

Von Willebrand Disease (VWF) Sequencing

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Von Willebrand disease (VWD) is a common inherited bleeding disorder that involves qualitative or quantitative abnormalities in von Willebrand factor (VWF), a large multimeric glycoprotein that plays a critical role in hemostasis. Diagnosis generally includes hemostasis tests and VWD assays. Genetic testing may be used to confirm a phenotypic diagnosis of VWD, distinguish VWD type 2N from mild hemophilia A, and distinguish VWD type 2B from platelet type VWD (PT-VWD) caused by pathogenic *GP1BA* gene variants. It can also be used to evaluate family members of individuals with known VWF variants.

For additional information on testing for VWD, refer to the ARUP Consult [Von Willebrand Disease - VWD](#) topic.

Disease Overview

Epidemiology

- Prevalence of symptomatic VWD is estimated at 1 in 10,000¹
 - VWD type 1: 1-5/10,000²
 - VWD type 2: 1-5/10,000³
 - VWD type 3: 1-9/1,000,000⁴
- Of individuals with VWD, approximately 30% have type 1, 60% have type 2, and less than 10% have type 3⁵

Symptoms

Patients with VWD may demonstrate the following⁵:

- Mucocutaneous bleeding after brushing or flossing teeth
- Unexplained bruising
- Prolonged repeated nosebleeds
- Menorrhagia
- Prolonged bleeding following childbirth, trauma, or surgery

Featured ARUP Testing

[von Willebrand Disease \(VWF\) Sequencing 3004379](#)

Method: Massively Parallel Sequencing

- Molecular test to confirm a phenotypic diagnosis of VWD types 1, 2A, 2B, 2M, 2N, or 3
- Use for carrier screening for autosomal recessive forms of VWD.

Additional test options, including VWD subclassification tests, are available. If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate. Refer to the [Laboratory Test Directory](#) for additional information.

Clinical Characteristics of Subtypes

Type	Defect	Clinical Presentation	Treatment
Type 1	Partial deficiency of VWF Type 1C increased VWF clearance leading to low VWF levels	Mild mucocutaneous bleeding	Desmopressin or VWF/FVIII clotting factor concentrates; usually only needed for surgery or major trauma <ul style="list-style-type: none"> 1C: may not be good candidates for desmopressin due to the significantly decreased half-life of their native VWF; thus, VWF replacement therapy may be considered
Type 2	Structurally or functionally abnormal VWF	Highly variable 2A: mild to moderate mucocutaneous bleeding; may have thrombocytopenia 2B: mild to moderate mucocutaneous bleeding; thrombocytopenia may be present; enhanced ability of VWF to bind platelet receptor GP1BA, causes removal of the platelet/VWF complex	2A: VWF/FVIII clotting factor concentrates; responsiveness to desmopressin variable; treatment for severe bleeding episodes may require clotting factor concentrates 2B: clotting factor concentrates needed to treat severe bleeding; desmopressin therapy may worsen the thrombocytopenia 2M: clotting factor concentrates needed; response to desmopressin is usually very poor; may require clotting

VWF:RCo, ratio of VWF to ristocetin cofactor, a measure of the ability of VWF to agglutinate platelets in response to initiation by the antibiotic ristocetin

Source: GeneReviews, 2021⁵

Type	Defect	Clinical Presentation	Treatment
		2M: mild to moderate mucocutaneous bleeding; bleeding episodes may be severe, especially in cases of very low or absent VWF:RCo 2N: symptoms are similar to hemophilia A, but with predominant mucocutaneous bleeding	factor concentrates 2N: desmopressin for minor bleeding; severe bleeding requires concentrate with both VWF and FVIII
Type 3	Complete absence of VWF	Severe mucocutaneous and musculoskeletal bleeding	Requires repeated infusions of clotting factor concentrates

VWF:RCo, ratio of VWF to ristocetin cofactor, a measure of the ability of VWF to agglutinate platelets in response to initiation by the antibiotic ristocetin

Source: GeneReviews, 2021⁵

Genetics

Gene

VWF (NM_000552)

Inheritance

- Autosomal dominant: types 1, 2B, 2M, and most cases of type 2A
 - Rare individuals with type 1 VWD caused by biallelic variants typically have more severe disease than heterozygotes.
- Autosomal recessive: types 2N, 3, and 20% of type 2A cases

Penetrance

Autosomal dominant types 1, 2A, 2B, and 2M

- Incomplete penetrance when VWF antigen (VWF:Ag) and VWF:RCo levels are between 30 and 50 IU/dL⁵
- Full penetrance is expected when VWF:Ag and VWF:RCo levels are <30 IU/dL⁵
- Heterozygous carriers of type 3 VWD or type 2N are often asymptomatic; however, some individuals may show mild bleeding symptoms and be diagnosed with type 1 VWD.⁵

Test Description

Clinical Sensitivity

VWD Type 1: 80%⁵

VWD Type 2A, 2B, 2M, or 2N: 90%⁵

VWD Type 3: 90%⁵

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate ^a (%)	Analytic Sensitivity (PPA) 95% Credibility Region ^a (%)
SNVs	99.2	96.9-99.4
Deletions, 1-10 bp	93.8	84.3-98.2

^aGenes included in this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Variant Class	Analytic Sensitivity (PPA) Estimate ^a (%)	Analytic Sensitivity (PPA) 95% Credibility Region ^a (%)
Deletions, 11-44 bp	99.9	87.8-100
Insertions, 1-10 bp	94.8	86.8-98.5
Insertions, 11-23 bp	99.9	62.1-100

^aGenes included in this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a diagnosis of VWD.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- 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 will not be evaluated:
 - Variants outside the coding regions and intron-exon boundaries of targeted genes
 - Regulatory region and deep intronic variants
 - Noncoding transcripts
 - Large deletions/duplications
 - The following regions are not sequenced due to technical limitations of the assay:
 - VWF(NM_000552) exon(s) 26, 34
- The following may not be detected:
 - Deletions/duplications/insertions of any size by massively parallel sequencing
 - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
 - Low-level somatic variants

References

1. Ng C, Motto DG, Di Paola J. [Diagnostic approach to von Willebrand disease](#). *Blood*. 2015;125(13):2029-2037.
2. Orphanet. [Von Willebrand disease type 1](#). Last updated Feb 2009; accessed Aug 2021.
3. Orphanet. [Von Willebrand disease type 2](#). Last updated Feb 2009; accessed Aug 2021.
4. Orphanet. [Von Willebrand disease type 3](#). Last updated Feb 2009; accessed Aug 2021.
5. Goodeve A, James P. [von Willebrand Disease](#). In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*. University of Washington, Seattle. Updated Oct 2017; accessed Feb 2022.

Related Information

[Von Willebrand Disease - VWD](#)
[Von Willebrand Disease Testing Algorithm](#)

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