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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1752
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

von Willebrand Disease, Type 2N (VWF) Sequencing

ARUP test code 2005494

VWD Type 2N (VWF) Sequencing Specimen: Whole Blood

VWD Type 2N (VWF) Sequencing Interp: **Positive** *

TEST PERFORMED - 2005494
TEST DESCRIPTION - von Willebrand Disease, Type 2N (VWF) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
Two apparent copies of a likely pathogenic variant were detected in the VWF gene.

DNA VARIANT
Classification: Likely Pathogenic
Gene: VWF
Nucleic Acid Change: c.2447G>A; Homozygous
Amino Acid Alteration: p.Arg816Gln

INTERPRETATION
Two apparent copies of a likely pathogenic variant, c.2447G>A; p.Arg816Gln, were detected in the von Willebrand factor (VWF) gene by targeted bidirectional sequencing of exons 4, 9, 17, 18, 19, 20, 21, 24, 25, and 27. This result is consistent with being affected with von Willebrand disease (VWD) type 2N. Since this condition is inherited in an autosomal recessive manner, all offspring of this individual are predicted to be at least carriers.

Sequence analysis is unable to detect large deletions; therefore, this individual either has two copies of the identified variant or a single copy of the variant and a large deletion on the opposite chromosome. Parental testing could determine which of the above scenarios is correct for the purposes of testing other family members.

Evidence for variant classification: The VWF c.2447G>A; p.Arg816Gln variant (rs62643634), also known as Arg53Gln in the mature protein, is reported in the literature in individuals affected with von Willebrand disease type 2N (Mazurier 2001, Michiels 2009). Additionally, another variant in this codon, p.Arg816Trp, is one of the most common VWD type 2N pathogenic variants (Gaucher 1991, Mazurier 2001, Michiels 2009, Qin 2014). The c.2447G>A; p.Arg816Gln variant is found on only two chromosomes (2/277164 alleles) in the Genome Aggregation Database. The arginine at codon 816 is highly conserved, it occurs in the F8 binding domain (Mazurier 2001), and computational algorithms (PolyPhen2, SIFT) predict this variant

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

is deleterious. Based on available information, this variant is classified as likely pathogenic.

RECOMMENDATIONS
Medical management should rely on clinical and phenotypic laboratory findings as well as family history. At-risk family members should be offered testing for the identified variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Genetic consultation is recommended.

COMMENTS
Reference Sequence: GenBank # NM_000552.3 (VWF)
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
Gaucher C et al. Identification of two point mutations in the von Willebrand factor gene of three families with the 'Normandy' variant of von Willebrand disease. Br J Haematol. 1991 Aug;78(4):506-14.

Mazurier C et al. Type 2N von Willebrand disease: clinical manifestations, pathophysiology, laboratory diagnosis and molecular biology. Best Pract Res Clin Haematol. 2001 Jun;14(2):337-47.

Michiels JJ et al. Recessive von Willebrand disease type 2 Normandy: variable expression of mild hemophilia and VWD type 1. Acta Haematol. 2009;121(2-3):119-27.

Qin HH et al. Similarity in joint and mucous bleeding syndromes in type 2N von Willebrand disease and severe hemophilia A coexisting with type 1 von Willebrand disease in two Chinese pedigrees. Blood Cells Mol Dis. 2014 Apr;52(4):181-5.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: von Willebrand Disease, Type 2N (VWF) Sequencing

CHARACTERISTICS: Mucocutaneous bleeding after brushing or flossing teeth, unexplained bruising, prolonged repeated nosebleeds, menorrhagia, and prolonged bleeding following childbirth, trauma or surgery. Symptoms of type 2N are similar to mild hemophilia A.
INCIDENCE: Approximately 1 in 100 to 1 in 1000 individuals.
INHERITANCE: Autosomal recessive.
CAUSE: Pathogenic VWF mutations.
CLINICAL SENSITIVITY: Unknown for VWD type 2N.
METHODOLOGY: Bidirectional sequencing of VWF exons 4, 9, 17, 18, 19, 20, 21, 24, 25, and 27 and the corresponding 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 large deletion/duplications will not be detected. Mutations lying outside of VWF exons 4, 9, 17, 18, 19, 20, 21, 24, 25, and 27 will not be evaluated.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
VWD Type 2N (VWF) Sequencing Specimen	19-336-112305	12/2/2019 1:12:00 PM	12/2/2019 1:14:20 PM	12/4/2019 8:55:00 AM
VWD Type 2N (VWF) Sequencing Interp	19-336-112305	12/2/2019 1:12:00 PM	12/2/2019 1:14:20 PM	12/4/2019 8:55:00 AM

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