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Updated global prevalence and ethnic diversity of von Willebrand disease based on population genetics analysis

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EHC european haemophilia consortium

EAHAD European Association for Haemophilia and Allied Disorders

ERN | EuroBloodNet

VWD classification - VWF scientific and standardization committee (SSC) from the ISTH

ISTH VWF SSC (2026)

- **type 1 VWD** — **(partial) quantitative** VWF deficiency
  - **type 1C VWD** — **(partial) quantitative** VWF deficiency
- **type 2 VWD** — **qualitative VWF** deficiency
  - **2A:** decrease VWF-dependent platelet adhesion; loss of HMWM
  - **2B:** increased affinity for platelet glycoprotein Ib
  - **2M:** decrease VWF-dependent platelet adhesion; normal multimer
  - **2N:** markedly decreased binding affinity for factor VIII
- **type 3 VWD** — **(complete) quantitative** VWF deficiency

HMWM: High-Molecular-Weight Multimers

Sadler JE et al, *JTH*. 2006

Prevalence of a disease

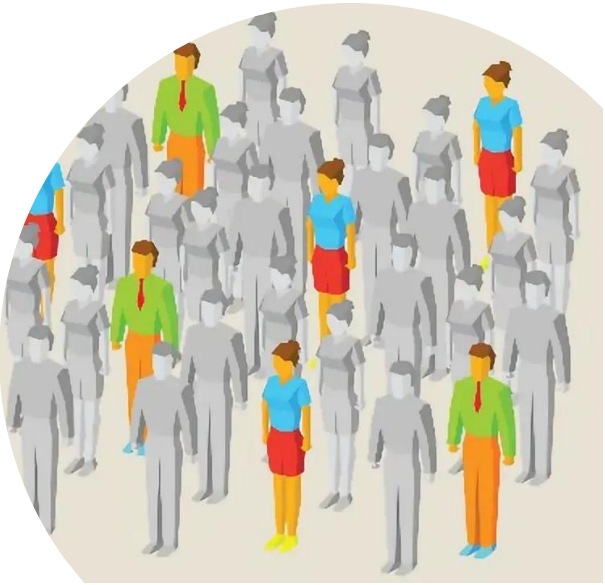
The total number of people affected by a disease in a population, including both new and existing cases

Why understanding the prevalence of disorders is important?

- Resource Allocation
- Healthcare Planning and Education
- Public Health Initiatives
- Research Focus
- Health Disparities
- Improving Outcomes

Traditional methods to estimate disease's prevalence

- Counting cases of known affected individuals in medical records
- Screening programs (eg, newborn screening)
- Population survey and disease registries
- Case reporting



Limitations

- Underreporting (by patients or clinicians)
- Sampling bias (Surveys and sample-based methods)
- Data inaccuracy: (Medical records or self-reported surveys)
- Small geographic areas and limited number of cases

VWD prevalence using traditional approaches: 3 seminal studies

"VWD affects up to 1% of the general population, with approximately 1 in 1,000 individuals experiencing symptoms".

VWD prevalence: 0.82% (0.57%-1.1%)

- Italy
- 1,218 children
- Type 1 VWD

Rodeghiero F, et al. Blood. 1987

VWD prevalence: 1.3%

- USA
- 600 children
- No ethnic difference (black vs white)

Werner EJ, et al. J. Pediatr. 1993

VWD prevalence: 1 per 1000 (0.001%)

- Canada
- 10,258 individuals
- (type 1= 7, 2B= 1, 2M= 1)

Bowman M, et al. JTH. 2010

Genetic prevalence:

The estimated proportion of a population that has a causal genotype for a genetic disorder

(when genotype-phenotype correlation exists)

All VWD types, except type 1 cases with VWF levels 30-50 IU/dL

Advantages of genetic prevalence

- Population scale
- Diverse ethnicities
- Provides more accurately estimation (variant's frequency)

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Population-based prevalence and mutational landscape of von Willebrand disease using large-scale genetic databases

Omid Seidizadeh, Andrea Cairo, Luciano Baronciani, Luca Valenti & Flora Peyvandi

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Updated global prevalence and ethnic diversity of von Willebrand disease based on population genetics analysis

Omid Seidizadeh, Andrea Cairo, Camilla Oriani & Flora Peyvandi

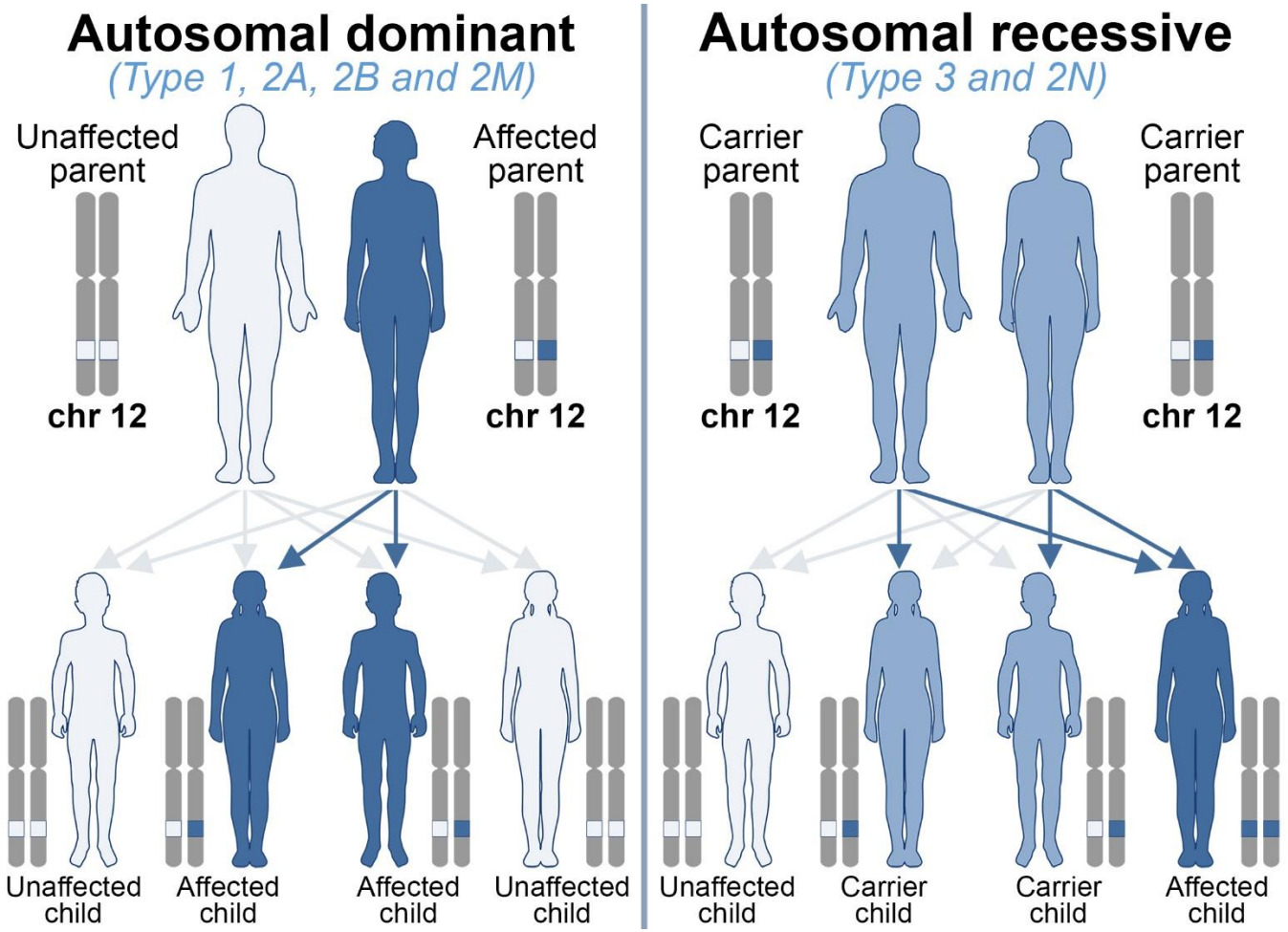
The Genome Aggregation Database (gnomAD)

- **Exome sequencing** : 730,947 (416,555 UK Biobank)
- **Genome sequencing** : 76,215

	ExAC	gnomAD v2	gnomAD v3	gnomAD v4*		
	#	#	#	#	%	Fold increase from v2
Admixed American	5,789	17,720	7,647	30,019	3.72%	1.7x
African	5,203	12,487	20,744	37,545	4.65%	3x
Ashkenazi Jewish	-	5,185	1,736	14,804	1.83%	2.9x
East Asian	4,327	9,977	2,604	22,448	2.78%	2.3x
European^	36,667	77,165	39,345	622,057	77.07%	8.1x
Middle Eastern	-	-	158	3,031	0.38%	New
Remaining Individuals^	454	3,614	1,503	31,172	3.93%	8.8x
South Asian	8,256	15,308	2,419	45,546	5.64%	3x
Total	**60,706**	**141,456**	**76,156**	**-**	**807,162**	**-**

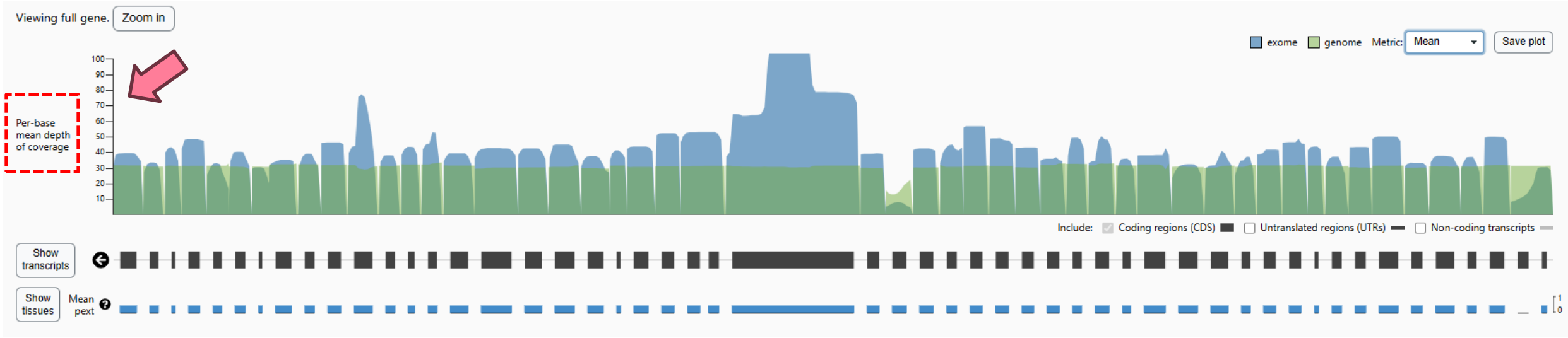
*v4 includes all v3 samples
^ Due to small sample sizes Finnish was included in European and Amish was included in Remaining Individuals

The inheritance pattern of VWD



Seidizadeh O, et al. J Thromb Haemost. 2024

VWF gene mean depth of coverage
gnomAD v4.1



An example of a type 2B VWD variant (p.Arg1306Gln)

Genetic Ancestry Group Frequencies

gnomAD | HGDP | 1KG | Local Ancestry

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
African/African American	1	74926	0	0.00001335
South Asian	1	91080	0	0.00001098
Admixed American	0	59994	0	0.000
Ashkenazi Jewish	0	29604	0	0.000
East Asian	0	44886	0	0.000
European (Finnish)	0	64012	0	0.000
Middle Eastern	0	6078	0	0.000
European (non-Finnish)	0	1179876	0	0.000
Amish	0	912	0	0.000
Remaining	0	62468	0	0.000
XX	2	812374	0	0.000002462
XY	0	801462	0	0.000
Total	**2**	**1613836**	**0**	**0.000001239**

Include: Exomes Genomes

Methods

- *VWF* variants were obtained from the **gnomAD (v4.1.1)**
- gnomAD: **730,947 exome** and **76,215 genome**
- Individuals with severe pediatric disease and their first-degree relatives are excluded

- Identify all previously reported *VWF* variants associated with VWD using:
- HGMD, LOVD, ClinGen, and ClinVar

Seidizadeh O, et al. *Sci Rep*. 2026

Seidizadeh, O et al. *npj Genomic Medicine. 2023*

From Variant Databases to Ancestry-Stratified Allele Frequencies

STAGE 1

VWD Variant Databases

↓

VWF Variants Associated with VWD

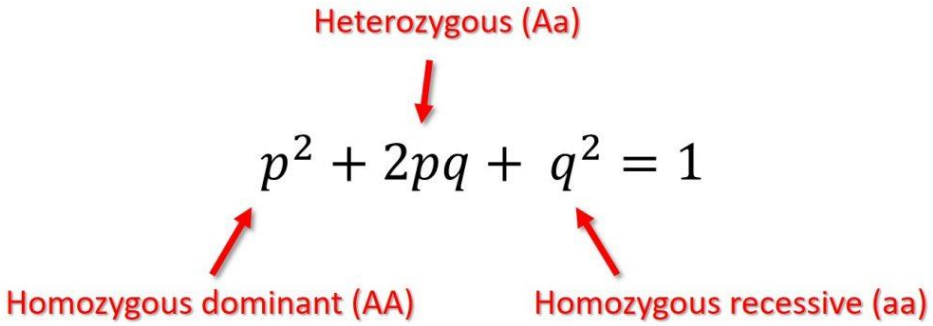
STAGE 2

gnomAD v4.1.1

↓

Allele Frequency Analysis by Ancestry

Hardy-Weinberg principle



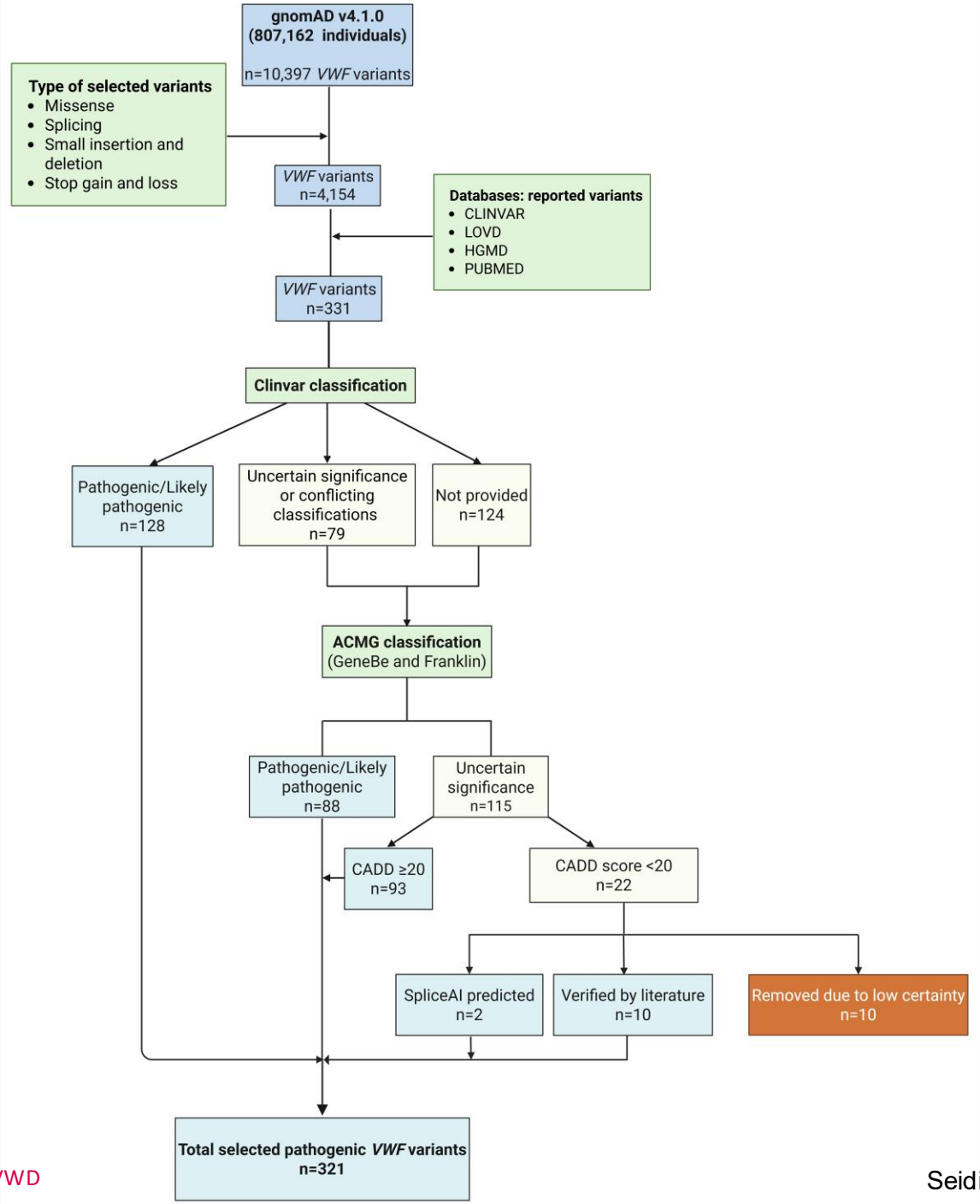
$$Q^2 = \left(\sum_i q_i\right)^2 = \sum_i q_i^2 + 2\sum_{\{i<j\}q_i} q_j$$

gnomAD population

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

Seidizadeh O, et al. *Sci Rep*. 2026

Flowchart of the data analysis pipeline used to identify previously reported pathogenic variants causing VWD



Seidizadeh O, et al. *Sci Rep*. 2026

Global prevalence of type 1 VWD

- VWF level of <30 IU/dL regardless of bleeding
- VWF level of <50 IU/dL with abnormal bleeding

James et al, Blood Advs (2021)

gnomAD v4.1 (807, 162)

↓

10.6/1000 (1.1%)

↓

All variants associated with VWD type 1 (VWF <30 IU/dL)

↓

Fully penetrant phenotype (accurate prevalence)

Type 1 VWD
(gnomAD v4.1)

population	Prevalence/1000
General	**10.6** (10.4–10.8)
African/African American	**8.2** (7.3–9.1)
Admixed American	**7.2** (6.3–8.2)
Ashkenazi Jewish	**7.3** (6.0–8.7)
East Asian	**4.4** (3.6–5.3)
European (Finnish)	**8.2** (7.3–9.2)
Middle Eastern	**10.5** (6.9–14.4)
European (non-Finnish)	**12.0** (11.7–12.2)
South Asian	**3.3** (2.8–3.8)
Remaining	**9.7** (8.6–10.8)

Values in parentheses represent 95% confidence intervals (Cis)

Seidizadeh O, et al. *Sci Rep*. 2026

Determinants of developing VWD

7.4% of the population carry variants associated with Low VWF/type 1 VWD, but only **1.1%** are likely to develop the condition

Seidizadeh O, et al. RPTH. 2025

Global prevalence of type 2 VWD

gnomAD v4.1
(807, 162)

2A = 1.3/1000 (0.13%)
2B = 1.7/1000 (0.17%)
2M = 1.5/1000 (0.15%)

Fully penetrant phenotype

Type 2 VWD/1000

(gnomAD v4.1)

population	2A	2B	2M
General	**1.3** (1.2–1.4)	**1.7** (1.6–1.8)	**1.5** (1.4–1.6)
African/African American	**1.0** (0.7–1.4)	**0.5** (0.3–0.8)	**0.7** (0.5–1.0)
Admixed American	**2.9** (2.3–3.6)	**2.5** (1.9–3.0)	**1.4** (1.0–1.9)
Ashkenazi Jewish	**0.3** (0.07–0.5)	**6.6** (5.3–7.9)	**0.1** (0–0.2)
East Asian	**4.4** (3.6–5.3)	**0.04** (0–0.13)	**1.0** (0.6–1.4)
European (Finnish)	**1.7** (1.2–2.1)	**8.9** (7.8–9.9)	**0.03** (0–0.09)
Middle Eastern	**2.3** (0.7–4.3)	**1.0** (0–2.3)	**3.0** (1.3–4.9)
European (non-Finnish)	**1.1** (1.0–1.2)	**1.3** (1.2–1.4)	**1.0** (1.0–1.1)
South Asian	**1.1** (0.8–1.4)	**0.9** (0.7–1.2)	**9.7** (8.8–10.6)
Remaining	**2.1** (1.6–2.7)	**1.9** (1.4–2.4)	**2.2** (1.7–2.7)

Values in parentheses represent 95% confidence intervals (Cis)

Seidizadeh O, et al. *Sci Rep*. 2026

Global prevalence of type 2N VWD

- 2N/2N (homozygous)
- 2N/2N (compound)
- 2N/null variants

gnomAD v4.1 (807, 162)

2N= 26/million (2N/2N)[a]
2N = 31/million (2N/null)[b]

p.Arg854Gln

XX	4062	812494	11	0.004999
XY	3938	801720	15	0.004912
Total	**8000**	**1614214**	**26**	**0.004956**

VWF variant p.Arg854Gln/ p.Arg854Gln → 26 cases in 807, 162 => **32 per million have type 2N**

Type 2N/million

(gnomAD v4.1)

population	Type 2N[a]	Type 2N[b]
General	26	31
African/African American	2.8	3.5
Admixed American	9.5	10.5
Ashkenazi Jewish	1.7	2
East Asian	0.004	0.05
European (Finnish)	31	43
Middle Eastern	1	2.2
European (non-Finnish)	37	42
South Asian	2.3	4
Remaining	20	24

Seidizadeh O, et al. *Sci Rep*. 2026

Global prevalence of type 3 VWD

gnomAD v4.1
(807, 162)

Type 3 = 1/million (type 3/type 3)
Type 3 = 1.3/million (type 3/type 1 null)

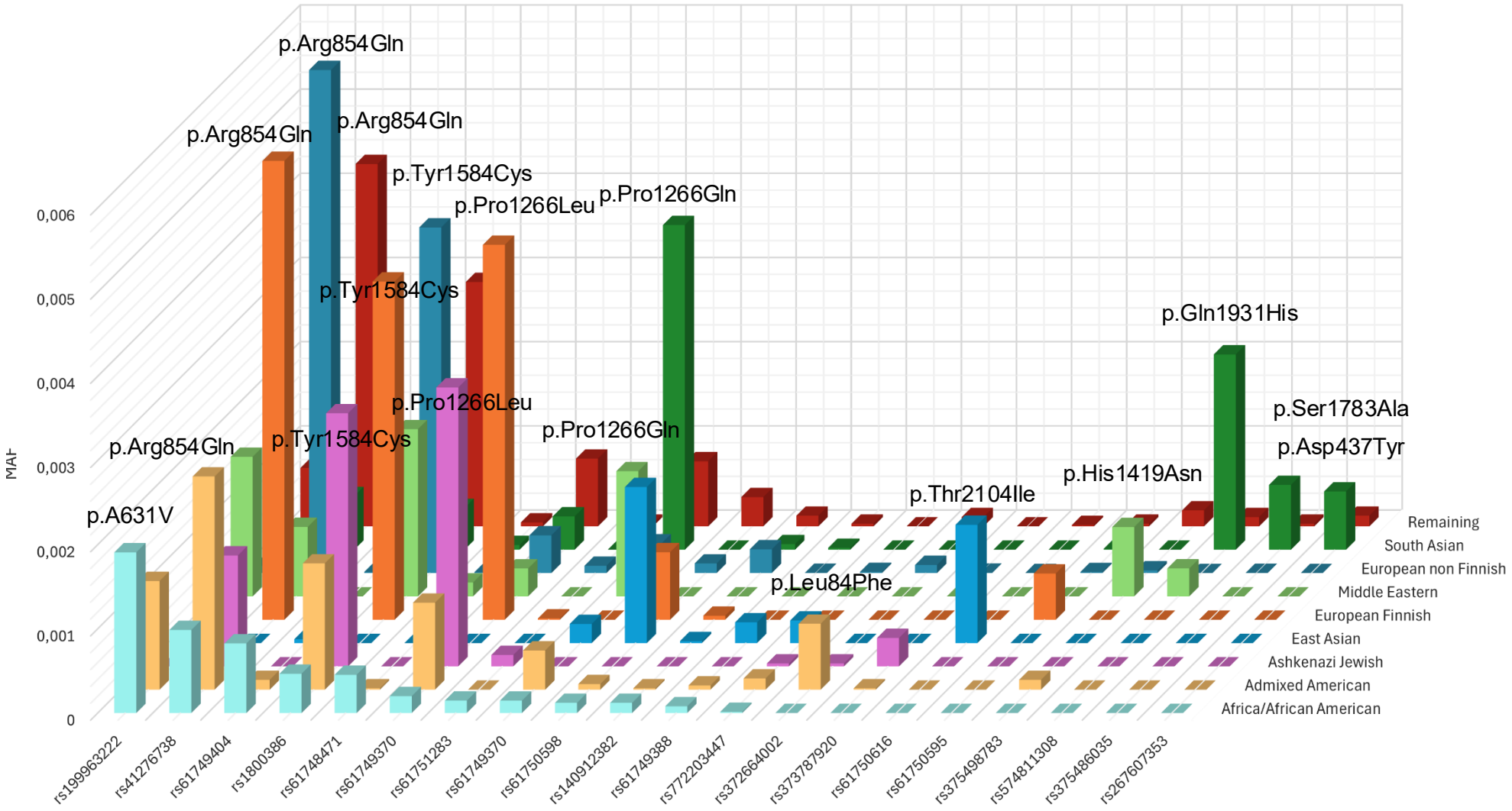
Type 3 VWD/million
(gnomAD v4.1)

population	Type 3
General	**1.3** (1.2–1.5)
African/African American	**0.4** (0.2–0.7)
Admixed American	**0.2** (0.08–0.4)
Ashkenazi Jewish	**0.01** (0–0.06)
East Asian	**0.4** (0.2–0.8)
European (Finnish)	**1.3** (0.8–2.1)
Middle Eastern	**0.7** (0.03–2.7)
European (non-Finnish)	**1.0** (0.9–1.2)
South Asian	**19.5** (16.0–23.6)
Remaining	**1.3** (0.8–2.0)

Values in parentheses represent 95% confidence intervals (Cis)

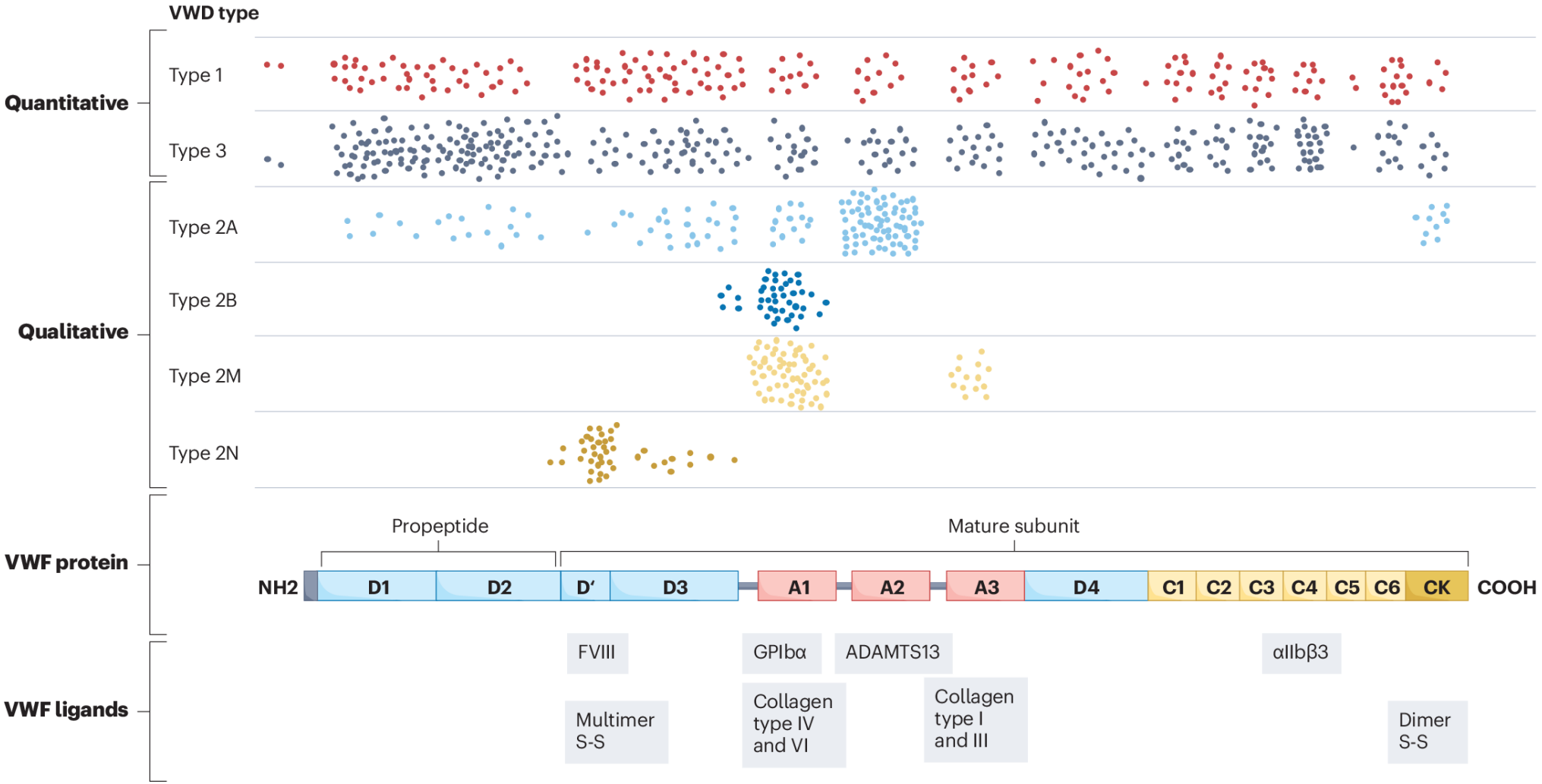
Seidizadeh O, et al. *Sci Rep*. 2026

Most frequent VWD variants associated with VWD



Seidizadeh O, et al. *Sci Rep*. 2026

Domain distribution of variants associated with VWD (2023)

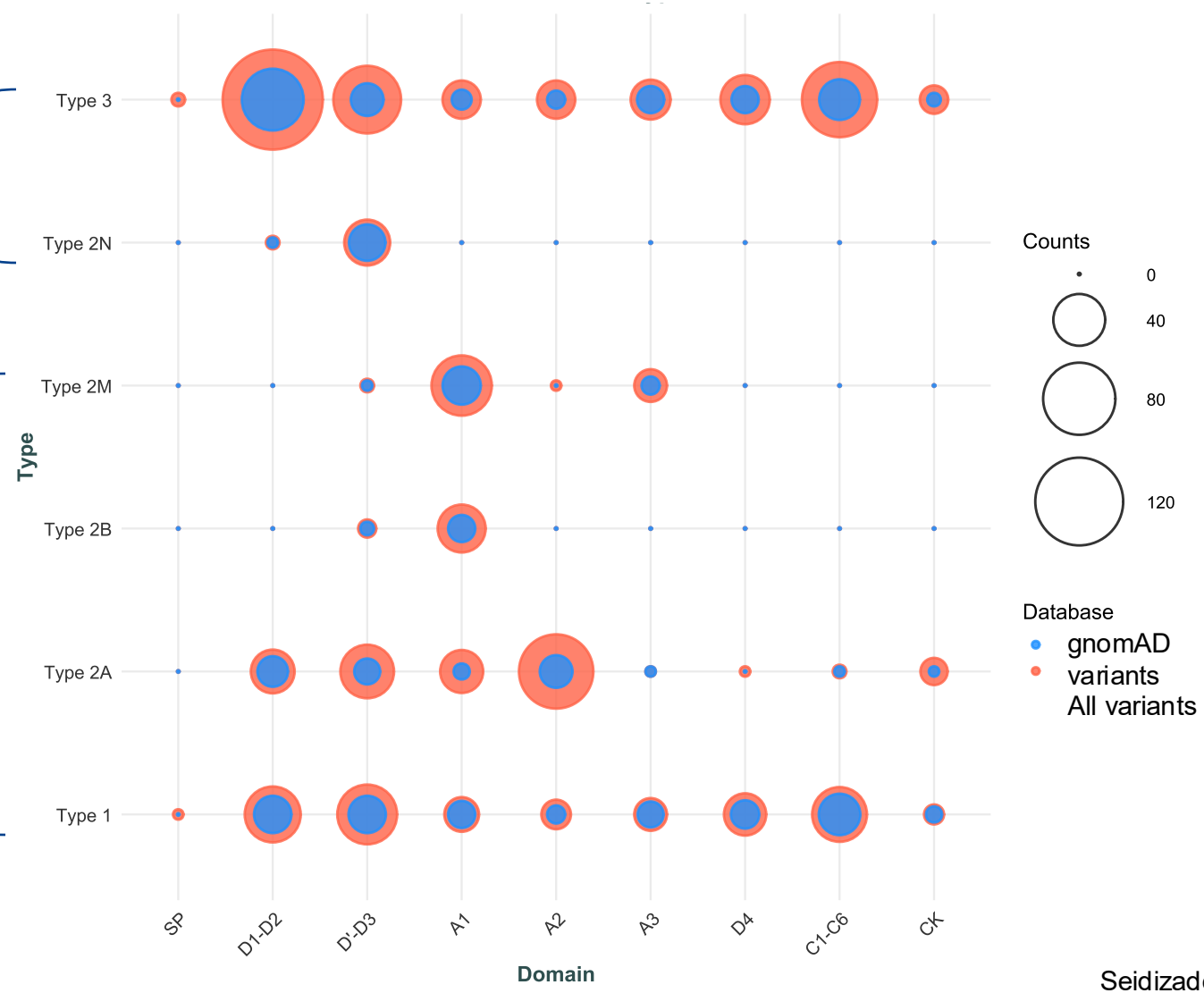


Seidizadeh, O et al. *Nature Reviews Disease Primers. 2024*

Domain distribution of variants associated with VWD (2025)

Recessive types **VWD**

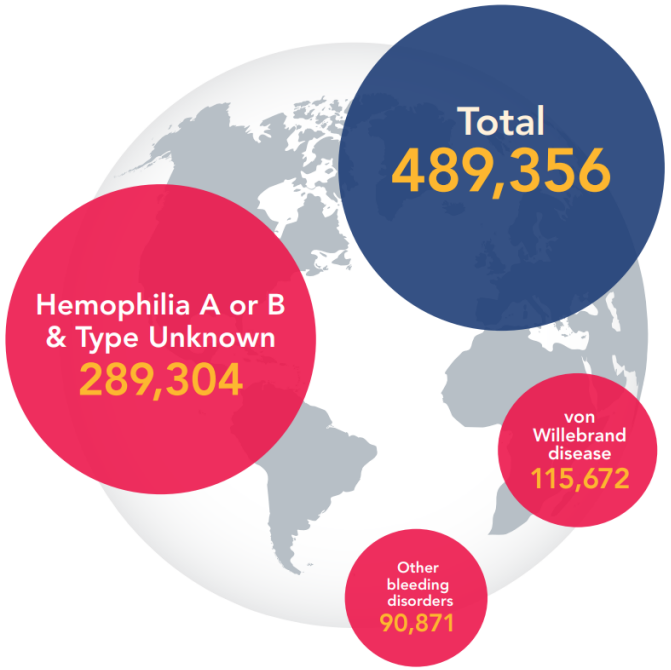
Dominant types **VWD**



Seidizadeh O, et al. *Sci Rep*. 2026

Global number of VWD cases

World Federation of Hemophilia Report on the **Annual Global Survey 2024**



Global registry-reported prevalence averages only **25.6** per million

J.S. Stonebraker A et al. *Haemophilia*. 2023

Bowman M, et al. *JTH*. 2010

1 per 1000

8.3 million in 8.3 billion

Bowman M, et al. *JTH*. 2010

Seidizadeh O, et al. *Sci Rep*. 2026

Type 1 = ~11 per 1000
Type 2A, 2B, 2M = ~1.5 per 1000
Type 2N = ~34 per million
Type 3 = ~1.3 per million

Type 1 = ~91.3 million
Type 2A, 2B, 2M = ~12.5 million
Type 2N = ~410, 000
Type 3 = ~10, 800

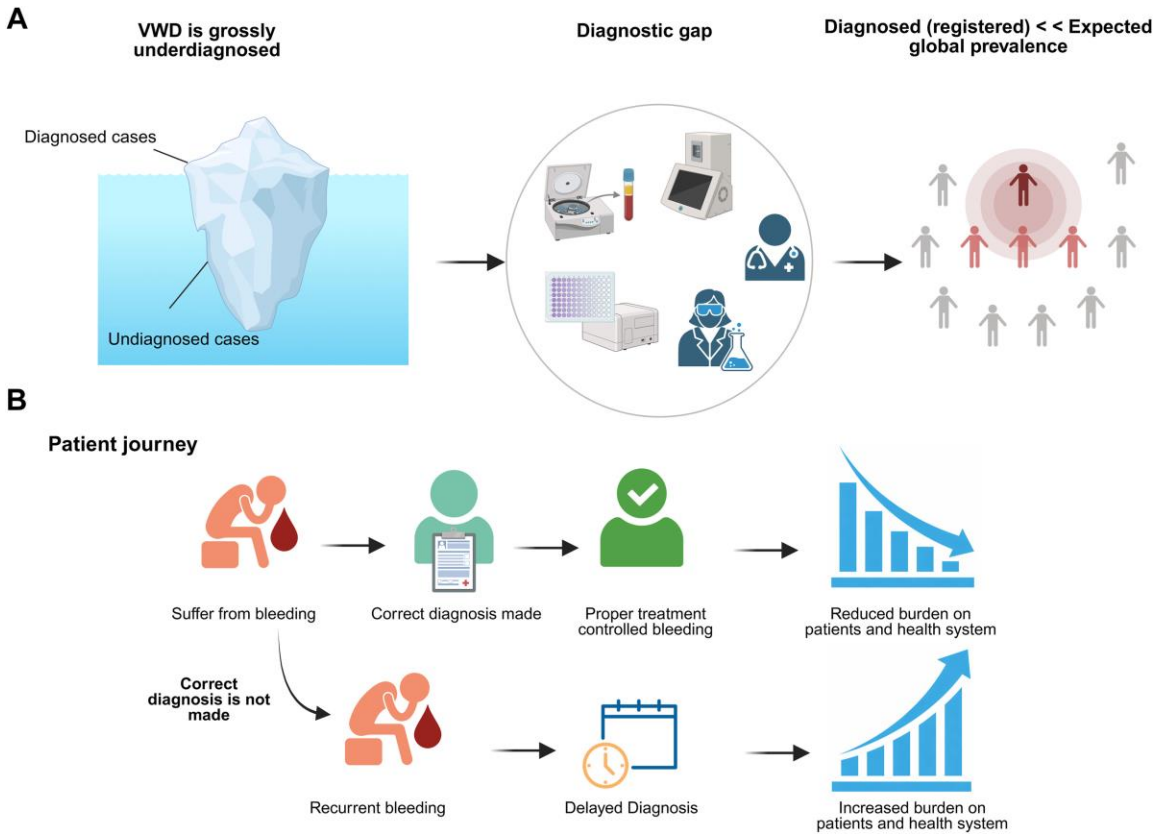
Seidizadeh O, et al. *Sci Rep*. 2026

Research and Practice in Thrombosis and Haemostasis
Volume 10, Issue 1, January 2026, 103359

Review Article

Beyond a century of discovery: the global and persistent burden of underdiagnosis in von Willebrand disease

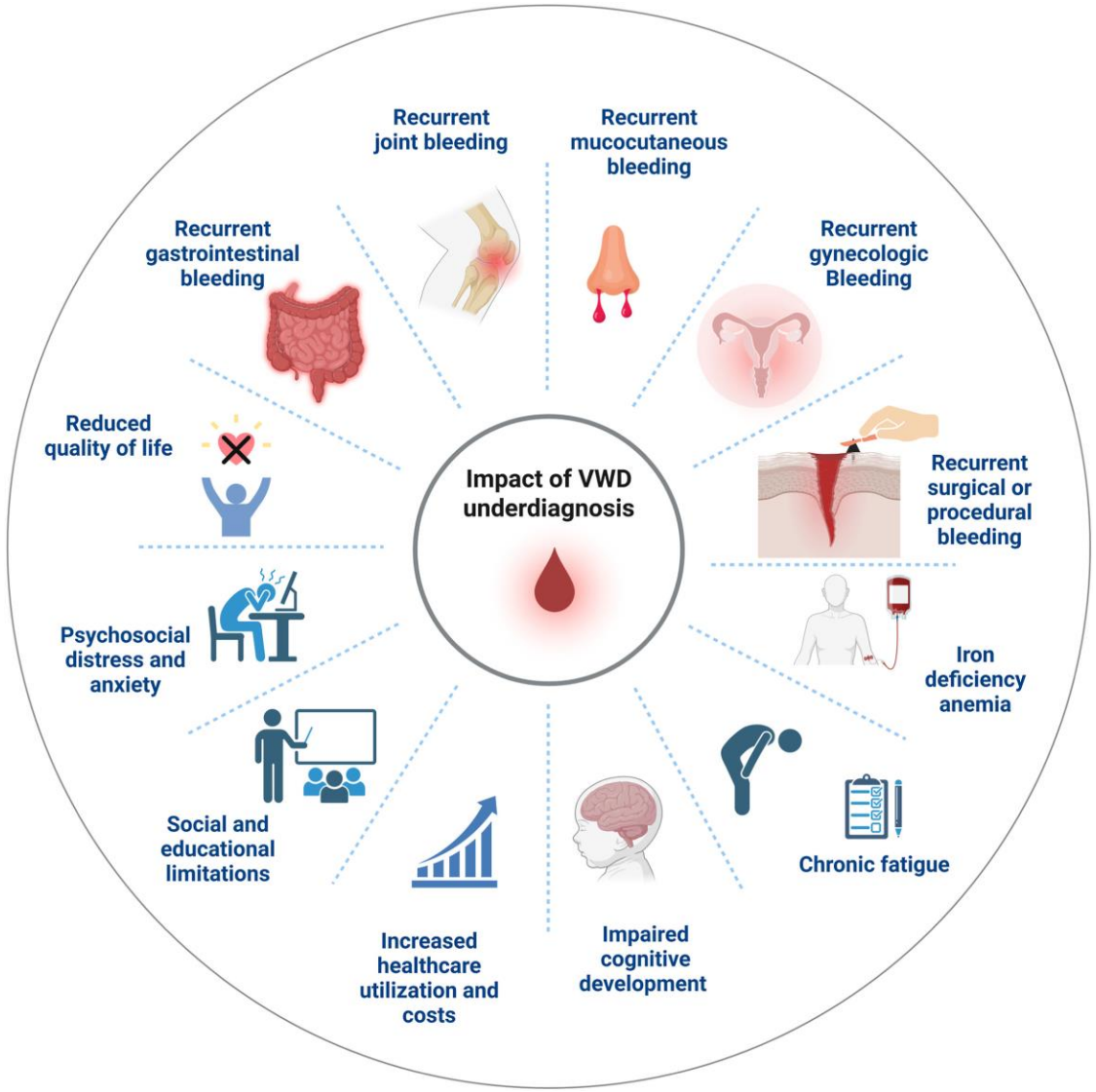
Omid Seidizadeh [1], Rezan Abdul-Kadir [2 3 4], Pier Mannuccio Mannucci [1], Flora Peyvandi [1 5]



Seidizadeh O, et al. *RPTH*. 2026

VWD is still underdiagnosed after 100 years

Median diagnostic delay in women can exceed **14 years**
(J. Shelton et al, *RPTH*, 2024)



Why von Willebrand Disease Remains Underdiagnosed Worldwide

Despite more than a century of progress, VWD remains underdiagnosed across all regions due to several overlapping factors.

1 Limited awareness among providers

- Suboptimal VWD knowledge among specialists and non-specialists, incl. obstetricians/gynaecologists
- Standardised tools (ISTH-BAT) rarely used
- Low public awareness delays or misses diagnoses

2 Poor access to specialised testing

- VWF-specific assays scarce in low/middle-income settings
- Reliance on basic coagulation tests → missed/incorrect diagnoses
- High assay costs; genetic testing underused globally

3 Biological variability

- VWF levels fluctuate with age, exercise, stress, hormones, inflammation, and blood group
- These influences can mask mild disease and complicate result interpretation

4 Heterogeneity & complexity of VWD

- 12+ phenotypes grouped into 6 major categories
- Severity ranges from mild/asymptomatic to life-threatening
- Variability complicates recognition and classification

5 Diagnostic & assay variability

- Diagnosis requires multiple assays of VWF quantity and function — no single confirmatory test
- Results affected by sample handling, assay and lab variability
- Inter-laboratory variation drives 7–33% diagnostic error rates

6 Misdiagnosis as other bleeding disorders

- Clinical overlap with platelet function disorders and haemophilia A causes confusion
- Misclassification → delayed/inappropriate management and missed targeted therapy

Seidizadeh O, et al. *RPTH*. 2026

Strategies to Reduce Global Underdiagnosis of von Willebrand Disease

Improving recognition and diagnosis of VWD requires coordinated clinical, laboratory, and policy action, with particular attention to LMICs.

1 Increase awareness & education

- Integrate VWD education into medical, nursing, and laboratory curricula
- Continuing education for GPs, ob/gyn, ER, pediatric, dental and hematology-oncology providers
- Public health campaigns on abnormal bleeding symptoms

2 Strengthen diagnostic capacity

- Expand access to labs performing FVIII, VWF antigen and activity assays
- Support regional reference centres (hub-and-spoke) for QA/standardisation
- Global proficiency testing; technology transfer and mentorship

3 Standardise diagnostic algorithms

- Adopt ISTH- and society-endorsed diagnostic pathways
- Use the ISTH-BAT in initial clinical history evaluation
- Promote reflex testing algorithms for VWF testing/interpretation

4 Enhance lab quality & standardisation

- Implement validated assay protocols with defined reference ranges
- Inter-laboratory collaborations to harmonise VWF assays
- Invest in digital/automated systems to cut analytical variability

5 Leverage population & genetic data

- Integrate genetic testing for difficult diagnoses, especially where access is limited
- Develop gene-specific variant interpretation frameworks to reduce misclassification

6 Address health-system inequities

- Improve access to diagnostic tools and hemostasis expertise in LMICs
- Global partnerships and funding to close diagnostic gaps
- Make diagnostic equity core to policy; leverage telemedicine for specialist support

Seidizadeh O, et al. *RPTH*. 2026

Conclusions

- The global genetic prevalence of VWD is higher than previously estimated.
- Type 1 VWD is the most common form across populations.
- VWF pathogenic variants exhibit marked ethnic and ancestry-specific diversity.
- Population-scale genomic data provide valuable insights into the epidemiology of VWD.

EAHAD
European Association for Haemophilia and Allied Disorders

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