG1, RAG2, RASGRP1, RBCK1, REL, RELA, RELB, RFX5, RFXANK,

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RFXAP, RHOH, RMRP (NME1), RNF168, RNF31, RNU4ATAC, SEC61A1, SEMA3E, SH2D1A, SKIV2L (SKIC2), SMARCAL1, SP110, STAT3, STAT5B, STIM1, STK4, TAP1, TAP2, TAPBP, TAZ (TAFAZZIN), TBX1, TFRC, TNFRSF4, TRAC, TTC37 (SKIC3), TTC7A, WAS, WIPF1, ZAP70 and ZBTB24

DISCLAIMER

Clinical Correlations

The gene(s) analyzed by this test may have more than one associated phenotype or inheritance pattern. Additionally, the genetic variants detected may have reduced penetrance, variable expressivity, or different classifications based on disease state. Classification and reporting of the variants detected is based on the intended disease state of the test ordered. For more information regarding the phenotypic spectrum which may be involved for a specific gene, see OMIM (www.ncbi.nlm.nih.gov/omim) or GeneReviews (www.genereviews.org).

An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710.

Technical Limitations

Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. The clinical phenotype observed in this individual and/or family may be due to genetic variants not targeted by this test. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected

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variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Combined Humoral and Cell-Mediated Immunodeficiency Gene Panel, Varies in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID COMID) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.

TEST CLASSIFICATION
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

RELEASED BY

Ann Marie Moyer, M.D., Ph.D.

IS THIS BONE MARROW

No

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