Von Willebrand disease (VWD) is the most common inherited bleeding disorder and is classified into three major types: type 1, type 2, and type 3.1 Von Willebrand factor (VWF) is a large multimeric glycoprotein that plays a critical role in hemostasis. VWF binds factor VIII (FVIII) to protect it from premature degradation, which causes platelet recruitment via the GP1BA receptor and facilitates clot formation. Type 1 results from a partial quantitative deficiency of normal plasma VWF, type 2 results from a qualitative defect of VWF, and type 3 results from a severe quantitative VWF deficiency (virtual absence). 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. After diagnosis, subtyping may be indicated. Analysis of VWF multimers using a qualitative assay may help determine the type, but molecular genetic testing may be required to distinguish among certain types and subtypes. Genetic testing may be used to evaluate family members of individuals with known VWF variants or 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. An accurate phenotypic diagnosis helps guide therapeutic decision-making.

For more guidance, see The Diagnosis, Evaluation and Management of von Willebrand Disease report from the National Heart, Lung, and Blood Institute.

### Disease Overview

#### Epidemiology

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

#### Symptoms

Patients with VWD may demonstrate the following:

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

<table>
<thead>
<tr>
<th>Clinical Characteristics of Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
</tr>
</tbody>
</table>

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

### Tests to Consider

**von Willebrand Disease (VWF) Sequencing**

- **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

**Familial Targeted Sequencing**

- **Method**: Massively Parallel Sequencing
  - Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member's test result documenting the familial gene variant is REQUIRED.
  - To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.

**Related Subclassification Tests**

**von Willebrand Panel with Reflex to von Willebrand Multimeric Analysis**

- **Method**: Electrophoresis/Clotting/Microlatex Particle-Mediated Immunoassay/Platelet Agglutination
  - Recommended panel to subclassify VWD when high suspicion for VWD exists
  - Contains VWF multimers, factor VIII activity, VWF antigen, and VWF activity (ristocetin cofactor [RCo])
  - Multimeric testing is performed when RCo, VWF antigen, or factor VIII activity is low or if the ratio of RCo to VWF antigen is <0.7.

**von Willebrand Factor Multimers**

- **Method**: Qualitative Electrophoresis
  - Use to assist with diagnosis and subclassification of inherited or acquired VWD in conjunction with factor VIII activity, VWF antigen, and VWF activity

See Related Diagnostic Tests
<table>
<thead>
<tr>
<th>Type</th>
<th>Defect</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Partial deficiency of VWF</td>
<td>Mild mucocutaneous bleeding</td>
<td>Desmopressin or VWF/FVIII clotting factor concentrates; usually only needed for surgery or major trauma</td>
</tr>
<tr>
<td></td>
<td>Type 1C increased VWF clearance leading to low VWF levels</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- 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</td>
</tr>
<tr>
<td>Type 2</td>
<td>Structurally or functionally abnormal VWF</td>
<td>Highly variable</td>
<td>2A: VWF/FVIII clotting factor concentrates; responsiveness to desmopressin variable; treatment for severe bleeding episodes may require clotting factor concentrates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2A: mild to moderate mucocutaneous bleeding, may have thrombocytopenia</td>
<td>2B: clotting factor concentrates needed to treat severe bleeding; desmopressin therapy may worsen the thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td>2M: clotting factor concentrates needed; response to desmopressin is usually very poor; may require clotting factor concentrates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2M: mild to moderate mucocutaneous bleeding; bleeding episodes may be severe, especially in cases of very low or absent VWF:RCo</td>
<td>2N: desmopressin for minor bleeding; severe bleeding requires concentrate with both VWF and FVIII</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2N: symptoms are similar to hemophilia A, but with predominant mucocutaneous bleeding</td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td>Complete absence of VWF</td>
<td>Severe mucocutaneous and musculoskeletal bleeding</td>
<td>Requires repeated infusions of clotting factor concentrates</td>
</tr>
</tbody>
</table>

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

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/dL.
- Full penetrance is expected when VWF:Ag and VWF:RCo levels are <30 IU/dL.
- 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.

Test Description
Clinical Sensitivity

VWD Type 1: 80%

VWD Type 2A, 2B, 2M, or 2N: 90%

VWD Type 3: 90%

Analytical Sensitivity

For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate (%)</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
</tr>
<tr>
<td>Deletions, 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
</tr>
<tr>
<td>Deletions, 11-44 bp</td>
<td>99.9</td>
<td>87.8-100</td>
</tr>
<tr>
<td>Insertions, 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
</tr>
<tr>
<td>Insertions, 11-23 bp</td>
<td>99.9</td>
<td>62.1-100</td>
</tr>
</tbody>
</table>

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


Related Information

Von Willebrand Disease - VWD
Von Willebrand Disease Testing Algorithm

Related Tests

von Willebrand Panel 0030125
Method: Electromagnetic Mechanical Clot Detection/Platelet Agglutination/Microlatex Particle-Mediated Immunoassay

Factor VIII, Activity 0030095
Method: Electromagnetic Mechanical Clot Detection

von Willebrand Factor Antigen 0030285
Method: Microlatex Particle-Mediated Immunoassay

von Willebrand Factor Activity (Ristocetin Cofactor) 0030250
Method: Platelet Agglutination

von Willebrand Modified Panel 0030284
Method: Platelet Agglutination/Microlatex Particle-Mediated Immunoassay

von Willebrand Multimeric Panel 0030002
Method: Electrophoresis/Clothing/Microlatex Particle-Mediated Immunoassay/Platelet Agglutination

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