MAYO CLINIC

1-800-533-1710

# F9 Gene, Full Gene NGS

# GNHMB

| PATIENT NAME | | | | ORDER NUMBER |
|---|---|---|---|---|
| **TESTRNV, IMPLEMENTATION** | | | | **M727000384** |
| PATIENT ID<br>SA00158437 | DATE OF BIRTH<br>02/19/1968 | AGE<br>55 Y | SEX<br>Male | REQUESTED BY<br>CLIENT CLIENT |
| COLLECTED<br>2/27/2023, 6:00 AM | RECEIVED<br>2/27/2023, 1:06 PM | REPORTED<br>2/27/2023, 1:33 PM | | |
| The collected, received, and reported dates and times on the report are in the time zone of the performing location.<br>7028846<br>MCL RochesterCampus<br>Rochester MN 55901 | | | | CLIENT ORDER NUMBER<br>SA00158437<br>CLIENT MRN<br>SA00158437 |

## TEST DESCRIPTION

Evaluation of the F9 gene associated with hemophilia B (also known as factor IX deficiency).

## SPECIMEN

WB Whole Blood

## RESULT SUMMARY

Pathogenic Variant Detected

## RESULT

| Gene (Transcript) | Variant | Zygosity | Classification |
|---|---|---|---|
| F9<br>NM_000133.4 | c.316G>A<br>p.Gly106Ser<br>ChrX:g.138623273G>A | hemizygous | PATHOGENIC |

The following hemizygous PATHOGENIC variant was detected:
F9 (NM_000133.4), chrX(GRCh37):g.138623273G>A, c.316G>A, p.Gly106Ser (p.G106S)

## INTERPRETATION

F9 c.316G>A (p.Gly106Ser), PATHOGENIC
The hemizygous c.316G>A (p.Gly106Ser) missense variant in the F9 gene (MIM:300746) is classified as pathogenic. Pathogenic variants in the F9 gene have been associated with X-linked recessive hemophilia B (1). This variant has been reported as a pathogenic variant in several unrelated individuals with a clinical diagnosis of hemophilia B (2-4). Furthermore, functional studies have been performed to support the pathogenicity of this variant. Functional studies demonstrate this alteration results in defective folding of the domain (5). 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 heterozygous state in 1 out of 3,576 individuals in the subpopulation Other (minor allele frequency [MAF] = 0.02%) and at lower frequencies (MAF of 0.01%, 0.004%, and 0.001%) in the African/African-American, Latino/Admixed American, and the European (non-Finnish) subpopulations, respectively (6,7). This result is supportive of a diagnosis of hemophilia B for this individual. 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

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laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:
1) GeneReviews: Hemophilia B (https://www.ncbi.nlm.nih.gov/books/NBK1495/) (PMID: 20301668)
2) Ketterling RP, Bottema CD, Phillips JA 3rd, Sommer SS. Evidence that descendants of three founders constitute about 25% of hemophilia B in the United States. Genomics. 1991;10(4):1093-1096. doi:10.1016/0888-7543(91)90207-u (PMID 1916816)
3) Chen SH, Thompson AR, Zhang M, Scott CR. Three point mutations in the factor IX genes of five hemophilia B patients. Identification strategy using localization by altered epitopes in their hemophilic proteins. J Clin Invest. 1989;84 (1):113-118. doi:10.1172/JCI114130 (PMID 2472424)
4) Denton PH, Fowlkes DM, Lord ST, Reisner HM. Hemophilia B Durham: a mutation in the first EGF-like domain of factor IX that is characterized by polymerase chain reaction. Blood. 1988;72(4):1407-1411. (PMID 3262389)
5) Whiteman P, Downing AK, Smallridge R, Winship PR, Handford PA. A Gly --> Ser change causes defective folding in vitro of calcium-binding epidermal growth factor-like domains from factor IX and fibrillin-1. J Biol Chem. 1998;273 (14):7807-7813. doi:10.1074/jbc.273.14.7807 (PMID 9525872)
6) 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)
7) 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 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 GNHMB) for details regarding genes with regions not routinely covered.

## GENES ANALYZED

F9

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**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.

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

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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**

SHANDA VOELTZ

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