



von Willebrand Disease

Synonym: von Willebrand Factor Deficiency

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Summary

Clinical characteristics

Von Willebrand disease (VWD), a congenital bleeding disorder caused by deficient or defective plasma von Willebrand factor (VWF), may only become apparent on hemostatic challenge, and bleeding history may become more apparent with increasing age.

Recent guidelines on VWD have recommended taking a VWF level of 30 or 40 IU/dL as a cut-off for those diagnosed with the disorder. Individuals with VWF levels greater than 30 IU/dL and lower than 50 IU/dL can be described as having a risk factor for bleeding. This change in guidelines significantly alters the proportion of individuals with each disease type.

Type 1 VWD (~30% of VWD) typically manifests as mild mucocutaneous bleeding.

Type 2 VWD accounts for approximately 60% of VWD. Type 2 subtypes include:

- Type 2A, which usually manifests as mild-to-moderate mucocutaneous bleeding;
- Type 2B, which typically manifests as mild-to-moderate mucocutaneous bleeding that can include thrombocytopenia that worsens in certain circumstances;
- Type 2M, which typically manifests as mild-moderate mucocutaneous bleeding;
- Type 2N, which can manifest as excessive bleeding with surgery and mimics mild hemophilia A.

Type 3 VWD (<10% of VWD) manifests with severe mucocutaneous and musculoskeletal bleeding.

Diagnosis

The diagnosis of VWD typically requires characteristic results of assays of hemostasis factors specific for VWD and/or identification of a heterozygous, homozygous, or compound heterozygous pathogenic variant(s) in *VWF* by molecular genetic testing. In addition, the diagnosis requires (in most cases) a positive family history. In those

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with a risk factor for bleeding (VWF levels >30 and <50 IU/dL), family history may not be positive because of incomplete penetrance and variable expressivity.

Management

Treatment of manifestations: Affected individuals benefit from care in a comprehensive bleeding disorders program. The two main treatments are desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) and clotting factor concentrates (recombinant and plasma-derived) containing both VWF and FVIII (VWF/FVIII concentrate). Indirect hemostatic treatments that can reduce symptoms include fibrinolytic inhibitors; hormones for menorrhagia are also beneficial. Individuals with VWD should receive prompt treatment for severe bleeding episodes. Pregnant women with VWD are at increased risk for bleeding complications at or following childbirth.

Prevention of primary manifestations: Prophylactic infusions of VWF/FVIII concentrates in individuals with type 3 VWD to prevent musculoskeletal bleeding and subsequent joint damage.

Prevention of secondary complications: Cautious use of desmopressin (particularly in those age <2 years because of the potential difficulty in restricting fluids in this age group). Vaccination for hepatitis A and B.

Surveillance: Follow up in centers experienced in the management of bleeding disorders. Periodic evaluation by a physiotherapist of those with type 3 VWD to monitor joint mobility.

Agents/circumstances to avoid: Activities involving a high risk of trauma, particularly head injury; medications with effects on platelet function (ASA, clopidogrel, or NSAIDs). Circumcision in infant males should only be considered following consultation with a hematologist.

Evaluation of relatives at risk: If the familial pathogenic variant(s) are known, molecular genetic testing for at-risk relatives to allow early diagnosis and treatment, if needed.

Pregnancy management: As VWF levels increase throughout pregnancy, women with baseline VWF and FVIII levels greater than 30 IU/dL are likely to achieve normal levels by the time of delivery. However, those with a basal level lower than 20 IU/dL and those with baseline VWF:RCo or other VWF activity measurement/VWF:Ag ratio <0.6 are likely to require replacement therapy. Desmopressin has been successfully used to cover delivery in women with type 1 VWD and a proportion of pregnant women with type 2 VWD; delayed, secondary postpartum bleeding may be a problem.

Genetic counseling

VWD types 2B and 2M are inherited in an autosomal dominant manner. VWD types 1 and 2A are typically inherited in an autosomal dominant manner but may also be inherited in an autosomal recessive manner. VWD types 2N and 3 are inherited in an autosomal recessive manner.

- *AD inheritance.* Most affected individuals have an affected parent. The proportion of cases caused by *de novo* pathogenic variants is unknown. Each child of an individual with AD VWD has a 50% chance of inheriting the pathogenic variant.
- *AR inheritance.* At conception, each sib of an individual with AR VWD has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for family members at risk for AR VWD is possible once the pathogenic variants have been identified in the family.

Prenatal testing and preimplantation genetic diagnosis are possible if the pathogenic variant(s) in the family are known.

GeneReview Scope

von Willebrand Disease: Included Phenotypes

- Type 1 von Willebrand disease
- Type 2A von Willebrand disease
- Type 2B von Willebrand disease
- Type 2M von Willebrand disease
- Type 2N von Willebrand disease
- Type 3 von Willebrand disease

For synonyms and outdated names see Nomenclature.

Diagnosis

Several guidelines and testing algorithms have been published [Keeney et al 2008, Nichols et al 2008, Lassila et al 2011, Laffan et al 2014]. See Figures 1 and 2.

Von Willebrand disease (VWD) is caused by deficient or defective plasma von Willebrand factor (VWF), a large multimeric glycoprotein that plays a pivotal role in primary hemostasis by mediating platelet hemostatic function and stabilizing blood coagulation factor VIII (FVIII).

There are three types of VWD [Sadler et al 2006]:

- **Type 1.** Partial quantitative deficiency of essentially normal VWF
- **Type 2.** Qualitative deficiency of defective VWF; divided into four subtypes depending on VWF function perturbed: 2A, 2B, 2M, 2N
- **Type 3.** Complete quantitative deficiency of (virtually absent) VWF

Suggestive Findings

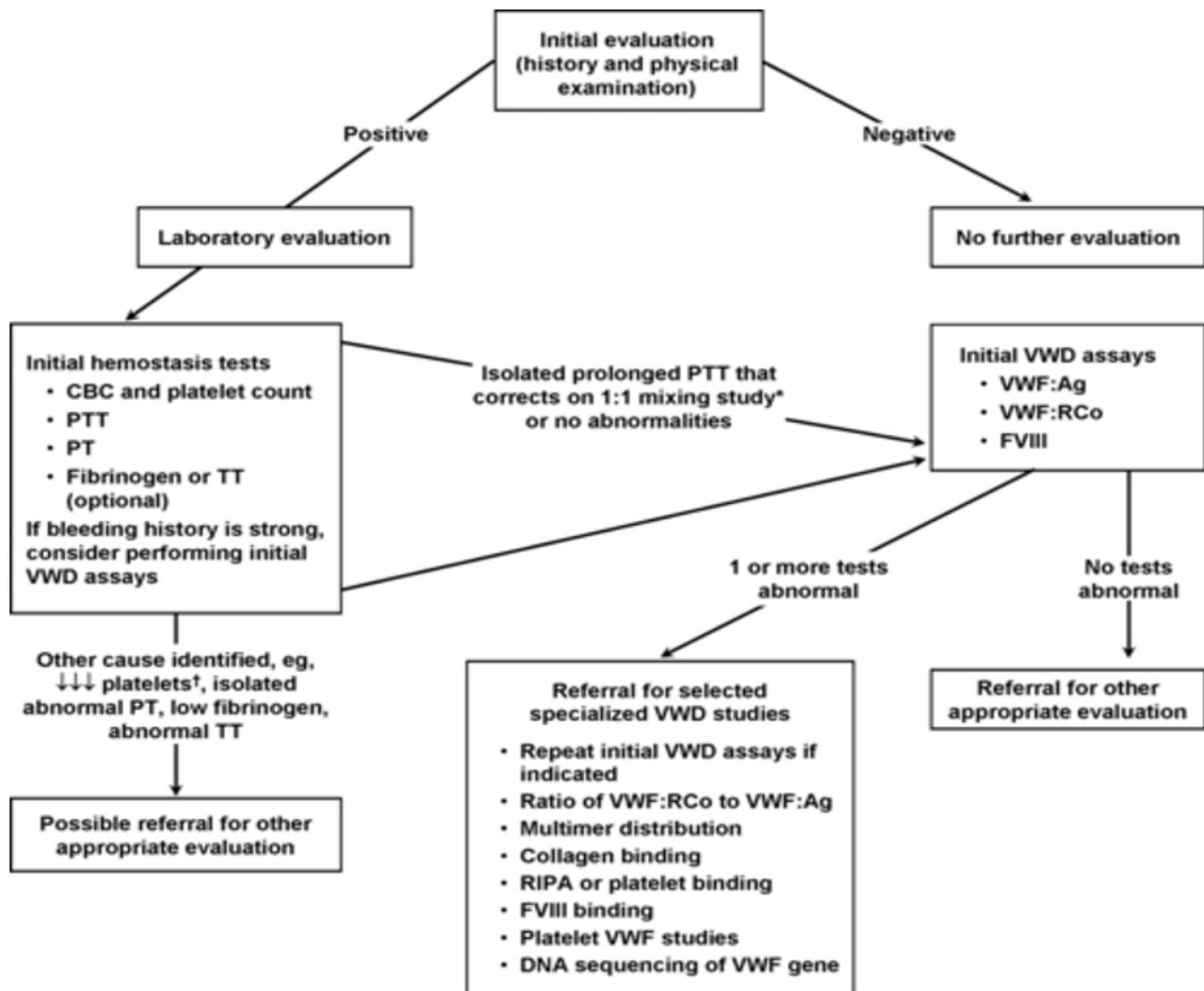
Von Willebrand disease (VWD) **should be suspected** in individuals with excessive mucocutaneous bleeding including the following:

- Bruising without recognized trauma
- Prolonged, recurrent nose bleeds
- Bleeding from the gums after brushing or flossing teeth or prolonged bleeding following dental cleaning or dental extractions
- Menorrhagia, particularly if occurring since menarche
- Prolonged bleeding following surgery, trauma, or childbirth
- Gastrointestinal bleeding

The utility of standard clinical assessment tools to score occurrence of symptoms and their severity as part of VWD diagnosis is increasingly recognized [Tosetto et al 2006, Rodeghiero et al 2010, Elbatarny et al 2014, Mittal et al 2015]. These tools can: determine if there is more bleeding than in the general population; justify the diagnosis of a bleeding disorder; quantify the extent of symptoms; indicate situations requiring clinical intervention; and be used to indicate that a bleeding disorder is unlikely [Tosetto et al 2011]. Additionally, bleeding severity assessment correlates with the long-term probability of bleeding [Tosetto 2016].

Establishing the Diagnosis

The diagnosis of VWD is **established** in a proband with excessive mucocutaneous bleeding and characteristic results of assays of hemostasis factors specific for VWD (see Clinical Laboratory Testing and Table 1) and/or



Laboratory assessment for von Willebrand disease (VWD) or other bleeding disorders. If the clinical evaluation suggests a bleeding disorder, the initial haemostasis tests should be ordered, followed by or along with the initial VWD assays indicated in the algorithm. Referral to a haemostasis specialist is appropriate for help in interpretation, repeated testing and specialized tests.

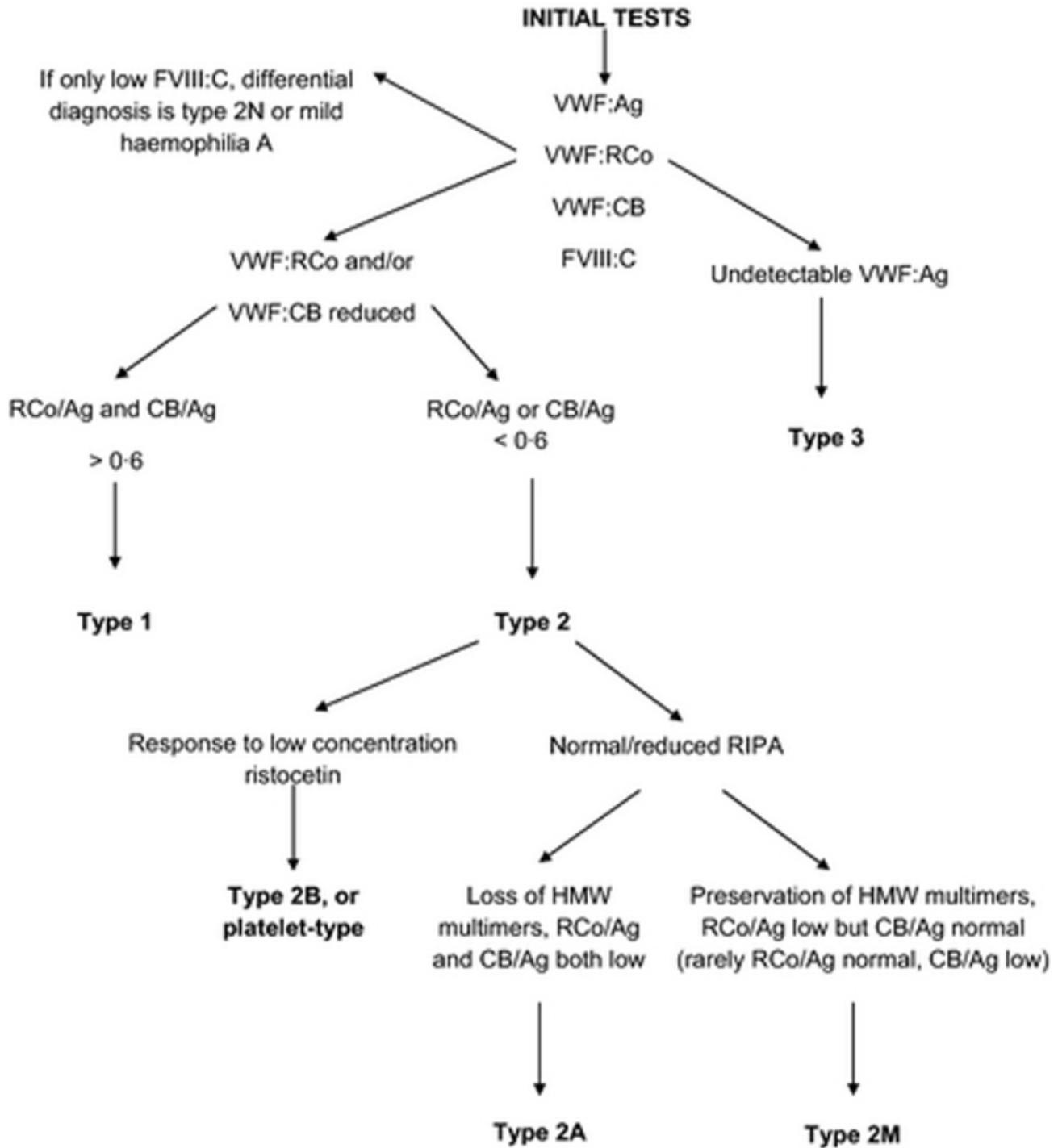
*Correction of the PTT mixing study immediately and after 2-h incubation removes a FVIII inhibitor from consideration. Investigation of other intrinsic factors and lupus anticoagulant may also be indicated.

†Isolated decreased platelets may occur in VWD type 2B.

CBC, complete blood cell count; FVIII, factor VIII; PT, prothrombin time; PTT, partial thromboplastin time; RIPA, ristocetin-induced platelet aggregation; TT, thrombin time; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity

Figure 1. Initial testing algorithm for von Willebrand disease

From Nichols et al [2008]. Reprinted with permission of John Wiley and Sons.



An algorithm for the investigation of suspected von Willebrand disease

VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWF:RCo, ristocetin cofactor activity; VWF:CB, collagen binding activity; FVIII, factor VIII; FVIII:C, Factor VIII coagulant activity; GPIb, glycoprotein Ib; HMW, high molecular weight; RIPA, ristocetin-induced platelet agglutination.

Figure 2. Algorithm for additional testing for von Willebrand disease subtype
 From Laffan et al [2014]. Reprinted with permission of John Wiley and Sons.

identification of a heterozygous, homozygous, or compound heterozygous pathogenic variant(s) in *VWF* by molecular genetic testing (see Table 2).

In addition, the diagnosis requires (in most cases) a positive family history. Note: In those with a risk factor for bleeding (*VWF* levels >30 and <50 IU/dL), family history may not be positive because of incomplete penetrance and variable expressivity.

Clinical Laboratory Testing

Screening tests

- **Complete blood count (CBC)** may be normal, but could also show a microcytic anemia (if the individual is iron deficient) or a low platelet count (thrombocytopenia), specifically in type 2B VWD.
- **Activated partial thromboplastin time (aPTT)** is often normal, but may be prolonged when the factor VIII (FVIII:C) level is reduced to below 30-40 IU/dL, as can be seen in severe type 1 VWD, type 2N VWD, or type 3 VWD. The normal range for FVIII:C clotting activity is approximately 50-150 IU/dL.
- **Prothrombin time** is normal in VWD.
- **Other.** Although some laboratories may also include a skin bleeding time and platelet function analysis (PFA closure time) in their evaluation of an individual with suspected VWD, these tests lack sensitivity in persons with mild bleeding disorders.

Hemostasis factor assays. The following specific hemostasis factor assays (see Table 1) should be performed even if the screening tests are normal in an individual in whom VWD is suspected [Budde et al 2006]. Note: Normal ranges are determined by the individual laboratory and thus are indicative only.

The International Society on Thrombosis and Haemostasis has recently published new guidance on assays that measure von Willebrand factor activity (*VWF:Act*) [Bodó et al 2015]. These tests include:

- **VWF:RCo.** Ristocetin cofactor activity: all assays that use platelets and ristocetin. Ability of *VWF* to agglutinate platelets, initiated by the antibiotic ristocetin (normal range ~50-200 IU/dL)
- **VWF:GPIbR.** All assays that are based on the ristocetin-induced binding of *VWF* to a recombinant WT GPIb fragment
- **VWF:GPIbM.** All assays that are based on the spontaneous binding of *VWF* to a gain-of-function variant GPIb fragment
- **VWF:Ab.** All assays that are based on the binding of a monoclonal antibody (mAb) to a *VWF* A1 domain epitope
- **VWF:Ag.** Quantity of *VWF* protein (antigen) in the plasma, measured antigenically using enzyme-linked immunosorbant assay (ELISA) or by latex immunoassay (LIA) [Castaman et al 2010a] (normal range ~50-200 IU/dL). A reduced ratio (<0.6) of *VWF:Act* to *VWF:Ag* can indicate loss of high-molecular-weight (HMW) multimers.
- **Factor VIII:C level.** Functional FVIII assay (i.e., activity of FVIII in the coagulation cascade) (normal range ~50-150 IU/dL)

If abnormalities in the tests above are identified, specialized coagulation laboratories may also perform the following assays to determine the subtype of VWD:

- **VWF multimer analysis.** SDS-agarose electrophoresis used to determine the complement of *VWF* oligomers in the plasma. Normal plasma contains *VWF* ranging from dimers to multimers comprising more than 40 dimers and molecular weight into gigadaltons. Multimers are classified as low (1-5-dimer), intermediate (6-10-dimer), and high (≥ 10 -dimer) molecular weight. HMW multimers are decreased or missing in type 2A VWD and often in 2B VWD; intermediate MW may also be lost in type 2A VWD. Abnormalities in satellite (“triplet”) band patterns can give clues as to pathogenesis and help to classify subtypes of type 2 VWD [Budde et al 2008].

- **Ristocetin-induced platelet agglutination (RIPA).** Ability of VWF to agglutinate platelets at two to three concentrations of ristocetin. Agglutination at a low concentration (~0.5-0.7 mg/mL) is abnormal and may indicate type 2B or platelet-type pseudo VWD (PT-VWD) caused by pathogenic variants in *GP1BA* (see Differential Diagnosis), in which enhanced VWF-platelet binding is present.
- **Binding of FVIII by VWF (VWF:FVIII B).** Ability of VWF to bind FVIII. Useful, but not widely used to identify type 2N VWD
- **Collagen binding assay (VWF:CB).** Ability of VWF to bind to collagen (a sub-endothelial matrix component). Used to help define functional VWF discordance (i.e., to help distinguish types 1 and 2 VWD) [Flood et al 2013]. Collagen I/III mixture is often used, but isolated deficient binding to collagen types IV and VI has recently been recognized [Flood et al 2012]. Normal range is approximately 50-200 IU/dL. A reduced ratio of VWF:CB/VWF:Ag can indicate loss of HMW multimers.
- **VWF:GP1BA.** Functional tests are used to determine how well VWF binds to GpIba. Previously, this was assessed using the VWF:RCo assay. Currently, this analysis is undertaken as part of the newer activity assays.

Table 1. Classification of VWD Based on Specific VWF Tests

VWD Type	VWF:Act ¹	VWF:Ag ¹	Act/Ag	FVIII:C IU/dL ¹	Multimer Pattern ²	Other
1	Low	Low	Equivalent	~1.5x VWF:Ag	Essentially normal	
2A	Low	Low	VWF:Act < VWF:Ag	Low or normal	Abnormal ↓ HMW	↓ VWF:GP1BA binding
2B	Low	Low	VWF:Act < VWF:Ag	Low or normal	Often abnormal ↓ HMW	↑ RIPA ³ (↓ platelet count)
2M	Low	Low	VWF:Act << VWF:Ag	Low or normal	No loss of HMW	↓ VWF:GP1BA binding ↓ VWF:collagen binding ⁴
2N	Normal/low	Normal/low	Equivalent	<40	Normal in most cases	↓ VWF:FVIII B ⁵
3	Absent	Absent	NA	<10	Absent	

1. Relative to the reference range (approximate values); VWF:Act (50-200 IU/dL), VWF:Ag (50-200 IU/dL), FVIII:C (50-150 IU/dL). VWF activity (VWF:Act) includes VWF:RCo and the newer VWF activity assays in this instance.

2. HMW multimers

3. Increased agglutination at low concentrations of ristocetin

4. Reduction in the ability of VWF to bind to collagen. Types I/III are bound by the A3 domain while types IV and VI are bound by the A1 domain. The latter types are not commonly analysed.

5. Ability of VWF to bind and protect FVIII is reduced. VWF and FVIII levels can look exactly like those in males with mild [hemophilia A](#) or in symptomatic hemophilia A carrier females.

Molecular Genetic Testing

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *VWF* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *VWF* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for

each gene vary by laboratory and over time. 2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Note: Analysis of exons 23 to 34 of *VWF* is complicated by the presence of a partial pseudogene, *VWFP1*.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g. mutation of a different gene or genes that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 2. Molecular Genetic Testing Used in von Willebrand Disease (VWD)

Gene ¹	VWD Type(s) ²	Proportion of VWD Attributed to This Type	Test Method	Proportion of Probands with a Pathogenic Variant ³ Detectable by This Method
<i>VWF</i>	1	~30%	Sequence analysis ⁴	80% ⁵
			Gene-targeted deletion/duplication analysis ⁶	6% ⁷
	All type 2 forms	~60%	Sequence analysis ⁴	~90% ⁷
			Gene-targeted deletion/duplication analysis ⁶	0.2% ⁷
	3	<10% ⁸	Sequence analysis ⁴	~90% ⁷
			Gene-targeted deletion/duplication analysis ⁶	3.7% ⁷

1. See Table A. Genes and Databases for chromosome locus and protein.

2. Recent changes in the von Willebrand factor (VWF) level used for diagnosis have significantly altered the proportion of patients classified with each disease type [Lassila et al 2011, Castaman et al 2013, Laffan et al 2014].

3. See Molecular Genetics for information on allelic variants detected in this gene.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

5. Cumming et al [2006], Goodeve et al [2007], James et al [2007a], Yadegari et al [2012], Veyradier et al [2016]

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. Veyradier et al [2016]

8. In populations with frequent consanguineous partnerships, the rate of recessive forms of VWD may be elevated and type 3 VWD comprises a larger proportion of affected individuals.

Clinical Characteristics

Clinical Description

Von Willebrand disease (VWD) is a congenital bleeding disorder; however, symptoms may only become apparent on hemostatic challenge and bleeding history may become more apparent with increasing age. Thus, it may take some time before a bleeding history becomes apparent.

Recent guidelines on VWD have recommended taking von Willebrand factor (VWF) levels of 30 or 40 IU/dL as a cut-off for those diagnosed with the disorder. Individuals with VWF levels greater than 30 IU/dL and lower than 50 IU/dL can be described as having a risk factor for bleeding. This change in guidelines significantly alters the proportion of individuals with each disease type [Lassila et al 2011, Castaman et al 2013, Laffan et al 2014].

Bleeding history also depends on disease severity; type 3 VWD is often apparent early in life, whereas mild type 1 VWD may not be diagnosed until midlife, despite a history of bleeding episodes.

Individuals with VWD primarily manifest excessive mucocutaneous bleeding (e.g., bruising, epistaxis, menorrhagia) and do not tend to experience musculoskeletal bleeding unless the FVIII:C level is lower than 10 IU/dL, as can be seen in type 2N or type 3 VWD.

Bleeding score. In general, there is an inverse relationship between the VWF level and the severity of bleeding [Tosetto et al 2006]. Bleeding scores (BS) have been documented in several cohort studies and give an indication of the range of bleeding severity associated with different VWD types:

Table 3. Bleeding Scores (BS) Reported in VWD by Type

Patient Group	Study	# of Patients	BS Median	BS Range
Type 1	Goodeve et al [2007]	150	9	-1-24
Type 2A	Castaman et al [2012]	46	11	6-16
Type 2B	Federici et al [2009]	40	5	4-24
Type 2M	Castaman et al [2012]	61	7	4-28
Type 3	Solimando et al [2012]	9	15	6-26
Type 3	Bowman et al [2013]	42	13	3-30

The higher the bleeding score, the greater the bleeding severity

Note: While the studies reported have all used similar bleeding assessment tools, slight variations in the tools and their application may have contributed to differences in bleeding scores.

Recently established cutoffs for an abnormal BS (≥ 4 for adult males, ≥ 6 for adult females, ≥ 3 for children) can be utilized to objectively assess the affected status of individuals tested using the ISTH-bleeding assessment tool (BAT) in a standard fashion [Elbatarny et al 2014].

BS in adults has also been shown to be a predictor of future bleeding [Federici et al 2014].

Type 1 VWD accounts for approximately 30% of all VWD in populations with infrequent consanguineous partnerships [Batlle et al 2016, Veyradier et al 2016]. It typically manifests as mild mucocutaneous bleeding; however, symptoms can be more severe when VWF levels are lower than 15 IU/dL. Epistaxis and bruising are common symptoms among children. Menorrhagia is the most common finding in women of reproductive age [Ragni et al 2016].

Type 2 VWD accounts for approximately 60% of all VWD. The relative frequency of the subtypes is 2A>2M>2N>2B in European populations [Batlle et al 2016, Veyradier et al 2016].

- **Type 2A VWD.** Individuals with type 2A VWD usually present with mild to moderate mucocutaneous bleeding [Veyradier et al 2016].
- **Type 2B VWD.** Individuals typically present with mild-moderate mucocutaneous bleeding. Thrombocytopenia may be present. A hallmark of type 2B VWD is a worsening of thrombocytopenia during stressful situations, such as severe infection or during surgery or pregnancy, or if treated with desmopressin [Federici et al 2009].
- **Type 2M VWD.** Individuals typically present with mild-moderate mucocutaneous bleeding symptoms, but bleeding episodes can be severe, particularly in the presence of very low or absent VWF:RCO [Castaman et al 2012, Larsen et al 2013].
- **Type 2N VWD.** Symptoms are essentially the same as those seen in mild hemophilia A and include excessive bleeding at the time of surgery or procedures as both disorders result from reduced FVIII:C [van Meegeren et al 2015].

Type 3 VWD accounts for up to 10% of VWD (except in areas where consanguineous partnerships are common, where a higher proportion may be found). It manifests with severe bleeding including both excessive mucocutaneous bleeding and musculoskeletal bleeding [Metjian et al 2009, Ahmad et al 2013, Kasatkar et al 2014].

Associated complications

- Gastrointestinal angiodysplasia occurs most commonly in middle-aged/elderly individuals with types 2A and 3 VWD and affects the colon, small intestine, and stomach [Franchini & Mannucci 2014]. Lack of VWF in Weibel-Palade bodies promotes angiogenesis in endothelial cells [Starke et al 2011]. The disorder has also been reported in types 1 and 2B VWD [Hertzberg et al 1999, Siragusa et al 2008].
- Menorrhagia is experienced by a large proportion of women with VWD.
- The development of alloantibodies against VWF is an uncommon but serious complication of VWD treatment. An estimated 5%-10% of individuals with type 3 VWD may experience this complication. Affected individuals present with reduced or absent response to infused VWF concentrates or, in rare cases, with anaphylactic reaction. Individuals who have had multiple transfusions are at highest risk for this complication.

Genotype-Phenotype Correlations

The three phenotypes reflect a partial (type 1 VWD) or complete (type 3 VWD) quantitative deficiency of VWF or qualitative deficits (type 2 VWD) of VWF. See Molecular Genetics, **Pathogenic variants** for details regarding the genotypes associated with each subtype of VWD.

Individuals with large deletions of *VWF* are at highest risk for alloantibody development, although some with other null alleles have also been reported to develop this complication [James et al 2013].

Penetrance

Type 1 VWD (AD)

- **VWF level.** Pathogenic variants resulting in plasma VWF levels lower than 25 IU/dL are mostly fully penetrant. Those resulting in higher VWF levels are often incompletely penetrant.
- **ABO blood group** appears to be an important contributor to penetrance and reduced VWF level in type 1 VWD [Goodeve et al 2007, James et al 2007a]. Blood group contributes approximately 25% of the variance in plasma VWF level; ABO glycosylation of VWF influences its rate of clearance [Jenkins & O'Donnell 2006]. Individuals with non-O blood groups have higher VWF levels than those with O blood group; those with group AB have the highest levels.

Other AD types (2A, 2B, and 2M). Pathogenic variants are often fully penetrant.

Nomenclature

Changes in nomenclature:

- von Willebrand's disease has been replaced by von Willebrand disease.
- vWF has been replaced by VWF.
- vWD has been replaced by VWD.
- RiCof (ristocetin cofactor activity) has been replaced by VWF:RCo [Mazurier & Rodeghiero 2001].
- FVIII RAg (FVIII related antigen) has been replaced by VWF:Ag.
- Platelet-type pseudo von Willebrand (PT-VWD), also called pseudo-VWD, is caused by pathogenic variants in *GP1BA* and, thus, is not a form of VWD (see Differential Diagnosis).
- Acquired von Willebrand syndrome (AVWS), previously known as acquired VWD, is the preferred terminology for defects in VWF concentration, structure, or function that are neither inherited nor reflective of pathogenic variants in *VWF*, but arise as consequences of other medical conditions (see brief discussion of AVWS under Differential Diagnosis).

See also Mazurier & Rodeghiero [2001] and Bodó et al [2015].

Prevalence

VWD affects 0.1% to 1% of the population; 1:10,000 seek tertiary care referral.

VWD type 3 affects 0.5:1,000,000-6:1,000,000 population, increasing with the rate of consanguinity.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *VWF*.

Differential Diagnosis

Two disorders can be difficult to distinguish phenotypically from von Willebrand disease (VWD):

- **Mildhemophilia A**, caused by pathogenic variants in *F8*, resembles **type 2N VWD** in that reduced levels of FVIII:C (~5-40 IU/dL) and normal-to-borderline low levels of VWF can be seen in both disorders. In families with reduced FVIII:C, an X-linked pattern of inheritance can help identify those with mild hemophilia A.

The VWF:FVIIIIB test, which determines the ability of VWF to bind FVIII, can be used to discriminate between the two disorders [Casonato et al 2007] and a commercial assay is now available [Veyradier et al 2011], although on a limited basis. Alternatively, molecular genetic testing can be used to distinguish the two disorders. Both molecular and phenotypic testing have some fallibilities in interpretation.

- **PT-VWD (pseudo VWD)** (OMIM 177820), caused by pathogenic variants in *GP1BA*, may be difficult to distinguish from **type 2B VWD**; one study identified pathogenic variants in *GP1BA* in up to 15% of persons diagnosed with 2B VWD [Hamilton et al 2011]. The two disorders can be distinguished by mixing patient/control plasma and platelets to determine which component is defective [Othman et al 2016] or by molecular testing.

PT-VWD has been shown to be less severe than type 2B VWD using a bleeding assessment tool [Kaur et al 2014].

The two disorders require different treatment. In PT-VWD, VWF concentrate is needed to correct the reduced VWF level, but platelet transfusion may also be required if there is significant thrombocytopenia.

The half-life of replaced VWF is reduced as a result of binding to the abnormal GpIb α , necessitating more frequent administration of VWF concentrate than in VWD.

Acquired von Willebrand syndrome (AVWS) is a mild-moderate bleeding disorder that can occur in a variety of conditions [Sucker et al 2009, Federici et al 2013, Mital 2016] but is not caused by pathogenic variants in *VWF*. It is most often seen in persons older than age 40 years with no prior bleeding history. AVWS has diverse pathology and a number of possible causes:

- Lymphoproliferative or plasma cell proliferative disorders, paraproteinemias (monoclonal gammopathy of unknown significance [MGUS]), multiple myeloma, and Waldenstrom macroglobulinemia. Antibodies against VWF have been detected in some of these cases.
- Autoimmune disorders including systemic lupus erythematosus (SLE), scleroderma, and antiphospholipid antibody syndrome
- Shear-induced VWF conformational changes leading to increased VWF proteolysis (e.g., aortic valve stenosis, ventricular septal defect)
- Markedly increased blood platelet count (e.g., essential thrombocythemia or other myeloproliferative disorders)
- Removal of VWF from circulation by aberrant binding to tumor cells (e.g., Wilm's tumor or certain lymphoproliferative disorders)
- Decreased VWF synthesis (e.g., hypothyroidism)
- Certain drugs (e.g., valproic acid, ciprofloxacin, griseofulvin, hydroxyethyl starch)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with von Willebrand disease (VWD), the following evaluations are recommended:

- A personal and family history of bleeding to help predict severity and tailor treatment. Use of a bleeding assessment tool can facilitate standardized assessment [Kaur et al 2016, Toretto 2016, [ISTH-BAT](#)].
- A joint and muscle evaluation for those with type 3 VWD (Musculoskeletal bleeding is rare in types 1 and 2 VWD.)
- Screening for hepatitis B and C as well as HIV if the diagnosis is type 3 VWD or if the individual received blood products or plasma-derived clotting factor concentrates before 1985
- Baseline serum concentration of ferritin to assess iron stores, as many individuals with VWD (particularly women with menorrhagia) are iron deficient
- Gynecologic evaluation for women with menorrhagia [Rodeghiero 2008]
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

See Nichols et al [2008] ([full text](#)), Castaman et al [2013] ([full text](#)), and Laffan et al [2014] ([full text](#)) for treatment guidelines.

Individuals with VWD benefit from referral to a comprehensive bleeding disorders program for education, treatment, and genetic counseling.

Medical Treatments

The two main treatments are desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) and clotting factor concentrates (recombinant and plasma-derived) containing both VWF and FVIII (VWF/FVIII concentrate).

Indirect hemostatic treatments are also beneficial. Individuals with VWD should receive prompt treatment for severe bleeding episodes.

Desmopressin

- Most individuals with type 1 VWD and some with type 2 VWD respond to intravenous or subcutaneous treatment with desmopressin [Castaman et al 2008, Federici 2008, Leissinger et al 2014], which promotes release of stored VWF and raises levels three- to fourfold. Intranasal preparations are also available.
- Following VWD diagnosis, a desmopressin challenge is advisable to assess VWF response.
- Desmopressin is the treatment of choice for acute bleeding episodes or to cover surgery.
- It has been used successfully to cover delivery in women with type 1 VWD and also for a proportion of pregnant women with type 2 VWD (where a desmopressin trial has previously proved efficacious) [Castaman et al 2010b] (see Pregnancy Management).
- Desmopressin is contraindicated in individuals with arteriovascular disease and in those older than age 70 years, for whom VWF/FVIII concentrate is required.
- In persons who do not tolerate desmopressin or who have a poor VWF response, clotting factor concentrate is required.

Note: Because desmopressin can cause hyponatremia (which can lead to seizures and coma), fluid intake should be restricted for 24 hours following its administration to minimize this risk.

Intravenous infusion of VWF/FVIII clotting factor concentrates

- In those who are non-responsive to desmopressin (i.e., VWF deficiency is not sufficiently corrected) and for those in whom desmopressin is contraindicated (see Treatment by VWD Type), bleeding episodes can be prevented or controlled with intravenous infusion of recombinant VWF or virally inactivated plasma-derived clotting factor concentrates containing both VWF and FVIII [Castaman & Linari 2016, Windyga et al 2016a, Windyga et al 2016b].
- Plasma-derived concentrates are prepared from pooled blood donations from many donors. Virus inactivation procedures eliminate potential pathogens.
- Recombinant VWF Vonvendi[®] was licensed for use in adults (18+ years) by the US FDA in December 2015 [Franchini & Mannucci 2016].

Indirect treatments. In addition to treatments that directly increase VWF levels, individuals with VWD often benefit from indirect hemostatic treatments, including:

- Fibrinolytic inhibitors (i.e., tranexamic acid for treatment or prevention of bleeding episodes);
- Hormonal treatments (i.e., the combined oral contraceptive pill for the treatment of menorrhagia).

Combined treatments for menorrhagia. Current treatments and a proposed future treatment trial are described by Ragni et al [2016]. 1321 women with VWD were assessed between 2011 and 2014, and of these 816 (61.8%) had menorrhagia.

- Treatments used most commonly were combined oral contraceptives, tranexamic acid, and desmopressin as first and second-line therapies, whereas VWF concentrate was the most common third-line therapy used by 13 women (1.6%).
- Review of information on 88 women from six published studies showed that a VWF dose of 33-100 IU kg⁻¹ reduced menorrhagia on days one to six of the menstrual cycle in 101 women.

Treatment by VWD Type

Type 1 VWD. Treatments that directly increase VWF levels (e.g., desmopressin or VWF/FVIII clotting factor concentrates) are usually only needed for the treatment or prevention of severe bleeding, as with major trauma or surgery.

Indirect treatment with fibrinolytic inhibitors or hormones is often effective.

Type 2A VWD. Treatment with clotting factor concentrates is usually only required for the treatment or prevention of severe bleeding episodes such as during surgery.

Responsiveness to desmopressin is variable and should be confirmed prior to therapeutic use.

Indirect treatments can be beneficial.

Type 2B VWD. Clotting factor concentrates are usually required to treat severe bleeding or at the time of surgery.

Treatment with desmopressin should be undertaken cautiously as it can precipitate a worsening of any thrombocytopenia. Individuals with mild or atypical type 2B VWD (caused by p.Pro1266Leu, p.Pro1266Glu, and p.Arg1308Leu variants), however, do not appear to develop thrombocytopenia when exposed to desmopressin [Federici et al 2009].

Indirect treatments (i.e., fibrinolytic inhibitors) can be useful.

Type 2M VWD. Because desmopressin response is generally poor, VWF/FVIII concentrate is the treatment of choice.

Type 2N VWD. Desmopressin can be used for minor bleeding, but because the FVIII level will drop rapidly (as FVIII is not protected by VWF), concentrate containing VWF **as well as** FVIII is required to cover surgical procedures.

Type 3 VWD. Treatment often requires the repeated infusion of VWF/FVIII clotting factor concentrates [Franchini & Mannucci 2016, Lavin & O'Donnell 2016, Lissitchkov et al 2017].

Desmopressin is not effective in type 3 VWD.

Indirect treatments may also be beneficial.

Pediatric Issues

Special considerations for the care of infants and children with VWD include the following:

- Infant males should be circumcised only after consultation with a pediatric hemostasis specialist.
- Desmopressin should be used with caution, particularly in those younger than age two years, because of the potential difficulty in restricting fluids in this age group.
- VWF levels are higher in the neonatal period [Klarmann et al 2010]; thus, phenotypic testing for milder forms of VWD should be delayed until later in childhood.

Prevention of Primary Manifestations

Individuals with type 3 VWD are often given prophylactic infusions of VWF/FVIII concentrates to prevent musculoskeletal bleeding and subsequent joint damage.

Prevention of Secondary Complications

Desmopressin should be used with caution, particularly in those younger than age two years, because of the potential difficulty in restricting fluids in this age group.

Individuals with VWD should be vaccinated for hepatitis A and B [Nichols et al 2008, Castaman et al 2013].

Prevention of chronic joint disease is a concern for individuals with type 3 VWD. However, controversy exists regarding the specific schedule and dosing of prophylactic regimens. An international trial that investigated prophylactic treatment for symptoms including joint bleeding, nosebleeds, and menorrhagia concluded that rates of bleeding within individuals during prophylaxis were significantly lower than levels prior to prophylaxis [Berntorp et al 2010, Abshire et al 2013]. Additionally, rates of bleeding were also significantly reduced in a trial of the recombinant VWF product Vonvendi[®], which was licensed for use in adults in 2015 [Franchini & Mannucci 2016].

Surveillance

Individuals with milder forms of VWD can benefit from being followed by treatment centers with experience in the management of bleeding disorders.

Individuals with type 3 VWD should be followed in experienced centers and should have periodic evaluations by a physiotherapist to monitor joint mobility.

Agents/Circumstances to Avoid

Activities with a high risk of trauma, particularly head injury, should be avoided.

Medications that affect platelet function (ASA, clopidogrel, or NSAIDs) should be avoided as they can worsen bleeding symptoms.

Infant males should be circumcised only after consultation with a pediatric hemostasis specialist.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic at-risk relatives of an affected individual to allow early diagnosis and treatment as needed [Goodeve 2016].

Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- VWD hemostasis factor assays if the pathogenic variant(s) in the family are not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

VWF levels increase throughout pregnancy with the peak occurring four hours after delivery [James et al 2015]. Nonetheless, pregnant women with VWD are at increased risk for bleeding complications and care should be provided in centers with experience in perinatal management of bleeding disorders [Pacheco et al 2010, Castaman 2013, Biguzzi et al 2015, Reynen & James 2016, Roth & Syed 2016].

Women with baseline VWF and FVIII levels higher than 30 IU/dL are likely to achieve normal levels by the time of delivery, whereas those with a basal level lower than 20 IU/dL and those with baseline VWF:Act/VWF:Ag ratio <0.6 are likely to require replacement therapy [Castaman et al 2010b, James et al 2015, Hawke et al 2016].

Although deliveries should occur based on obstetric indications, instrumentation should be minimized [Demers et al 2005].

Delayed, secondary postpartum bleeding may be a problem. VWF level rapidly returns to pre-pregnancy level following delivery [Castaman et al 2013].

Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and www.ClinicalTrialsRegister.eu in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Von Willebrand disease (VWD) types 2B and 2M are inherited in an autosomal dominant manner.

VWD types 1 and 2A are typically inherited in an autosomal dominant manner but may also be inherited in an autosomal recessive manner.

VWD types 2N and 3 are inherited in an autosomal recessive manner.

A single case of uniparental disomy has been reported in type 3 VWD. The two copies of the pathogenic variant resulted from maternal uniparental isodisomy [Boisseau et al 2011].

Risk to Family Members – Autosomal Dominant Inheritance

Parents of a proband

- Most individuals diagnosed with one of the autosomal dominant types of VWD have an affected parent.
- A proband with autosomal dominant VWD may have the disorder as the result of a *de novo* VWF pathogenic variant. The proportion of cases caused by a *de novo* VWF variant is unknown.
- If the VWF pathogenic variant causing autosomal dominant VWD found in the proband cannot be detected in the leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or *de novo* pathogenic variant in the proband. Neither possibility has been sufficiently investigated to comment on relative likelihood of occurrence. Unpublished data on type 1 VWD indicated that approximately 4% of individuals had a *de novo* pathogenic variant [Goodeve et al, unpublished data].
- The family history of some individuals diagnosed with AD VWD may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the recognition of symptoms, or delayed onset of significant hemostatic challenges in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations (e.g., VWD hemostasis factor assays and/or molecular genetic testing if the proband's pathogenic variant is known) have been performed on the parents of the proband.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.

- The sibs of a proband with clinically unaffected parents are still at increased risk for the disorder because of the possibility of reduced penetrance in a parent.
- If the *VWF* variant found in the proband cannot be detected in the leukocyte DNA of either parent, the empiric recurrence risk to sibs is approximately 1% because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant VWD has a 50% chance of inheriting the *VWF* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members may be at risk.

Risk to Family Members – Autosomal Recessive Inheritance

Parents of a proband

- The parents of an individual with autosomal recessive VWD are usually heterozygotes (i.e., carriers of one *VWF* pathogenic variant).
- Heterozygotes (carriers) of type 3 VWD are often asymptomatic. However, between 15% and 50% may show some mild bleeding symptoms and may be diagnosed with type 1 VWD [Nichols et al 2008, Bowman et al 2013].
- Heterozygotes (carriers) of type 2N VWD are often asymptomatic. However, a small proportion may show some mild bleeding symptoms and may be diagnosed with type 1 VWD.

Sibs of a proband

- When both parents are heterozygous for a *VWF* pathogenic variant, each sib of an individual with autosomal recessive VWD has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not a carrier.
 - Heterozygotes (carriers) of type 3 VWD are often asymptomatic. However, 15%-50% may show some mild bleeding symptoms and may be diagnosed with type 1 VWD [Nichols et al 2008, Bowman et al 2013].
 - Heterozygotes (carriers) of type 2N VWD are often asymptomatic. However, a small proportion may show some mild bleeding symptoms and may be diagnosed with type 1 VWD.
- Note: When only one parent is a carrier (in the case of uniparental isodisomy [Boisseau et al 2011]), the risk to sibs of a proband to be affected is unknown, but likely very low (<1%). However, each sib has a 50% chance of being heterozygous and a 50% chance of being unaffected and not a carrier.

Offspring of a proband. The offspring of an individual with autosomal recessive VWD are obligate heterozygotes (carriers) for a pathogenic variant in *VWF*.

Other family members. Each sib of the proband's parents is at 50% risk of being a carrier of a *VWF* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *VWF* pathogenic variant(s) in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *VWF* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for von Willebrand disease are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Medline Plus**
[von Willebrand disease](#)
- **National Heart, Lung, and Blood Institute (NHLBI)**
PO Box 30105
Bethesda MD 20824-0105
Phone: 301-592-8573; 240-629-3255 (TTY)
Fax: 240-629-3246
Email: nhlbiinfo@nhlbi.nih.gov
[Diagnosis, Evaluation and Management of von Willebrand Disease](#)
- **National Hemophilia Foundation (NHF)**
116 West 32nd Street
11th Floor
New York NY 10001
Phone: 212-328-3700
Fax: 212-328-3777
Email: handi@hemophilia.org
[von Willebrand disease](#)
- **National Library of Medicine Genetics Home Reference**

Von Willebrand disease

- **Canadian Hemophilia Society (CHS)**
400 - 1255 University Street
Montreal Quebec H3B 3B6
Canada
Phone: 800-668-2686 (toll-free); 514-848-0503
Fax: 514-848-9661
Email: chs@hemophilia.ca
www.hemophilia.ca
- **Haemophilia Society**
Petersham House
57a Hatton Garden
First Floor
London EC1N 8JG
United Kingdom
Phone: 020 7831 1020; 0800 018 6068 (Toll-free Helpline)
Fax: 020 7405 4824
Email: info@haemophilia.org.uk
www.haemophilia.org.uk
- **World Federation of Hemophilia**
1425 Rene Levesque Boulevard West
Suite 1010
Montreal Quebec H3G 1T7
Canada
Phone: 514-875-7944
Fax: 514-875-8916
Email: wfh@wfh.org
www.wfh.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

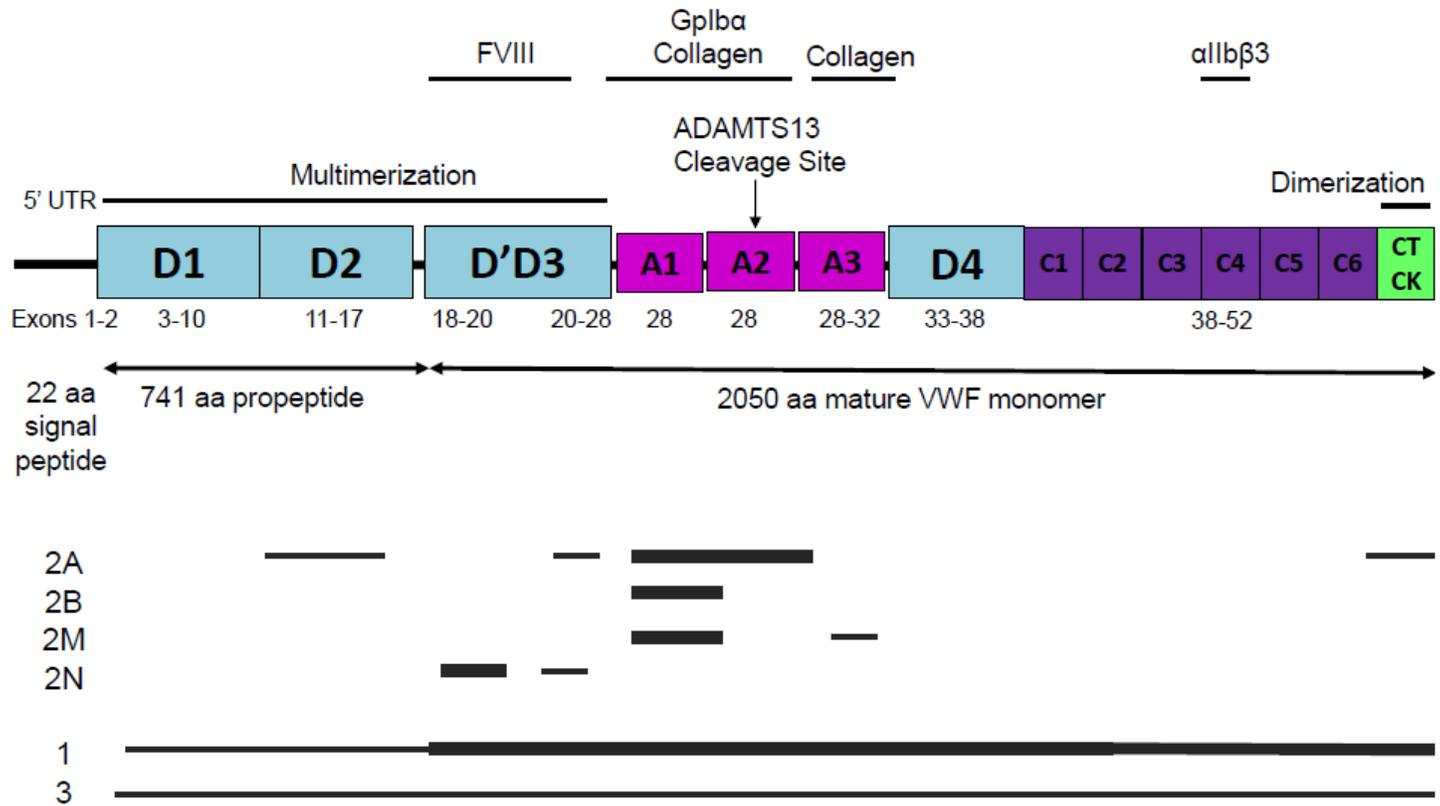


Figure 3. VWF protein structure [adapted from Zhou et al 2012] and location of VWF pathogenic variants by VWD type. Bold horizontal lines indicate the approximate position of exons where pathogenic variants are most prevalent; thinner lines indicate exons with variants of lower frequency. Pathogenic variants that result in type 2 VWD affect VWF function and cluster in domains primarily disrupted by missense variants.

Table A. von Willebrand Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>VWF</i>	12p13.31	von Willebrand factor	EAHAD von Willebrand Factor Database	VWF	VWF

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for von Willebrand Disease ([View All in OMIM](#))

193400	VON WILLEBRAND DISEASE, TYPE 1; VWD1
277480	VON WILLEBRAND DISEASE, TYPE 3; VWD3
613160	VON WILLEBRAND FACTOR; VWF
613554	VON WILLEBRAND DISEASE, TYPE 2; VWD2

Gene structure. *VWF* spans 178 kb of genomic DNA in 52 exons that encode an 8.8-kb mRNA and a 2813-amino-acid protein [Sadler 1998]. For a detailed summary of gene and protein information, see Table A, **Gene**.

VWF has a partial pseudogene, *VWFP1* (exons 23-34), which complicates analysis of these exons. Domain structure and exons encoding each VWF domain are shown in Figure 3.

Pathogenic variants. Most cases of VWD result from single-nucleotide variants; however, large deletions and gene conversion events have been described (Table 4, Figure 3) [James & Lillicrap 2006]. Pathogenic variants are cataloged in the [EAHAD VWF Database](#) (see Table 5). The types of variants most commonly associated with VWD subtypes are described here.

Type 1 VWD. Partial quantitative deficiency in type 1 VWD is mostly associated with missense variants. Pathogenic variants have been identified in an estimated 60%-65% of individuals with type 1 VWD [Cumming et al 2006, Goodeve et al 2007, James et al 2007a, Yadegari et al 2012]. However, with recent guidelines recommending a VWF level of 30 or 40 IU/dL as a cut-off for VWD, the detection rate is much higher. In a recent Spanish study of individuals with VWD, 133 (27.7%) had type 1 VWD [Batlle et al 2016]; in a French study, 25% had type 1 [Veyradier et al 2016]. Variants associated with type 1 include:

- Fully penetrant, dominantly inherited missense variants that are often identified when VWF:Ag and VWF:RCO levels are lower than 30 IU/dL;
- Incompletely penetrant, dominantly inherited missense variants (e.g., p.Tyr1584Cys), identified in approximately 50% of individuals whose VWF:Ag levels are 20-80 IU/dL [O'Brien et al 2003, Goodeve et al 2007].

Of note, approximately 50% of pathogenic variants in type 1 VWD are located between exons 18 and 28.

Missense variants, predominantly in the D3 and A1 domains [Haberichter et al 2008, Millar et al 2008, Eikenboom et al 2013], reduce the residence time of VWF in plasma by many fold. The so-called “Vicenza” variant, p.Arg1205His, is the best characterized and the most common of these pathogenic variants. Such pathogenic variants have been referred to as type 1 clearance (1C) [Haberichter et al 2006].

Type 2 VWD. Qualitative deficiency (type 2 VWD) results from pathogenic missense variants in functionally important areas of VWF. Most pathogenic variants seen in types 2A and 2M and all pathogenic missense variants in type 2B are located in exon 28.

- **Type 2A (AD & AR) VWD.** Pathogenic variants are predominantly located in exon 28, affecting the A2 domain and (to a lesser extent) the A1 domain. Pathogenic variants in the D3 assembly (exons 22 and 25-27) have been reported in dominant disease [Schneppenheim et al 2010].
In addition to exon 28, pathogenic missense variants have also been reported in exons 6-7, 11-16 (AR), and 52 (AD & AR).
- **Type 2B (AD) VWD.** Pathogenic missense variants associated with classic type 2B are located in exon 28 in or close to the A1 domain [Federici et al 2009, Castaman & Federici 2016]. Type 2B pathogenic variants such as p.Pro1266Leu and p.Arg1379Cys may demonstrate enhanced GpIba binding but no thrombocytopenia or HMW multimer loss [Federici et al 2009, Casonato et al 2010].
- **Type 2M (AD) VWD.** Pathogenic variants are predominantly located in exon 28 and impair binding to GpIba. Small numbers of variants that impair binding to collagen types I and III are located in the A3 domain encoded by exons 29-32 [Keeling et al 2012, Veyradier et al 2016] and in the A1 domain, where they impair binding to collagen types IV and VI [Flood et al 2012, Flood et al 2015].
- **Type 2N (AR) VWD.** Most pathogenic missense variants are located in exons 18-20; a much lower proportion have been reported in exons 17 and 24-25 [Mazurier & Hilbert 2005, van Meegeren et al 2010, Veyradier et al 2016].

The 2N pathogenic variant p.Arg854Gln is present in approximately 1% of northern European individuals; p.Arg816Trp is also relatively frequent in affected European individuals.

Type 3 VWD. Severe quantitative deficiency in type 3 VWD typically results from homozygosity or compound heterozygosity for null alleles, but also a small proportion of missense variants. Pathogenic variants associated

with type 3 VWD are found throughout the entire coding region of *VWF* (Figure 3). Sequence analysis of the entire coding region plus deletion/duplication analysis identifies two pathogenic variants in approximately 90% of individuals with type 3 VWD and a single heterozygous variant in the remaining approximately 10% [Kasatkar et al 2014, [EAHAD VWF Database](#)].

- 20% are missense variants.
- 80% are null alleles.

Deletion/duplication analysis of *VWF* detects approximately 2%-5% of pathogenic variants reported in individuals with VWD [[EAHAD VWF Database](#)]. Out-of-frame deletions predominate in type 3 VWD, while in-frame deletions of up to nine exons have also been reported in types 1 and 2 VWD [Sutherland et al 2009, Casari et al 2010]. Duplications of one or two exons have also been reported [Boisseau et al 2013, Obser et al 2016, Veyradier et al 2016].

Gene conversion events with *VWFPI* occur from the 3' end of intron 27 into the 5' end of exon 28 [Goodeve 2010]. There are sufficient differences between *VWF* and *VWFPI* to recognize a conversion event through two or more sequential sequence variants from the pseudogene sequence (*VWFPI*). Conversions of 6 bp to 335 bp are most commonly seen and have been reported in VWD types 1, 2B, 2M, and 3. They have been reported in both multiethnic and Indian populations in higher proportions than often found in other studies [Gupta et al 2005, Kasatkar et al 2014].

Table 4. Selected *VWF* Pathogenic Variants

VWD Type ¹	DNA Nucleotide Change	Predicted Protein Change	VWF Exon	Reference Sequences
1	c.3614G>A	p.Arg1205His	27	NM_000552.3 NP_000543.2
1	c.4751A>G	p.Tyr1584Cys	28	
2A	c.4517C>T	p.Ser1506Leu	28	
2A	c.4789C>T	p.Arg1597Trp	28	
2B	c.3797C>T	p.Pro1266Leu	28	
2B	c.3797C>A	p.Pro1266Glu	28	
2B	c.3916C>T	p.Arg1306Trp	28	
2B	c.3923G>T	p.Arg1308Leu	28	
2B	c.3946G>A	p.Val1316Met	28	
2B	c.4022G>A	p.Arg1341Gln	28	
2B	c.4135C>T	p.Arg1379Cys	28	
2M	c.3835G>A	p.Val1279Ile	28	
2M	c.4273A>T	p.Ile1425Phe	28	
2N	c.2372C>T	p.Thr791Met	18	
2N	c.2446C>T	p.Arg816Trp	19	
2N	c.2561G>A	p.Arg854Gln	20	
3	c.2435delC	p.Pro812ArgfsTer31	18	
3	c.4975C>T	p.Arg1659Ter	28	

Table 4. continued from previous page.

VWD Type ¹	DNA Nucleotide Change	Predicted Protein Change	VWF Exon	Reference Sequences
3	c.7603C>T	p.Arg2535Ter	45	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

1. Examples of the most frequent variants identified in each VWD type are shown. See [EAHAD VWF Database](#) for further information on allelic variants and frequencies.

Normal gene product. The 2813-amino-acid VWF protein comprises:

- 22-amino-acid signal peptide;
- 741-amino-acid propeptide;
- 2050-amino-acid mature protein (see Figure 3) [Sadler 1998, Zhou et al 2012, Valentijn & Eikenboom 2013].

VWF has two key functions:

- Binding collagen in the sub-endothelium at sites of vascular damage, which initiates repair through platelet recruitment and clot formation plus binding; and
- Protecting FVIII from premature proteolytic degradation and transporting it to sites where fibrin generation is required.

VWF has two sites of synthesis: endothelial cells and megakaryocytes, the precursors of platelets. During synthesis, tail-to-tail disulfide-linked dimers are formed through the CK domains, followed by head-to-head VWF oligomers of up to 40 dimers in length.

During multimer production, the propeptide (VWFpp) is cleaved by furin and is secreted into the plasma along with VWF. The ratio of VWFpp to mature VWF (von Willebrand factor antigen or VWF:Ag) can be used to estimate relative half-life of mature VWF [Haberichter et al 2008] and provide information about the mechanism of pathogenicity [Eikenboom et al 2013].

To render HMW VWF less thrombogenic, it is cleaved by ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif) between amino acids 1605 and 1606 following secretion. The pattern of multimer proteolysis products by agarose-SDS gel analysis can be suggestive of VWD subtype [Schneppenheim & Budde 2011].

Abnormal gene product. Abnormalities in VWF depend on the type of pathogenic variant. The protein and nucleotide abnormalities both play a role in determining VWD type:

- **Type 1.** Missense variants predominate but may affect VWF through different mechanisms. Intracellular retention is a common mechanism for type 1 VWD pathogenicity [Eikenboom et al 2009, Eikenboom et al 2013]. Haploinsufficiency resulting from a heterozygous null allele results in reduced VWF expression in a small proportion of cases.
- **Type 2A.** Missense variants result in a loss of high- and sometimes intermediate-molecular-weight multimers through a number of mechanisms that may act together: (1) impaired dimer assembly, (2) impaired multimer assembly, (3) enhanced susceptibility to VWF cleaving protease encoded by *ADAMTS13* [Hassenpflug et al 2006], and (4) intracellular retention [Schneppenheim et al 2010]. All result in the loss of HMW forms of VWF with fewer GpIba binding sites and less effective platelet clot formation.

- **Type 2B.** Missense variants (see **Pathogenic variants** for specific examples) that allow spontaneous binding of VWF to platelet glycoprotein GpIb α , without the conformational change in VWF precipitated by its binding to collagen following subendothelial damage, are associated with type 2B. The platelet-VWF complex is removed from the circulation and can result in mild-moderate thrombocytopenia in up to 50% of individuals [Castaman & Federici 2016]. Higher-molecular-weight multimers bind platelets preferentially, favoring their loss. VWF platelet binding can also enhance susceptibility to the VWF cleaving protease (encoded by *ADAMTS13*), contributing to the loss of HMW multimers.
- **Type 2M.** Missense variants (often in the A1 domain) that result in poor binding of VWF to GpIb α (see Figure 3) alter protein conformation and render the domain incapable of binding GpIb α , but without the loss of HMW multimers associated with type 2A [James et al 2007b]. Missense variants in the A1 domain, and less commonly the A3 domain, may also reduce affinity for subendothelial collagen types I/III (A3 domain) and IV/VI (A1 domain) [Flood et al 2012, Flood et al 2015].
- **Type 2N.** Affinity of VWF for FVIII is reduced as a result of alteration of key amino acids in the FVIII binding site or of conformational change having an indirect effect on VWF-FVIII binding (through lack of cleavage of the propeptide from mature VWF).
- **Type 3.** Both alleles are affected by pathogenic variants (null or missense) that result in lack of VWF secretion from the cell. Most individuals with type 3 VWD have two null alleles and therefore produce no significant quantity of VWF. Approximately 20% of alleles have missense variants (see Figure 3). Some may impair VWF multimerization, resulting in intracellular retention and lack of secretion into plasma.

EAHAD VWF Variant Database summary. The von Willebrand factor LOVD database currently lists more than 700 unique variants representing more than 1400 affected individuals. Table 5 summarizes the numbers of affected individuals with propeptide and mature VWF pathogenic variants and the ratio between the two.

Table 5. EAHAD VWF Mutation Database Summary (January 2017)

VWD Type	Protein Location		All
	Propeptide	Mature protein	
1	24	144	168
2A	17	104	121
2B	0	40	40
2M	0	50	50
2N	4	46	50
3	121	148	269
Total	166	532	698
% by VWF location	24%	76%	100%

Summary of separate patient entries per VWD type. Only a single entry for each patient is included; multiple entries are omitted.

References

Published Guidelines / Consensus Statements

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Chapter Notes

Author Notes

[Professor Goodeve's web page](#)

[Professor James's web page](#)

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Revision History

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- 26 October 2010 (cd) Revision: deletion/duplication analysis available clinically
- 4 June 2009 (et) Review posted live
- 4 December 2008 (ag) Original submission

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