

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB: 2/17/2005
Sex: Female
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Collection Date: 01/01/2017 12:34

Hemophilia A (F8) Sequencing

ARUP test code 3004241

Hemophilia A (F8) Specimen	whole Blood
Hemophilia A (F8) Interp	<p>Positive</p> <p>RESULT One pathogenic variant was detected in the F8 gene.</p> <p>PATHOGENIC VARIANT Gene: F8 (NM_000132.4) Nucleic Acid Change: c.1094A>G; Heterozygous Amino Acid Alteration: p.Tyr365Cys Inheritance: X-linked</p> <p>INTERPRETATION One pathogenic variant, c.1094A>G; p.Tyr365Cys, was detected in the F8 gene by massively parallel sequencing; thus, this individual is a carrier of hemophilia A. Approximately 30 percent of female carriers have factor VIII activity levels of less than 40 percent and are at-risk for bleeding symptoms typically consistent with mild hemophilia A. This individual's offspring have a 50 percent chance of inheriting the variant regardless of sex.</p> <p>Please refer to the background information included in this report for the methodology and limitations of this test.</p> <p>Evidence for variant classification: The F8 c.1094A>G; p.Tyr365Cys variant (rs375241473), also known as Tyr346Cys, is published in the medical literature and in gene-specific databases in several individuals with mild hemophilia (see link to FVIII database, Bowyer 2011, Cutler 2002, Hill 2005). This variant is found in the Genome Aggregation Database in the non-Finnish European population with an allele frequency of 0.015% (12/81864 alleles, including 6 hemizygotes). The tyrosine at this position is conserved across species and computational algorithms (PolyPhen2, SIFT) predict this variant is deleterious. Considering available information, this variant is considered pathogenic.</p> <p>RECOMMENDATIONS A baseline factor VIII clotting activity assay should be performed to determine if this individual is at increased risk for bleeding. Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic F8 variant (Familial Targeted Sequencing, ARUP test code 3005867).</p> <p>COMMENTS Unless otherwise specified, confirmation by Sanger sequencing</p>

H=High, L=Low, *=Abnormal, C=Critical

Unless otherwise indicated, testing performed at:

was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not reported. Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations: None

REFERENCES

Link to F8 database: <http://f8-db.eahad.org/>
Bowyer AE et al. p.Tyr365Cys change in factor VIII: haemophilia A, but not as we know it. *Br J Haematol*. 2011 Sep;154(5):618-25.
Cutler JA et al. The identification and classification of 41 novel mutations in the factor VIII gene (F8C). *Hum Mutat*. 2002 Mar;19(3):274-8.
Hill M et al. Mutation analysis in 51 patients with haemophilia A: report of 10 novel mutations and correlations between genotype and clinical phenotype. *Haemophilia*. 2005 Mar;11(2):133-41.

This result has been reviewed and approved by [REDACTED]

BACKGROUND INFORMATION: Hemophilia A (F8) Sequencing

CHARACTERISTICS: Hemophilia A is characterized by deficiency of factor VIII clotting activity. Less than 1 percent factor VIII activity results in severe deficiency associated with spontaneous joint or deep muscle bleeding. Moderate deficiency (1-5 percent activity) and mild deficiency (6-40 percent activity) are associated with prolonged bleeding after tooth extractions, surgery, or injuries, and recurrent or delayed wound healing. Female carriers of hemophilia A may have increased bleeding tendencies.

EPIDEMIOLOGY: 1 in 5,000 live male births worldwide

CAUSE: Pathogenic F8 germline variants

INHERITANCE: X-linked recessive. In the estimated 30 percent of cases that appear to be de novo, the mother is found to be a carrier at least 80 percent of the time.

PENETRANCE: 100 percent in males. Approximately 30 percent of female carriers have factor VIII activity levels of less than 40 percent and are at risk for bleeding symptoms typically consistent with mild hemophilia A.

CLINICAL SENSITIVITY: Sequencing detects 76-98 percent of variants causing mild or moderate hemophilia A and 43-51 percent of variants causing severe hemophilia A.

GENE TESTED: F8 (NM_000132.4)

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the F8 gene, followed by massively parallel sequencing. Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of or carrier status for hemophilia A. This test only detects variants within the coding regions and intron-exon boundaries of the F8 gene. Variants in regions that are not included in the preferred transcript are not detected. This assay will not detect the common intron 22-A and intron 1 inversions.

Regulatory region variants and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. In males, lack of massively parallel sequencing coverage of one or more F8 exons may suggest the presence of a large deletion; however, this should be confirmed by a validated method. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions.

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Unless otherwise indicated, testing performed at:

ARUP LABORATORIES | 800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Jonathan R. Genzen, MD, PhD, Laboratory Director

Patient: Patient, Example
ARUP Accession: 25-149-146578
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
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This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Hemophilia A (F8) Specimen	25-149-146578	5/29/2025 3:44:00 PM	5/31/2025 11:57:46 AM	6/6/2025 12:31:00 PM
Hemophilia A (F8) Interp	25-149-146578	5/29/2025 3:44:00 PM	5/31/2025 11:57:46 AM	6/6/2025 12:31:00 PM

END OF CHART

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