MAYO CLINIC

1-800-533-1710

Postmortem HLH Gene Panel

PMHLH

PATIENT NAME				ORDER NUMBER
TESTRNV, TESTING A				**N425000326**
PATIENT ID X100430258	DATE OF BIRTH 02/19/1968	AGE 55 Y	SEX Male	REQUESTED BY CLIENT TESTING
COLLECTED 9/25/2023, 7:00 AM	RECEIVED 9/25/2023, 2:04 PM	REPORTED 10/1/2023, 3:04 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 X100430258 CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 23 genes associated with primary hemophagocytic lymphohistiocytosis

SPECIMEN

Tissue Scroll

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	Heterozygous	Likely Pathogenic

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

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 heterozygous 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. This result is supportive of at minimum carrier status for XIAP deficiency. Female carriers of X-linked conditions are at risk

PATIENT NAME				ORDER NUMBER
TESTRNV, TESTING A				**N425000326**
PATIENT ID X100430258	DATE OF BIRTH 02/19/1968	AGE 55 Y	SEX Male	REQUESTED BY CLIENT TESTING
COLLECTED 9/25/2023, 7:00 AM	RECEIVED 9/25/2023, 2:04 PM	REPORTED 10/1/2023, 3:04 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 X100430258 CLIENT MRN 321

for having affected children and in some cases may have features related to the disease. Clinical correlation is recommended.

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/

ADDITIONAL INFORMATION

TISSUE ID: Testing539294

METHOD

Next generation sequencing (NGS) was performed to test for the presence of sequence variants in coding regions and intron/exon boundaries of the genes analyzed. The human genome reference GRCh37/hg19 build was used for sequence read alignment. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. See www.mayocliniclabs.com (TEST ID PMHLH) for details regarding genes with regions not routinely covered.

GENES ANALYZED

PATIENT NAME	TESTRNV, TESTING A	23-41852

PATIENT NAME				ORDER NUMBER
TESTRNV, TESTING A				**N425000326**
PATIENT ID X100430258	DATE OF BIRTH 02/19/1968	AGE 55 Y	SEX Male	REQUESTED BY CLIENT TESTING
COLLECTED 9/25/2023, 7:00 AM	RECEIVED 9/25/2023, 2:04 PM	REPORTED 10/1/2023, 3:04 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 X100430258 CLIENT MRN 321

ADA, AP3B1, AP3D1, BLOC1S6, CD27, CD70, CDC42, CORO1A, CTPS1, IFNAR2, ITK, LYST, MAGT1, MVK, NLRC4, PRF1, RAB27A, SH2D1A, SLC7A7, STX11, STXBP2, UNC13D and XIAP

DISCLAIMER

Sample Quality:

This test is intended for use when EDTA whole blood is not available and formalin-fixed, paraffin-embedded (FFPE) tissue is the only available sample. DNA extracted from FFPE tissue can be degraded, which results in a higher failure rate for next-generation sequencing when compared to DNA extracted from whole blood. Due to the quality of DNA extracted from FFPE, the acceptable coverage threshold may be lower than that of the equivalent blood assays. Coverage of at least 20X is expected for most regions assessed but may be adjusted on a case-by-case basis at the discretion of the laboratory director.

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.

Deletion/duplication analysis is not performed due to technical limitations of the FFPE sample type. In addition, there may be regions of genes that cannot be effectively evaluated for sequencing analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of NGS results by Sanger sequencing is typically not performed for this test. 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

PATIENT NAME				ORDER NUMBER
TESTRNV, TESTING A				**N425000326**
PATIENT ID X100430258	DATE OF BIRTH 02/19/1968	AGE 55 Y	SEX Male	REQUESTED BY CLIENT TESTING
COLLECTED 9/25/2023, 7:00 AM	RECEIVED 9/25/2023, 2:04 PM	REPORTED 10/1/2023, 3:04 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 X100430258 CLIENT MRN 321

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 Postmortem HLH 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 PMHLH) 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

Linnea M. Baudhuin, Ph.D.

Code : MCR Laboratory : Mayo Clinic Laboratories - Rochester Main Campus Address : 200 FIRST STREET SW
Lab Director : WILLIAM G MORICE MD, PHD CLIA Certificate : 24D0404292 ROCHESTER MN 55905