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ORIGINAL ARTICLE

Global prevalence of platelet-type von Willebrand disease

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Abstract

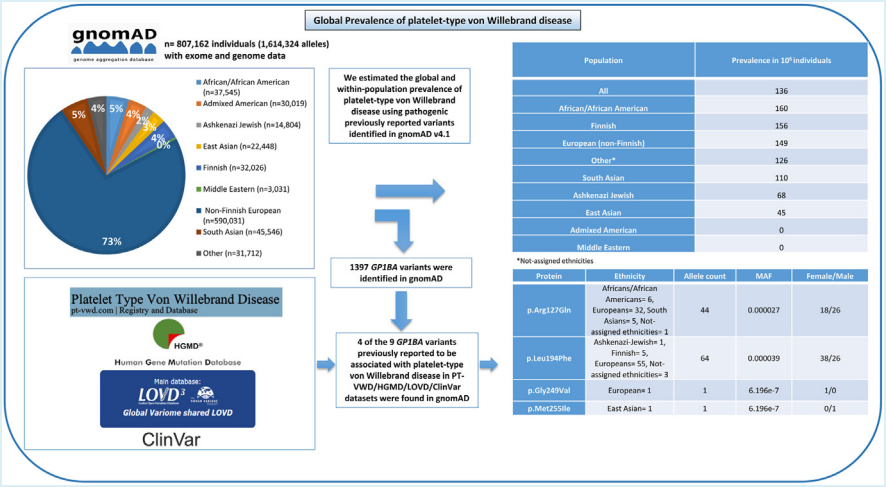
Background: Platelet-type von Willebrand disease (PT-VWD) is a rare autosomal dominant disorder. It is caused by gain-of-function gene variants in the platelet *GP1BA*, which results in excessive binding between GPIbα and von Willebrand factor (VWF). The prevalence of PT-VWD is unknown.

Objectives: To establish the worldwide and within distinct ethnic groups prevalence of PT-VWD.

Methods: We used available exome and genome sequencing data of 807,162 (730,947 exomes and 76,215 genomes) subjects from the Genome Aggregation Database (gnomAD-v4.1).

Results: Among the 1,614,324 alleles analyzed in the gnomAD population, there were 1397 distinct *GP1BA* variants. Of them, 4 variants (p.Arg127Gln, p.Leu194Phe, p.Gly249Val, and p.Met255Ile) have been previously reported to cause PT-VWD. Considering these 4 known pathogenic variants, we estimated a global PT-VWD prevalence of 136 cases/10^6. The highest estimated prevalence of PT-VWD was found in Africans/African Americans (160/10^6), Finnish (156/10^6), Europeans (149/10^6), and South Asians (110/10^6), followed by Ashkenazi Jewish (68/10^6) and East Asian (45/10^6) ethnicities. In the population with no assigned ethnicity, a prevalence of 126/10^6 was estimated. Since no pathogenic *GP1BA* variants that were previously reported to cause PT-VWD were found in Admixed American and Middle Eastern ethnicities, we were unable to estimate the PT-VWD prevalence in these 2 populations. We found a global prevalence of 2.5/10^6 for severe PT-VWD and 134/10^6 for the mild form.

Conclusion: This population-based genetic epidemiology analysis indicates a substantially higher than expected frequency of PT-VWD. This novel finding suggests that a large number of PT-VWD patients are still under- or misdiagnosed.



KEYWORDS
gnomAD, GP1BA, platelet disorders, prevalence, PT-VWD, VWD

Essentials

- The prevalence of platelet-type von Willebrand disease (PT-VWD) is unknown.
- Sequencing data of 807,162 exomes/genomes from gnomAD-v4.1 were used to estimate PT-VWD prevalence.
- We estimated a global PT-VWD prevalence of 136 cases/10^6.
- This finding suggests that a large number of PT-VWD patients are under- or misdiagnosed.

1 | INTRODUCTION

von Willebrand factor (VWF) is a large adhesive multimeric glycoprotein that is exclusively synthesized in endothelial cells and megakaryocytes [1]. Among the many functions of VWF, it is best known for supporting platelet adhesion to the exposed collagen at the site of the injured vessel and acting as a chaperone for coagulation factor VIII (FVIII) [2]. This interaction of VWF with platelets happens through 2 receptors, glycoprotein Ibα (GPIbα), which binds to the VWF A1 domain, and integrin $\alpha_{IIb}\beta_3$, which binds to the VWF C4 domain [2,3]. There are 2 pathological conditions recognized to cause enhanced binding of either the VWF A1 to GPIbα, known as type 2B von Willebrand disease (VWD) [3,4], or GPIbα to the A1 domain, known as platelet-type von Willebrand disease (PT-VWD) [5,6].

Type 2B VWD is well-known, with relatively extensive information available on its pathophysiology, clinical characterization, and genetic background [7,8], whereas this is not the case for PT-VWD [9]. This is because nearly only 60 cases with PT-VWD have been described so far [10]. PT-VWD, inherited as an autosomal dominant platelet functional defect, is unique among platelet disorders as it is characterized by platelet hyperresponsiveness rather than decreased function [9]. It is caused by gain-of-function gene variants in the platelet GP1BA gene coding for the platelet GPIbα receptor [11]. This results in excessive binding between GPIbα–VWF, subsequently leading to the removal of the platelet–VWF complex from circulation and hence the loss of high molecular weight (HMW) VWF multimers as well as thrombocytopenia (typically mild) [9,11]. The clinical and laboratory features of PT-VWD are similar to those of type 2B VWD: mild-to-moderate mucocutaneous bleeding such as nosebleeds, bleeding after tooth extraction or postsurgical operations, reduced platelet-dependent VWF activity, and characteristically, enhanced ristocetin-induced platelet agglutination (RIPA). In the absence of proper laboratory testing (ie, RIPA or better RIPA mixing study) [12] or genetic evaluation of *VWF* and *GP1BA* [13], PT-VWD is often misdiagnosed as type 2B VWD or idiopathic thrombocytopenic purpura or is underdiagnosed [14].

Type 2B VWD is more common than its counterpart, PT-VWD. A recent genetic epidemiologic population-based study newly estimated the prevalence of type 2B to be 3 cases in 1000 people worldwide [15]. This estimation was based on the allele frequency of several type 2B VWD-associated variants (p.Leu1460Phe, p.Arg1379Cys, p.Ile1372Ser, p.Arg1341Gln, p.Arg1341Trp, p.Pro1337Leu, p.Arg1308Leu, p.Val1279Ile, p.Pro1266Leu, p.Pro1266Gln, and p.Tyr1258Cys) in >141,000 of the general population [15].

However, the prevalence of PT-VWD is unknown, and only about 60 patients with this disorder have been reported globally (https://pt-vwd.com/). To evaluate more accurately the worldwide prevalence of PT-VWD and also the prevalence within distinct ethnic groups, we

used, for the first time, exome and genome sequencing data of 807,162 subjects reported recently in the Genome Aggregation Database (gnomAD-v4.1).

2 | METHODS

2.1 | GP1BA gene variants in the population-based gnomAD

All variants identified in the GP1BA gene (NM_000173.7) from the gnomAD population (v4.1), which is composed of 730,947 whole exomes (416,555 individuals from the UK Biobank) and 76,215 genomes from around the world were extracted and analyzed. These sequencing data are from various population genetic studies, totaling 807,162 individuals, and were aligned to GRCh38 of the human reference genome. A wide range of ethnicities around the globe is represented in this population-based database, including 8 major ethnicities (African/African American, Admixed American, Ashkenazi Jewish, East Asian, Finnish, Middle Eastern, non-Finnish European, and South Asian), making a unique population for prevalence estimation of genetic diseases. The dataset has undergone extensive quality control measures by the gnomAD investigators aiming to remove sequences with a poor-quality and to flag those variants with questionable reliability. Accordingly, only those *GP1BA* variants that had passed quality controls (using the gnomAD random forest filters) were considered for our evaluation.

Among the *GP1BA* variants identified in the 807,162 gnomAD population, we considered the following as pathogenic: all variants reported to be associated with PT-VWD in the Platelet Type von Willebrand Disease Registry (https://pt-vwd.com/), and/or the Human Gene Mutation Database (HGMD, https://www.hgmd.cf.ac.uk/ac/index.ph), and/or the Leiden Open Variation Database (LOVD, https://databases.lovd.nl/shared/variants/GP1BA/), and/or ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/?term=adamts13%5Bgene%5D&redir=gene), and/or PubMed (https://pubmed.ncbi.nlm.nih.gov/).

2.2 | Identification of previously reported *GP1BA* variants associated with PT-VWD

We searched PubMed for articles describing PT-VWD to identify all previously reported *GP1BA* variants that are associated with PT-VWD. Furthermore, variants reported to be associated with PT-VWD in the PT-VWD Registry (accessed 2024), HGMD (accessed 2024), or the LOVD (accessed 2024) were included. Finally, we searched for *GP1BA* variants in ClinVar that have been associated with PT-VWD. Two independent authors checked all previously reported variants to select only those that had been confirmed to be associated with PT-VWD. We classified these variants into 2 groups of severe and mild PT-VWD considering the laboratory and clinical results of previously reported cases with these variants. Compared with the mild form, severe PT-VWD cases were those with loss of HMW VWF multimers, respond to a lower dose of ristocetin in the RIPA assay, pronounced thrombocytopenia, severe clinical presentation, as well as having a lower frequency in the general population.

2.3 | Calculation of PT-VWD prevalence

The worldwide and within-population prevalence of PT-VWD was calculated using 2 different approaches. First, we calculated the prevalence by counting cases with pathogenic variants in the *GP1BA* identified in the gnomAD population; these variants have been previously reported to be associated with PT-VWD in the available genetic databases (HGMD, LOVD, or ClinVar) or in the literature. In the second approach, we calculated the estimated prevalence using the Hardy-Weinberg equation ($p^2 + 2pq + q^2 = 1$), where p is the population frequency of the major allele, 2pq is the incidence of an autosomal dominant condition, and q is the population frequency of the minor allele. Since PT-VWD inheritance is autosomal dominant (1 copy of a mutated GP1BA gene from 1 parent can cause the disease), we estimated the prevalence of individuals heterozygous (ie, 2pq) for *GP1BA* variants. Furthermore, we estimated the PT-VWD prevalence considering the severity of the variants associated with PT-VWD in the 2 categories of severe and mild forms.

3 | RESULTS

3.1 | Mutation spectrum of all previously reported *GP1BA* variants associated with PT-VWD

To identify all previously reported *GP1BA* variants associated with PT-VWD, we searched PubMed, PT-VWD Registry, HGMD, LOVD, and ClinVar. We found 9 distinct *GP1BA* variants that have been reported to cause PT-VWD (Table 1) [16–24]. For these 9 variants, 8 (89%) were missense (p.Arg127Gln, p.Leu194Phe, p.Trp246Leu, p.Gly249Val, p.Gly249Ser, p.Asp251Tyr, p.Met255Val, and p.Met255Ile), and 1 (11%) was a small deletion (p.Thr436_Ala444del). Table 1 summarizes the characteristics of these variants.

3.2 | Global mutation spectrum of *GP1BA* gene

High-quality sequencing data of the GP1BA gene was collected from the gnomAD population of 807,162 subjects (1,614,324 alleles) with different ethnicities (Table 2). The population includes African/African American (n = 37,545), Ashkenazi Jewish (n = 14,804), East Asian (n = 22,448), Finnish (n = 32,026), Middle Eastern (n = 3031), non-Finnish European (n = 590,031), South Asian (n = 45,546), and Remaining (n = 31,712), with no assigned ethnicity. The average depth of sequencing coverage per base in exon 2 of the GP1BA gene was almost always greater than 30× and 25× for exome and genome sequencing, respectively (Supplementary Figure), indicating adequate coverage.

TABLE 1 List of all variants reported in association with PT-VWD.

cDNA	Protein	Severity of PT-VWD	Characteristics	Reference
c.380G>A	p.Arg127Gln	Mild-moderate; bruising, recurrent epistaxis, occasional gum bleeding, ISTH-BAT= 4	A 14-y-old boy, VWF levels were normal, PLT = 208 × 10^9/L, MPV = 12 fL, RIPA = 0.6-0.7 mg/mL	Bury et al. 2022 [16]
c.580C>T	p.Leu194Phe	Mild-moderate; easy bruising and recurrent epistaxis, ISTH-BAT= 3	A 17-y-old boy, VWF:Ag = 105 IU/dL, VWF:RCo = 66, VWF:RCo/VWF:Ag = 0.62, MPV = 14.2 fL, PLT = 127 × 10^9/L, RIPA = 0.5 mg/mL	Monteiro et al. 2023 [17]
c. 3805G>T	p.Trp246Leu	Severe; epistaxis, gum bleeding, major bleeding after dental extraction, muscle hematoma. BS= 11	Macrothrombocytopenia, PLT = 41 and 75 × 10^9/L, VWF:Ag = 47 and 61 IU/dL, VWF:RCo <10 IU/dL, VWFpp/VWF:Ag= 1.65, RIPA = 0.3 and 0.4 mg/mL	Woods et al. 2014 [18]
c.746G>T	p.Gly249Val	Severe; associated with significant bleeding manifestations following minor trauma or in association with the surgical process	Mild thrombocytopenia, decreased VWF:RCo and VWF:RCo/VWF:Ag ratio, loss of HMW VWF multimers, increased RIPA at low concentrations of ristocetin	Miller et al. 1991 [19]
c.746G>A	p.Gly249Ser	-	A 3-y-old boy, loss of HMW VWF multimers, moderate thrombocytopenia, RIPA = 0.5 mg/mL	Matsubara et al. 2003 [20]
c.752G>T	p.Asp251Tyr	Severe; severe gum bleeding at the age of 27, abnormal bleeding post-traumatic nasal fracture	The index case was a 50-y-old man, low VWF:RCo and VWF:RCo/VWF:Ag ratio, loss of HMW VWF multimers. PLT = 108-227 × 10^9/L, RIPA = 0.75 mg/mL	Enayat et al. 2012 [21]
c.764A>G	p.Met255Val	Severe; epistaxis, ecchymoses, gingival bleeding, and bleeding during shedding of teeth or after dental extractions	A 4-year-old patient, thrombocytopenia, reduced HMW VWF multimers and VWF:RCo, RIPA < 0.5 mg/mL	Takahashi et al. 1995 [22]
c.765G>A	p.Met255Ile	Severe; ISTH= 7, neonatal bleeding (scalp bleeding after puncture), easy bruising, and rare severe epistaxis episodes	Reported in a child being compound heterozygote for type 2B "Malmö/New York"/PT-VWD (p.Pro1266Leu/p.Met255Ile), severe thrombocytopenia at birth, MPV = 11.6 fL, VWF:RCo <13 IU/dL, VWF:Ag= 60 IU/dL, reduced HMW VWF multimers, RIPA = 0.3 mg/mL	Lavenu-Bombled et al. [23]
c.1326_1334 del	p.Thr436_Ala444del	Severe; recurrent epistaxis, postoperative and dental bleeding, menorrhagia	A 37-y-old female with a long history of bleeding since the age 4 y, PLT = 216 × 10^9/L, reduced VWF levels, loss of HMW VWF multimers, RIPA = 0.5 mg/mL	Othman et al. 2005 [24]

ISTH-BAT, International Society on Thrombosis and Haemostasis-bleeding assessment tool; HMW, high molecular weight; MPV, mean platelet volume; PLT, platelet count; PT-VWD, platelet-type von Willebrand disease; RIPA, ristocetin-induced platelet aggregation; VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWFpp, VWF propeptide; VWF:RCo, VWF ristocetin co-factor.

The less covered region of the GP1BA gene is due to the presence of variable number tandem repeats.

Among the 1,614,324 alleles analyzed in the gnomAD population, there were 1397 distinct *GP1BA* variants. Of then, 4 variants (p.Arg127Gln, p.Leu194Phe, p.Gly249Val, and p.Met255Ile) have been previously reported to cause PT-VWD (Figure). Thus, these 4 variants were classified as pathogenic and were considered for our prevalence estimation. Of the 4 pathogenic variants identified in the gnomAD

TABLE 2 The gnomAD population stratified by ethnicity.

Population	Total
All	807,162
African/African American	37,545
Admixed American	30,019
Ashkenazi Jewish	14,804
East Asian	22,448
Finnish	32,026
Middle Eastern	3031
European (non-Finnish)	590,031
South Asian	45,546
Remaining[a]	31,712

[a]Remaining, population with no assigned ethnicity.

population, 2 variants were identified in only 1 subject. Considering all 1,614,324 analyzed alleles, 110 alleles were carrying the 4 pathogenic variants, always due to missense mutations (Figure).

3.3 | Population-based prevalence of PT-VWD

First, we counted the individual cases that carry the 4 pathogenic variants that were identified in the gnomAD and were previously reported to cause PT-VWD. The global prevalence of observed patients with PT-VWD was 110 cases in 807,162 gnomAD people, corresponding to a worldwide prevalence of 136.3/10^6. Considering these 110 cases with pathogenic variants, the frequency of observed patients with PT-VWD among different ethnicities was 6 in 37,545 cases for Africans/African Americans, 5 in 32,026 cases for Finnish, 88 in 590,031 cases for European population, 4 in 31,712 cases in not-specified population, 5 in 45,546 cases for South Asians, 1 in 14,804 cases for Ashkenazi Jewish, and 1 in 22,448 cases for East Asians (Table 3). We found no patients carrying the previously reported *GP1BA* variants associated with PT-VWD in 30,019 cases of Admixed Americans and in 3031 cases of Middle Eastern ethnicity.

In the second approach, we estimated the PT-VWD prevalence (Hardy-Weinberg equation; $p^2 + 2pq + q^2 = 1$) using the allele frequency of the 4 *GP1BA* variants that were found in gnomAD and were previously reported to cause PT-VWD (totaling 110 alleles). Accordingly, the global prevalence of PT-VWD was estimated to be 136/10^6 (Table 3). The highest estimated prevalence of PT-VWD was found in Africans/African Americans (160/10^6), Finnish (156/10^6), European population (149/10^6), and South Asians (110/10^6), followed by Ashkenazi Jewish (68/10^6) and East Asians (45/10^6). In the population with no assigned ethnicity, a prevalence of 126/10^6 was estimated. Since no pathogenic *GP1BA* variants that were previously reported to cause PT-VWD were found in Admixed American and Middle Eastern ethnicities, we were unable to estimate the PT-VWD prevalence in these 2 populations. Considering the severity of identified variants associated with PT-VWD in gnomAD, we found a global prevalence of 2.5 per 10^6 for severe PT-VWD and 134 per 10^6 for the mild form.

Among the 110 cases with PT-VWD, 57 (52%) were females and 53 (48%) were males. The age distribution was available for 62 of 110 cases (Supplementary Table).

3.4 | The most frequent pathogenic variants in the gnomAD population stratified by ethnicity

Of the 9 previously reported variants in the GP1BA gene that have been associated with PT-VWD, 4 were found in the gnomAD population, including p.Arg127Gln, p.Leu194Phe, p.Gly249Val, and p.Met255Ile (Figure). The variant p.Arg127Gln was found in 44 cases, including 6 Africans/African Americans, 32 non-Finnish Europeans, 5 South Asians, and 1 case with no assigned ethnicity. The variant p.Leu194Phe was found in 64 cases; 1 Ashkenazi Jewish, 5 Finnish European, 55 non-Finnish Europeans, and 3 cases with no assigned ethnicity. Variants p.Gly249Val and p.Met255Ile were found in only 1 non-Finnish European and 1 East Asian case, respectively.

4 | DISCUSSION

PT-VWD is currently considered to be an extremely rare disorder, with only approximately 60 patients being described so far [10]. No information on the global and within distinct ethnicity prevalence of PT-VWD is available. The prevalence may be underestimated because PT-VWD is often misdiagnosed as type 2B VWD or idiopathic thrombocytopenic purpura or is underdiagnosed [14,25]. The assumption that PT-VWD is very rare diminishes the consideration of its diagnosis in patients with characteristic clinical features of thrombocytopenia and mucocutaneous bleeding. Nowadays, by leveraging the current genetic epidemiology methodologies that define valid prevalence estimations for population-based scales, we can more accurately estimate the prevalence of genetic disorders [26]. We previously established the global and within distinct ethnicity prevalence of VWD [15] and hereditary thrombotic thrombocytopenic purpura [27], and our results suggested a substantially higher prevalence than previous reports. The advent of next generation sequencing has revolutionized genetic epidemiology because data from large international consortia are now increasingly available [28], and the prevalence can be estimated using the allele frequency of pathogenic variants [26].

Our comprehensive genetic epidemiology investigation provides, for the first time, a global and within-population estimation of PT-VWD prevalence using genome and exome data from 807,162 individuals. Based on the allele frequency of 4 documented gain-of-function pathogenic variants in the GP1BA gene, the worldwide prevalence of PT-VWD was estimated to be 136/10^6 people. Considering that only approximately 60 cases of PT-VWD have been documented so far, this prevalence is substantially higher than what has been previously assumed. Indeed, among 807,162 gnomAD

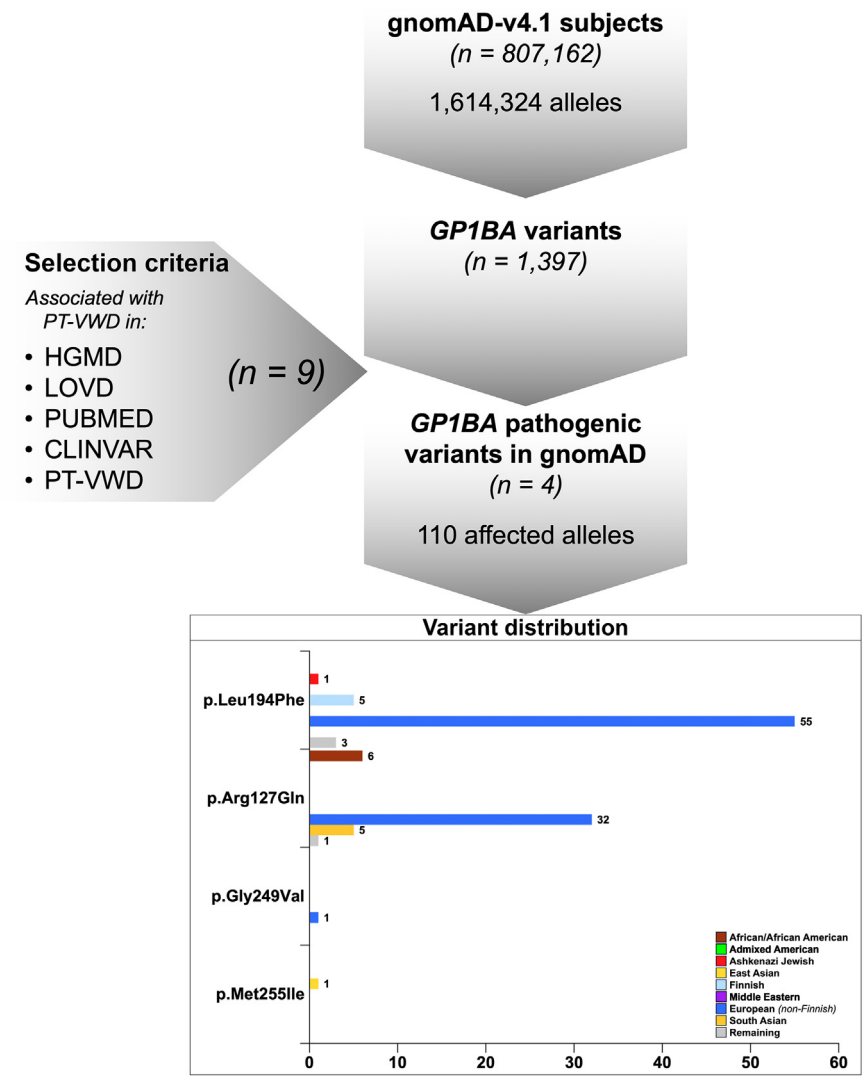


FIGURE Flowchart of data analyses. The gnomAD data set includes 807,162 subjects (1,614,324 alleles). Among this population, 1397 distinct *GP1BA* variants were identified, of which 4 variants were previously confirmed to be associated with PT-VWD. A total of 110 alleles were affected by these 4 variants and their distribution is illustrated in the bar charts. PT-VWD, platelet-type von Willebrand disease.

subjects, we identified 110 new cases with 4 pathogenic variants, and considering the autosomal dominant nature of PT-VWD, all these people should have been diagnosed as having PT-VWD.

Our study newly demonstrated that the prevalence of PT-VWD differs among various populations. We found the highest prevalence of PT-VWD in Africans/African Americans ($160/10^6$), Finnish ($156/10^6$), European population ($149/10^6$), and South Asians ($110/10^6$). This was followed by Ashkenazi Jewish ($68/10^6$) and East Asians ($45/10^6$). However, we did not find any pathogenic *GP1BA* variants that were previously reported to cause PT-VWD in Admixed American and Middle Eastern ethnicities; thus, we were unable to estimate the PT-VWD prevalence in these 2 populations. This suggests that PT-VWD is likely less frequent in these 2 ethnicities, or the genetic variants responsible for PT-VWD are much less investigated in these populations, leading us to not find them in the gnomAD population.

We found only 4 of the 9 previously reported variants associated with PT-VWD in the gnomAD population (p.Arg127Gln, p.Leu194Phe, p.Gly249Val, and p.Met255Ile). p.Arg127Gln was reported in a 14-year-old boy with mild to moderate bleeding who experienced bruising, recurrent epistaxis, and occasional gum bleeding [16]. VWF levels and platelet count were normal with mean platelet volume (MPV) of 12 fL. The RIPA was increased [16]. This variant was found in 44 cases of gnomAD population including 18 females and 26 males. p.Leu194Phe was reported in a 17-year boy with a moderate bleeding phenotype (easy bruising and recurrent epistaxis requiring cauterization), and mild thrombocytopenia. The patient had a slightly reduced VWF ristocetin co-factor (VWF:RCo)/VWF antigen (VWF:Ag) ratio, increased MPV, and an increased RIPA at a low ristocetin concentration. Interestingly, platelet glycoprotein levels, assessed by flow cytometry, were decreased for GPIbα (CD42b, 58% N) and GPIX (CD42a, 73.3% N) [17]. This variant was found in 64 cases of the gnomAD population (38 females vs 26 males). p.Gly249Val was originally reported in a family with PT-VWD in 1991 [19]. In all 5 members of the family, a history of significant bleeding manifestations after minor trauma or in association with surgery, decreased VWF:RCo/VWF:Ag ratio, loss of HMW VWF multimers, as well as increased RIPA were found [6,29]. Patients also showed mild thrombocytopenia. We found only 1 case with the p.Gly249Val variant in the gnomAD

TABLE 3 Global and within-population prevalence of platelet-type von Willebrand disease.

Population	Total number of alleles	Total number of affected alleles	Collective frequency of variants	Heterozygote frequency	Prevalence per 10^6
All	1,614,324	110	0.00007	0.00014	136
African/African American	75,090	6	0.00008	0.00016	160
Finnish	64,052	5	0.00008	0.00016	156
European (non-Finnish)	1,180,062	88	0.00007	0.00015	149
Remaining	63,424	4	0.00006	0.00013	126
South Asian	91,092	5	0.00005	0.00011	110
Ashkenazi Jewish	29,608	1	0.00003	0.00007	68
East Asian	44,896	1	0.00002	0.00004	45
Admixed American	60,038	0	0	0	0
Middle Eastern	6062	0	0	0	0

population, suggesting that this variant is associated with the severe PT-VWD phenotype. p.Met255Ile has been reported in an interesting family with combined PT-VWD and type 2B VWD due to VWF p.Pro1266Leu/GP1BA p.Met255Ile variants [23]. The proband was a baby who, after birth, presented with profound thrombocytopenia, severe bleeding, increased MPV, severely reduced VWF:RCo/VWF:Ag ratio, and reduced HMW VWF multimers. The RIPA was observed even at low ristocetin concentrations down to 0.3 mg/mL [23]. We found only 1 case with p.Met255Ile in the gnomAD population, suggesting that this variant is likely also associated with severe PT-VWD, similar to p.Gly249Val.

Since among these 4 pathogenic variants identified in gnomAD, 2 are associated with mild PT-VWD and the other 2 are associated with severe PT-VWD, we also estimated a PT-VWD prevalence according to disease severity. We found a global prevalence of 2.5 per 10^6 for severe PT-VWD and 134 per 10^6 for mild PT-VWD. These results raise concern that most patients with the mild form of PT-VWD are likely at great risk of being mis- or underdiagnosed compared with those with the severe disease phenotype. When the specific laboratory test is not performed (ie, RIPA or RIPA mixing study) or *VWF* and *GP1BA* are not evaluated, PT-VWD is often misdiagnosed and/or underdiagnosed [12–14].

The autosomal (dominant) inheritance pattern of PT-VWD results in an equal distribution of affected males and females. However, it has been reported that PT-VWD is more common in females than in males [25]. In this population-scale study, among 110 cases with PT-VWD, we found almost an equal distribution of females (n = 57, 52%) vs males (n = 53, 48%), suggesting that both sexes are affected by this condition. Because of the specific hemostatic challenges related to women during menstruation, pregnancy, and after childbirth, it is anticipated that more females are being diagnosed with the disease.

A limitation of our study was that we could not predict novel variants in the gnomAD population with gain-of-function features (PT-VWD characteristic). In addition, no clinical data or laboratory results were available in gnomAD for the cases carrying the previously reported pathogenic variants associated with PT-VWD. While p.Arg127Gln, p.Leu194Phe, and p.Gly249Val have been previously well characterized at family and functional levels, p.Met255Ile has not been experimentally tested; therefore, our estimated prevalence should be interpreted cautiously since it may significantly influence the study's conclusions.

In conclusion, we have attempted for the first time to establish the worldwide and within-population prevalence of PT-VWD using the largest available genome and exome sequencing data by analyzing 807,162 individuals from gnomAD. This population-based genetic epidemiology analysis indicates a substantially higher than expected frequency of PT-VWD. This new finding suggests that a large number of PT-VWD patients, especially those with the mild form of the disease, are still under- or misdiagnosed and thus are not adequately treated.

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AUTHOR CONTRIBUTIONS

O.S. designed the study. O.S. and A.C. collected and analyzed data. O.S. wrote the manuscript. M.O. and F.P. critically revised the manuscript. All authors have approved the final manuscript.

RELATIONSHIP DISCLOSURE

F.P. reports participation in educational meetings of Takeda and Spark and on the advisory boards of CSL Behring, Biomarin, Roche, Sanofi, and Sobi. The other authors state that they have no conflicts of interest.

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SUPPLEMENTARY MATERIAL

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