Von Willebrand Disease [VWD] - Summary

Subtype	Inheritance	Prevalence	Bleeding Phenotype	APTT	VIII:C	VWF:Ag	VWF:RCo	[VWF:Ag]: VWF:RCo] Ratio	FVIII Binding	RIPA - Low Dose1	RIPA - High Dose1	Platelet Count	PFA-100	Multimers	Comments
Normal	**-**	**-**	**-**	**Normal**	**Normal**	**Normal**	**Normal**	**1**	**Normal**	**Absent**	**Normal**	**Normal**	**Normal**		
1 [Partial quantitative deficiency]	Autosomal domina	Common - accounts for 80% of cases of VWD. Prevalent in the general population may be as high as	Mild to moderate	May be normal or abnormal- depends upon the severity of the disorder and the level of VIII:C	Normal or ↓	↓ or ↓↓	↓ or ↓↓		Usually Normal	Absent	Often Normal	Normal	Normal or ↑	Normal distribution	There are a wide spectrum of mutations associated with Type 1 VWD. Mutations include those that interfere with the intracellular transport of VWF, or which accelerate the clearance of VWF from the plasma e.g Type 1 Vicenza.
2A [Qualitative deficiency: Decreased VWF-dependent platelet adhesion with selective loss of HMWM]	Autosomal dominant [or recessive]	Uncommon	Variable - usually moderate	Normal or ↑	Normal or ↓	↓	↓↓ or ↓↓↓		Normal	Absent	↓	Normal	↑↑↑	High and intermediate molecular weight multimers absent. Frequent abnormal triplet sub-bands	Type 2A VWD is due to a qualitative abnormality of VWF in which the proportion of HMW multimers is reduced. Type 2A VWD can be caused by mutations that interfere with VWF assembly or by mutations that increase its susceptibility to proteolytic cleavage in plasma. Mutations that affect multimer assembly usually lead to the secretion of multimers that are unable to bind to platelets efficiently. Homozygous mutations in the VWF prepropeptide interfere with multimer assembly within the Golgi of the cell - historically this was classified as Type IIC VWD. Heterozygous mutations within the cysteine knot region of VWF [XXXX] can impair dimerisation of VWF within the ER and lead to a phenotype historically known as Type IID VWD. Heterozygous mutations within the D3 domain can
2B [Qualitative deficiency: Increased affinity for platelet GpIb]	Autosomal dominant		Variable - usually moderate	Usually Normal or ↑	Normal or ↓	Normal or ↓	↓↓		Normal	↑↑↑	Usually normal	Usually ↓ but may be normal	↑↑↑	Variable loss of high-molecular weight multimers. Occasionally multimer distribution is normal with all high-molecular weight multimers present.	Type 2B VWD is caused by mutations that increase platelet-VWF binding leading to proteolytic degradation and depletion of HMW functional VWF multimers. This is similar to Pseudo/platelet type VWD in which mutation in the GpIb receptor leads to an increased affinity for VWF leading to a depletion of the HMWM in the plasma. Type 2B mutations occur within or adjacent to Domain 1. These mutations appear to stabilise platelet-VWF interaction so enhancing platelet binding.
2M [Qualitative deficiency: Decreased VWF-dependent platelet adhesion without selective deficiency	Autosomal dominant [or recessive]	Uncommon	Variable - usually moderate	Usually Normal or ↑	↓↓	Usually ↓	↓↓		Normal	Absent	↓	Normal	↑	The full range of VWF multimers is present. Occasionally ultra-large multimers are present	Type 2M mutations reduce the interaction of VWF with platelet GpIb of with connective tissue and do not substantially impair multimer assembly. Mutations in Type 2M have been reported in the A1 domain and in the A3 domain.
2N [Qualitative deficiency: Markedly decreased binding affinity for FVIII]	Autosomal recessive	Uncommon	Variable - usually moderate	↑↑	↓↓	Normal	Normal	1	Abnormal	Absent	Normal	Normal	Normal	Normal distribution	Type 2N VWD is due to homozygous mutations that impair binding to FVIII leading to a reduction in circulating FVIII. 2N VWD was frequently mistaken as mild-moderate haemophilia A as the VWF levels are normal but FVIII is reduced. However, the pattern of inheritance in 2N VWD is autosomal recessive whilst in Haemophilia it is X-linked. Most mutations causing 2N VWD lie in either the D' or
3 [Virtually complete deficiency of VWF]	Autosomal recessiv	Rare 1:250,000 - 1:1,000,000. Possibly as high as 6:1,000,000 where consanguinity is common	Severe	↑↑↑	↓↓↓	↓↓↓	↓↓↓		Normal	Absent	Absent	Normal	↑↑↑	No multimers visualized. May be faint low-molecular weight bands present.	No consistent genetic abnormality has been identified in Type 3 VWD. Individuals with complete gene deletions may be at risk of developing inhibitors following treatment with VWF-containing concentrates. Individuals who are heterozygous for mutations that when present either in the homozygous state or compound heterozygous state may have none or only
Pseudo/Platelet-Type VWD [Abnormality of the Platelet membrane GpIb receptor]		Rare						Normal	Normal	↑↑↑		↓		Presence of ultra HMWM	A mutation [Arg1205His] leads to the accelerated clerance of the variant VWF from the plasma. VWF:RCo is reduced [commonly around 15 IU/dL]. Measuring the VWFpp:XXXX ratio can be of value in establishing the presence of a variant VWF with an accelerated clearance.
VWD Vicenza															