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: 1-5/10,000[2]
- Platelet-type VWD: <1/1,000,000[3]

Symptoms

Patients with VWD may demonstrate the following[4]:

- 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/dL[4]
- Full penetrance is expected when VWF:Ag and VWF:RCo levels are <25 IU/dL[4]

Structure/Function

Tests to Consider

von Willebrand Disease, Type 2A (VWF) Sequencing Exon 28 with Reflex to 9 Exons (Temporary Referral as of 02/10/21) 2005480

Method: Polymerase Chain Reaction/Sequencing

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

von Willebrand Disease, Type 2B (VWF) Sequencing (Temporary Referral as of 02/10/21) 2005486

Method: Polymerase Chain Reaction/Sequencing

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

von Willebrand Disease, Type 2M (VWF) Sequencing (Temporary Referral as of 02/10/21) 2005490

Method: Polymerase Chain Reaction/Sequencing

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

von Willebrand Disease, Type 2N (VWF) Sequencing (Temporary Referral as of 02/10/21) 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

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

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

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
Type 2N (*VWF*) Sequencing	Positive	2 pathogenic variants detected	Individual is predicted to be affected with VWD
		1 pathogenic VWF gene variant detected	Individual is at least a carrier and may be affected if an undetected VWF variant is present

Test	Result	Variant(s) Detected	Interpretive Data
	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
GP1BA Variant Detection	Positive	1 pathogenic variant detected	Individual predicted to be affected with PT-VWD
	Negative	Negative for 4 variants tested in the GP1BA gene	Risk for PT-VWD is reduced, but not eliminated Individual may have a rare GP1BA 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 VWF	Mild mucocutaneous bleeding	Desmopressin or VWF/FVIII clotting factor concentrates; usually only needed for surgery or major trauma

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[4]

Type	Defect	Clinical Presentation	Treatment

Type 2: ~60% of cases
 	
Subtype frequency in the White population: 2A>2M>2N>2B
	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 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, 2017[4]

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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Content Review March 2020 | Last Update August 2020