MAYO CLINIC

1-800-533-1710

F8 Gene, Full Gene NGS

GNHMA

PATIENT NAME				ORDER NUMBER
GNHMA, ABNORMAL				**M724000351**
PATIENT ID SA00158410	DATE OF BIRTH 12/12/1956	AGE 66 Y	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 2/23/2023, 12:00 AM	RECEIVED 2/24/2023, 2:36 PM	REPORTED 2/28/2023, 8:42 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 SA00158410 CLIENT MRN SA00158410

TEST DESCRIPTION

Evaluation of the F8 gene associated with hemophilia A (also known as factor VIII deficiency).

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
F8 NM_000132.3	c.2167G>A p.Ala723Thr ChrX:g.154159898C>T	heterozygous	PATHOGENIC

The following heterozygous PATHOGENIC variant was detected:
F8 (NM_000132.3), chrX(GRCh37):g.154159898C>T, c.2167G>A, p.Ala723Thr (p.A723T)

INTERPRETATION

F8 c.2167G>A (p.Ala723Thr), PATHOGENIC
The heterozygous c.2167G>A (p.Ala723Thr) missense variant in the F8 gene (MIM:300841) is classified as pathogenic. Pathogenic variants in the F8 gene have been associated with X-linked recessive hemophilia A (1). This variant has been reported as a pathogenic variant in several unrelated individuals with a clinical diagnosis of hemophilia A (2-9). However, functional studies have not been performed to either support or refute the pathogenicity of this variant. This variant occurs in an established functional domain and an in silico meta-predictor suggests that this amino acid change may impact protein function. This alteration is observed in the large population genetics database gnomAD in the hemizygous state in 1 out of 15,251 South Asian individuals (minor allele frequency [MAF] = 0.005%) and not in any other subpopulation (10,11). This result is supportive of at minimum carrier status for X-linked recessive hemophilia A. Female carriers of X-linked conditions are at risk for having affected children and in some cases may have features related to the disease. Clinical correlation is recommended.

Individuals may have a pathogenic variant in the F8 gene that is not detectable by the methods utilized. Additionally, pathogenic variants in other genes not interrogated by this assay may cause a similar phenotype.

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

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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:

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6) Villarreal-Martínez L, Ibarra-Ramirez M, Calvo-Anguiano G, et al. Molecular genetic diagnosis by next-generation sequencing in a cohort of Mexican patients with haemophilia and report of novel variants. Blood Cells Mol Dis. 2020;83:102423. doi:10.1016/j.bcmd.2020.102423 (PMID 32224444)
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10) 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)
11) 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

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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 gene 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 >30X. Sensitivity is estimated at >99% for single nucleotide variants, >94% for indels up to 39 base pairs, >95% for deletions up to 75 base pairs and insertions up to 47 base pairs. NGS and/or a PCR-based quantitative method was performed to test for the presence of deletions and duplications in the gene analyzed. See the Genes Analyzed field for a list of gene(s) 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 GNHMA) for details regarding genes with regions not routinely covered.

GENES ANALYZED

F8

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.

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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.

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