MAYO CLINIC

1-800-533-1710

F11 Gene, Full Gene NGS

GNF11

PATIENT NAME				ORDER NUMBER
GNF11, AB				**M724000388**
PATIENT ID SA00158422	DATE OF BIRTH 10/14/1975	AGE 47 Y	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 2/23/2023, 12:00 AM	RECEIVED 2/24/2023, 2:40 PM	REPORTED 2/28/2023, 9:02 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 SA00158422 CLIENT MRN SA00158422

TEST DESCRIPTION

Evaluation of the F11 gene associated with factor XI deficiency.

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
F11 NM_000128.4	c.901T>C p.Phe301Leu Chr4:g.187201412T>C	heterozygous	PATHOGENIC

The following heterozygous PATHOGENIC variant was detected:
F11 (NM_000128.4), chr4(GRCh37):g.187201412T>C, c.901T>C, p.Phe301Leu (p.F301L)

INTERPRETATION

F11 c.901T>C (p.Phe301Leu), PATHOGENIC
The heterozygous c.901T>C (p.Phe301Leu) missense variant in the F11 gene (MIM:264900) is classified as pathogenic. Pathogenic variants in the F11 gene have been associated with autosomal recessive and autosomal dominant forms of factor XI deficiency. This variant has been reported in the homozygous state and in the compound heterozygous state with other pathogenic F11 variants in many unrelated individuals with a clinical diagnosis of autosomal recessive factor XI deficiency (1-4). Furthermore, functional studies have been performed to support the pathogenicity of this variant. Functional studies demonstrate this alteration introduces a defect in dimerization that reduces factor XI secretion to about 8% of normal factor XI (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 4 homozygotes and 239 heterozygotes out of 5,184 Ashkenazi Jewish individuals (minor allele frequency [MAF] = 2.38%) and is a known founder variant in the Ashkenazi Jewish population. It is also present at lower frequencies (MAF < 0.18%) in the population Other in both the homozygous and heterozygous states and in the European (non-Finnish) and Latino/Admixed American populations exclusively in the heterozygous state (6,7). This result is supportive of carrier status for autosomal recessive factor XI deficiency. However, the presence of an undetectable second variant cannot be ruled out. Clinical correlation is recommended.

Individuals may have a pathogenic variant in the F11 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.

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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) Asakai R, Chung DW, Davie EW, Seligsohn U. Factor XI deficiency in Ashkenazi Jews in Israel. N Engl J Med. 1991;325(3):153-158. doi:10.1056/NEJM199107183250303 (PMID 2052060)
2) Asakai R, Chung DW, Ratnoff OD, Davie EW. Factor XI (plasma thromboplastin antecedent) deficiency in Ashkenazi Jews is a bleeding disorder that can result from three types of point mutations. Proc Natl Acad Sci U S A. 1989;86 (20):7667-7671. doi:10.1073/pnas.86.20.7667 (PMID 2813350)
3) Tiscia GL, Favuzzi G, Lupone MR, et al. Factor XI gene variants in factor XI-deficient patients of Southern Italy: identification of a novel mutation and genotype-phenotype relationship. Hum Genome Var. 2017;4:17043. Published 2017 Nov 9. doi:10.1038/hgv.2017.43 (PMID 29138690)
4) Rimoldi V, Paraboschi EM, Menegatti M, et al. Molecular investigation of 41 patients affected by coagulation factor XI deficiency. Haemophilia. 2018;24(2):e50-e55. doi:10.1111/hae.13378 (PMID 29178608)
5) Meijers JC, Davie EW, Chung DW. Expression of human blood coagulation factor XI: characterization of the defect in factor XI type III deficiency. Blood. 1992;79(6):1435-1440. (PMID 1547342)
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.

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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 GNF11) for details regarding genes with regions not routinely covered.

GENES ANALYZED

F11

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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Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID GNF11) 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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