haematologica
Journal of the Ferrata Storti Foundation

When genotype precedes phenotype: incidental findings in inherited disorders of hemostasis

by Omid Seidizadeh

Received: August 25, 2026.
Accepted: August 28, 2026.

Citation: Omid Seidizadeh.
When genotype precedes phenotype: incidental findings in inherited disorders of hemostasis.
Haematologica. 2026 Sept 3. doi: 10.3324/haematol.2026.301864 [Epub ahead of print]

When genotype precedes phenotype: incidental findings in inherited disorders of hemostasis

Omid Seidizadeh

Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

Correspondence

Omid Seidizadeh, Ph.D.

Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Via Pace 9, 20122 Milan, Italy.

Email: omid.seidizadeh@unimi.it, omidseidi93@gmail.com, phone: +390250320288

Acknowledgements

O.S. acknowledges partial support from the Italian Ministry of Health through the *Bando Ricerca Corrente*. The Hemostasis & Thrombosis Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico is a member of the European Reference Network on Rare Hematological Diseases (ERN-EuroBloodNet, Project ID No. 101157011). ERN-EuroBloodNet is partly co-funded by the European Union under the Fourth EU Health Program.

Conflict of interest

O.S.: None

The integration of clinical exome sequencing into routine medical practice has fundamentally changed the diagnostic pathway for rare genetic disorders.[1] Clinical exome sequencing is increasingly performed for patients with neurological, cardiovascular, immunological, and multisystem conditions, often revealing pathogenic variants unrelated to the original indication for testing.[2] In this issue of *Haematologica*, D'Apolito et al.[3] provide the first systematic estimate of pathogenic or likely pathogenic variants across the complete International Society on Thrombosis and Haemostasis (ISTH) Tier 1 gene set in individuals undergoing exome sequencing for conditions unrelated to inherited disorders of hemostasis. Their findings offer an important perspective on how frequently genetic predisposition to bleeding, thrombotic, and platelet disorders may be encountered outside hematology practice.

The results are striking. Among 1,135 consecutive individuals undergoing clinical exome sequencing, 103 carried pathogenic or likely pathogenic variants in ISTH Tier 1 genes, corresponding to an overall frequency of 7.5%. After consideration of the established inheritance pattern and the expected biological consequences of each genotype, 47 individuals (4.1%) were classified as carrying potentially clinically actionable incidental findings.[3] These figures should not be interpreted as estimates of disease prevalence. Rather, they demonstrate that disease-associated genetic variation in hemostasis genes is encountered with appreciable frequency during routine genomic testing, even among individuals who were not referred because of a suspected bleeding, thrombotic, or platelet disorder.

These findings also raise the possibility that inherited bleeding disorders, particularly mild forms, remain clinically underrecognized. The absence of a recognized bleeding phenotype does not necessarily exclude an underlying disorder, as mild bleeding may become apparent only during major hemostatic challenges such as surgery, trauma, dental procedures, or pregnancy. This may be particularly relevant in individuals who have not previously encountered circumstances capable of revealing a bleeding tendency. The identification of disease-associated variants in apparently unaffected individuals therefore suggests that the burden of genetic susceptibility to bleeding disorders may exceed that captured by current clinical diagnoses and highlights the potential value of genotype-first approaches in facilitating their recognition. This concept is consistent with previous reports suggesting that von Willebrand disease (VWD), rare bleeding disorders, hemophilia A/B in female carriers, and inherited platelet disorders may be substantially underdiagnosed.[4-8]

This issue is particularly relevant in VWD. Sixteen individuals in the present cohort carried pathogenic or likely pathogenic *VWF* variants, including variants associated with type 1, type 2B, type 2N VWD, and low VWF. Population-based studies have suggested that reduced VWF levels and disease-associated *VWF* variants are more common than clinically diagnosed VWD.[4] The present findings reinforce the concept that VWD occupies a broad biological and clinical spectrum, ranging from individuals with little or no spontaneous bleeding to those with clinically significant hemorrhagic manifestations. The phenotype associated with a given *VWF* genotype may be influenced by variant-specific effects as well as by additional genetic, environmental, and hemostatic modifiers, further complicating the interpretation of incidental findings.[4]

An important distinction is that the classification of findings as potentially actionable was based on the expected disease-associated genotype and the established inheritance pattern of each gene, rather than on demonstrated clinical penetrance.[3] Thus, heterozygous variants in autosomal recessive disorders were considered carrier states and were not classified as actionable incidental findings, whereas genotypes compatible with disease were retained. Nevertheless, a disease-associated genotype does not necessarily imply a fully penetrant clinical disorder. This may be especially relevant in inherited disorders of hemostasis, where genotype–phenotype relationships can be highly variable, for example, in disorders caused by variants in *SERPINC1*, *PROC*, *PROS1*, *F12*, *F11*, *F7*, *VWF*, fibrinogen genes (*FGA, FGB, FGG*), and *F5/F2* thrombophilia variants.[9] Because the study of D'Apolito et al [3] was not designed to evaluate genotype–phenotype correlations, these findings should be interpreted alongside personal and family history as well as laboratory phenotype whenever possible.

The study also highlights an important gap in the current framework for secondary genomic findings. Despite the clinical relevance of inherited bleeding, thrombotic, and platelet disorders, genes responsible for these conditions are not currently included in the American College of Medical Genetics and Genomics (ACMG) recommended secondary finding list.[10] This likely reflects the substantial variability in penetrance, expressivity, and clinical actionability across these disorders rather than a lack of clinical importance. Although several findings identified by D'Apolito et al.[3] may have implications for perioperative management, pregnancy, invasive procedures, thrombotic risk assessment, surveillance, and family counseling, potential clinical relevance should not be equated with established actionability. Determining which hemostasis genes and more importantly, which

specific variants or genotypes should be reported as secondary findings remains unresolved. Defining these criteria will become increasingly important as genomic testing becomes more widely accessible and incidental findings are encountered more and more frequently in routine clinical practice.

The work further underscores a broader shift occurring throughout medicine. Traditionally, inherited disorders of hemostasis have been diagnosed through a phenotype-first pathway, in which bleeding history, thrombotic events, family history, and laboratory abnormalities drive genetic investigation. Genome-scale sequencing may reverse this paradigm, placing the genotype at the beginning rather than the end of the diagnostic process. However, the emerging genotype-first model should not become a genotype-only model. Rather, incidental genomic findings should be viewed as signals prompting targeted clinical evaluation, laboratory investigation, and, where appropriate, family assessment. In this context, genetic findings complement rather than replace careful clinical phenotyping.[11]

Ultimately, the study by D'Apolito et al.[3] should not be viewed simply as a catalogue of incidental variants. It highlights a fundamental question for contemporary hematology: determining what a pathogenic genotype means when it is identified before a clinical phenotype. As clinical exome sequencing becomes increasingly integrated into medical practice, the interpretation of these findings will require close collaboration between geneticists, hematologists, and laboratory specialists. The expanding availability of genomic information should reinforce rather than replace rigorous clinical assessment. In inherited disorders of hemostasis, the significance of a genotype ultimately lies not only in whether a variant is pathogenic, but in how that genotype translates into an individual's actual bleeding, thrombotic, or platelet phenotype.

References

1. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA. 2014;312(18):1880-1887.
2. Green Rc, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15(7):565-574.
3. D'Apolito M, D'Andrea G, Palladino GP, et al. Incidental findings of inherited thrombosis and hemostasis disorders in clinical exomes with unrelated indications. Haematologica. xxxxx
4. Seidizadeh O, Abdul-Kadir R, Mannucci PM, Peyvandi F. Beyond a century of discovery: the global and persistent burden of underdiagnosis in von Willebrand disease. Res Pract Thromb Haemost. 2026;10(1):103359.
5. Meijer K, van Heerde W, Gomez K. Diagnosis of rare bleeding disorders. Haemophilia. 2021;27 Suppl 3:60-65.
6. Xing S, Batt K, Kuharic M, Bullano M, et al. Evaluation of clinical characteristics, health care resource utilization, and cost outcomes of hemophilia A carriers and noncarriers in the United States: A real-world comparative analysis. J Manag Care Spec Pharm. 2023;29(6):626-634.
7. Bury L, Falcinelli E, Gresele P. Learning the ropes of platelet count regulation: inherited thrombocytopenias. J Clin Med. 2021;10(3):533.
8. Seidizadeh O, Cairo A, Othman M, Peyvandi F. Global prevalence of platelet-type von Willebrand disease. Res Pract Thromb Haemost. 2025;9(1):102682.
9. Franchini M, Mannucci PM. Interactions between genotype and phenotype in bleeding and thrombosis. Haematologica. 2008;93(5):649-652.
10. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(8):100866.
11. Downes K, Megy K, Duarte D, et al. Diagnostic high-throughput sequencing of 2396 patients with bleeding, thrombotic, and platelet disorders. Blood. 2019;134(23):2082-2091.