Von Willebrand Disease Genetic Subtyping, Type 2 and Platelet Type

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. After diagnosis, subtyping may be indicated. Analysis of von Willebrand factor (VWF) multimers using a qualitative assay may help determine the type, but additional molecular genetic testing may be required to distinguish among certain types and subtypes. These genetic tests may be used to evaluate family members of individuals with known variants or confirm a phenotypic diagnosis of VWD types 2A, 2B, 2M, 2N, or platelet type, helping to distinguish type 2N from mild hemophilia A, and type 2B from platelet type VWD (PT-VWD). An accurate phenotypic diagnosis helps guide therapeutic decision-making.

### Disease Overview

#### Incidence

- **VWD type 2:** 1-5/10,000
- **Platelet-type VWD:** <1/1,000,000

#### 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

For clinical characteristics of subtypes, see table.

### Genetics

#### Genes

- **Type 2:** VWF
- **Platelet type:** GP1BA

#### Inheritance

- Autosomal dominant: most type 2A cases, types 2B and 2M, and PT-VWD
- Autosomal recessive: types 2N, 20% of type 2A cases

#### Penetrance

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

- Incomplete penetrance when VWF:Ag and VWF:RCo levels are 25-50 IU/dL
- Full penetrance is expected when VWF:Ag and VWF:RCo levels are <25 IU/dL

#### Structure/Function

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.

Variants

**GP1BA variants**

- c.746 G>T (p.Gly249Val)
- c.746 G>A (p.Gly249Ser)
- c.763A>G (p.Met255Val)
- c.1306del27 (p.436_444 del 9)

### Test Interpretation

#### Sensitivity/Specificity

- **Clinical sensitivity**
  - 80% for VWD types 2B and 2M
  - 99% for 2A
  - Unknown for other VWD subtypes
- **Analytical specificity and sensitivity**: 99% for type 2

#### Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Variant(s) Detected</th>
<th>Interpretive Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 2A (VWF)</strong></td>
<td>Positive</td>
<td>1 pathogenic type 2A VWF gene variant detected</td>
<td>Individual may be affected if the variant is dominant.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If the variant is recessive, individual is at least a carrier of VWD.</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>No pathogenic VWF gene variant detected</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
<td>1 variant of uncertain significance was detected</td>
<td>Significance unknown.</td>
</tr>
<tr>
<td><strong>Type 2B (VWF)</strong></td>
<td>Positive</td>
<td>1 pathogenic variant detected</td>
<td>Individual is at risk to be affected with type 2B VWD.</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>Individual may still be affected with VWD if an undetected pathogenic variant is present</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
<td>1 variant of uncertain significance was detected</td>
<td>Significance unknown.</td>
</tr>
<tr>
<td><strong>Type 2M (VWF)</strong></td>
<td>Positive</td>
<td>1 pathogenic variant detected</td>
<td>Individual is at risk to be affected with type 2M VWD.</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>Individual may still be affected with VWD if an undetected pathogenic variant is present</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
<td>1 variant of uncertain significance was detected</td>
<td>Significance unknown.</td>
</tr>
<tr>
<td><strong>Type 2N (VWF)</strong></td>
<td>Positive</td>
<td>2 pathogenic variants detected</td>
<td>Individual is predicted to be affected with VWD.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 pathogenic VWF gene variant detected</td>
<td>Individual is at least a carrier and may be affected if an undetected VWF variant is present</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>No pathogenic variants detected</td>
<td>Individual appears to be neither a carrier of or affected with type 2N VWD.</td>
</tr>
</tbody>
</table>

A negative result for type 2N sequencing would be expected in patients with hemophilia A.
Limitations

- A negative result does not eliminate the possibility of VWD, as undetected pathogenic variant(s) may be present in one of the unsequenced exons, a noncoding region, or the promoter
- VWF sequencing may identify sequence variants with uncertain clinical significance
- VWF variants, other than those in exons tested, will not be detected
- Large VWF deletions/duplications will not be detected
- No GP1BA variants, other than the four targeted, are detected by analysis for PT-VWD
- Rare diagnostic errors may occur due to primer-site variants

### Clinical Characteristics of Subtypes

<table>
<thead>
<tr>
<th>Type</th>
<th>Defect</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1: ~30% of cases</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>
</tbody>
</table>
| Type 2: ~60% of cases | Structurally or functionally abnormal VWF | Highly variable | 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 factor VIII |
| Type 3: <10% of cases | Complete absence of VWF | Severe mucocutaneous and musculoskeletal bleeding | Requires repeated infusions of clotting factor concentrates |

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

Source: GeneReviews, 2017
### Type | Defect | Clinical Presentation | Treatment
--- | --- | --- | ---
PT-VWD or pseudo VWD | Abnormal high-affinity interaction between platelet glycoprotein Ib/V/IX complex and VWF | Often indistinguishable from VWD type 2B | 

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

Source: GeneReviews, 2017

---

### References


---

### Related Information

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

---

### Related Tests

- **Familial Mutation, Targeted Sequencing 2001961**
  - Method: Polymerase Chain Reaction/Sequencing

- **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

- **Chromogenic Factor VIII, Activity 3002343**
  - Method: Chromogenic

---

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108 | (800) 522-2787 | (801) 583-2787

Content Review March 2020 | Last Update March 2020

© 2020 ARUP Laboratories. All Rights Reserved.