MAYO CLINIC

1-800-533-1710

SCID Gene Panel

SCIDP

PATIENT NAME				ORDER NUMBER
TESTRNV, IMPLEMENTATION				**N022000307**
PATIENT ID X100420058	DATE OF BIRTH 02/19/1968	AGE 55 Y	SEX Male	REQUESTED BY CLIENT TEST
COLLECTED 5/22/2023, 6:33 AM	RECEIVED 5/22/2023, 12:22 PM	REPORTED 5/24/2023, 10:49 AM		
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 X100420058 CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 50 genes associated with severe combined immunodeficiency (SCID)

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
LIG4 (NM_002312.3)	c.1904del p.Lys635Argfs*10 (p.K635Rfs*10) Chr13(GRCh37):g.108861713del	Heterozygous	Pathogenic

The following heterozygous PATHOGENIC variant was detected:
LIG4 (NM_002312.3), chr13(GRCh37):g.108861713del, c.1904del, p.Lys635Argfs*10 (p.K635Rfs*10)

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

LIG4 c.1904del (p.Lys635Argfs*10), PATHOGENIC
The heterozygous c.1904del (p.Lys635Argfs*10) single base pair deletion in the LIG4 gene (MIM:601837) is classified as pathogenic. The LIG4 gene encodes DNA Ligase 4, a protein essential for DNA double strand break repair through non-homologous end joining. Pathogenic variants in this gene are associated with autosomal recessive DNA ligase IV deficiency (also called LIG4 syndrome), a condition with a wide range of clinical manifestations including sensitivity to ionizing radiation, severe combined immunodeficiency, congenital microcephaly, growth failure, developmental delay, skeletal malformations, progressive bone marrow failure, and predisposition to hematological malignancy. This variant is predicted to cause premature protein truncation due to a frameshift and is expected to result in loss-of-function. Other truncating variants in the LIG4 gene have also been associated with disease. This variant has been reported in two individuals with LIG4-related conditions who carried both the p.Lys635Argfs*10 pathogenic variant and another LIG4 variant; in at least one of these individuals the variants were proven to be in trans (on opposite chromosomes) through family studies (1,2). This variant was also reported with a second pathogenic loss of function LIG4 variant in a patient with suspected hereditary bone marrow failure (3). This variant has been observed at a very low frequency in exome and/or genome sequencing data gathered from large, multi-ethnic cohorts, suggesting it is a rare variant (4,5). This result is supportive of carrier status for autosomal recessive DNA ligase IV deficiency. However, the presence of an undetectable

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second variant cannot be ruled out. Clinical correlation is recommended.

Individuals may have a pathogenic variant in one of the interrogated genes that is not detectable by the methods utilized. Additionally, the clinical phenotype that is observed in this individual and/or family may be due to a pathogenic variant or variants in another gene not targeted by this test.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

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. 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) IJspeert H, Warris A, van der Flier M, et al. Clinical spectrum of LIG4 deficiency is broadened with severe dysmaturity, primordial dwarfism, and neurological abnormalities. Hum Mutat. 2013;34(12):1611-1614. doi:10.1002/humu.22436 (PMID 24027040)
2) Brunet BA, Dave N. Unique heterozygous presentation in an infant with DNA ligase IV syndrome. Ann Allergy Asthma Immunol. 2017;119(4):379-380. doi:10.1016/j.anai.2017.07.017 (PMID 28866308)
3) Bluteau O, Sebert M, Leblanc T, et al. A landscape of germ line mutations in a cohort of inherited bone marrow failure patients. Blood. 2018;131(7):717-732. doi:10.1182/blood-2017-09-806489 (PMID 29146883)
4) dbSNP: www.ncbi.nlm.nih.gov/snp; Sherry ST, Ward M and Sirotkin K. dbSNP-Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation. Genome Res. 1999;9:677-679 (PMID 10447503)
5) gnomAD Browser: gnomad.broadinstitute.org/; Karczewski K, Francioli LC, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020; 581(7809):434-443 (PMID 32461654)

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.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis

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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 SCIDP) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ADA, AK2, ATM, BCL11B, CARD11, CD247, CD3D, CD3E, CD3G, CD8A, CHD7, CIITA, CORO1A, DCLRE1C, DOCK2, DOCK8, EXTL3, FOXN1, IKZF1, IL2RA, IL2RG, IL7R, JAK3, LAT, LCP2, LIG4, MTHFD1, NBN, NHEJ1, ORAI1, PAX1, PNP, POLE2, PRKDC, PTPRC, RAC2, RAG1, RAG2, RFX5, RFXANK, RFXAP, RMRP, SEMA3E, SMARCAL1, STIM1, TBX1, TTC7A, WAS, WIPF1 and ZAP70

DISCLAIMER

Clinical Correlations
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. 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.

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Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the SCID Genetic Panel in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID SCIDP) 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

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