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

Physician: Doctor, Example

Patient: Patient, Example

DOB	[redacted]
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hemophilia A (F8) Sequencing

ARUP test code 2001747

F8 FGS Specimen: Whole Blood

Hemophilia A (F8) Sequencing Interp: **Positive** *

Section 79-1 of New York State Civil Rights Law requires informed consent be obtained from patients (or their legal guardians) prior to pursuing genetic testing. These forms must be kept on file by the ordering physician. Consent forms for genetic testing are available at www.aruplab.com. Incidental findings are not reported unless clinically significant but are available upon request.

TEST PERFORMED - 2001747
TEST DESCRIPTION - Hemophilia A (F8) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the F8 gene.

DNA VARIANT
Classification: Pathogenic
Gene: F8
Nucleic Acid Change: c.6089G>A; Hemizygous
Amino Acid Alteration: p.Ser2030Asn
Also Known As: p.Ser2011Asn

INTERPRETATION
One copy of a pathogenic variant, c.6089G>A; p.Ser2030Asn, was detected through bidirectional sequencing of all coding regions and intron/exon borders of the factor 8 (F8) gene. This result is consistent with a diagnosis for hemophilia A. Symptoms of hemophilia A are highly variable and variants detected by this assay may result in mild, moderate or severe disease. All of his daughters will be carriers but none of his sons will inherit the variant.

Evidence for variant classification: The F8 c.6089G>A; p.Ser2030Asn variant (rs369414658), also known as p.Ser2011Asn, is reported in the literature in multiple individuals affected with mild hemophilia A (Lannoy 2015, Liu 1998, Markoff 2009, Repesse 2007) and is considered a founder mutation in the Belgian population (Lannoy 2015). This variant is reported in ClinVar (Variation ID: 439683). This variant is found in the non-Finnish European population with an allele frequency of 0.006% (5/81740 alleles, including 3 hemizygotes) in the Genome Aggregation Database. The serine at codon 2030 is highly conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. Based on available information, this variant is considered to be pathogenic.

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

RECOMMENDATIONS
This patient should be followed at a hemophilia treatment center. Genetic counseling, including a discussion of medical screening and management, is indicated. At-risk family members should be offered testing for the identified variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_000132.3 (F8)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not included in this report, but are available upon request.

REFERENCES
European Association of Haemophilia and Allied Disorders (EAHAD)-Factor VIII Variant Database: http://f8-db.eahad.org/newstructure.php
Lannoy N et al. Overrepresentation of missense mutations in mild hemophilia A patients from Belgium: founder effect or independent occurrence? Thromb Res. 2015 135:1057-1063.
Liu M et al. A domain mutations in 65 haemophilia A families and molecular modelling of dysfunctional factor VIII proteins. Br J Haematol. 1998 103:1051-1060.
Markoff A et al. Combined homology modelling and evolutionary significance evaluation of missense mutations in blood clotting factor VIII to highlight aspects of structure and function. Haemophilia. 2009 15:932-941.
Repesse Y et al. Factor VIII (FVIII) gene mutations in 120 patients with hemophilia A: detection of 26 novel mutations and correlation with FVIII inhibitor development. J Thromb Haemost. 2007 5:1469-1476.

This result has been reviewed and approved by Rong Mao, M.D.

BACKGROUND INFORMATION: Hemophilia A (F8) Sequencing

CHARACTERISTICS: Severe deficiency of factor VIII clotting activity leading to spontaneous joint or deep muscle bleeding. Moderate to mild deficiency is associated with prolonged bleeding after tooth extractions, surgery, or injuries and recurrent or delayed wound healing.
INCIDENCE: 1 in 4,000-5,000 live male births worldwide, rare in females.
INHERITANCE: X-linked recessive. Of simplex cases, 85 percent of mothers are carriers and 10-15 percent of boys have a de novo mutation.
PENETRANCE: 100 percent in males and 10 percent in females.
CAUSE: Deleterious F8 gene mutations.
CLINICAL SENSITIVITY: 98 percent of mutations causing mild to moderate hemophilia A and 43 percent of severe hemophilia A mutations are detected by sequencing.
METHODOLOGY: Bidirectional sequencing of the entire F8 coding region and intron-exon boundaries.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations, deep intronic mutations and gene duplications will not be detected in patients of either sex; large deletions will not be detected in females.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
F8 FGS Specimen	19-308-110227	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Hemophilia A (F8) Sequencing Interp	19-308-110227	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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