MAYO CLINIC

1-800-533-1710

Viral Susceptibility Gene Panel

VIRID

PATIENT NAME				ORDER NUMBER
TESTRNV, IMPLEMENTATION				**M702000288**
PATIENT ID X100407769	DATE OF BIRTH 02/19/1968	AGE 54 Y	SEX Male	REQUESTED BY ATLAS TEST
COLLECTED 2/2/2023, 8:33 AM	RECEIVED 2/7/2023, 3:06 PM	REPORTED 2/24/2023, 4:49 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 X100407769 CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 30 genes associated with a hereditary form of viral susceptibility

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Likely Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
XIAP (NM_001167.3)	c.562G>A p.Gly188Arg (p.G188R) ChrX(GRCh37):g.123020074G>A	Hemizygous	Likely Pathogenic

The following hemizygous LIKELY PATHOGENIC variant was detected:
XIAP (NM_001167.3), chrX(GRCh37):g.123020074G>A, c.562G>A, p.Gly188Arg (p.G188R)

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

XIAP c.562G>A (p.Gly188Arg), LIKELY PATHOGENIC
The hemizygous c.562G>A (p.Gly188Arg) missense variant in the XIAP gene (MIM:300079) is classified as likely pathogenic. The XIAP gene encodes for the X-linked inhibitor of apoptosis protein, which regulates programmed cell death as well as inflammatory signaling, immunity, and several other cell processes. Pathogenic variants in this gene are associated with X-linked lymphoproliferative syndrome 2 (XLP2), which is also known as XIAP deficiency. This variant has been previously reported in at least three individuals with XIAP deficiency (1,2). The Gly188 codon is a critical residue in the BIR2 domain, which is important to protein function (3). There is another missense variant, p.Gly188Glu, at this codon that has been demonstrated to cause XIAP deficiency and is classified as pathogenic by this lab. A functional study has been performed that supports the pathogenicity of the p.Gly188Arg variant detected in the individual tested here (4). This variant has not been observed in exome or genome sequencing data gathered from large, multi-ethnic cohorts, suggesting it is a rare variant (5). This amino acid is highly conserved across species and there is a moderate physicochemical difference between glycine (Gly) and arginine (Arg). An in silico meta-predictor suggests that this amino acid change may impact protein function. However, computational program predictions are not sufficient to determine pathogenicity. Taken together, these findings suggest that the identified XIAP p.Gly188Arg variant is likely pathogenic. The finding of a likely pathogenic XIAP variant is likely supportive of a diagnosis of X-linked lymphoproliferative disease (XLP) for this individual but should be correlated with clinical findings. Appropriate screening and/or management procedures should be considered.

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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) Gifford CE, Weingartner E, Villanueva J, et al. Clinical flow cytometric screening of SAP and XIAP expression accurately identifies patients with SH2D1A and XIAP/BIRC4 mutations. Cytometry B Clin Cytom. 2014;86(4):263-271. doi:10.1002/cyto.b.21166 (PMID 24616127)
2) Ji J, Shen L, Bootwalla M, et al. A semiautomated whole-exome sequencing workflow leads to increased diagnostic yield and identification of novel candidate variants. Cold Spring Harb Mol Case Stud. 2019;5(2):a003756. Published 2019 Apr 1. doi:10.1101/mcs.a003756 (PMID 30755392)
3) Damgaard RB, Fiil BK, Speckmann C, et al. Disease-causing mutations in the XIAP BIR2 domain impair NOD2-dependent immune signalling. EMBO Mol Med. 2013;5(8):1278-1295. doi:10.1002/emmm.201303090 (PMID 23818254)
4) Engel K, Rudelius M, Slawska J, et al. USP9X stabilizes XIAP to regulate mitotic cell death and chemoresistance in aggressive B-cell lymphoma. EMBO Mol Med. 2016;8(8):851-862. Published 2016 Aug 1. doi:10.15252/emmm.201506047 (PMID 27317434)
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 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 VIRID) for details regarding genes with regions not routinely covered.

GENES ANALYZED

CARMIL2, CD27, CD70, CIB1, CTPS1, CXCR4, DBR1, IFIH1, IFNAR1, IFNAR2, IRF3, IRF7, IRF9, MAGT1, POLR3A, POLR3C, PRKCD, RASGRP1, SH2D1A, STAT1, STAT2, TLR3, TLR7, TLR8, TMC6, TMC8, TNFRSF9, TRAF3,

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UNC93B1 and XIAP

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.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Viral Susceptibility Gene 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 VIRID) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation

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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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