Von Willebrand disease: classification and epidemiology

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Received: April 30, 2025.
Accepted: June 25, 2025.

https://doi.org/10.3324/haematol.2024.286058

Abstract

Von Willebrand disease (VWD) is a highly heterogeneous inherited bleeding disorder caused by reduced levels or activity of von Willebrand factor (VWF). VWD is associated with a wide spectrum of clinical and laboratory phenotypes, but diagnosis is based on three main criteria: a positive bleeding history, low levels of circulating VWF and autosomal inheritance patterns. VWD is classified into quantitative VWF deficiencies (type 1, partial and type 3, almost total) and peculiar qualitative defects (type 2 A, B, M, and N). The prevalence of VWD has been estimated by epidemiological investigations to be ~1%, but a clear-cut diagnosis in clinical practice is often not possible because of several confounding factors influencing plasma VWF levels, especially in mild cases. The prevalence of clinically relevant VWD could range from 1/1,000-10,000 inhabitants based on patients referred to tertiary care centers. Recent genetic prevalence data however suggest that pathogenic *VWF* variants or putative disease alleles may be significantly more common than 1%.

Introduction

In 1926 Erik von Willebrand investigated a family with a new bleeding disorder, named thereafter von Willebrand disease (VWD) in recognition of his pioneering discovery.[1] At that time, he was unaware that he was studying what has been recognized 100 years later as the most frequent inherited hemorrhagic disorder. VWD should always be considered first in the differential diagnosis of patients presenting with mild bleeding symptoms since the prevalence of this disease was estimated to be around 1% in a population-based epidemiological investigation conducted in Italy in 1987.[2] However, a clear-cut diagnosis of VWD often remains difficult or elusive, because of the wide spectrum of clinical and laboratory manifestations as well as variable penetrance and expressivity. In this regard, genetic testing has limited diagnostic value in mild type 1 VWD (in which von Willebrand factor [VWF] levels are >30 U/dL), whereas it remains useful in other types of VWD.

For these reasons, the actual prevalence of clinically significant cases of VWD is uncertain despite the increasing number of diagnostic laboratory tools. Prevalence estimates are in fact critically influenced by the clinical criteria used to select candidate subjects, the populations investigated and by the laboratory criteria to confirm the diagnosis. Moreover, the assessment of the bleeding history is often more difficult in an epidemiological context than in a clinical setting. Physicians must rely on a patient's bleeding history, which is confounded by personal recollection (recall bias), unless the subject has suffered from severe bleeding episodes, possibly leading to hospitalization. Until recently, no clinical tools were available to objectively quantitate mild or intermediate bleeding symptoms, apart from surgical bleeding and menorrhagia.[3] The number and severity of symptoms reported by a patient may be influenced by his or her education, social and cultural context, family setting (e.g., some symptoms may be under-reported by subjects belonging to a bleeding family) and personality, but also by the type of data ascertainment.[4,5] Hence, stringent clinical criteria and standardized questionnaires to assure inter-observer reproducibility have the highest likelihood of achieving accurate assessment.[6] Thus, potential pitfalls may arise in prevalence estimates of VWD in relation to its clinical presentation. The use of different methods to estimate prevalence may indeed result in much lower prevalence figures in hospital-based investigations than in population-based investigations, since different categories of subjects are considered.

Classification of von Willebrand disease

VWD is classified into three main types categorizing quantitative (types 1 and 3) or qualitative (type 2) VWF abnormalities (Table 1).[7,8]

In type 1 VWD (60-70% of cases) there is partial quantitative VWF deficiency (10-30 U/dL), with normal or slightly reduced levels of factor VIII (FVIII). The ratio between VWF activity (VWF:Act) and its concentration (VWF:Ag) is >0.7. The inheritance is autosomal dominant and most of the causative variants are due to missense amino acid changes.[9,10] However, although rare, recessive forms of type 1 VWD have also been reported.[11] Patients with VWF levels between 30-50 U/dL are often included in the "Low VWF" category, since in several of them a true *VWF* variant is rarely detected, although this category seems to be part of the type 1 heterogeneous phenotypes if bleeding symptoms are confirmed.[12,13] A type 1 subtype called 1C includes patients with increased VWF clearance.[14] These patients are characterized by severe reduction of VWF level, increased VWF propeptide/VWF antigen ratio and short-lived response to desmopressin.

VWF is virtually absent in patients with type 3 VWD (≈5% of cases), and FVIII levels are usually very low (<5 U/dL). The inheritance is autosomal recessive and most of these patients are homozygous or compound heterozygous mostly for null alleles in the *VWF* gene.[15]

The remaining 20-25% of patients have type 2 VWD, which is further divided into four variants according to distinct pathophysiological mechanisms and laboratory features.[7] Type 2A is caused by *VWF* variants resulting in decreased binding to platelet glycoprotein Ib (GPIb) receptor caused by the absence or significant reduction of high- and intermediate-molecular-weight VWF multimers. In type 2B, the mutant(s) VWF shows a spontaneous increased affinity for platelet GPIb receptor, which can result in persistent, variable thrombocytopenia often aggravated when using desmopressin or during hemostatic triggers (cancer, infections, inflammation, pregnancy, surgery). A subset of these patients does however have normal platelet counts even after desmopressin or trigger factors, because of specific variants associated with this phenotype. Type 2M is characterized by a decrease in or absent binding to GPIb, with an apparently intact VWF multimer structure. Rare variants with collagen-binding defects are also included in this type. Type 2N (Normandy) shows a variable reduction of the ability of VWF to bind FVIII, resulting in a shortened FVIII half-life.

Most cases of type 2 VWD are usually inherited as a dominant trait with high penetrance and expressivity, apart from type 2N which is transmitted in a recessive manner. Type 2 VWD is suspected when the ratio between VWF:Act and VWF:Ag is <0.7, apart from type 2N in which the ratio is usually >0.7 while the ratio between FVIII and VWF:Ag is <0.5.[14]

Clinical phenotypes and von Willebrand disease classification

Typically, patients with VWD have excessive mucocutaneous bleeding including epistaxis, gum bleeding, heavy menstrual bleeding, and gastrointestinal bleeding. Bleeding after tooth extraction and surgery is also frequent. The bleeding tendency in VWD usually increases across the different types.[16,17] Clinical expression is usually mild in type 1 with VWF levels >30 U/dL. However, females experience more frequent bleeding episodes due to menstruation and during delivery and in the post-partum period. Women with VWD usually have a lower quality of life compared to that of males with VWD because of an increased bleed-

Table 1. Classification of von Willebrand disease. Table modified, with permission, from Sadler *et al*. 2006.[7]

	Quantitative deficiency of VWF (VWF:Act/VWF:Ag >0.7)
Type 1	Partial quantitative deficiency of VWF (~60-70% of all cases) - autosomal dominant transmission
Type 1C	Partial quantitative deficiency of VWF associated with an increased clearance of VWF - autosomal dominant transmission
Type 3	Virtually complete deficiency of VWF (~ 1-2% of all cases) - autosomal recessive transmission
	Qualitative deficiency of VWF (VWF:Act/VWF:Ag <0.7)
Type 2	Qualitative deficiency of VWF (~ 25-30% of all cases)
Type 2A	Qualitative variants with decreased platelet-dependent function associated with the absence of high- and intermediate-molecular-weight VWF multimers - autosomal dominant transmission
Type 2B	Qualitative variants with increased affinity for platelet GPIb - autosomal dominant transmission
Type 2M	Qualitative variants with decreased platelet-dependent function not caused by the absence of high-molecular-weight VWF multimers - autosomal dominant transmission
Type 2N	Qualitative variants with markedly decreased affinity for FVIII - autosomal recessive transmission. In this type, the FVIII/VWF ratio is <0.5 and VWF:Act/VWF:Ag is normal

VWF: von Willebrand factor; Act: activity; Ag: antigen; GPIb: glycoprotein Ib; FVIII: factor VIII.

ing tendency during childbearing age and chronic anemia requiring iron supplementation. Up to 70-80% of women with VWD may experience heavy menstrual bleeding and VWD is responsible for it in a significant proportion of women.[18-20] A recent study showed that a high percentage of infants and toddlers <2 years old with VWD may suffer from circumcision-related bleeding, oropharyngeal and even intra- and extracranial bleeding episodes.[21]

In general, the severity of bleeding correlates with the degree of the reduction of VWF and FVIII, the latter particularly for joint bleeding and bleeding during surgery. Some mucocutaneous bleeding (epistaxis especially during childhood, menorrhagia) may be rather frequent and may affect the quality of life. However, the rate of spontaneous bleeding can sometimes be low even in patients with significant VWF deficiency.[22] Bleeding after dental extraction is the most frequent post-operative bleeding manifestation. Hemarthrosis and deep muscle hematoma are rarely observed in type 1 and 2 VWD and are mainly post-traumatic because FVIII is usually >10-20 U/dL. In contrast, the bleeding phenotype of type 3 VWD may overlap that of moderate hemophilia, including the risk of late arthropathy.[23] In these patients the risk of severe bleeding, especially cerebral and joint bleeds, may be 10- to 20-fold greater than that of patients with type 1 VWD.[24] Gastrointestinal bleeding may be particularly frequent, recurrent and difficult to manage, especially when associated with angiodysplasia in patients with type 3 VWD or those lacking high-molecular-weight multimers in plasma, especially those with type 2A VWD.[25,26] Since FVIII/VWF levels tend to normalize at the end of pregnancy in most cases of type 1 and type 2N VWD, bleeding after delivery is infrequent.[18,27] In contrast, females with other type 2 and type 3 VWD usually need replacement therapy after delivery to prevent immediate or delayed bleeding because VWF levels do not correct.[18,28] Post-operative bleeding is not universally present and may sometimes not occur even in untreated, more severely affected type 1 patients,[28] whereas in types 2 and 3 prophylactic treatment is always required. However, patients with a significant bleeding history invariably require hemostatic prophylaxis also to avoid delayed bleeding.

Epidemiological data on von Willebrand disease prevalence and frequency of types

Prevalence of bleeding patients in the general population

Normal individuals may report hemorrhagic symptoms frequently, but the severity has not been investigated appropriately.[29-31] Using a self-report questionnaire, Friberg *et al*. found that about 25% of Swedish girls reported three or more hemorrhagic symptoms,[4] while this association was reported in less than 1% of normal controls through a physician-guided questionnaire.[6] Stringent criteria and clinical expertise are therefore always advisable in collecting a bleeding history, and the use of appropriate tools may ensure inter-observer reproducibility.[14,32]

Based on the results of physician-conducted interviews in an epidemiological investigation,[2] 49 families (at least two members of the genetic lines with at least two hemorrhagic symptoms) were classified as bleeders, with a prevalence of about 4.5%, while 2% of the investigated children had two or more bleeding symptoms. Notwithstanding the lack of a grading of the severity of bleeding symptoms reported, this figure represents the only estimation of the prevalence of a family bleeding tendency in the general population.

Prevalence according to clinical phenotypes

According to clinical presentation and diagnostic approach, three distinct groups of VWD patients may be identified (Table 2).

In the first group (group A), patients present with a lifelong history of severe to moderate bleeding symptoms,

Table 2. Clinical classification and prevalence of von Willebrand disease according to clinical presentation and diagnostic approach.

Classification	Severe VWD (group A)	Intermediate VWD (group B)	Mild VWD (group C)
Bleeding severity	Severe to moderate	Moderate	Mild
Co-segregation (linkage) of symptoms with low VWF/*VWF* haplotype-variant	Invariable	Variable	Inconsistent
VWF levels*	About 10 U/dL or less	20-30 U/dL	30-50 U/dL
Diagnosis	Easy	Repeated testing may be needed	Not always possible; not clinically useful in some cases
VWD types	Type 3, 2A, 2B, 2M, 1 recessive, 1C, rare 2N	Type 1, some type 2, including most type 2N	Most type 1
Epidemiological ascertainment	Referral-based: appropriate	Referral-based: underestimated	Cross-sectional: overestimated

* For type 2N, factor VIII level must be considered instead. VWD: von Willebrand disease; VWF: von Willebrand factor.

often requiring hospitalization for specific treatment, including replacement therapy and surgical interventions (e.g., nose packing/cauterization for epistaxis, curettage/hormonal treatment in women for menorrhagia). Iron-deficiency anemia is also common, especially in women. Laboratory investigations show VWF activity levels below or around 10 U/dL. Linkage with a mutant *VWF* gene is usually complete as well as the likelihood of detecting a specific *VWF* variant.[10,33] This group of patients includes those with recessive type 3 VWD, some dominant type 1 patients with full penetrance and expressivity (including the Vicenza type), and most type 2A and 2B VWD patients. Prevalence estimates for these patients may be reliably obtained from hospital-based cohorts, as it is highly unlikely that these patients have never been referred to a specialized secondary coagulation center, at least in Western countries.

The second group of patients (group B) comprises subjects with a milder but still definite bleeding phenotype. These patients may have frequent spontaneous bleeding episodes (such as muco-cutaneous bleeding) and may be referred for bleeding after trauma or minor surgery, especially when mucous membranes are involved. Laboratory investigations typically show VWF activity levels around 20-30 U/dL. Linkage analysis with mutations in the *VWF* gene is consistent with an autosomal dominant disease with variable penetrance in most cases.[10,33] Most subjects with type 1 and some with type 2 VWD are included in this group. Prevalence is partly underestimated from hospital-based cohorts, because some patients may never look for hospital advice, resulting in a falsely low prevalence. Very large, cross-sectional (population-based) investigations should be used to identify this cohort.

The third group of patients (group C) comprises patients with a mild hemorrhagic phenotype. Bleeding symptoms are occasional, sometimes absent even after trauma or minor surgery. Laboratory investigations show VWF activity levels around 30-50 U/dL, and repeated measurements to achieve an accurate diagnosis are often required. VWF normalization with age is very frequent.[13,14] Linkage analysis fails to detect association with a *VWF* haplotype in up to 50% of the families, indicating a possibly spurious association.[34] Family investigations and standardized diagnostic tools (e.g., bleeding questionnaire) are critical in trying to achieve a definite diagnosis. Patients classified as "Low VWF" were included in this category,[34] but they are now considered as having true type 1 VWD if bleeding is present. Indeed, in most group C patients, using a Bayesian approach it has been demonstrated that even in the presence of two family members (including the proband) with VWF levels just below 40 U/dL) a final odds ratio of VWD of approximately 2.0 would be produced (false-positive equals true-positive rates).[35] This means that more stringent clinical criteria need to be established in order to achieve a "useful" diagnosis, thereby avoiding mislabeling with the stigma of a definite genetic diagnosis in subjects with a small risk of minor bleeding.

Prevalence of severe von Willebrand disease (group A)

Most cases of clinically moderate to severe VWD are represented by type 3, with cases of type 1, type 2A, and 2B VWD. The prevalence of type 3 VWD is very low, ranging from 0.1 to 5.3 per million in the population. In 1982, Weiss *et al.* reported a prevalence of severe VWD of 1.53 and 1.38 cases per million in Europe and North America, respectively, based on reports from 195 referral centers worldwide.[36] A subsequent re-evaluation of these subjects through measurement of VWF:Ag with a highly sensitive method (immunoradiometric assay) showed a prevalence of severe VWD (defined by an antigen level <1 U/dL) of 0.45 per million.[37] Significant differences in the prevalence of severe VWD were present in different countries, notably with a higher prevalence in Scandinavian countries (2.4-3.12 per million).[37] The highest prevalence of type 3 VWD was, however, observed in Arabs, in whom consanguinity is rather frequent, with an estimated prevalence of 5.3 per million.[38] No data are available about the prevalence of type 2 VWD, while that of severe type 1 (i.e., VWF level <10 U/dL) could be higher than previously believed. For example, VWD Vicenza (p.Arg1205His), an increasingly frequently recognized mutation across several countries, has been identified in 98 patients from a resident population of 807,000 inhabitants, leading to a rough estimation of 12 cases/100,000 inhabitants, substantially greater than the prevalence of hemophilia A (C*astaman, unpublished data*). This estimate appears to be reliable since all the patients and relatives undergo extended family studies to identify earlier potential patients who will require specific treatment or prophylaxis for invasive procedures. Of course, these estimates could be biased by the presence of a founder effect; nevertheless, this situation could occur with other mutations in other countries.

Prevalence of intermediate von Willebrand disease (group B)

As for severe VWD, prevalence estimates for intermediate VWD are available only from hospital-based cohorts: these are calculated as the number of patients registered at a single specialized center, divided by the total population served by the center. The first data published based on this methodology date back to 1984, when Nilsson estimated that there were about 530 known cases (230 families) of VWD in Sweden, corresponding to a prevalence of seven VWD patients per 100,000 inhabitants, the same figure as for hemophilia in that country (Table 3).[39] This study did, however, also include patients with type 3 VWD. In 1991, Bloom and Giddins[40] tried to indirectly estimate the prevalence of VWD. Information was received through a questionnaire from 63% of the centers contacted (37 countries) including 16,664 identified patients, of whom 7,534 were treated. The prevalence estimate was consequently very

heterogeneous in the various countries, ranging from 3.7 to 239 cases per million inhabitants (Table 3). Whatever the limitations of this approach, the prevalence of patients with intermediate VWD requiring specific treatment has been estimated to range from 40 to 100 cases per million,[39-42] a figure often quoted as a reliable estimation.[43]

Prevalence of mild von Willebrand disease (group C)

Four population-based studies are available (Table 4). Rodeghiero *et al.*[2] evaluated 1,218 schoolchildren aged 11-14 years in a well-defined territory of northern Italy. The diagnosis of VWD was considered "probable" in the following children: those with low VWF levels (VWF:RCo below an ABO-adjusted reference range) belonging to a family with more than two members, including or not the subject under investigation and those with a bleeding history consisting of two or more symptoms. A definite diagnosis was assigned if, in addition to these criteria, at least one other family member on the hemorrhagic side had a low VWF level. Ten children (four with probable and six with definite VWD) were classified as affected (0.82%). This figure could range from 7 (0.57%) to 14 (1.15%) considering the 90% confidence interval for the lower limit of the normal range. All these

Table 3. Historical prevalence of referred von Willebrand disease. Table modified, with permission, from Nilsson IM. 1984.[39]

Area	Population (million)	Patients reported	Corrected prevalence, per million
Scandinavia	21.5	4,749	239
Rest of Europe	441	6,514	23
Australasia	16	599	42
North America	237	2,263	22
Israel	3.5	106	60.4
Far East	286	1,673	8.1
South America	133	600	3.7
South Africa	24	80	7.4

Table 4. Estimates of the prevalence of von Willebrand disease determined by epidemiological investigations.

VWD severity	Study	Methodology	Population	Prevalence
Severe	Weiss *et al.*[36]	Mail survey to 354 hematology departments	USA, Canada, 17 European countries, Iran, Israel, all ages	1.38-1.51 per million
	Mannucci *et al.*[37]	Patients identified through a questionnaire; plasma VWF assay and recruitment of patients with VWF:Ag <1% by IRMA	Western European countries plus Israel, all ages	0.1-3.12 per million
	Berliner *et al.*[38]	Investigation of patients followed at a single center	Cases followed in Israel, all ages	5.3 per million among Arabs
Intermediate	Nilsson[39]	Cases registered at specialized centers in Sweden	230 Swedish families (530 patients) with VWD already known, all ages	70 cases per million inhabitants (about 15% severe type 3)
Mild	Rodeghiero *et al.*[2]	History + VWF:RCo Family study	Caucasian children	0.82% (8,200 per million)
	Miller*et al.*[45]	VWF:RCo	Adult blood donors	1.6% (0.2% bleeders)
	Meriane *et al.*[46]	History + VWF:RCo Family study	Arabic-Turkish Adult students	1.23%
	Werner *et al.*[44]	History + VWF:RCo Family study	Caucasian–Black Children	1.3% (1.15% Caucasian, 1.81% Black)
	Abu-Doleh *et al.*[48]	VWF:Ag + FVIII + Bleeding questionnaire	Saudi students	1.5 %
	Bowman *et al.*[49]	Primary practice History + VWF + Bleeding Score	Mostly Caucasian, patients investigated for bleeding	0.09% (95% CI: 0.03-0.15%)
	Bowman *et al.*[50]	Primary pediatric care History + VWF + Bleeding Score	4,592 parents/children investigated for bleeding, 223 (5%) answered yes, 41 of them were administered the validated Pediatric Bleeding Questionnaire + VWF testing	Approximately 1 in 1,000 (0.11%)

VWD: von Willebrand disease; VWF: von Willebrand factor; Ag: antigen; IRMA: immunoradiometric assay; RCo: ristocetin cofactor; 95% CI: 95% confidence interval.

children had at least one bleeding symptom. This translates into a prevalence of 0.57-1.15%, or 5,700-11,500 per million. Interestingly, in about half of the diagnosed families in this investigation, linkage was not subsequently confirmed.[34]
In 1993, Werner *et al*.[44] published the results of a similar investigation carried out in 600 American schoolchildren aged 12-18 years undergoing well-child or school physical examinations at the pediatric ambulatory clinics of the hospitals located in Virginia, Ohio, and Mississippi. The criteria were less restrictive and included all three of at least one bleeding symptom, a family member with at least one bleeding symptom and low VWF. The overall prevalence was estimated at 1.3%, with no racial difference (1.15% among Whites and 1.8% among Blacks). These data have been confirmed in two additional studies, not reported as full papers. Miller *et al*.[45] found a prevalence of VWD of 1.6% in adult blood donors from New York, with a prevalence of symptomatic subjects with low VWF:RCo of 0.2%. In an additional study, Meriane *et al*.[46] investigated the prevalence in Arabic-Turkish adult subjects. The figure was 1.23%, again with no racial differences. In all these studies the same functional test (VWF:RCo) and separate normal ranges according to blood groups were used, thus providing uniformity to the results. Although these figures appear high, it should be emphasized that the prevalence is probably even higher since the sensitivity of the functional test is about 50%. This assumption stems from the demonstration that among obligatory carriers for type 1 disease, only 42% had abnormal VWF activity on their initial test.[47]
As previously mentioned, most of these cases will resist a Bayesian approach as sufficiently proved VWD cases, in keeping with their lack of linkage with a *VWF* allele.[34]
More recently, in 2,000 university students in Riyadh (Saudi Arabia) a prevalence of 1.5% was demonstrated based on FVIII and VWF:Ag measurement results.[48] A recent Canadian study identified a prevalence of 0.09% (95% confidence interval: 0.03-0.15%) in a population of unselected, consecutive patients presenting to one of six multi-practitioner family practices (50 family physicians' offices in total) in Kingston, Canada, between September 2004 and January 2007.[49] Furthermore, the same group reported a prevalence of symptomatic VWD of approximately 1 in 1,000 (0.11%) in a pediatric primary care setting.[50]

Prevalence of von Willebrand disease: a global perspective

Limited investigations have been carried out in developing countries, based on voluntary reporting in mail questionnaire-based surveys through national or regional hemophilia centers.[43] Recently, data have been published from a 2018/2019 World Federation of Hemophilia annual global survey and a global perspective about VWD awareness and registration at Hemophilia Centers in low-, intermediate- and high-income countries.[51,52] These data provide a global perspective of VWD registration in different geographic areas. The mean VWD prevalence worldwide was 25.6 per million people.[51] The lowest registration rate was reported from South Asia (0.6 per million population) while it was the highest in Europe/Central Asia (50.9 per million).[51] These figures are very far from an expected 0.1% prevalence and do not differ significantly from data reported more than 30 years ago (Table 3). The prevalence of VWD is in general reported to be higher in high-income (60.3 per million) than in low-income countries (1.1 per million); the prevalence of type 3 VWD was 3.3 per million *versus* 0.7 per million, respectively. For all countries, the reported prevalence was greater in females than in males. In general, major under-reporting is evident compared with the expected prevalence, especially for low-income countries, but with a significantly higher percentage of type 3 VWD cases reported in low-income countries[52] due to diagnostic limitations and therapeutic resources being restricted to the most severe clinical cases

Prevalence of mutant *VWF* genes

Mild VWF deficiency is rather frequent in the general population, while an estimate of the prevalence of *VWF* gene variant(s) possibly causing disease has been unknown until recently. Some heterozygous variants are highly penetrant and with full expressivity (e.g., p.Arg1205His, p.Cys1130Phe, p.Arg1374His/Cys) giving a severe reduction of VWF levels, a clear-cut bleeding tendency and evident inheritance.[53,54] In contrast, the prevalence of heterozygous p.Arg854Gln may be as high as 1%, but bleeding presents only in a homozygous or compound heterozygous state.[11] Heterozygous type 3 VWD carriers or patients with recessive type 1 VWD are usually asymptomatic but they carry variants which produce a significant bleeding tendency in a compound heterozygous or homozygous state.[55] For example, in the Region of Veneto at least 120 subjects with a p.Cys2362Phe heterozygous variant have been identified through family studies, with significant bleeding manifestations in homozygous patients and in compound heterozygosity with a null allele.[56] These patients are truly recessive, although their features do not completely match with the usual classification of type 3 VWD, further adding to the complexity of the genetic basis of VWD.[57]
A fresh insight has recently been provided by Seidizadeh *et al*.[58] By analyzing exome and genome data of 141,456 individuals collected in the genome Aggregation Database (gnomAD) from different populations, a total of 4,313 variants were identified of which 505 were predicted to be pathogenic or already reported associated with VWD. The global prevalence of dominant VWD was thus 7.4 % for type 1, 0.3 % for type 2A, 0.3% for type 2B, and 0.6 % for type 2M VWD. The prevalence was 0.03% for recessive type 3 and 0.07 for type 2N.[58] In a recent study from the same group, the authors analyzed exome and genome sequencing data from 807,162 individuals (730,947 exomes and 76,215 genomes) included in gnomAD v4.1. Based on the allele frequencies

of 321 well-documented pathogenic VWF variants, the estimated global prevalence per 1,000 individuals was 11 for type 1 VWD (1.1%), 1.3 for type 2A (0.13%), 1.7 for type 2B (0.17%), and 1.5 for type 2M (0.15%). For the recessive forms, prevalence was estimated at 31 cases per million for type 2N and 1.2 per million for type 3 VWD. Notably, prevalence estimates varied across different ancestral populations.[59] Thus, putative pathogenic *VWF* gene variants appear to be rather frequent in the general population, producing the full range of different VWD phenotypes through their functional diversity.

Current perspectives: from classification and epidemiology to clinical practice

In summary, VWD is a highly heterogeneous inherited bleeding disorder caused by reduced activities of VWF. Type 3 VWD is a rare disorder, with a prevalence similar to that of other severe inherited bleeding disorders. However, clinically "severe" cases are more prevalent when considering recessive types 1 cases and type 1 and 2 with high penetrance and expressivity. The prevalence of clinically intermediate VWD is probably similar to that of the cumulative prevalence of hemophilia A and B, while that of mild VWD is still uncertain, but a reasonable estimate is possibly one case per 1,000 to 10,000 subjects. By a direct epidemiological approach, about 1% of the normal population could be diagnosed with VWD and genetic data seem to support an even higher prevalence of a putative VWD-associated allele. However, many of these subjects will experience only minor or trivial bleeding during their lifetime and will probably never be referred for specific medical assistance. The current diagnostic pathways appear to be incomplete still at several centers and in different countries so that most borderline cases remain undiagnosed or receive a delayed diagnosis. There is also limited awareness among non-expert clinicians about the appropriate diagnostic pathway at specialized centers for a patient with a mild bleeding tendency. Finally genetic tools may improve diagnosis, but these tools are available and interpretable only in a limited number of centers. On the other hand, it is of paramount importance to distinguish between a diagnosis satisfying only minimal criteria and a clinically meaningful diagnosis, which is important for quality of life and access to timely appropriate treatments.[60] It seems that in low-income countries several of these clinically relevant cases are still undiagnosed or unreported. Based on these considerations, more efforts should be made to improve access to diagnosis, to establish registries and reporting and to organize clinical prospective observations to determine the frequency and severity of bleeding events with the type of treatments especially in patients with moderate and mild VWD.

Disclosures

No conflicts of interest to disclose.

Contributions

GC drafted the initial manuscript, GC and ABF revised the paper and approved the final version.

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