Von Willebrand Disease (VWF) Sequencing

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.

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.

Disease Overview

Epidemiology

- Prevalence of symptomatic VWD is estimated at 1 in 10,000[1]
  - VWD type 1: 1-5/10,000[2]
  - VWD type 2: 1-5/10,000[3]
  - VWD type 3: 1-9/1,000,000[4]
- Of individuals with VWD, approximately 30% have type 1, 60% have type 2, and less than 10% have type 3[5]

Symptoms

Patients with VWD may demonstrate the following[5]:

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

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 • 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

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, 2021[5]

Type	Defect	Clinical Presentation	Treatment
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 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	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 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, 2021[5]

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 (VFW:Ag) and VWF:RCo levels are between 30 and 50 IU/dL[5]
- Full penetrance is expected when VWF:Ag and VWF:RCo levels are <30 IU/dL[5]
- 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
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

[a]Genes 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; 1993-2020. [Updated: Oct 2017; Accessed: Feb 2022]

Related Information

Von Willebrand Disease - VWD
Von Willebrand Disease Testing Algorithm

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