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 2B (VWF) Sequencing

ARUP test code 2005486

vWD2B (VWF) Specimen: Whole Blood

vWD Type 2B (VWF) Sequencing Interp: **Positive** *

TEST PERFORMED - 2005486
TEST DESCRIPTION - von Willebrand Disease, Type 2B (VWF) Sequencing
INDICATION FOR TEST - Not Provided

RESULT
One pathogenic variant was detected in the VWF gene.

DNA VARIANT
Classification: Pathogenic
Gene: VWF
Nucleic Acid Change: c.3797C>T; Heterozygous
Amino Acid Alteration: p.Pro1266Leu

INTERPRETATION
One pathogenic variant, c.3797C>T; p.Pro1266Leu, was detected in the von Willebrand factor (VWF) gene by targeted sequencing of exon 28. This result is consistent with a diagnosis of von Willebrand disease (VWD) type 2B. Clinical manifestations may include thrombocytopenia and mild to moderate mucocutaneous bleeding. Type 2B is inherited in an autosomal dominant pattern. Therefore, this individual's offspring are predicted to have a 50 percent risk of being affected.

Evidence for variant classification: The VWF c.3797C>T; p.Pro1266Leu variant (rs61749370), also known as Pro503Leu, has been described in the literature in individuals with von Willibrand disease (VWD) type 2B, though it is generally reported in individuals with normal VWF multimers (Casonato 2017, Federici 2009, Holmberg 1993, Veyradier 2016, Weiss 1986). This variant has been reported to co-segregate with disease in affected family members (Holmberg 1993, Weiss 1986), and disease is often described as mild (Federici 2009, Holmberg 1993). This variant is also commonly reported in cis to a p.Val1279Ile variant (James 2007). The p.Pro1266Leu variant is reported as pathogenic/likely pathogenic by several laboratories in ClinVar (Variation ID: 314), and it is found in the Finnish European population with an overall allele frequency of 0.37% (92/25086 alleles) in the Genome Aggregation Database. The proline at codon 1266 is moderately conserved but computational programs (PolyPhen2, SIFT) do not reach a consensus as to the effect of this variant on protein function. However, both patient samples and purified protein with the p.Pro1266Leu variant exhibit enhanced ristocitin-induced platelet aggregation relative to

wildtype, consistent with type 2B VWD (Holmberg 1993, Weiss 1986). Additionally, another variant at this codon (p.Pro1266Gln) has been described in families with VWD and is considered pathogenic (Casonato 2017, Federici 2009). Based on available information, the p.Pro1266Leu variant is considered to be pathogenic.

RECOMMENDATIONS
Since desmopressin therapy may worsen the thrombocytopenia associated with Type 2B VWD, it should be used cautiously. Clotting factor concentrates are typically required to treat severe bleeding episodes or at the time of surgery. Indirect treatments, such as hormone therapy or fibrinolytic inhibitors, may be helpful. A genetic consultation, 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_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
Casonato A et al. Type 2B von Willebrand disease with or without large multimers: A distinction of the two sides of the disorder is long overdue. PLoS One. 2017 Jun 22;12(6):e0179566.

Federici AB et al. Clinical and molecular predictors of thrombocytopenia and risk of bleeding in patients with von Willebrand disease type 2B: a cohort study of 67 patients. Blood. 2009 Jan 15;113(3):526-34.

Holmberg L et al. von Willebrand factor mutation enhancing interaction with platelets in patients with normal multimeric structure. J Clin Invest. 1993 May;91(5):2169-77.

James PD et al. The mutational spectrum of type 1 von Willebrand disease: Results from a Canadian cohort study. Blood. 2007 Jan 1;109(1):145-54.

Veyradier A et al. A Laboratory Phenotype/Genotype Correlation of 1167 French Patients From 670 Families With von Willebrand Disease: A New Epidemiologic Picture. Medicine (Baltimore). 2016 Mar;95(11):e3038

Weiss HJ and Sussman II. A new von Willebrand variant (type I, New York): increased ristocetin-induced platelet aggregation and plasma von Willebrand factor containing the full range of multimers. Blood. 1986 Jul;68(1):149-56.

This result has been reviewed and approved by [redacted]

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

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

CHARACTERISTICS: Mucocutaneous bleeding after brushing or flossing teeth, unexplained bruising, prolonged repeated nosebleeds, menorrhagia, and prolonged bleeding following childbirth, trauma or surgery.
INCIDENCE: Approximately 1 in 100 to 1 in 1000 individuals.
INHERITANCE: Autosomal dominant for types 2B, 2M and most of 2A; autosomal recessive for 20 percent of 2A.
PENETRANCE: Dominant mutations are incompletely penetrant when VWF:Ag and VWF:RCo levels are 25-50 IU/dL. Full penetrance is expected when VWF:Ag and VWF:RCo levels are less than 25 IU/dL.
CAUSE: Pathogenic VWF mutations in exon 28.
CLINICAL SENSITIVITY: 80 percent for vWD types 2A, 2B, and 2M; unknown for other vWD subtypes.
METHODOLOGY: Bidirectional sequencing of VWF exon 28 and its 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 exon 28 are not 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
vWD2B (VWF) Specimen	19-336-112303	12/2/2019 1:11:00 PM	12/2/2019 1:14:20 PM	12/4/2019 8:52:00 AM
vWD Type 2B (VWF) Sequencing Interp	19-336-112303	12/2/2019 1:11:00 PM	12/2/2019 1:14:20 PM	12/4/2019 8:52:00 AM

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