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REVIEW ARTICLE

Systematic review and bibliometric analysis of genetic factors influencing hematologic traits: Implications for blood donor screening

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ABSTRACT

Introduction: Genetic variation plays a role in blood disorders involving iron metabolism, hemoglobin regulation, and thrombophilia, all of which may influence blood donor health and the quality of donated blood. Understanding these genetic determinants across diverse populations is important for improving donor selection, supporting safer blood donation practices, and strengthening transfusion outcomes. This systematic review evaluates reported genetic variants associated with these disorders and their potential application in blood donor screening. **Methodology:** A systematic literature search was conducted in PubMed, Web of Science, and Scopus using Medical Subject Headings (MeSH) and keywords related to single nucleotide polymorphisms (SNPs).

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Studies published between January 2000 and September 2023 involving human participants written in English were eligible. Two independent reviewers screened titles, abstracts, and full texts according to predefined inclusion criteria, while disagreements were resolved by a third reviewer. Methodological quality was evaluated using the Newcastle–Ottawa Scale (NOS), and bibliometric analyses were performed using VOSviewer. **Results:** Among 1,292 retrieved records, 20 studies satisfied the inclusion criteria. Frequently reported SNPs included *HFE C282Y*, associated with hereditary hemochromatosis, *TMPRSS6*, linked to iron deficiency anemia, and *BTBD9*, implicated in thrombophilia and iron regulation. NOS quality scores ranged from 6 to 9, indicating generally moderate-high methodological quality. Bibliometric mapping, including bibliographic coupling, co-authorship, and keyword co-occurrence analyses, identified research themes, influential collaborations, and emerging trends in blood disorder genetics. The review demonstrated that several polymorphisms are consistently associated with hematological disorders and may serve as genetic markers for identifying blood donors at increased risk of iron deficiency, iron overload, or related conditions. **Conclusion:** Genetic factors contribute substantially to interpopulation differences in blood composition and disease susceptibility. Incorporating validated SNP markers into donor screening strategies may improve diagnostic accuracy, transfusion safety, and clinical management while supporting the development of population-specific genetic screening panels for blood donation programs.

1. INTRODUCTION

1.1 Background of study

Erythropoiesis, the production of red blood cells (RBCs), is intricately regulated by genetic and nutritional factors. Essential nutrients such as iron and folate are required at various stages of this process. Iron is vital for the synthesis of heme and hemoglobin—proteins that transport oxygen—and for DNA synthesis in RBC precursors. Similarly, folate is crucial for DNA synthesis and cell division. Deficiencies in either nutrient can disrupt erythropoiesis and lead to anemia. These considerations are especially important in the context of blood donation, where maintaining adequate RBC levels is essential for the safety of both donors and recipients [1].

Genetic variations play a significant role in hematologic traits, including iron metabolism, hemoglobin levels, and the efficiency of erythropoiesis. Single nucleotide polymorphisms (SNPs), the most prevalent type of genetic variation, can affect the expression or function of genes involved in these processes. For example, SNPs in the *HFE* gene, such as C282Y and H63D, are linked to hereditary hemochromatosis and iron overload [2]. Similarly, variations in the *TMPRSS6* gene can influence susceptibility to iron deficiency anemia [3]. Moreover, SNPs in genes like *BTBD9* have been associated with thrombophilia and disruptions in iron homeostasis [4]. These genetic factors can lead to variations in blood composition and may result in subclinical or latent abnormalities, even in individuals who appear healthy.

Beyond genetic variants, epigenetic modifications such as DNA methylation also play a role in regulating blood cell production and immune cell differentiation. Changes in methylation patterns can affect the development and function of T and B lymphocytes, thereby influencing immune responses [5]. Notably, the interaction between genetic variants, such as those in the *MTHFR* gene, and epigenetic changes has been associated with immune-related disorders, including autoimmune diseases like systemic lupus erythematosus (SLE) [6].

Despite advancements in blood screening protocols, current donor selection practices largely ignore genetic and epigenetic factors. Individuals with SNPs associated with iron deficiency, altered hemoglobin synthesis, or thrombophilia may not be detected by standard screening, potentially compromising donor health and transfusion safety. Incorporating genetic tools into blood donor screening could improve risk assessment, reduce adverse reactions, and support precision-medicine approaches in transfusion care. This study aims to achieve two main objectives:

(i) To systematically review the literature for genetic variants, particularly SNPs, related to erythropoiesis, iron metabolism, hemoglobin levels, and thrombophilia that may be relevant to apparently healthy individuals and blood donors; and
(ii) To conduct a bibliometric analysis to map research trends, key contributors, and thematic focuses within this field. This combined approach seeks to highlight existing knowledge, identify research gaps, and inform strategies for more personalized and safer blood donation practices.

1.2 Research Questions

(i) RQ1- What are the common genetic variations associated with altered iron metabolism among blood donors?
(ii) RQ2- How do interactions between genetic factors, sex, and lifestyle/environmental factors impact blood disorder risk among blood donors?
(iii) RQ3- Are there specific genetic markers that predispose blood donors to blood-associated disorders?

2. METHODOLOGY

2.1 Search Strategy

The search was conducted using MeSH terms and Boolean: blood donors (AND) single nucleotide polymorphism (AND) genetic risks (AND) disease. The source of search included the PubMed, Web of Science and Scopus electronic databases from January 2000 to September 2023.

2.2 Screening Process

Following the database search, all retrieved records were exported into Mendeley for deduplication. The screening process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7] and involved several distinct stages: identification, screening, eligibility, and inclusion, as illustrated in Figure 1.

During the identification stage, articles from PubMed, Web of Science, and Scopus were compiled, and duplicates were removed. In the screening phase, the titles and abstracts of the remaining studies were reviewed to assess relevance based on the predefined inclusion and exclusion criteria. The eligibility phase involved a full-text review of the articles that passed the initial screening to ensure they met all criteria regarding population, intervention, and outcome relevance. Finally, in the inclusion stage, studies that fulfilled all eligibility criteria were selected for systematic review and bibliometric analysis.

All screening steps were performed independently by two reviewers (AFS and TLK). Any discrepancies in article selection or inclusion were resolved through discussion, and if necessary, a third reviewer (MZS) was consulted to achieve consensus. This rigorous process was employed to minimize selection bias and enhance the reproducibility and reliability of the review.

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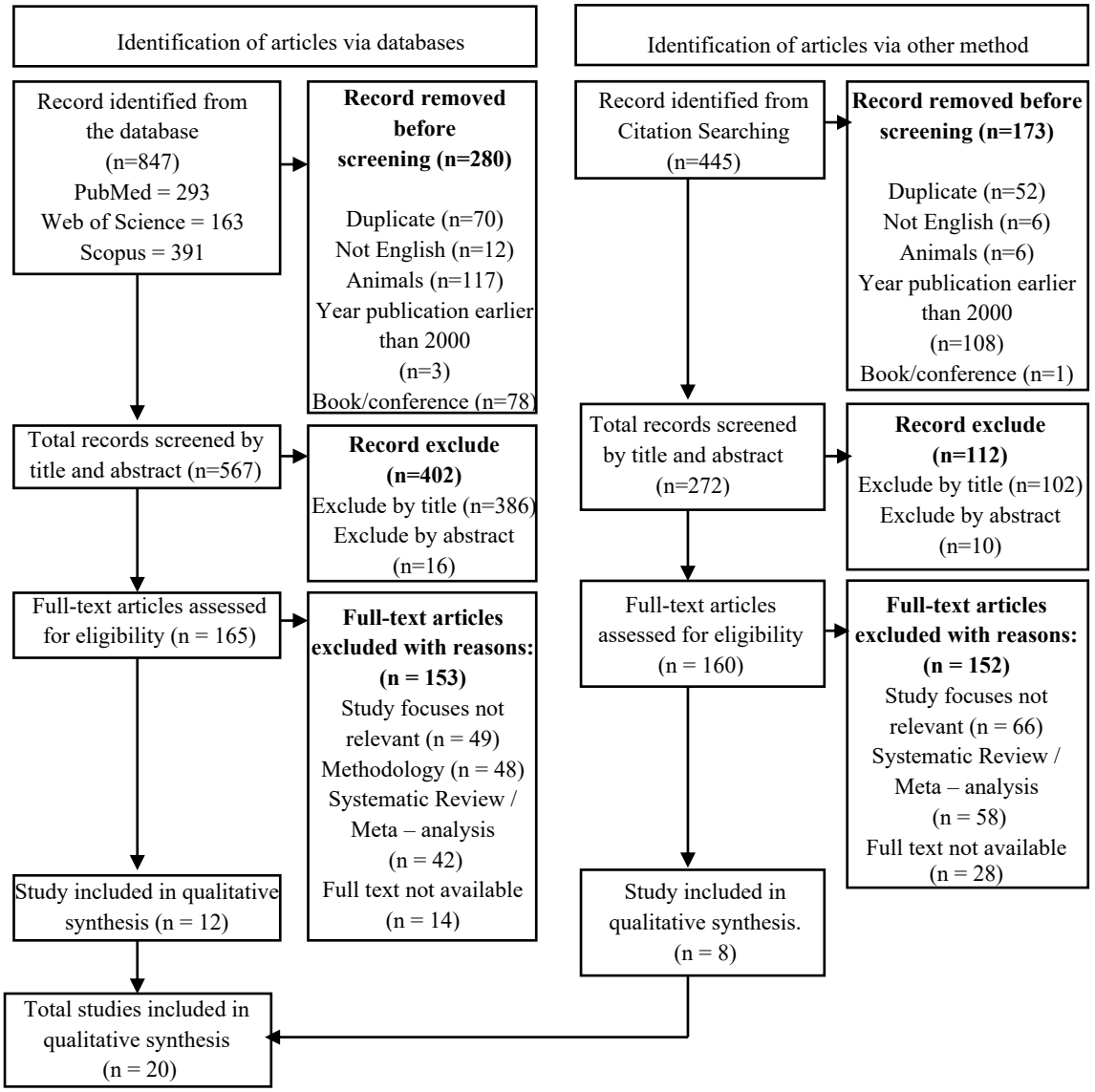

Fig 1. PRISMA flow diagram: identification, review, selection of articles included in the systematic review.

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2.3 Inclusion and Exclusion Criteria

The inclusion criteria for this study were as follows: (a) papers written in English; (b) studies focused on single nucleotide polymorphisms; (c) research involving human subjects; and (d) studies addressing blood disorders linked to genetic risks. The following types of studies were excluded: (a) opinion pieces and viewpoints; (b) books and book chapters; (c) articles unrelated to the research questions; (d) studies on transplantation, cancer, infectious diseases, and immune-related disorders; (e) articles utilizing sample types other than blood, such as biopsy tissues; and (f) systematic reviews and meta-analyses. The results of the PRISMA search are presented in Figure 1.

2.4 Quality assessment of Studies

Assessing the quality of studies included in systematic reviews is crucial for ensuring the reliability and validity of the evidence base. Quality evaluation was performed using the adapted Newcastle-Ottawa Scale (NOS) for observational studies [8]. NOS utilizes a star scoring system, allowing a maximum of nine stars for prospective and cross-sectional studies, and ten for case-control studies. This assessment encompasses three domains: subject selection, comparability, and outcome assessment, with scores allocated as follows: up to four stars for subject selection, two stars for comparability, and three stars for outcome assessment. Consequently, a study can achieve a total score of up to nine stars. The quality of each study was classified as low (0–3), moderate (4–6), or high (7–9). Two authors independently checked the quality assessments, and any discrepancies were resolved by a third author. Studies scoring 6 or higher were deemed high quality.

2.5 Characteristics of study

A detailed overview of the selected studies is presented to facilitate critical analysis and comparison. For each study, key data were systematically extracted to enable in-depth evaluation and comparison. Extracted variables include the first author and year of publication, study design, population characteristics such as sample size and demographic background, the genes or single nucleotide polymorphisms (SNPs) investigated, clinical or hematologic outcomes assessed such as iron status, hemoglobin concentration, or thrombophilia risk and the principal findings. This standardized extraction allows for a structured appraisal of the existing literature and highlights the diversity and consistency of findings across different study populations and genetic markers.

2.6 Bibliometric Analysis

We conducted a series of bibliometric analyses, a quantitative method that employs mathematical and statistical tools to assess the interrelationships and impacts of publications within a specific research area. This approach provides a broad overview of extensive academic literature [9]. Descriptive analysis focused on the number of publications per year, the most prolific authors, and the leading journals in the field. Citation analysis was used to identify highly cited papers, influential authors, and major journals. Co-authorship analysis examined collaboration patterns among researchers and institutions. Co-citation analysis helped identify relationships between papers and map the intellectual structure of the field. Finally, keyword analysis was utilized to identify research trends and hot topics.

2.6.1 Visualization Scientific Maps

Bibliometric maps were created using VOSviewer to visually represent the data. Network maps visualized co-authorship, co-citation, and keyword co-occurrence networks. Density maps showed the density of research activity or citations in specific areas. Temporal maps highlighted trends and changes over time in the field.

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3. RESULTS

3.1 Literature Search

A total of 1,292 publications were identified, 847 via electronic database search and 445 via other citation searching method (Figure 1). However, 453 publications were removed due to duplicates, not written in English; animal study; publish before year 2000 and articles are book or conferences. The remaining 839 publications were then screened and 489 articles were further excluded by title and 26 articles were excluded after abstract screening. Only 325 full-text articles were retrieved and reviewed in detail, 305 articles were excluded because of irrelevant study focus, different methodology used, systematic reviews or meta-analysis and no full-text was available. Only 20 articles met the inclusion criteria and were included in this systematic review

3.2 The Newcastle-Ottawa Scale score

The NOS score plays a pivotal role in assessing the dependability and validity of studies focused on diagnostic accuracy. Table 1 provides scoring criteria while Table 2 shows an overview of the NOS scores for the studies included in this review, highlighting both the strengths and weaknesses. While strengths include clear study objectives and appropriate design, weaknesses in methodological rigor were noted.

3.3 Characteristic Study

Moving to Table 3, it outlines the key characteristics of our study, offering insights into factors that influence the outcomes. These 20 articles underscore the significance of eleven (11) candidate genes linked to healthy blood synthesis: *BTB domain-containing protein* (*BTBD9*), *transmembrane serine protease S6* (*TMPRSS6*), *transferrin gene* (*TF*), *human hemochromatosis protein* (*HFE*), factor V (FV), factor II (F2), *methylenetetrahydrofolate reductase* (*MTHFR*), prothrombin, *Bone morphogenetic protein 2 (BMP2)*, *Transferrin receptor 2 (TfR2)*, and *glyceronephosphate O-acyltransferase* (*GNPAT*). The investigation involves the examination of specific polymorphisms within these genes, including *BTBD9* (rs9296249, rs3923809, rs9257271), *TMPRSS6* (rs4820268, rs855791), *TF* (G277S, rs1799852, rs2280673, rs11830084), *HFE* (H63D, S65C, C282Y), FV (g.1691 G>A, rs6025), F2 (g.20210 G>A, rs1799963), *MTHFR* (g.677 C>T, g.1298 A>C, rs1801133, rs1801131), prothrombin (20210 G>A), *BMP2* (rs235756), *TfR2* (rs7385804) and *GNPAT* (A>G, rs11558492).

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Table 1. Scores for the review based on Newcastle-Ottawa scale for genetic studies

Category	Scoring criteria
Selection (Maximum score: 4 stars)	Representation of blood donor population (maximum 1 star) - Population-based study with clear description of recruitment methods (1 star) - Convenience or non-representative sampling (0 star) - No description (0 stars) Ascertainment of exposure (maximum 2 star) - Use of reliable and valid methods for SNP genotyping (2 star) - Inadequate or poorly described genotyping methods (0 stars) - No description (0 stars) Selection of participants (maximum 1 star) Clear description of inclusion/exclusion criteria and sampling method (1 star) Unclear or inappropriate selection criteria (0 star)
Comparability (Maximum score: 2 stars)	Control for potential confounder (maximum 2 star) - Study adjusts for relevant confounders in the analysis (e.g., age, sex, ethnicity) (1 star) - Adequate control for confounders (1 stars) - Inadequate control for confounders (0 stars) - Incomparable control, confounders uncontrolled (0 stars)
Outcome (Maximum score: 3 stars)	Outcome assessment (maximum 1 star) - Clear definition and assessment of outcomes related to SNP genotype (1 stars) - Inadequate or poorly defined outcome assessment (0 star) Precision of outcome measurement (maximum 1 star) - Detailed description of SNP measurement techniques and validation (1 star) - Unclear or ambiguous outcome definition (0 stars) Statistical Analysis (maximum 1 star) Appropriate statistical methods used to analyse the association between SNP genotype and outcome (1 star) Inappropriate or inadequate statistical analysis (0 star)

Good quality: 3/4 stars for Selection, 1/2 stars for Comparability, 2/3 stars for Outcome. Fair quality: 2 stars for Selection, 1/2 stars for Comparability, 2/3 stars for Outcome. Poor quality: 0/1 star for Selection, 0 stars for Comparability, 1 star for Outcome.

Source: Norris et al. (2020)

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Table 2. Assessment of the studies included in the systematic review using a modified Newcastle-Ottawa scale

Study	Selection			Comparability	Outcome			Total
	Representation of blood donor population	Ascertainment of exposure	Selection of participants	Control for potential confounder	Outcome assessment	Precision of outcome measurement	Statistical Analysis	
Sørensen et al. 2012	*	**	*	*	*	*	*	8
Sørensen et al. 2015	*	**	*	**	*	*	*	9
Cukjati et al. 2007	*	**	*	**	*	*	*	9
Yang et al. 2011	-	**	*	*	*	*	*	7
Sørensen et al. 2018	*	**	*	*	*	*	*	8
Dick-Guareschi et al. 2021	*	**	*	**	*	*	*	9
Sabbagh et al. 2008	-	**	*	*	*	*	*	7
Hadhri et al. 2012	*	**	*	**	*	*	*	9
Greni et al. 2017	*	**	*	**	*	*	*	9
Rajkovic et al. 2000	-	**	*	*	*	*	*	7
Fawzy et al. 2021	*	**	*	**	*	*	*	9
Niewiadonski et al. 2015	*	**	*	**	*	*	*	9
Jackson et al. 2001	*	**	*	**	*	*	*	9
Lee et al. 2001	-	**	*	**	*	*	*	8
Chambers et al. 2003	*	**	*	**	*	*	*	9
Peng et al. 2001	-	**	*	*	*	*	*	7
Ji et al. 2018	*	**	*	**	*	*	*	9
Pei et al. 2014	-	**	*	**	*	*	*	8
An et al. 2012	-	**	*	**	*	*	*	8
Santos et al. 2010	*	**	*	**	*	*	*	9

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Table 3. Characteristics, scores on NOS and results found in the studies.

Article	Index Test	Study Design	Analysis	Results		Conclusion	NOS Score
				Gene	SNP /allele		
Sørensen et al. 2012 ….[10]	Total: 1302 donors female blood donors, adult population	Observational study, retrospective	-DNA extraction using a DNA blood kit, -SNP analysis using commercially available assays and sequence detection system, -Hardy-Weinberg equilibrium test. -logistic regression analyses -post hoc power calculations.	*BTBD9* *TMPRSS6* *TF*	rs9296249 rs3923809 rs4820268 rs855791 rs1799852	Genetic variants, especially rs9296249 (*BTBD9*), were significantly associated with serum ferritin levels in female blood donors. The paper also explored the relationship between restless legs syndrome (RLS) and serum ferritin. Additionally, it suggested that genetic polymorphisms related to iron metabolism could serve as markers to identify blood donors at risk of iron deficiency.	8
Sørensen et al. 2015 ….[11]	14,126 donors, including 7556 men and 6570 women, recurrent donors aged 18 to 67 years old	Observational, multi-site, retrospective, stratified by sex	-DNA extraction and genotyping by LGC genomics extraction service. -Measurement of plasma ferritin in blood donors. -Multiple linear and logistic regression analyses. -Tests for Hardy-Weinberg equilibrium using -AssoTest v0.4 - Statistical analyses using Stata/IC 11.2.	*HFE* *BTBD9* *TMPRSS6* *TF*	rs1800562 rs1799945 rs9357271 rs855791 rs2280673 rs11830084	The paper examined how genetic variants influence iron levels in blood donors, revealing associations between specific variants and serum ferritin levels, as well as the risk of iron deficiency. The authors emphasized the necessity for additional studies to evaluate the practicality of genetic testing in identifying donors who may be susceptible to or resistant against iron deficiency.	9
Cukjati et al. 2007…[12]	Total: 1303 Male blood donors: 934 Female blood donors: 348 Male HH patients: 20 Female HH patients: 1	Observational cross-sectional study	-Real-time PCR assay; TaqMan technology, -SNP-specific MGB probes, -PCR -restriction analysis -DNA sequencing, -ABI PRISM 7900HT Sequence Detection System, SDS 2.0 software DNA sequencing.	*HFE*	H63D, S65C and C282Y	The paper examines the development of a diagnostic assay for *HFE* mutations associated with hereditary hemochromatosis. Its primary objectives were to assess the frequencies of these mutations in the healthy population of Slovenia and to compare these frequencies with those in other European populations, particularly those of Slavic origin. The authors highlighted the significance of early detection and treatment of hereditary hemochromatosis as a crucial aspect of preventive medicine. The newly developed method is now accessible for routine diagnostic and screening procedures, potentially expanding opportunities in	9

						preventive healthcare and blood donor screening. The observed frequencies of the H63D, S65C, and C282Y mutations in the Slovenian population are consistent with those reported in Central European populations, although some variations were noted when compared to Slavic populations.	
Yang et al. 2011…[13]	Total: 320 Patients:265 Controls: 55	observational study	PCR, Restriction digestion, Cloning, RT-PCR, Electrophoretic mobility shift assays (EMSA), Splicing assays, Chain terminator sequencing	*HFE*	c.845G>A (p.C282Y), c.187C>G (p.H63D) c.193A>T (p.S65C), five SNPs rs2794720 rs2071303 rs1800758 rs1800708 rs1572982	The paper examined the prevalence of the c.845G>A (p.C282Y) substitution in individuals with hemochromatosis. It analyzed *HFE* using internal *HFE* SNPs and derived haplotypes, discussed the occurrence of the c.845G>A mutation on a progenitor haplotype, and its dissemination throughout the Caucasian population. Additionally, it addressed the significance of the g.4694C>G and c.1007G>A variations in assessing the risk for mild iron overload trait.	7
Sørensen et al. 2018 …[14]	Total: 15,567 Blood donors from the Danish Blood Donor Study, participants who had donated blood two or more times, 8333 men and 7234 women, differences in distribution of confounders between men and women.	Observational and cross-sectional with a longitudinal aspect	-DNA extraction and analysis, Ferritin level measurement. -Hardy-Weinberg equilibrium tests. -Statistical analyses. -T tests, Mann-Whitney U-tests, Chi-squared tests. -Multivariable linear regression analyses. -Multivariable logistic regression analyses.	*HFE* *BTBD9* *TMPRSS6* *TF*	rs1800562 rs1799945 rs9357271 rs855791 rs2280673 rs11830084	The paper summarized the study findings on the relationship between specific genetic variants and hemoglobin (Hb) levels, as well as the risk of Hb falling below deferral limits in blood donors. It emphasized the potential benefits of genetic testing for personalizing donation intervals. The study also highlights the differential effects of these genetic variants on Hb levels and the risk of Hb below deferral limits in men and women.	8
Dick-Guareschi et al. 2021…[15]	Total: 325 Male: 131 Female: 194 a mean age of 38.5 years.	Observational cross-sectional study	-Real-time polymerase chain reaction (PCR). -DNA isolation from capillary blood. -TaqMan assays for genotyping, -chi-square test of independence.	*FV* *F2* *MTHFR*	rs6025 g.1691G > A rs1799963 g.20210G > A rs1801133 rs1801131 g.677C>T g.1298A>C	The paper presented the frequencies of genetic variants linked to venous thrombosis and hyperhomocysteinemia among Brazilian blood donors. It also included demographic information about the study group and highlighted the importance of these findings in advancing our understanding of the genetic profiles of Brazilian blood donors.	9

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Sabbagh et al. 2008…[16]	Total : 205 blood donors 102 males and 103 females - Originating from different areas and religious communities of Lebanon	Randomized, single-site, retrospective, controlled laboratory procedure, quantitative analysis	CVD StripAssay, thermocycler program	*MTHFR*	A1298C	The paper summarizes the prevalence of *MTHFR* gene polymorphisms in the Lebanese population and highlights the unique genetic characteristics of this community.	7
Hadhri et al. 2012…[17]	Unrelated healthy Tunisian blood donors, 49% men and 51% women, mean age of 31.2 ± 8.1 years, no familial history of thromboembolism, subjects classified into two age groups: younger (< 40 years; n = 85) and older (≥ 40 years; n = 28).	Observational study	PCR, RFLP, PCR-RFLP, fluorescence polarization immunoassay	*FV* *Prothrombin* *MTHFR*	NA 20210G>A 677C>T 1298A>C	A brief summary was provided on the prevalence of specific genetic polymorphisms related to venous thromboembolism in the Tunisian population and their potential impact on venous thromboembolism occurrence, as well as the potential influence of independent founder mutations and migration of populations.	9
Greni et al. 2017…[18]	Total: 467 Patients: 298 Controls: 169 298 patients homozygous for p.C282Y in HFE, consisting of 205 men and 93 women with a median age of 48 years. The control group consists of 169 Italian health blood donors, all males.	Observational, cross-sectional, genetic association study	-DNA extraction using the Wizard Genomic DNA Purification kit and the ZR DNA-Card Extraction Kit. -Genotyping using tetra-primer ARMS-PCR and TaqMan 5'-nuclease assays. -statistical analyses using GraphPad Prism software.	*GNPAT*	rs11558492 A>G	*GNPAT* rs11558492 does not significantly influence iron status or correlate with liver fibrosis in patients with HFE-HH. In contrast, acquired factors like alcohol consumption, hepatic steatosis, obesity, and the presence of chronic viral hepatitis play a major role in modifying the clinical phenotype of HH..	9
Fawzy et al. 2021…[20]	Total : 197 Majority are men (90%) - Age range from 18 to 57 years old	Cross-sectional observational study	-Real-Time TaqMan genotyping assay -DNA extraction using QIAamp DNA Blood Mini kit -TaqMan Real-Time polymerase chain reaction (PCR) allelic discrimination assay	*HFE* *TMPRSS6* *BTBD9*	rs1800562 rs855791 rs9357271	The paper examined genetic variants linked to iron homeostasis and their potential effects on serum hepcidin and ferritin levels. The study specifically focused on the Middle Eastern blood donor population to analyze the genotype frequency and allelic distribution of three variants related to iron metabolism. It found that the *TMPRSS6* rs855791 (A/G) and *BTBD9*	9

						rs9357271 (C/T) variants were prevalent among this population and may affect serum hepcidin and/or ferritin levels.	
Niewiadonski et al. 2015… [21]	Total: 400 Blood donors from Fundação Pró-Sangue Hemocentro de São Paulo, 52.3% males and 47.7% females, mean age of 34.98 years old	Observational study with a cross-sectional design.	-OpenArray platform for genetic testing - TaqMan technology. -Primers and probes labelled with VIC and FAM fluorophores - Solid platform (chip) for multiple samples and targets -OpenArray AccuFill System for DNA and master mix incorporation	*FV* *F2* *MTHFR* *HFE*	G1691A rs6025 G20210A rs1799963 C677T rs1801133 A1298C rs1801131 C282Y rs1800562 H63 D rs1799945 S65C rs1800730	The paper evaluates the OpenArray platform for genetic testing of blood donors and examines the prevalence of mutations linked to thrombophilias and hemochromatosis within a Brazilian blood donor population. It highlights the necessity for a larger study to achieve a more precise frequency of the alleles and recognizes that the frequency of SNPs is similar to findings reported by other research groups.	9
Jackson et al. 2001…[22]	Total: 10,556 -Adults (mean age 35-38 years) - Majority white, with a minority (3%) of ethnic minorities (Asian, Black, Mediterranean) -Blood donors, with 12-16% being first-time donors who are younger (mean age 26-28 years) -Roughly equal numbers of men and women.	Observational study with a cross-sectional design.	- DNA extraction using the Dynabead DNA Direct System 1 - Genotyping using the PCR-SSP method - Measuring serum iron and unsaturated iron binding capacity using a microtitre plate method - Measuring serum ferritin concentrations using a method described by Worwood	*HFE*	C282Y H63 D	The paper concluded that while genetic testing can identify people at risk of haemochromatosis, many of those identified may never develop the disease, and the costs of counselling, testing, and investigating these individuals may outweigh the benefits until additional risk factors for iron overload are identified.	9
Lee et al. 2001…[23]	Total: 28,598 - White ethnicity - Menstruating women - Age under 60 years old - Presence or absence of iron deficiency anemia, defined as hemoglobin < 12 g/dL and ferritin < 20 mg/L - Normal HFE genotype (C282C/C282C	Retrospective study, multi-site, case-control, observational study that also includes a stratified analysis of individuals with	- Sequence analysis -Allele-specific oligonucleotide hybridization (ASOH)	*TF*	G277S	The G277S mutation in the transferrin gene increases the risk of iron deficiency anemia in menstruating women, likely due to reduced stability or iron affinity of the transferrin molecule. However, it does not contribute to iron overload in patients with hemochromatosis.	8

	and H63H/H63H or H63H/H63D)	the HFE C282Y mutation.					
Chambers et al. 2003…[24]	Total: 21,547 - Male blood donors - Divided into 4 age cohorts: <30, 30-39, 40-49, >50 years - Excluded donors with a history of jaundice or liver disease - Tested for hepatitis B and C	The study design is a cross-sectional observational study of a random sample.	-Bi-directional PCR amplification of specific alleles (BIPASA) for genotyping C282Y and H63D mutations -Ammonium chloride DNA precipitation for genomic DNA extraction - Measurement of serum iron, UIBC, and serum ferritin using commercial assays	*HFE*	C282Y H63D	The paper found that although the prevalence of C282Y heterozygosity decreased with age, there was no observed decline in C282Y homozygosity. Additionally, it provided evidence that C282Y and H63D heterozygosity may help protect against iron depletion resulting from repeated blood donations.	9
Peng et al. 2001…[25]	Total: 100 - Ethnicity: 50 Caucasian, 50 Hispanic (of Puerto Rican descent) - Health status: Generally healthy, undergoing routine blood tests - Age: Not specified - Sex: Not specified	Non-controlled, cross-sectional, observational study with a stratified sample.	- DNA extraction from peripheral blood leukocytes - PCR amplification of genomic DNA using specific primers - Restriction enzyme digestion of the PCR products (*Mboll* for A1298C, *Hinfi* for C677A) - Visualization of the digested PCR products by gel electrophoresis	*MTHFR*	A1298C C677T	The paper suggested that the *MTHFR* A1298C and C677T SNPs are very common in Caucasian and Hispanic populations, and that further large-scale studies are needed to understand their full effect on the pathogenesis of neural tube defects, while also cautioning that the high prevalence of these SNPs requires careful interpretation of their relationship to disease.	7
Ji et al. 2016…[25]	Total: 800 - Non-first-time blood donors in Queensland, Australia - 54% male, 46% female - Majority (61%) over 45 years old - Majority (54%) had donated within the last 3 months - Varying levels of iron loss, with 31% having less than 1 whole blood donation's worth of iron loss in the last 12 months, and 28% having 2-4 whole blood donations' worth of iron loss	Observational, non-controlled, cross-sectional study.	- Plasma ferritin quantification using an ELISA kit and plate reader - Genomic DNA extraction from whole blood using a commercial kit - SNP genotyping using TaqMan assays and real-time PCR	*BTBD9* *BMP2* *TMPRSS6*	rs3923809 rs235756 rs4820268	The study found that three genetic variants (SNPs) - rs3923809, rs235756, and rs4820268 - were associated with ferritin levels in blood donors, and the authors suggest these genetic factors could be useful for developing individualized donor management strategies to maintain iron levels.	9

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Pei et al. 2014…[27]	Total: 174 -Women of reproductive age - IDA patients were significantly older than controls (39.5 vs. 32.7 years on average) - Menorrhagia (heavy menstrual bleeding) was more common in the IDA group (80.0%) compared to the control group (65.4%) -Genotype distribution of TMPRSS6 rs855791 polymorphism showed a borderline difference between groups	Case-control observational study.	- Genomic DNA extraction from peripheral leukocytes - Polymerase chain reaction (PCR) - Restriction fragment length polymorphism (RFLP) analysis - Direct sequencing of 10% of the samples	*TMPRSS6*	rs855791	The *TMPRSS6* rs855791 CC genotype plays a protective role against iron deficiency anemia, particularly in women experiencing menorrhagia.	8
An et al. 2012…[28]	Total: 2,139 - Elderly women aged 50-70 years old - Majority Han Chinese and Zhuang ethnic groups - Anemic women had lower hemoglobin, serum iron, serum ferritin, and transferrin saturation levels, as well as higher free erythrocyte protoporphyrin levels and ratios compared to non-anemic controls	population-based case-control study	- DNA extraction from blood samples using a commercial kit - Genotyping of SNPs rs3811647, rs7385804, rs235756, rs855791, and rs4820268 using TaqMan assays and real-time PCR - Measurement of hemoglobin, serum iron, serum ferritin, serum transferrin, free erythrocyte protoporphyrin (FEP), and total iron-binding capacity (TIBC)	*TF* *TFR2* *BMP2* *TMPRSS6*	rs3811647 rs7385804 rs235756 rs855791 rs4820268	The key finding of this paper is that *TMPRSS6* polymorphisms are genetic risk factors for iron deficiency and iron-deficiency anemia (IDA). The association is stronger with the risk of IDA than with the risks of anemia or iron deficiency alone. These findings may enhance our understanding of the functional roles of *TMPRSS6* in other iron-related diseases.	8
Santos et al. 2010…[29]	Total: 542 - Brazilian healthy blood donors - Aged 18 or older (hematocrit cutoffs imply adults) -Diverse racial/ethnic background (White,	cross-sectional observational study	- DNA extraction from whole blood using a salting-out method - Genotyping of *HFE* C282Y, *HFE* H63D, *HFE* S65C, *TFR2* Y250X, and *TFR2* Q690P mutations using PCR-RFLP	*HFE*	C282Y H63 D	The *HFE* 282Y and 65C alleles were rare among Brazilian blood donors, whereas the *HFE* H63D allele was common. The *HFE* C282Y and H63D mutations were linked to changes in iron status, but this association was observed only in male blood donors. Further prospective studies are needed to assess the	9

Intermediate, Black, Yellow) - Divided into first-time, frequent, and sporadic blood donors - Excluded those with liver dysfunction or hepatitis C	- Primer design for *HFE* H63D, *HFE* S65C, and *TFR2* Q690P using Primer Premier software - Restriction digestion of PCR products using various enzymes (*RsaI, MboI, HinfI, BfaI, BfaI* and *HpaII*) - Gel electrophoresis to analyze the restriction fragments (2% agarose for *HFE* mutations, 8% polyacrylamide for *TFR2* Q690P)		impact of environmental factors and their interactions with these mutations.

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3.4 A bibliometric analysis

The bibliometric analysis conducted on 847 publications used databases with MeSH terms and Boolean operators, enabling researchers to thoroughly explore and analyze the existing body of literature. This analysis helped identify influential authors and important papers, as well as track citations to evaluate their impact and lasting relevance. The study also revealed research gaps, providing insights into the historical development of ideas in the field. Furthermore, it offered valuable insights into prevalent research methodologies. Researchers have gained a deeper comprehension of the existing knowledge base, identified areas that require further investigation, and established a roadmap for future research endeavours by applying these findings.

3.4.1 Bibliographic coupling between articles

Bibliographic coupling evaluates the relationship between two articles by examining their shared references. A higher number of shared references suggests greater similarity, which can be theoretical, methodological, or related to other specific characteristics [30]. The "size" of an item corresponds to the number of citations for the articles; thus, articles with more citations will display larger labels and circles (Figure 2).

The articles by the authors; Smolen et al. [31], Criswell et al. [32], Abadie et al. [33], Barker [34], and Cooper et al. [35] were the most cited during the research period. These are articles that discussed the genetics associated with diseases such as rheumatoid arthritis, autoimmune and diabetes [31,32,34]. Studies by Abadie et al. [33]; Cooper et al. [35] on the other hands discusses about pathogenesis of genetic and immunological integration and understanding of the molecular basis of human inherited diseases.

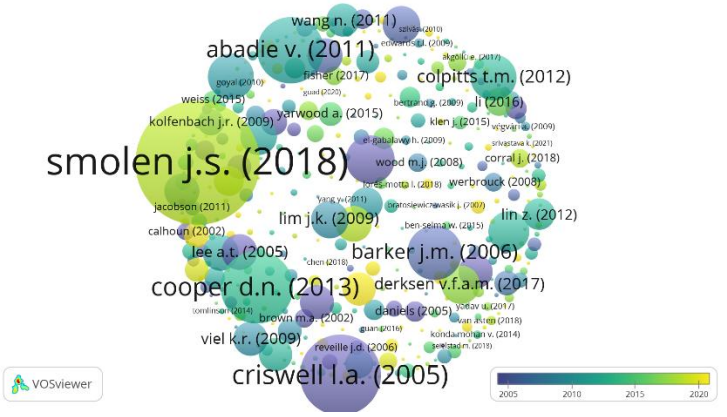

Fig 2. Bibliographic Coupling: Overlay View for Articles from 2000 to September 2023.

3.4.2 Co-authorship between articles

The network visualization map analyzes the social interactions and relationships among authors and their affiliations, highlighting their collective impact on the development of the research field. The strength of a link represents the number of authors shared between two publications [9] (Figure 3). Table 4 provides information on articles with at least 300 citations, along with their corresponding total binding strength values derived from the authors' information. It is important to note that the total link strength value is not directly related to the number of citations an article receives; instead, it reflects the network of authors connected by at least one common publication between two documents.

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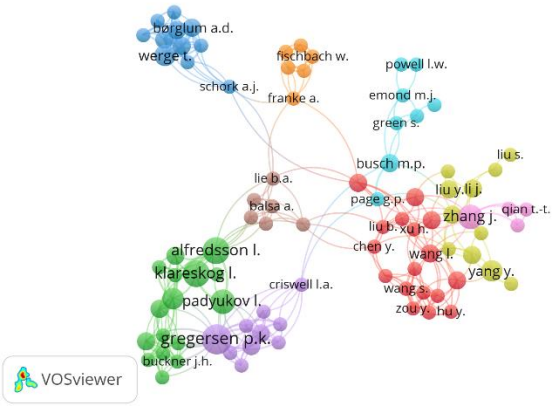

Fig. 3 Co-authorship: A network visualization map illustrating the authors.

Table 4. Authors with at least 300 citations and their corresponding total link strength values.

Authors	Document	Citation	Total link strength
Gregersen P.K.	7	1051	35
Firestein G.S.	2	1043	2
Barton A.	2	945	7
Emery P.	2	891	2
Lee A.T.	3	720	16
Behrens T.W.	3	707	16
Begovich A.B.	2	670	10
Li W.	2	670	10
Klareskog L.	6	551	19
Ortmann W.	2	550	13
Kern M.	2	516	8
Alfredsson L.	6	506	24
Criswell L.A.	2	505	9
Huizinga T.W.J.	4	482	1

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Padyukov L.	5	476	13
Karlson E.W.	4	344	20
Werge T.	4	323	23
Børglum A.D.	3	322	22
Hougaard D.M.	3	322	22
Mortensen P.B.	3	322	22

3.4.3 Co-occurrence of keywords analysis

Network Visualization of Keyword Co-Occurrence is based on the idea that words often appear together and share thematic relationships [36]. VOSviewer analyzes these relationships to illustrate the strength of connections between items, resulting in distance-based maps where shorter distances indicate stronger relationships between terms. Lines connecting the items represent these relationships, with more prominent items in the graph signifying greater significance within the studied context [9]. To identify potential research keywords, a network was constructed based on keyword co-occurrence, establishing a minimum threshold of ten occurrences per keyword. This process yielded a total of 161 keywords used to create the network graph in VOSviewer, as shown in Figure 4. An analysis of item relationships, depicted by the connecting lines, revealed the formation of four distinct clusters, each highlighted by different colours on the visualization map.

The grouping of terms allowed for the identification of existing relationships within the research field of gene polymorphism (cluster 1, in red). Cluster 2 (green) encompassed search terms related to disease mechanisms, treatments, and conditions. Cluster 3 (blue) focused on outcomes or impacts of donor transplantation, while cluster 4 (yellow) involved research on genome-wide association studies related to gene expression.

Co-occurrence links indicate the strength of relationships between items, represented by a positive relevance score. At least 40 occurrences with relevance scores are identified in VOSviewer (Table 5). A higher score indicates a stronger link, reflecting the number of publications in which two terms co-occur. The most frequently shared keywords from 2000 to September 2023 included donor, gene polymorphism, mechanism, treatment, mutation, and frequency, highlighting prominent research topics related to blood disorders.

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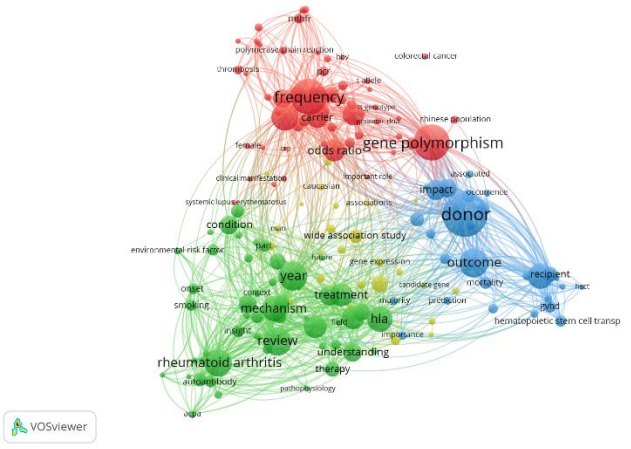

Fig 4. Keyword Co-occurrence Network Visualization Based on Publication Counts.

Table 5. Keyword occurrences with at least 40 occurrences with relevance score

Keywords	Occurrences	Relevance score
Donor	101	0.7879
Frequency	81	0.9688
Gene Polymorphism	81	0.6063
Year	65	0.1866
Outcome	64	0.7147
Review	63	0.6312
Rheumatoid Arthritis	61	1.5193
Mutation	60	0.7905
Transplantation	57	2.0761
HLA	56	0.355
Mechanism	56	0.4362
Treatment	51	0.2446
Response	50	0.3193
Approach	50	0.2333
Aim	48	0.5944
Odds Ratio	48	0.4984
Carrier	44	0.7802
Function	44	0.2001
Impact	44	0.4794
Understanding	41	0.4412

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3.4.4 Journal Co-Citation Map

The journal co-citation map illustrates the structure of the researched scientific areas. To create the map, selected journals with a minimum of two citations, resulting in a total of 119 journals included. Figure 5 presents a density view, where each point on the map is colour-coded according to the journal's citation density. Notably, the following journals—Blood, PLOS One, Biology of Blood and Marrow Transplant, Genetics Testing and Molecular, and Frontiers in Immunology—exhibit dense, highlighted areas on the map, indicating a higher number of citations during the investigated period. Additionally, their proximity on the map suggests that these journals are linked to closely related research fields.

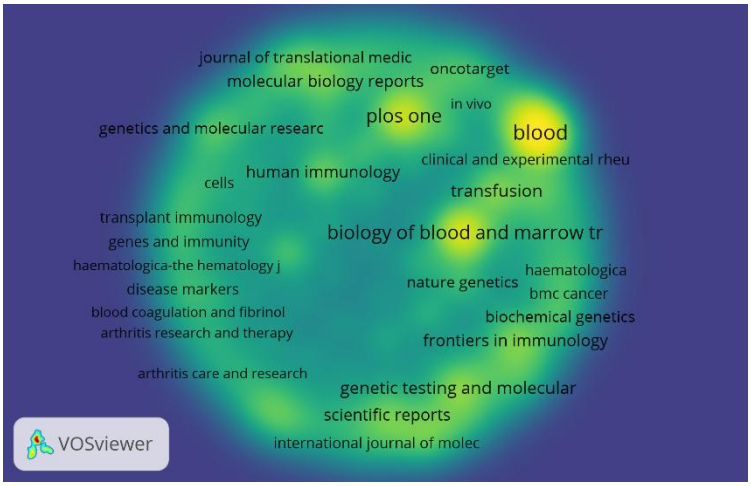

Fig.5 Density visualization map for co-citation of journals, with a minimum of two citations. The most prominent areas highlight the journals that received the highest number of citations.

Analyzing the scientific topics addressed by these journals reveals the connections among them. Table 6 highlights key journals frequently cited in studies on blood disorders, particularly focuses on hematology; genetics fields; multidisciplinary biology. Notably, research related to gene associations in blood disorders is prominent, with journals like Blood, Nature Genetics, PLOS One, and Human Genetics being significant in this regard (Table 6). This analysis offers insights into the interrelations among journals and their intellectual connections, as depicted in the co-citation map, highlighting the network's impact through the visualization of the density map.

Table 6. Journal with at least 120 citations

Journal	Citation	Document
Blood	628	27
Nature Genetics	622	5
Plos One	518	16
Human Genetics	510	2
Molecular Psychiatry	376	5
Annals of the Rheumatic Diseases	307	6
Journal of Autoimmunity	278	2
Arteriosclerosis, Thrombosis, and Vascular Biology	265	4
Nature Reviews Rheumatology	263	4

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Genes and Immunity	248	3
Seminars in Immunopathology	237	2
American Journal of Gastroenterology	199	2
Lupus	186	3
Molecular Medicine	173	2
Bone Marrow Transplantation	162	6
Best Practice and Research: Clinical Rheumatology	162	4
Arthritis Care and Research	152	2
Autoimmunity Reviews	134	2
Frontiers in Immunology	133	8
International Angiology	126	2

4. DISCUSSION

The systematic review revealed several significant genetic factors that influence iron metabolism, hemoglobin levels, and thrombophilia. Key genetic polymorphisms, such as the *HFE* C282Y mutation, were found to be strongly associated with iron metabolism disorders like hereditary hemochromatosis. Other genes, including *TMPRSS6* and *BTBD9*, were linked to variations in hemoglobin levels and iron storage. The review identified major themes in the literature, including the impact of genetic variability on blood donors' health, the role of genetic screening in donation practices, and the interplay between genetics and donor deferral criteria. Patterns emerged showing a focus on understanding genetic predispositions to thrombophilia and their implications for donor safety and recipient health.

The influence of genetic variability on iron metabolism, hemoglobin, thrombophilia, and related conditions in blood donors. Several studies have delved into the influence of genetic variability on various aspects of iron metabolism, hemoglobin levels, thrombophilia, and related conditions among blood donors. Thrombophilia, characterized by an increased tendency to form clots inappropriatelyF, can be attributed to genetic factors such as deficiencies in antithrombin or protein S, gene mutations, and other hereditary or acquired factors [37]. The *HFE* C282Y mutation, associated with hereditary hemochromatosis, a disorder of iron metabolism, is one such gene variant linked to thrombophilia [21]. Additionally, research has explored the impact of low iron status, particularly in female donors under 50 years of age who are often deferred from donation due to this reason, on their quality of life and cognitive abilities [38]. Moreover, frequent blood donors have been observed to have reduced body iron stores, potentially affecting vascular function [39]. These findings collectively underscore the importance of genetic variability in blood donors, which can influence both donor health and the quality of donated blood.

Iron deficiency is a common consequence of blood donation. Research by Sørensen et al. [10,11,14] has identified significant associations between serum ferritin levels among female blood donors and the rs9296249 variant in the *BTBD9* gene. Elevated ferritin levels were found in individuals homozygous for the A allele of *HFE* rs1800562, regardless of sex, and in men homozygous for the G allele of *HFE* rs179945. However, no significant correlation was observed between rs1799852 in the *TF* gene and serum ferritin levels, despite earlier associations with serum transferrin and ferritin [25,20]. This lack of significance may be due to statistical limitations. The research highlights the roles of *HFE* and T*MPRSS6* in influencing hemoglobin levels and the risk of hemoglobin dropping below the deferral threshold, indicating the potential benefits of genetic testing for personalized donation intervals [26]. Additionally, preliminary findings suggest that the *TMPRSS6* rs855791 (A/G) and *BTBD9* rs9357271 (C/T) variants may be associated with serum hepcidin and/or ferritin levels in an initial sample of Middle Eastern blood donors [20].

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Impact of genetic variability on iron metabolism. Genetic variability exerts a significant influence on iron metabolism. Hepcidin, a crucial hormone governing iron absorption and distribution, is susceptible to genetic variations, which can modulate its expression and consequently contribute to phenotypic disparities in iron metabolism [40]. For instance, the *HFE* C282Y mutation has been implicated in hereditary hemochromatosis, a hereditary disorder characterized by aberrant iron metabolism [41,42]. Furthermore, a recent study has explored the impact of gene variants on iron metabolism among anemic adolescent girls, identifying specific genetic variations associated with diminished iron status [43]. Findings also show that *HFE* gene variations are detected in healthy blood donors in the Slovenian [12] and Caucasian populations [13], and that C282Y and H63D heterozygosity may protect against iron depletion from repeated blood donation [24], though this effect is seen only in Brazilian male donors [29].

Certain genetic conditions are known to increase the risk of venous thromboembolism. This genetic predisposition to thrombosis varies among different ethnicities, reflecting the diverse social and political contexts of various regions [44]. Venous thromboembolic events arise from an imbalance between fibrinolysis and thrombosis. This coagulation abnormality can result from acquired factors like obesity, smoking, and immobility, as well as inherited factors, including genetic variations in factor V, prothrombin, and methylenetetrahydrofolate reductase [15,17,21].

Expanded Bibliometric Analysis. This bibliometric analysis further supported these findings by mapping the research landscape. Bibliographic coupling analysis identified key articles by authors such as Smolen et al. [31] and Criswell et al. [32], which shared numerous references, indicating theoretical and methodological similarities. Co-authorship analysis revealed prominent authors like Gregersen P.K. and Firestein G.S. as central figures in the research network, emphasising their influences on the field. Keyword co-occurrence analysis identified thematic clusters focusing on gene polymorphism, disease mechanisms, donor transplantation outcomes, and genome-wide association studies. The journal co-citation map indicated that journals like "Blood," "Nature Genetics," and "PLOS One" were central to the research landscape, highlighting their role in disseminating significant findings. Trends showed an increasing number of publications over recent years, with research hotspots in North America and Europe. Collaboration networks revealed strong connections between hematologists, geneticists, and epidemiologists, underscoring the interdisciplinary nature of this research area. The analysis also highlighted emerging topics such as the use of genetic testing for personalized donation intervals and the exploration of genetic factors affecting long-term donors' health.

Significant correlations were found between certain genetic polymorphisms and serum ferritin levels among female blood donors, indicating the critical role that genetic factors play in blood composition, particularly iron metabolism, and thrombophilia. Enhanced therapeutic approaches and personalized healthcare rely on comprehending genetic factors. Changes in genetics impact blood composition, donated blood quality, and necessitate refined therapeutic strategies and screening protocols for blood-related diseases.

Identifying Gaps in the Literature on Genetic Variability Among Blood Donors and Directions for Future Research. Additional studies are needed to understand the functional significance of specific genetic variants in blood donors, particularly those related to iron metabolism, hemoglobin levels, and thrombophilia. This understanding could offer insights for personalized healthcare and interventions. Further research is also necessary to explore the long-term health outcomes associated with genetic variability, including its impact on chronic diseases like cardiovascular disorders and hematological malignancies, informing screening procedures and healthcare strategies.

Studying the interactions among different genetic variants affecting blood composition and related parameters could provide a more comprehensive understanding of the genetic landscape in blood donors. Investigating gene-gene interactions and their influence on phenotypic outcomes may uncover novel insights into the complexity of genetic factors influencing blood traits. Future research should also focus on addressing potential gaps in diversity and representation within genetic studies of blood donors. Ensuring inclusivity across diverse populations can enhance the generalizability of findings and promote equitable healthcare practices.

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5. CONCLUSION

This study highlights the significant impact of genetic variation on blood composition among donors. The interplay of genetic factors, sex, and environmental influences contributes to individual susceptibility to blood-related disorders. We identified genetic markers associated with an increased risk of iron-related conditions, thrombophilia, and hereditary hemochromatosis [1]. Notably, variants in the *TMPRSS6* and *BTBD9* genes were linked to iron deficiency, underscoring their roles in iron absorption and regulation [2]. For hereditary hemochromatosis, we found pathogenic variants in the *HFE* gene, specifically C282Y and H63D, which are known to cause excessive iron accumulation. Additionally, we identified variants in coagulation-related genes such as *F5* (*Factor V Leiden*) and *F2* (*Prothrombin* G20210A), suggesting a genetic predisposition to thrombophilia.

These findings illustrate that genetic risk extends beyond iron metabolism to encompass broader hematological conditions. Incorporating genetic screening into blood donor programs could enhance transfusion safety, optimize donation frequency, and inform targeted prevention strategies. Ultimately, a deeper understanding of the genetic landscape among blood donors can facilitate more personalized and effective healthcare interventions.

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6. GENERATIVE A.I DISCLOSURE STATEMENT

No A.I generative tools were used.

7. CONFLICT OF INTEREST

The authors agree that this research was conducted in the absence of any self-benefits, commercial or financial conflicts and declare the absence of conflicting interests with the funders.

8. AUTHORS' CONTRIBUTION

All authors contributed significantly to the manuscript. AFS led the conceptualization, literature review, bibliometric analysis, and manuscript drafting. MZS provided supervision, conceptual guidance, and critical manuscript revision. NAMNH handled validation and manuscript review. MSR contributed to data curation and manuscript editing. Authors MMMZ, TMD, and NAAH participated in manuscript review and provided critical intellectual input. All was responsible for visualization and manuscript editing. TLK served as the corresponding author, overseeing study supervision, manuscript revision, and ensuring research integrity. All authors reviewed and approved the final manuscript, agreeing to its accuracy and integrity.

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