MAYO CLINIC

1-800-533-1710

Inborn Errors of Immunity GenePanel

IEICP

PATIENT NAME				ORDER NUMBER
IEICP, ABNORMAL				**P413000490**
PATIENT ID X100498920	DATE OF BIRTH 10/30/1990	AGE 34 Y	SEX Male	REQUESTED BY PROVIDER UNKNOWN
COLLECTED 5/13/2025, 8:00 AM	RECEIVED 5/14/2025, 12:37 PM	REPORTED 5/14/2025, 1:33 PM		
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TEST DESCRIPTION

Evaluation of 383 genes associated with associated with inborn errors of immunity (IEI)

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variants Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
NCF1 (NM_000265.6)	c.75_76del p.Tyr26Hisfs*26 (p.Y26Hfs*26) (GRCh37):g.74191615_74191616del	homozygous	PATHOGENIC

The following PATHOGENIC variant was detected:
NCF1 (NM_000265.6), chr7(GRCh37):g.74191615_74191616del, c.75_76del, p.Tyr26Hisfs*26 (p.Y26Hfs*26), 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

NCF1 c.75_76del (p.Tyr26Hisfs*26), PATHOGENIC
A homozygous deletion in the NCF1 gene on chromosome 17 was detected and is classified as pathogenic. The NCF1 gene encodes neutrophil cytosolic factor 1, a component of the NADPH oxidase complex that is activated to produce superoxide anion. Pathogenic variants in this gene are associated with autosomal recessive chronic granulomatous disease 1 (CGD 1). This variant, which is also known as the "delta GT" deletion, is reported to be the most common cause of autosomal recessive chronic granulomatous disease, has been reported in the homozygous and compound heterozygous state with a second pathogenic variant in NCF1 in many unrelated individuals with CGD 1, and has segregated with disease in several affected families (1-5). This variant is created by a recombination event between NCF1 and its pseudogenes and is predicted to cause premature protein truncation due to a frameshift and is expected to result in loss of function (6,7).

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Taken together, the evidence supports a classification of pathogenic for this variant. The finding of this homozygous pathogenic NCF1 deletion is supportive of a diagnosis of autosomal recessive chronic granulomatous disease 1 (CGD 1) for this individual but should be correlated with clinical findings. Appropriate screening and/or management procedures should be considered.

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.

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) Görlach A, Lee PL, Roesler J, et al. A p47-phox pseudogene carries the most common mutation causing p47-phox-deficient chronic granulomatous disease. J Clin Invest. 1997;100(8):1907-1918. doi:10.1172/JCI119721 (PMID 9329953)
2) Noack D, Rae J, Cross AR, et al. Autosomal recessive chronic granulomatous disease caused by defects in NCF-1, the gene encoding the phagocyte p47-phox: mutations not arising in the NCF-1 pseudogenes. Blood. 2001;97(1):305-311. doi:10.1182/blood.v97.1.305 (PMID 11133775)
3) Roos D, de Boer M, Köker MY, et al. Chronic granulomatous disease caused by mutations other than the common GT deletion in NCF1, the gene encoding the p47phox component of the phagocyte NADPH oxidase. Hum Mutat. 2006;27(12):1218-1229. doi:10.1002/humu.20413 (PMID 16972229)
4) Kuhns DB, Alvord WG, Heller T, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010;363(27):2600-2610. doi:10.1056/NEJMoa1007097 (PMID 21190454)
5) Kuhns DB, Hsu AP, Sun D, et al. NCF1 (p47phox)-deficient chronic granulomatous disease: comprehensive genetic and flow cytometric analysis. Blood Adv. 2019;3(2):136-147. doi:10.1182/bloodadvances.2018023184 (PMID 30651282)
6) Casimir CM, Bu-Ghanim HN, Rodaway AR, Bentley DL, Rowe P, Segal AW. Autosomal recessive chronic

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granulomatous disease caused by deletion at a dinucleotide repeat. Proc Natl Acad Sci U S A. 1991;88(7):2753-2757. doi:10.1073/pnas.88.7.2753 (PMID 2011585)
7) Roesler J, Curnutte JT, Rae J, et al. Recombination events between the p47-phox gene and its highly homologous pseudogenes are the main cause of autosomal recessive chronic granulomatous disease. Blood. 2000;95(6):2150-2156. (PMID 10706888)

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. Supplemental PCR-based methods were used to test for the presence of a large deletion in IKBKG and an inversion in UNC13D. Supplemental droplet digital PCR methods were used to detect deletions and duplications in IGHM and C1R and to test for the presence of the c.75_76del; p.Tyr26Hisfs*26 (delta GT) disease-causing variant in NCF1.

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.mayoclinicslabs.com (TEST ID IEICP) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ACD, ACP5, ADA, ADA2, ADAM17, ADAR, AICDA, AIRE, AK2, ALPI, ANGPT1, ANKZF1, AP3B1, AP3D1, ARPC1B, ASAH1, ATM, ATP6AP1, BACH2, BCL10, BCL11B, BLM, BLNK, BLOC1S6, BTK, C1QA, C1QB, C1QC, C1R, C1S, C2, C3, C5, C6, C7, C8A, C8B, C9, CARD11, CARD14, CARD9, CARMIL2, CASP10, CASP8, CCBE1, CD19, CD247, CD27, CD28, CD3D, CD3E, CD3G, CD40, CD40LG, CD46, CD48, CD55, CD59, CD70, CD79A, CD79B, CD81, CD8A, CDC42, CDCA7, CEBPE, CFB, CFD, CFH, CFI, CFP, CFTR, CHD7, CIB1, CIITA, CLCN7, CLPB, COPA, CORO1A, CR2, CSF2RA, CSF2RB, CSF3R, CTC1, CTLA4, CTPS1, CTSC, CXCR2, CXCR4, CYBA, CYBB, CYBC1, DBR1, DCLRE1C, DDX58 (RIGI), DEF6, DGAT1, DKC1, DNAJC21, DNASE1, DNASE1L3, DNASE2, DNMT3B, DOCK2, DOCK8, DUOX2, EFL1, ELANE, EPG5, ERBIN, ERCC6L2, EXTL3, F12, FADD, FAS, FASLG, FAT4, FCHO1, FERMT1, FERMT3, FOXN1, FOXP3, G6PC (G6PC1), G6PC3, G6PD, GATA2, GFI1, GINS1, GLA, HAVCR2, HAX1, HELLS, HMOX1, HPS1, HPS3,

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HPS4, HPS6, ICOS, ICOSLG, IFIH1, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IGHM, IGLL1, IKBKB, IKBKG, IKZF1, IKZF3, IL10, IL10RA, IL10RB, IL12B, IL12RB1, IL12RB2, IL17F, IL17RA, IL17RC, IL1RN, IL21, IL21R, IL23R, IL2RA, IL2RB, IL2RG, IL36RN, IL6R, IL6ST, IL7R, IRAK4, IRF2BP2, IRF3, IRF7, IRF8, IRF9, ISG15, ITCH, ITGB2, ITK, ITPKB, JAGN1, JAK1, JAK3, KDM6A, KMT2A, KMT2D, KNG1, LACC1, LAT, LCK, LCP2, LIG1, LIG4, LPIN2, LRBA, LSM11, LYN, LYST, MAGT1, MALT1, MAP3K14, MASP2, MCM10, MEFV, MOGS, MRTFA, MS4A1, MSN, MTHFD1, MVK, MYD88, MYSM1, NBAS, NBN, NCF1, NCF2, NCF4, NCSTN, NFE2L2, NFKB1, NFKB2, NFKBIA, NHEJ1, NHP2, NLRC4, NLRP1, NLRP12, NLRP3, NOD2, NSMCE3, OAS1, ORAI1, OSTM1, OTULIN, PARN, PAX1, PEPD, PGM3, PIK3CD, PIK3R1, PLCG2, PLG, PMM2, PNP, POLA1, POLD1, POLE, POLE2, POLR3A, POLR3C, POMP, PRF1, PRKCD, PRKDC, PSENEN, PSMA3, PSMB10, PSMB4, PSMB8, PSMB9, PSMG2, PSTPIP1, PTPRC, RAB27A, RAC2, RAG1, RAG2, RASGRP1, RBCK1, RBM8A, REL, RELA, RELB, RFX5, RFXANK, RFXAP, RHOH, RIPK1, RMRP (NME1), RNASEH2A, RNASEH2B, RNASEH2C, RNF168, RNF31, RNU4ATAC, RNU7-1, RORC, RPSA, RTEL1, SAMD9, SAMD9L, SAMHD1, SBDS, SEC61A1, SEMA3E, SERPING1, SH2D1A, SH3BP2, SH3KBP1, SKIV2L (SKIC2), SLC29A3, SLC35C1, SLC37A4, SLC39A7, SLC46A1, SLC7A7, SMARCAL1, SMARCD2, SNX10, SP110, SPINK5, SPPL2A, SRP54, STAT1, STAT2, STAT3, STAT5B, STIM1, STING1, STK4, STX11, STXBP2, SYK, TAP1, TAP2, TAPBP, TAZ (TAFAZZIN), TBX1, TCF3, TCIRG1, TCN2, TERC, TERT, TET2, TFRC, TGFB1, TGFBR1, TGFBR2, THBD, TINF2, TIRAP, TLR3, TLR7, TLR8, TMC6, TMC8, TNFAIP3, TNFRSF11A, TNFRSF13B, TNFRSF13C, TNFRSF1A, TNFRSF4, TNFRSF9, TNFSF11, TNFSF12, TNFSF13, TOP2B, TPP2, TRAC, TRAF3, TRAF3IP2, TREX1, TRNT1, TTC37 (SKIC3), TTC7A, TYK2, UNC13D, UNC93B1, UNG, USB1, USP18, VPS13B, VPS45, WAS, WDR1, WIPF1, WRAP53, XIAP, ZAP70, ZBTB24, ZNF341 and ZNFX1

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.

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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 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 Inborn Errors of Immunity Comprehensive 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 IEICP) 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.

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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

Code : MCR Laboratory : Mayo Clinic Laboratories - Rochester Main Campus Address : 200 FIRST STREET SW
Lab Director : NIKOLA A BAUMANN PHD CLIA Certificate : 24D0404292 ROCHESTER MN 55905