Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: arup, arup

Patient: Genomics, VWF NGS 2

DOB	
Sex:	Male
Patient Identifiers:	36429
Visit Number (FIN):	36748
Collection Date:	2/23/2022 09:21

von Willebrand Disease (VWF) Sequencing

ARUP test code 3004379

von Willebrand Disease Specimen	Whole Blood
von Willebrand Disease Interp	Positive

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

PATHOGENIC VARIANT
Gene: VWF (NM_000552.5)
Nucleic Acid Change: c.4931G>A; Homozygous
Amino Acid Alteration: p.Trp1644Ter
Inheritance: Autosomal recessive

INTERPRETATION
Two apparent copies of a pathogenic variant, c.4931G>A; p.Trp1644Ter, were detected in the VWF gene by massively parallel sequencing. This result is consistent with a diagnosis of von Willebrand disease (VWD) type 3 (MIM: 277480). VWD type 3 typically presents with severe mucocutaneous and musculoskeletal bleeding. Since this condition is inherited in an autosomal recessive manner, all offspring of this individual are predicted to be at least carriers. Because this assay is not able to detect large VWF deletions, this individual either has two copies of the detected pathogenic 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 purpose of testing other family members.

No additional pathogenic variants were identified in the VWF gene by massively parallel sequencing. Please refer to the background information included in this report for limitations of this test.

Evidence for variant classification: The VWF c.4931G>A; p.Trp1644Ter variant (rs1591862022) is reported in the literature in a homozygous individual affected with a coagulation disorder (Downes 2019). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. VWF loss-of-function is an established mechanism of disease, and truncating variants downstream of p.Trp1644Ter have been reported in individuals affected with type 3 von Willebrand disease and are considered disease-causing (Kasatkar 2014). Based on available information, the p.Trp1644Ter variant is considered to be pathogenic.

RECOMMENDATIONS
Referral to a comprehensive bleeding disorders program is

recommended. Desmopressin therapy is not effective in VWD type 3; thus, treatment often requires repeated infusion of VWF/FVIII clotting factor concentrates. Indirect treatments may also be beneficial. Genetic consultation is indicated, including a discussion of medical screening and management. Parental testing should be considered to confirm the specific pathogenic variant in each family lineage. At-risk family members should be offered testing for the identified pathogenic VWF variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). This individuals reproductive partner should be offered carrier screening for VWD.

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants, other than the benign c.4414G>C; p.Asp1472His variant, are not reported.

REFERENCES
Downes K et al. Diagnostic high-throughput sequencing of 2396 patients with bleeding, thrombotic, and platelet disorders. Blood. 2019 Dec 5;134(23):2082-2091. PMID: 31064749.

Kasatkar P et al. Genetic heterogeneity in a large cohort of Indian type 3 von Willebrand disease patients. PLoS One. 2014 Mar 27;9(3):e92575. PMID: 24675615.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: von Willebrand Disease (VWF) Sequencing

CHARACTERISTICS: Von Willebrand disease (VWD) is the most common inherited bleeding disorder and is classified into three major types: type 1, type 2, and type 3. VWF is a large multimeric glycoprotein that plays a critical role in hemostasis. VWF binds factor VIII to protect it from premature degradation, which causes platelet recruitment via the GP1BA receptor and facilitates clot formation. VWD type 1 results from a partial quantitative deficiency of normal plasma von Willebrand factor (VWF), type 2 results from a qualitative defect of VWF, and type 3 results from severe quantitative VWF deficiency. Type 2 VWD is divided into 4 subtypes: type 2A is characterized by reduced or absent high-molecular weight VWF, type 2B results from gain of function in VWF that increases affinity for platelets or collagen, type 2M is caused by reduced VWF interactions with platelets or collagen, and type 2N results from reduced binding of VWF to FVIII. Individuals with VWD may experience excessive mucocutaneous bleeding including, bruising without trauma, bleeding from gums, prolonged recurrent nosebleeds, menorrhagia, gastrointestinal bleeding, and prolonged bleeding following childbirth, trauma, or surgery.

EPIDEMIOLOGY: Prevalence of symptomatic VWD is estimated at 1 in 10,000. Of individuals with VWD, approximately 30 percent have type 1, 60 percent have type 2, and less than 10 percent have type 3.

CAUSE: Pathogenic germline variants in the VWF gene.

INHERITANCE: Autosomal dominant: types 1, 2B, 2M, and most cases of type 2A. Autosomal recessive: types 2N, 3, and 20 percent of type 2A cases.

PENETRANCE: For autosomal dominant types 1, 2A, 2B, and 2M, penetrance is incomplete when VWF:Ag and VWF:RCo levels are between 30 and 50 IU/dL. Full penetrance is expected when VWF:Ag and VWF:RCo levels are less than 30 IU/dL. Heterozygous carriers of type 3 or type 2N are often asymptomatic; however, some individuals may show mild bleeding symptoms.

CLINICAL SENSITIVITY: 80 percent for VWD type 1 and 90 percent for VWD types 2 and 3.

GENE TESTED: VWF (NM_000552)
Exons 26 and 34 are not covered by sequencing, and deletion/duplication analysis is not available for this gene.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the VWF gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

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 von Willebrand disease. This test only detects variants within the coding regions and intron-exon boundaries of the VWF gene. 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. 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. 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. Variants interpreted as pathogenic, likely pathogenic, and of uncertain significance will be reported, as will the benign variant VWF c.4414G>C; p.Asp1472His; other likely benign or benign variants are not reported.

The following regions are not sequenced due to technical limitations of the assay: VWF (NM_000552) exon(s) 26, 34

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
von Willebrand Disease Specimen	22-054-101654	2/23/2022 9:21:00 AM	2/23/2022 9:21:10 AM	2/23/2022 9:22:00 AM
von Willebrand Disease Interp	22-054-101654	2/23/2022 9:21:00 AM	2/23/2022 9:21:10 AM	2/23/2022 9:22:00 AM

END OF CHART

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