

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 3.¹ 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: 1-5/10,000²
- Platelet-type VWD: <1/1,000,000³

Symptoms

Patients with VWD may demonstrate the following⁴:

- 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^{3,4}
- 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/dL⁴
- Full penetrance is expected when VWF:Ag and VWF:RCo levels are <25 IU/dL⁴

Tests to Consider

[von Willebrand Disease, Type 2A \(VWF\) Sequencing Exon 28 with Reflex to 9 Exons 2005480](#)

Method: Polymerase Chain Reaction/Sequencing

Molecular test to confirm a phenotypic diagnosis of VWD type 2A

[von Willebrand Disease, Type 2B \(VWF\) Sequencing 2005486](#)

Method: Polymerase Chain Reaction/Sequencing

Molecular test to distinguish VWD type 2B from PT-VWD

[von Willebrand Disease, Type 2M \(VWF\) Sequencing 2005490](#)

Method: Polymerase Chain Reaction/Sequencing

Molecular test to confirm a phenotypic diagnosis of VWD type 2M

[von Willebrand Disease, Type 2N \(VWF\) Sequencing 2005494](#)

Method: Polymerase Chain Reaction/Sequencing

Molecular test to distinguish VWD type 2N from hemophilia A

[von Willebrand Disease, Platelet Type \(GP1BA\) 4 Mutations 2005476](#)

Method: Polymerase Chain Reaction/Sequencing/Fragment Analysis

Molecular test to distinguish VWD type 2B from PT-VWD

Related Subclassification Tests

[von Willebrand Panel with Reflex to von Willebrand Multimeric Analysis 2003387](#)

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)
- Multimeric testing is performed when ristocetin cofactor, VWF antigen, or factor

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

Test	Result	Variant(s) Detected	Interpretive Data
Type 2A (VWF) Sequencing	Positive	1 pathogenic type 2A VWF gene variant detected	Individual may be affected if the variant is dominant If the variant is recessive, individual is at least a carrier of VWD
	Negative	No pathogenic VWF gene variant detected	n/a
	Uncertain	1 variant of uncertain significance was detected	Significance unknown
Type 2B (VWF) Sequencing	Positive	1 pathogenic variant detected	Individual is at risk to be affected with type 2B VWD
	Negative	Negative	Individual may still be affected with VWD if an undetected pathogenic variant is present
	Uncertain	1 variant of uncertain significance was detected	Significance unknown
Type 2M (VWF) Sequencing	Positive	1 pathogenic variant detected	Individual is at risk to be affected with type 2M VWD
	Negative	Negative	Individual may still be affected with VWD if an undetected pathogenic variant is present
	Uncertain	1 variant of uncertain significance was detected	Significance unknown

VIII activity is low or if the ratio of ristocetin cofactor to VWF antigen is <0.7

[von Willebrand Factor Multimers 0092281](#)

Method: Qualitative Electrophoresis

Order to assist with diagnosis and subclassification of inherited or acquired von Willebrand disease in conjunction with factor VIII activity, VWF antigen, and VWF activity

[von Willebrand Multimeric Panel 0030002](#)

Method: Electrophoresis/Clotting/Microlatex Particle-Mediated Immunoassay/Platelet Agglutination

- Not recommended except in suspected cases of acquired VWD or high suspicion of VWD
- Contains VW factor multimeric analysis, factor VIII activity, VWF antigen, VWF activity (ristocetin cofactor)

See [Related Diagnostic Tests](#)

Test	Result	Variant(s) Detected	Interpretive Data
Type 2N (<i>VWF</i>) Sequencing	Positive	2 pathogenic variants detected	Individual is predicted to be affected with VWD
		1 pathogenic <i>VWF</i> gene variant detected	Individual is at least a carrier and may be affected if an undetected <i>VWF</i> variant is present
	Negative	No pathogenic variants detected	Individual appears to be neither a carrier of or affected with type 2N VWD A negative result for type 2N sequencing would be expected in patients with hemophilia A
<i>GP1BA</i> Variant Detection	Positive	1 pathogenic variant detected	Individual predicted to be affected with PT-VWD
	Negative	Negative for 4 variants tested in the <i>GP1BA</i> gene	Risk for PT-VWD is reduced, but not eliminated Individual may have a rare <i>GP1BA</i> variant

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			
Type	Defect	Clinical Presentation	Treatment
Type 1: ~30% of cases	Partial deficiency of <i>VWF</i>	Mild mucocutaneous bleeding	Desmopressin or <i>VWF</i> /FVIII clotting factor concentrates; usually only needed for surgery or major trauma

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

Source: GeneReviews, 2017⁴

Type	Defect	Clinical Presentation	Treatment
Type 2: ~60% of cases Subtype frequency in the Caucasian population: 2A>2M>2N>2B	Structurally or functionally abnormal VWF	Highly variable <ul style="list-style-type: none"> • 2A <ul style="list-style-type: none"> ◦ Mild to moderate mucocutaneous bleeding ◦ May have thrombocytopenia • 2B <ul style="list-style-type: none"> ◦ Mild to moderate mucocutaneous bleeding ◦ Thrombocytopenia may be present ◦ Enhanced ability of VWF to bind platelet receptor GPIBA, causes removal of the platelet/VWF complex • 2M <ul style="list-style-type: none"> ◦ 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 	<ul style="list-style-type: none"> • 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
PT-VWD or pseudo VWD	Abnormal high-affinity interaction between platelet glycoprotein Ib/V/IX complex and VWF Caused by GPIBA variants	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, 2017⁴

References

1. Ng C, Motto DG, Di Paola J. [Diagnostic approach to von Willebrand disease](#). Blood. 2015;125(13):2029-2037. PubMed
2. Orphanet. [Von Willebrand disease type 2](#). [Last Updated: Feb 2009; Accessed: Mar 2020]
3. Orphanet. [Pseudo-von Willebrand disease](#). [Last Updated: Mar 2020; Accessed: Mar 2020]
4. 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 2020]

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

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