

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

Physician: Doctor, Example

Patient: Patient, Example

DOB: 7/29/2012
Gender: Male
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Collection Date: 01/01/2017 12:34

von Willebrand Disease, Type 2M (VWF) Sequencing

ARUP test code 2005490

vWD Type 2M (VWF) Sequencing Specimen whole Blood

vWD Type 2M (VWF) Sequencing Interp

Positive *

TEST PERFORMED - 2005490
TEST DESCRIPTION - von Willebrand Disease, Type 2M (VWF) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One likely pathogenic variant was detected in the VWF gene.

DNA VARIANT
Classification: Likely Pathogenic
Gene: VWF
Nucleic Acid Change: c.4195C>T; Heterozygous
Amino Acid Alteration: p.Arg1399Cys

INTERPRETATION
One copy of a likely pathogenic variant, c.4195C>T; p.Arg1399Cys, was detected in the von Willebrand factor (VWF) gene by targeted sequencing of exons 28, 30, and 31. Additionally, one copy of a benign variant, c.4196G>A; p.Arg1399His, was also detected by sequencing. If these variants are on the same chromosome (in cis), this would result in a different variant, c.4195_4196delinsTA; p.Arg1399Tyr. However, the benign c.4196G>A variant is polymorphic in several subpopulations, and has not been observed in cis with the c.4195C>T variant; therefore these two variants are likely to be on opposite chromosomes. Parental testing could confirm the chromosomal origin of these variants. Overall, this molecular result is consistent with a diagnosis of von Willebrand disease (vWD) if the c.4195C>T; p.Arg1399Cys variant is confirmed to be pathogenic. Clinical manifestations are highly variable. Future offspring of this individual have a 50% chance of inheriting the c.4195C>T; p.Arg1399Cys variant.

Evidence for variant classification: The VWF c.4195C>T; p.Arg1399Cys variant (rs61750077) is reported in the literature in multiple individuals affected with an unclassifiable type of von Willebrand disease (Fidalgo 2016, Michiels 2006, Schneppenheim 2007, Wang 2012). This variant is reported in ClinVar (Variation ID: 100337), and is only observed on eight alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. The arginine at codon 1399 is moderately conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. In vitro functional analyses demonstrate a smeary multimer pattern that suggests the

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

Unless otherwise indicated, testing performed at:

ARUP LABORATORIES | 800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Tracy I. George, MD, Laboratory Director

Patient: Patient, Example
ARUP Accession: 19-275-401648
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Page 1 of 3 | Printed: 1/28/2021 2:38:10 PM
4848

introduced cysteine residue may interfere with disulfide bonds (Fidalgo 2016, Schneppenheim 2007), and at least one patient had vWF activity below the level of detection (Michiels 2006). Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS

This molecular result should be correlated with hematologic indices, including von willebrand antigen and activity, factor VIII level and vw multimeric pattern. 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). To determine the chromosomal origin of the identified variants, parental testing is recommended (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
Any other likely benign and benign variants are not included in this report.

REFERENCES

Fidalgo T et al. Genotype-phenotype correlation in a cohort of Portuguese patients comprising the entire spectrum of VWD types: impact of NGS. *Thromb Haemost.* 2016 Jul 4;116(1):17-31.

Michiels JJ et al. Classification and characterization of hereditary types 2A, 2B, 2C, 2D, 2E, 2M, 2N, and 2U (unclassifiable) von Willebrand disease. *Clin Appl Thromb Hemost.* 2006 Oct;12(4):397-420.

Schneppenheim R et al. Molecular Background of "Smearly" von willebrand Factor Multimers. *Blood.* 2007 110(11):2711.

Wang JW et al. Biogenesis of Weibel-Palade bodies in von willebrand's disease variants with impaired von willebrand factor intrachain or interchain disulfide bond formation. *Haematologica.* 2012 Jun;97(6):859-66.

This result has been reviewed and approved by [REDACTED]

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Page 2 of 3 | Printed: 1/28/2021 2:38:10 PM
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BACKGROUND INFORMATION: von Willebrand Disease, Type 2M (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 type 2M.
 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 exons 28, 30, and 31.
 CLINICAL SENSITIVITY: 80 percent for vWD types 2A, 2B, and 2M; unknown for other vWD subtypes.
 METHODOLOGY: Bidirectional sequencing of VWF exons 28, 30, 31 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 exons 28, 30, and 31 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 2M (VWF) Sequencing Specimen	19-275-401648	10/2/2019 11:26:00 AM	10/3/2019 4:18:00 PM	10/27/2019 10:01:00 AM
vWD Type 2M (VWF) Sequencing Interp	19-275-401648	10/2/2019 11:26:00 AM	10/3/2019 4:18:00 PM	10/27/2019 10:01:00 AM

END OF CHART

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

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