The evolution of hemostasis genetics: from monogenic disorders to complex traits. A historical perspective

Augusto Di Castelnuovo

Research Unit of Epidemiology and Prevention, IRCCS Neuromed, Pozzilli (IS), Italy

ABSTRACT

The genetics of hemostasis factors has evolved over the past five decades, transitioning from the study of rare Mendelian disorders to the exploration of complex traits influencing cardiovascular disease risk. Early research focused on single-gene mutations responsible for bleeding disorders. By the 1990s, candidate gene studies identified associations between common polymorphisms and thrombotic risk. However, inconsistencies across studies highlighted the need for more robust approaches. The completion of the Human Genome Project in 2003 represented a turning point, enabling genome-wide association studies and the identification of novel loci involved in hemostasis and thrombosis. This era also introduced gene-gene and gene-environment interactions, as well as large multicenter studies that improved the reproducibility of findings. Subsequent years saw the development of polygenic risk scores, integrating the cumulative effect of numerous variants to refine individual risk prediction. Advances in pharmacogenomics further demonstrated how genetic polymorphisms modulate responses to antithrombotic therapies, paving the way for personalized treatment strategies. More recently, Mendelian randomization studies have provided compelling evidence of causal relationships between hemostatic factors and cardiovascular outcomes. Simultaneously, machine learning and artificial intelligence approaches have begun to uncover complex genetic networks, offering new perspectives in precision medicine. This review traces the chronological development of genetic research in hemostasis and thrombosis, emphasizing key methodological breakthroughs and their impact on cardiovascular risk assessment. By integrating genetics with emerging technologies, the field moves closer to personalized prevention and therapeutic interventions in thrombotic diseases.

Introduction

Hemostasis is a physiological process that maintains the equilibrium between bleeding and clot formation. The genetic basis of hemostasis has been studied for over a century, initially focusing on rare monogenic bleeding disorders such as hemophilia. However, as investigators recognized that common cardiovascular diseases (CVD) often arise from complex interactions between multiple genetic and environmental factors, research on the genetics of hemostasis expanded beyond simple Mendelian inheritance.

Early research identified single-gene defects in coagulation proteins, whereas later studies began to study multiple variants and gene-environment interactions. With the publication of the first draft of the human genome in 2003, the field shifted from candidate-gene approaches and small-scale association studies to genome-wide association studies (GWAS) and, more recently, to polygenic risk scores and machine learning (Figure 1).

This review provides a historical overview of key milestones in the genetics of hemostasis and thrombosis, describing major methodological advances.

Correspondence: Augusto Di Castelnuovo, Research Unit of Epidemiology and Prevention, IRCCS Neuromed, Via dell'Elettronica, 86077 Pozzilli (IS), Italy.
E-mail: dicastel@moli-sani.org

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Early insights (1970s-1980s): Mendelian thinking and first steps into complex disease

One of the earliest comprehensive discussions of genetic markers in atherosclerosis can be traced to Mortons 1976 review on *Genetic markers in atherosclerosis.*[1] While evidence was suggestive of a genetic component, such analyses were far from conclusive. A decade later, research on insulin-dependent diabetes mellitus (type 1 diabetes) offered indications into how Mendelian approaches could be extended to multifactorial conditions.[2] During this period, however, cardiovascular disease (CVD) genetics remained relatively unexplored. In 1987, an early review on the genetic aspects of hemostasis appeared in an Italian journal, reflecting a growing national interest in the genetic regulation of coagulation factors and their link to thrombotic diseases.[3] This underscored the expanding awareness that

genetic polymorphisms might be pivotal in determining individual risk profiles.

A cornerstone in understanding multifactorial, non-Mendelian diseases came from the work of Boerwinkle and Sing in the mid-1980s. They pioneered the integration of measured genotype information into the study of quantitative traits, moving beyond simple family-based inheritance models to more complex frameworks.[4] Notably, they highlighted how the apolipoprotein E polymorphism influences plasma lipid levels, heralding a new era in which specific genetic variants were linked to modulations in key cardiovascular risk factors.

Around the same time, Bernardi *et al.* provided critical insights into the genetics of von Willebrand factor, demonstrating novel restriction fragment length polymorphisms and allowing more detailed molecular analyses of von Willebrand disease.[5]

Studies by De Stefano *et al*. and others highlighted the significance of antithrombin deficiency in pregnancy, illustrating one of the earliest clinical applications of genetic knowledge in hemostasis.[6] Such work bridged monogenic conditions (e.g., antithrombin deficiency) with the growing realization that many thrombotic disorders display more complex genetic architectures.

The 1990s: emergence of candidate gene studies and early meta-analyses

Single-polymorphism investigations

By the early 1990s, single-gene polymorphism studies were rapidly expanding, widely published. A landmark study by Cambien *et al*., published in Nature in 1992,[7] provided compelling evidence of the association between a polymorphism in the angiotensin-converting enzyme (ACE) gene and cardiovascular disease risk. This study demonstrated that the insertion/deletion polymorphism in the ACE gene influenced plasma ACE levels and was associated with an increased risk of myocardial infarction. The publication in Nature gave the study great visibility and paved the way for further research of this kind, underscoring the potential of genetic markers in cardiovascular risk stratification and setting the stage for future investigations into gene-disease associations in hemostasis and vascular biology. The landmark discovery of the Factor V Leiden (F5 G1691A) mutation in 1994 definitively linked a single genetic alteration to elevated venous thrombotic risk[8] and shortly thereafter, the identification of the prothrombin G20210A variant further expanded the spectrum of common genetic risk factors for venous thrombosis.[9]

Early studies on Factor VII (FVII) also appeared, investigating whether FVII polymorphisms contributed to myocardial infarction (MI) risk. A key 1995 study published in Atherosclerosis[10] demonstrated that the investigated polymorphisms influenced plasma FVII levels; however, the association between these genetic variants and MI risk was not consistent across all populations examined. In contrast, Iacoviello *et al*. reported a substantial link in The New England Journal of Medicine,[11] showing that the association between the genetic variants studied and MI risk was entirely mediated by their effect on plasma FVII levels. This work introduced the concept of mediation analysis in this field, highlighting the importance of disentangling direct genetic effects from those exerted through intermediate phenotypic traits.

Observed inconsistencies in the case of FVII polymorphisms—later documented for several other single-gene candidates—likely reflected differences in population characteristics, sample sizes, and study designs, all of which are common challenges in genetic epidemiology. Such limitations, particularly in terms of statistical power and heterogeneity, contributed to the broader difficulty in replicating early candidate-gene associations in complex diseases.

In parallel with investigations of Factor VII, early genetic research also extended to other hemostatic components. For instance, several studies focused on the PLA1/A2 polymorphism of platelet glycoprotein IIb/IIIa, examining its possible association with coronary artery disease and restenosis after percutaneous transluminal coronary angioplasty.[12] Another analysis of the angiotensin-converting enzyme gene suggested that the deletion polymorphism could be associated with a higher risk of stroke, particularly when high tissue-type plasminogen activator levels were present.[13] Meanwhile, variations in fibrinogen gene loci were shown to modulate plasma fibrinogen concentrations, linking inflammatory stimuli and gene regulation to the pathogenesis of atherosclerotic complications.[14] Together, these find-

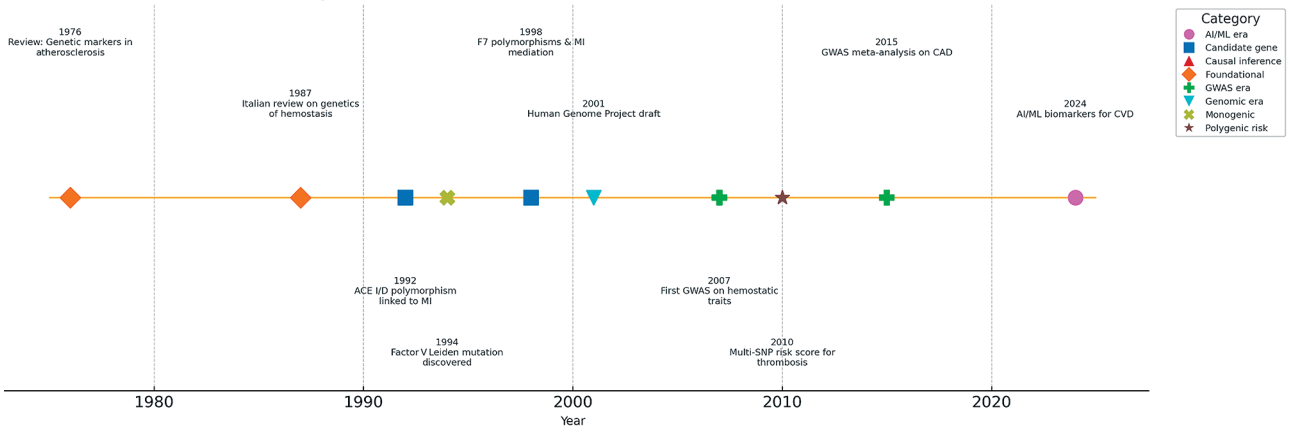

Figure 1. Chronological evolution of genetic research in hemostasis and thrombosis.

ings broadened the scope of early genetic studies on thrombosis, indicating that multiple loci can influence cardiovascular outcomes through varied mechanisms.

Rise of meta-analyses

Because many candidate-gene studies yielded inconsistent or non-replicable results, meta-analyses emerged as a powerful tool. Among the earliest in this domain was one by Iacoviello *et al*. on the 4G/5G polymorphism in the PAI-1 gene,[15] followed by Di Castelnuovo *et al*. evaluating the PLA1/PLA2 polymorphism in platelet glycoprotein IIIa.[16] These endeavors represented critical steps toward consolidating heterogeneous findings and set the stage for more robust, large-scale analyses.

Special populations and explorations beyond coagulation factors

Seeking explanations for conflicting results, investigators explored unique cohorts. For example, Mannucci *et al*. studied centenarians to identify potential protective genetic factors in hemostasis.[17] Meanwhile, Koeleman *et al*. shifted attention to mapping 26 coagulation-related genes on the human genetic linkage map, facilitating multi-gene interaction analyses.[18] These efforts highlighted the need for large-scale studies, illustrated by early European consortia like HIFMECH Study Group.[19,20]

The early 2000s: expanding methodologies and the human genome sequence

Human genome publication and its impact

The publication of the first draft of the human genome by Venter *et al.* in 2001 represented a major advancement for the field.[21] The unprecedented scale of genomic information led to a shift from studying single variants in isolation to investigating thousands—even millions—of polymorphisms simultaneously. This development enabled systematic, hypothesis-free screening for genetic determinants of hemostatic factors in cardiovascular genetics.

Growing evidence for gene-environment and gene-gene interactions

During this period, numerous studies reinforced the importance of gene-environment interactions. Investigations on Factor VII, PAI-1, and cigarette smoking[22-24]showed that genetic predispositions could be significantly modulated by lifestyle or environmental exposures. Researchers also began addressing gene-gene (epistatic) interactions, an approach exemplified by D'Angelo *et al*., who examined interactions among genetic polymorphisms involved in mild hyperhomocysteinemia and their influence on thrombotic risk.[25]

Consolidating or disproving candidate-gene associations

As collaborative consortia expanded, some large-scale studies did not confirm earlier candidate-gene associations. An example is the Atherosclerosis Thrombosis and Vascular Biology Italian Study Group, which in 2003 found no association between nine polymorphisms in hemostatic genes and acute myocardial infarction in young individuals.[26] Similar null findings for factor XI deficiency[27] reinforced skepticism about many initial "positive" reports, further motivating a transition away from single-candidate approaches.

Early signs of multi-locus and haplotypic analyses

Simultaneously, researchers began deploying multi-locus and haplotype-based strategies. Van der Neut Kolfschoten *et al*. demonstrated the importance of haplotypes (e.g., R2-haplotype in factor V) rather than single polymorphisms.[28] Investigators also introduced "tag SNP" approaches to capture genetic diversity across larger genomic regions - Grisoni *et al*. used this method for IL-18 gene analysis in the MORGAM Project.[29] These novel methods allowed more robust assessments of the combined effect of variants within a gene or locus.

The GWAS era and beyond (mid-2000s–present)

First genome-wide association studies

By 2007, the first GWAS investigating hemostatic factors had emerged, such as Yang *et al*.'s work in the Framingham Heart Study[30] and parallel efforts on lipoprotein(a).[31] These studies moved beyond predefined candidate genes, scanning the entire genome to identify potential risk loci. The approach greatly enhanced the discovery of previously unrecognized genetic determinants.

From multi-locus analyses to complex network interactions

Researchers like Zee *et al*. moved beyond single-locus designs toward multi-locus candidate-gene polymorphisms and risk assessment.[32] The importance of gene-gene interactions also became clearer as demonstrated by Gong *et al*. in the context of lupus nephritis and microthrombosis.[33]. These strategies addressed the need to address the complex, polygenic nature of thrombotic and cardiovascular diseases.

Large consortia and meta-analyses of GWAS

As sample sizes rose—often aided by international collaborations - the field witnessed the advent of GWAS meta-analyses for CVD and related hemostatic traits. Landmark examples include: i) Nikpay *et al*., examining coronary artery disease;[34] ii) de Vries *et al*., identifying new loci for fibrinogen concentration;[35] iii) Ehret *et al*., studying the genetics of blood pressure regulation in over 300,000 individuals.[36] These consortium-driven studies provided robust statistical power, uncovering numerous novel variants that had eluded smaller candidate-gene efforts.

Polygenic risk scores

In parallel with GWAS expansion, polygenic risk scores (PRS) emerged as a way to combine many loci of small effect

into a single predictive measure.[37] While some PRS focused on intermediate phenotypes like LDL cholesterol levels,[38] others tackled clinical outcomes such as coronary artery disease[39] or ischemic stroke. The concept broadened to include interplay with environmental or lifestyle factors, further refining personalized risk assessment.

Pharmacogenomics of hemostasis

Beyond disease risk, genetic polymorphisms also influence therapeutic response. Early studies on aspirin resistance (e.g., PlA2 allele in glycoprotein IIIa) showed how specific genotypes might reduce the efficacy of antiplatelet therapy.[40,41] Further research by Giusti *et al*. and others expanded the scope of pharmacogenetics to clopidogrel metabolism (e.g., CYP2C19 loss-of-function variants) and glycoprotein receptors involved in platelet aggregation.[42,43]

Subsequent investigations extended pharmacogenetic approaches to anticoagulant therapies. For vitamin K antagonists (VKAs) like warfarin, polymorphisms in the CYP2C9 and VKORC1 genes were shown to influence both drug metabolism and sensitivity, prompting the development of genotype-guided dosing algorithms.[44,45] More recently, attention has turned to direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban. Although DOACs are generally less affected by genetic variability than VKAs, studies have explored the roles of CES1, ABCB1, and CYP3A5 variants in modulating drug levels and bleeding risk, albeit with more modest clinical impact.[46]

Together, these pharmacogenetic findings underscore the potential for tailoring anticoagulant and antiplatelet therapy to individual genetic backgrounds - an evolving area that may improve efficacy, reduce adverse events, and enhance overall safety in thrombotic disease management.

Mendelian randomization

Mendelian randomization (MR) is an epidemiological method that uses genetic variants as instrumental variables to infer causal relationships between modifiable risk factors and disease outcomes. By leveraging the random assortment of alleles at conception, MR minimizes confounding and reverse causation common in observational studies. For instance, the study[47] applied a three-step MR strategy to assess the role of plasminogen activator inhibitor type 1 (PAI-1) in coronary heart disease. Initially, a systematic meta-analysis of observational studies showed that individuals with the highest blood levels of PAI-1 had a markedly higher risk of CHD compared with those in the lowest quantile. In the subsequent MR analysis, summary statistics from large-scale genome-wide association studies were used to demonstrate that a genetically determined increase in PAI-1 levels was causally associated with elevated CHD risk. Moreover, the study provided evidence that higher PAI-1 may exert its adverse cardiovascular effects partly by influencing metabolic traits such as blood glucose and high-density lipoprotein cholesterol levels. This work underscores how MR can clarify the causal impact of hemostatic factors on cardiovascular outcomes and guide the development of targeted preventive and therapeutic strategies.[48]

Machine learning and AI: the next frontier

Most recently, the integration of artificial intelligence (AI) and machine learning (ML) represents a new area in discovering genetic risk markers and predictive models for CVD. For example, DeGroat *et al.* used ML algorithms to achieve up to 96% accuracy in predicting cardiovascular disease based on transcriptomic data.[49] Similarly, Venkat *et al*. employed ML to identify genes associated with heart failure and atrial fibrillation, underscoring the promise of advanced computational techniques in unveiling complex gene-gene and gene-environment networks.[50] This integration of genomics, big data, and AI is advancing cardiovascular precision medicine, enhancing granularity and predictive power.

Non-inherited genetic mechanisms

Although traditionally considered as inherited conditions, it is now well established that certain thrombotic disorders arise from acquired (somatic) genetic mutations. Notable examples include paroxysmal nocturnal hemoglobinuria (PNH), driven by somatic mutations in the PIGA gene affecting hematopoietic stem cells, and myeloproliferative neoplasms (MPNs) characterized by the acquired JAK2 V617F mutation, both of which substantially increase thrombotic risk.[51,52] These cases illustrate how the boundary between inherited and acquired genetic contributions to thrombosis has become increasingly blurred.

Conclusions

Over the past five decades, the genetics of hemostasis has evolved from early, often inconclusive, markers-based analyses to a complex field integrating monogenic and polygenic concepts, gene-environment and gene-gene interactions, Genome-Wide Association Studies, meta-analyses, polygenic risk scores, and machine learning. Initial Mendelian discoveries - like Factor V Leiden and prothrombin G20210A - demonstrated how single genetic variants can profoundly alter thrombotic risk in some conditions. Yet, inconsistent replication and the realization that CVD and thrombosis are multifactorial led to larger, consortium-driven studies and increasingly sophisticated analytical techniques.

The completion of the Human Genome Project in 2001 and subsequent technological advances enabled the high-throughput genotyping and whole-genome scanning that underpin modern research. Today, the focus has shifted to integrative approaches - encompassing multiple genes, extensive consortia, big data, and AI-driven analytics - to dissect the intricate genetic architecture of hemostasis. These approaches improve prevention, diagnosis, and therapy, bringing the field closer to personalized cardiovascular medicine.

However, despite the substantial advances in the genetic dissection of thrombotic and hemorrhagic disorders, the impact on routine clinical management has been relatively limited. Polygenic risk scores, while valuable for population-level stratification, have yet to gain widespread use in individual patient care. Similarly, pharmacogenetic tests—though informative in selected contexts, such as clopidogrel metabolism—are not systematically employed to guide antithrombotic therapy. These gaps underscore the need for further translational efforts to bridge genetic discoveries and clinical utility.[53,54]

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