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The Role of Genetics in the Pathogenesis and Diagnosis of Type 1 von Willebrand Disease

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Abstract

Purpose of review: Von Willebrand disease (VWD) is a common bleeding disorder, but diagnosis of VWD is challenging, particularly with type 1 VWD. While most clinicians use specific tests of von Willebrand factor (VWF) activity to classify patients with VWD, genetic testing for *VWF* defects is another potential method of diagnosis.

Recent findings: Studies of patients with type 1 VWD report consistently that many, but not all, subjects have *VWF* gene defects. Certain populations, including those with VWF levels < 30 IU/dL and those with clearance defects, are more likely to have a *VWF* sequence variant. In addition, a number of loci outside the *VWF* gene have been shown to affect VWF levels, including *ABO*, *CLEC4M*, *STXBP5* and *STAB2*.

Summary: Genetic defects in *VWF* are common, but not all defects lead to disease. Type 1 VWD in particular does not always have an associated *VWF* sequence variant. New data stemming from genome wide association studies on modifier genes suggests that the etiology of type 1 VWD is multifactorial.

Keywords

von Willebrand disease; von Willebrand factor; genetic

Introduction

Type 1 von Willebrand disease (VWD) is the most common form of VWD which is in turn the most common inherited bleeding disorder (1). Unlike other coagulation factor deficiencies, however, VWD is notoriously hard to diagnose, and type 1 VWD is the most

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Conflicts of Interest

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challenging group. Part of this difficulty stems from the need to perform multiple assays of von Willebrand factor (VWF) function, and part stems from the controversy around the appropriate cut-off VWF level to use for diagnosis of type 1 VWD (2). Some studies argue for use of a cut-off VWF level of 30 IU/dL (3,4) while many groups classify patients as type 1 if their VWF levels are lower than the lower limit of the normal range (<50 IU/dL) . It should be noted that regardless of the cutoff used, low VWF does appear to be a risk factor for bleeding, as recent studies from Ireland demonstrate increased bleeding and sustained decreased VWF levels in a cohort of subjects with VWF levels between 30–50 IU/dL (5).

Current VWF testing includes both testing for total protein (VWF antigen, or VWF:Ag) and platelet binding function (either by ristocetin cofactor activity assay [VWF:RCo] or GPIb binding assays [VWF:GPIbM or VWF:GPIbR]) (3). While the VWF:Ag assay is relatively straightforward, the VWF:RCo assay is prone to error due to high inter- and intra- laboratory variability, and the effect of sequence variants in the VWF gene on VWF binding to ristocetin (6–8). The high variability in the VWF:RCo has led to some institutions replacing it with a GPIb binding assay (9–11). The current assays most commonly use a gain-of-function GPIb to induce VWF binding to GPIb independent of ristocetin (11). The International Society on Thrombosis and Haemostasis has recommended using the nomenclature VWF:GPIbM for such assays (12).

The limitations of laboratory testing call for improved methods of diagnosis. Given the ready availability and decreasing cost of gene sequencing, it would seem that genetic diagnosis of type 1 VWD would solve this problem. Several issues, however, preclude the clinical utility of genetic diagnosis, at least in type 1 patients. New findings in the area of type 1 VWD genetics, however, continue to improve our understanding of VWF function and type 1 VWD.

Genetic defects in VWF

In type 2 VWD, defects in VWF function map to specific regions of the VWF protein, and therefore the genetic defects tend to be found in the DNA region corresponding to the affected functional domain (13). In types 1 and 3 VWD, however, defects have been reported across the coding region of the gene (13). These range from point mutations that cause missense or nonsense mutations to deletions and insertions of varying size (13). In some cases, the latter may not be detected on conventional sequencing (14). Copy number variant assays, such as comparative genomic hybridization, can detect how many alleles are present for specific regions of the *VWF* gene (15,16). In some cases, patients receive whole exome or whole genome sequencing while in other cases, if a specific coagulation defect is under evaluation, the VWF gene may be analyzed specifically.

The most common deletion appears to be one affecting exons 4 and 5 (14). Several other deletions have been described, many of which appear to be unique to the affected family (17). Interestingly, while patients with type 3 VWD likely have two genetic defects causing their VWD, their obligate carrier parents may or may not exhibit findings consistent with type 1 VWD (18). This means that a deletion, in and of itself, does not necessarily confer low VWF levels.

Another problem with sequence variants found in type 1 VWD stems from the highly polymorphic nature of *VWF*. In healthy individuals, relatively high frequencies of genetic variants have been reported (19). Of note, several variants were seen at high frequency, particularly in the African American population, and some of these variants had been previously considered as causative of disease. This highlights the need for caution when interpreting novel variants. The advent of larger, more diverse cohorts of genetic data has improved our ability to understand ethnic differences, but unique novel variants still may not necessarily cause disease.

One cautionary tale is that of the *VWF* p.D1472H variant. This variant has been associated with decreased VWF:RCo, and decreased VWF:RCo/VWF:Ag ratios across several studies, yielding levels that could result in a diagnosis of type 2M VWD (8,20). However, when VWF-platelet interactions are examined using other assays (either the VWF antibody assay or assays such as the VWF:GPIbM that do not require ristocetin), normal results are obtained (8,10,21). This “mutation” is actually a common variant, found at high frequencies in the African American population (up to 60% of subjects) but also present at not insubstantial frequencies in the Caucasian population (8). Another variant in the same region has been reported, p.P1467S, but so far described in only one family (22).

Recent VWF genetic findings

A recent study from Spain by Borras and colleagues demonstrated genetic defects in 91% of type 1 subjects (23). Interestingly in their study of 556 subjects a total of 155 novel variants were found, highlighting the high rate of variability in *VWF* (23). The high rate of genetic variants observed in type 1 VWD in their study can be attributed in part to their stringent entry criteria (VWF levels < 30 IU/dL on two occasions) in contrast to previous reports including patients with levels < 50 IU/dL where rates of genetic variants ranged between 55 and 70% (24–28).

A new comprehensive study in patients with “Low VWF” (VWF levels between 30–50 IU/dL) by Lavin and colleagues showed only 40% of patients had genetic variants in the *VWF* gene predicted to be damaging, although 60% of the cohort had at least one sequence variant observed (5). This cohort is remarkable for having reproducible low VWF levels (measured on at least 2 occasions) and comprehensive bleeding score data available on their subjects to confirm that a bleeding phenotype was present (5).

While many variants reduce VWF expression, some variants have been shown to increase VWF expression. Several VWF D’D3 variants, *VWF* c.2880G>A and *VWF* c.2365A>G(;)c.2385T>C, have been linked with increased VWF levels and therefore a decreased risk of diagnosis of type 1 VWD (29). These results are important to demonstrate that not all changes in *VWF* gene sequence result in VWD.

Genetic modifiers outside the VWF locus

While variants in *VWF* logically can cause VWD, a number of genes outside the *VWF* locus have also been implicated in altering VWF levels (table 1). Perhaps the most well characterized is ABO blood group. Gill and colleagues reported in 1987 that individuals with blood type O had lower VWF levels than those individuals with other blood types (30).

The normal range for healthy individuals with blood group O was actually reported as 36–157 IU/dL (30). This is important for two reasons. First, patients with type O are over-represented in studies of type 1 VWD. Second, the diagnosis of VWD typically utilizes levels of <50 IU/dL, and some healthy individuals with type O will fall into this category. For the physician faced with a patient who has bleeding symptoms and low VWF levels, this may be an academic distinction, as low levels of VWF could certainly cause bleeding regardless of the mechanism. It has been pointed out, however, that VWF exists on a continuum, and perhaps low VWF is better considered a risk factor for bleeding as opposed to a definite cause of bleeding (31).

Over the last few years, a number of other genes have been reported to affect *VWF* gene expression (32,33). Some of these have now been characterized and their mechanism of action described, while others are simply the result of genome-wide association studies with exact pathology to be determined. Further details on those best characterized in terms of mechanism and association with true VWD are discussed below.

CLEC4M in particular has been shown to associate with low VWF levels (32,34). CLECM is a lectin receptor that has been shown to both bind and internalize VWF, thus functioning to clear VWF from plasma (35). A recent study by Manderstedt and colleagues showed enrichment of two *CLEC4M* genotypes in the Swedish type 1 VWD population (36). Recent work shows that CLEC4M also clears FVIII, both with and without associated VWF (37). Such findings may have implications beyond just diagnosis of VWD, with potential utility in improving treatment of both VWD and hemophilia.

STXBP5 is another gene associated with low VWF levels (32,34). This gene encodes for syntaxin binding protein 5, and is known to inhibit endothelial cell exocytosis (38). Work from the Netherlands demonstrated an association of variants in *STX2* and *STXBP5* in patients with type 1 VWD and bleeding symptoms (39). Data from Sweden now show that the p.N436S variant in the *STXBP5* gene is associated with type 1 VWD (40). No other potentially causative variants were found in this group, but it is possible that other ethnicities may have different variants in *STXBP5* affecting VWF regulated secretion from endothelial cells.

STAB2 was also identified by GWAS as a potential influencer of VWF levels (32). *STAB2* encodes a protein known as stabilin-2, which is a scavenger receptor. Swystun and colleagues have now demonstrated the mechanism for the effect of stabilin-2, which appears to work as both a clearance receptor and as an immunoregulatory receptor (41). The clinical implications for stabilin-2 are exciting, given that it appears that absence of stabilin-2 prolongs the half-life of VWF, and by association, FVIII (41).

Genome wide association studies continue to implicate additional factors (32). Recent data by Sabater-Lleal show 11 new genes that may affect VWF levels, including *PDHB/PXK/KCTD6*, *SLC39A8*, *FCHO2/TMEM171/TNPO1*, *HLA*, *GIMAP7/GIMAP4*, *OR13C5/NIPSNAP*, *DAB2IP*, *C2CD4B*, *RAB5C-KAT2A*, *TAB1/SYNGR1*, and *ARSA* (42). Functional characterization of these new candidate genes will be required to better understand their role in VWD.

Utility of genetics in VWD diagnosis

Given the issues above, use of genetic diagnosis in type 1 VWD is difficult. Other genes beyond *VWF* may affect VWF levels, so lack of a pathogenic mutation in *VWF* does not exclude the diagnosis of VWD. On the other hand, the frequency of variants in the *VWF* gene is such that discovery of a variant does not necessarily equate to a diagnosis of VWD. The one potential caveat is discovery of a clearance defect.

Those variants that cause type 1C VWD are of potential interest from a therapy standpoint. Patients with type 1C VWD clear their VWF more rapidly than normal (43). Desmopressin, while causing a temporary increase in VWF level, will not result in a sustained rise in these patients (43), so treatment for type 1C VWD typically requires administration of VWF concentrate. If a variant previously reported to cause type 1C VWD is found on sequencing, desmopressin may not the best therapy for that patient. However, other assays such as the VWF propeptide (VWFpp) or results of a desmopressin trial including late (2–4 hour) timepoints may be sufficient to make this diagnosis. A VWFpp/VWF:Ag ratio greater than 3 supports the diagnosis of type 1C VWD without an extended desmopressin trial (44).

Otherwise, utility of sequencing for type 1 VWD is debatable. In general, diagnosis is made based on symptoms and VWF level, and the addition of *VWF* gene sequencing will not usually provide any additional actionable information. Sequencing *VWF* remains of use from a research standpoint, as we seek to understand more about the myriad functions of the VWF protein, but is less helpful from a clinical standpoint.

Sequencing in type 2 VWD, on the other hand, may be very useful. Differentiation of type 2 VWD subtypes in the current classification system requires plasma based assays, including VWF multimers, FVIII binding, and platelet binding, which may not be readily available at some centers. DNA sequencing technology is now widespread, and may provide quicker answers. If a type 2 variant of VWD is part of the differential diagnosis, VWD sequencing could yield a therapeutically meaningful result, as most type 2 variants would also require treatment with von Willebrand concentrate rather than desmopressin.

Conclusion

In summary, sequence variants are common in type 1 VWD, but their location throughout the *VWF* gene and the difficulties surrounding classification of pathogenicity of novel variants limit utility of genetic testing for type 1 VWD. When other types of VWD are part of the differential however, *VWF* gene sequencing may be the fastest method of excluding a potential type 1C or type 2 variant (figure 1). It is important to remember that not all type 1 VWD patients will have a genetic defect in the *VWF* gene, and further work needs to be done to understand the importance of modifier genes in the pathogenesis of type 1 VWD. However, new studies demonstrating the novel effects of modifier genes continue to expand our knowledge of VWF secretion and clearance and may have promise for future therapeutic improvements for patients with VWD.

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Key Points:

1. The *VWF* gene is highly polymorphic.
2. Not all patients with type 1 VWD have genetic variants found in the *VWF* gene.
3. Genetic variants outside the *VWF* locus have also been associated with VWD.

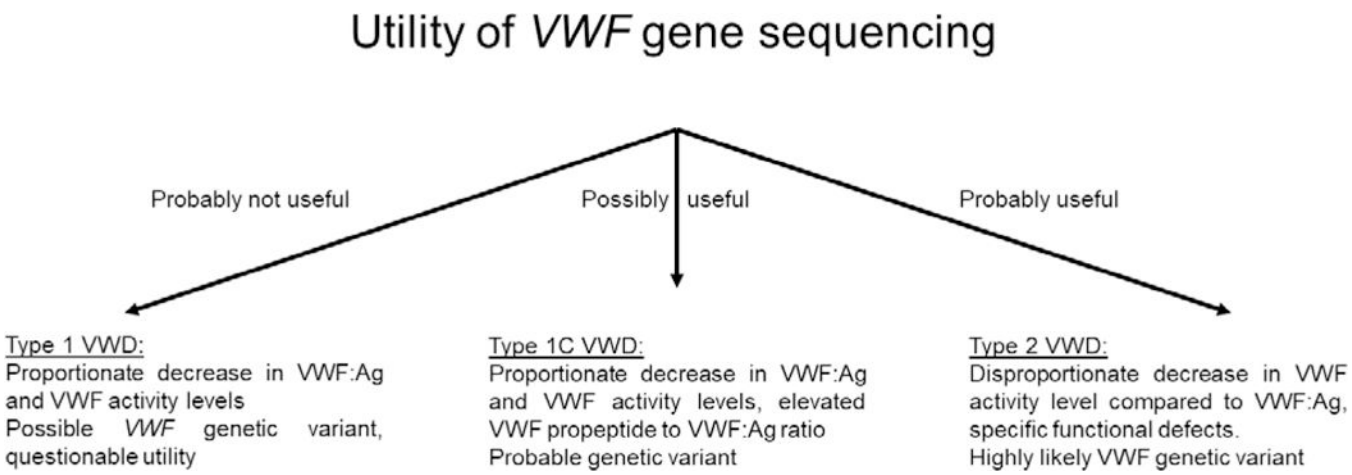

Figure 1. Utility of *VWF* gene sequencing.

The figure shows typical laboratory results for several types of VWD and the likely utility of *VWF* gene sequencing for these diagnoses.

Table:

Modifier genes with defined pathology implicated in VWD

Modifier gene	Putative function
ABO	Clearance
CLEC4M	Clearance
STXBP5	Endothelial cell exocytosis
STAB2	Clearance, immunoregulation