Journal of Thrombosis and Thrombolysis (2021) 51:359–369
https://doi.org/10.1007/s11239-020-02203-7

The genetics of venous thromboembolism: a systematic review of thrombophilia families

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Published online: 4 July 2020

Abstract

Genetic risk factors are important for the occurrence and prognosis of venous thromboembolism (VTE). The studies of thrombophilia families are important for dissecting the genetic background of the thrombotic disease. We conducted the systematic review of all published family-based studies on VTE genetics across all racial groups through PubMed and Embase prior to 13th April 2020. This systematic review of 287 families (including 225 Caucasian families, 52 East Asian families, and families of other ethnicities) revealed a total of 21 different genes; the five most reported mutated genes were *F5* (88/287, 30.7%), *SERPINC1* (67/287, 23.3%), *PROC* (65/287, 22.6%), *F2* (40/287, 13.9%) and *PROS1* (48/287, 16.7%). For Caucasian families, *F5* mutations were most frequently reported at 37.8% (85/225), while *PROS1* mutations were most frequently reported, at 40.4% (21/52), for East Asian families (Chinese, Japanese and Korean). Factor V Leiden was reported more frequently in Caucasians than in East Asians. Missense mutations were reported frequently in the *SERPINC1*, *PROC* and *PROS1* genes. In conclusion, our study found the most likely mutated genes associated with VTE among different ethnic groups and provided indications for VTE genetic testing and research in the future.

Keywords Venous thromboembolism · Family study · Systematic review · Genes

Abbreviation

APCR	Activated protein C resistance
AT	Antithrombin
DVT	Deep venous thrombosis
FVL	Factor V Leiden
GWAS	Genome wide association study
PAI-1	Plasminogen activator inhibitor-1
PC	Protein C
PCR	Polymerase chain reaction
PS	Protein S
PTE	Pulmonary thromboembolism
SNPs	Single nucleotide polymorphisms
VTE	Venous thromboembolism
WES	Whole exome sequencing
IIa	Activated FactorII
Va	Activated FactorV

Dr. Yu Zhang and Zhu Zhang contribute equally to this study.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11239-020-02203-7) contains supplementary material, which is available to authorized users.

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VIIa Activated FactorVII
Xa Activated FactorX

Highlights

- This is the first systematic review of all published family-based studies on venous thromboembolism (VTE) genetics of all racial groups.
- This study concluded that *F2*, *F5*, *SERPINC1*, *PROC* and *PROS1* were the most frequently identified genes in VTE families.
- For East Asian families (China, Japan and Korea), the mutations of *PROS1* were the most frequently reported than other genes. For Caucasian families, however, mutations of *F5* were revealed to be the most frequent compared to other genes.
- Our review analyzed the type and prevalence of gene mutations associated with VTE among different ethnical groups, therefore, provided useful genetic information for future testing and research on VTE. Large samples may be needed for more accurate and comprehensive conclusion.

Introduction

Venous thromboembolism (VTE), comprising pulmonary thromboembolism (PTE) and deep venous thrombosis (DVT), has become a major global health problem such as stroke and myocardial infarction [1]. The global disease burden of VTE has increased steadily over the last decade, with approximately 75–269 patients per 100,000 individuals in the United States and Europe [2] and 10–30 patients per 100,000 individuals in China [3].

VTE is well-known as a multifactorial disease, but predisposing genetic factors play an important role in the occurrence and prognosis of the disease [4]. The genetic burden of VTE is characterized by a sibling relative risk of 2.5 and a strong heritability estimated from 35 to 60%, according to various studies [5].

VTE gene variations that strongly affect the VTE risk are rarely reported [5]. Notably, most causal gene mutations associated with the risk of VTE were detected in family-based studies. Moreover, family studies are generally more powerful than case–control studies as the inheritance pattern among families implies that genetics play a more important role in the pathogenesis of VTE [6].

Therefore, we conducted this comprehensive review of all published family-based studies on VTE genetics of all racial groups, aiming to identify the mutation patterns of VTE-related genes among different ethnic groups and to provide a foundation for the diagnosis of and research related to VTE. To our knowledge, our analysis is one of the most comprehensive findings on the genetics of VTE through the family-based study to date.

Method

Search strategy

We searched PubMed, Embase for articles published in English until 13th April 2020. The following search terms and their similar terms were used: “thrombosis”, “mutation” and “family”(Detailed search strategy in Supplementary material). The systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

Selection criteria

Titles and abstracts of potentially relevant family studies were checked independently by two investigators (Yu Zhang and Zhu Zhang) for eligibility of full paper evaluation. For a conflicting evaluation, a third reviewer (Shi Shu) was consulted and a consensus was reached by discussion. Studies of all genetic backgrounds were included.

Identified studies satisfied the following criteria: (1) evaluating any candidate gene defect in association with VTE; (2) family studies (at least two VTE patients in one family); (3) containing sufficient information on clinical features and VTE gene mutations. The major reasons for exclusion of studies were as follows: non-English publications, reviews, duplicate publications, inherited deficiency confined to proteins levels.

Data extraction

The information was carefully extracted from all eligible literature independently by Yu Zhang and Zhu Zhang. For each selected study, information was extracted mainly on genes, genotyping method, mutation information, ethnicity, the number of families.

Result

Study selection and characteristics

Using our search strategies, 220 potentially relevant studies were initially selected (Fig. 1). On applying the inclusion and exclusion criteria, we identified 150 studies eligible for this analysis. In addition, four more studies were manually added to our research. A total of 154 studies involving 287

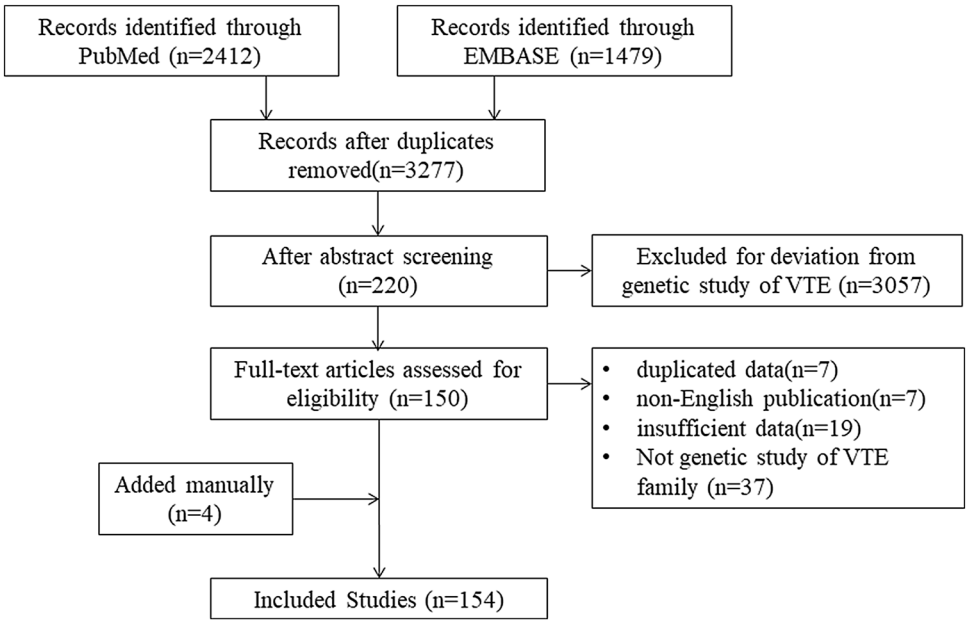

Fig. 1 Study flow diagram. Using our search strategies, 220 potentially relevant studies were initially identified. After applying the inclusion and exclusion criteria, 150 studies were identified. In addition, we added four studies manually. A total of 154 studies involving 287 families with VTE were included. *VTE* venous thromboembolism

families with VTE were included (225 Caucasian families, 52 East Asian families, four Arab families, two Latino families, two African families, and others; Table 1; detailed data is shown in Supplementary Table 1.1 to Supplementary Table 1.7). However, few studies have reported on clear ancestries (Supplementary Table 2). Thus, the ancestry of most families is assumed based on the country of origin. A total of 21 genes associated with VTE (Table 2) were reported among the families included in this study. The five most frequently reported genes were: *F5* (88/287, 30.7%), *SERPINC1* (67/287, 23.3%), *PROC* (65/287, 22.6%), *F2* (40/287, 13.9%), *PROS1* (48/287, 16.7%; Table 3). Moreover, *MTHFR* polymorphisms have been reported in 26 families. *SERPINE1, FGA, THBD* and *FGB* gene defects were also reported in 9, 5, 4, and 3 unrelated families, respectively. The *MTHFR* C677T and plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphisms were reported to be associated with VTE only in combination with other genetic defects. The other genes had only been reported in one or two families. The mechanisms underlying the mutations that lead to the development of thrombophilia are shown in Fig. 2.

The reported number of families with thrombophilia is smaller among the Asian populations than among the Caucasians. There are differences in the type and frequency of gene mutations between these two ethnic groups. For East Asian families (Chinese, Japanese and Korean), we found the defect of *PROS1* at 40.4% (21/52), *PROC* at 21.2% (11/52), *SERPINC1* at 19.2% (10/52), and *F2* at 15.4% (8/52). Only one family from China was identified with a novel mutation of p.Glu666Asp in *F5* [7]. However, for Caucasian families, the mutations in *F5* were most frequently reported at 38.2%

Table 1 Numbers of families from different countries

Population[a] (no.)	Country/ethnicity (no.)
Caucasian (225)	France (46), Netherlands/Belgium (37), Britain (19), Italy (17), Spain (17), Portugal (16), America (16), Hungary (15), Germany (9), Denmark (8), Serbia (4), Poland (4), Australia (3), Sweden (3), Bulgaria (1), Ireland (1), Norway (1), Turkey (1), Kurd (1), Romania(1), New Zealand(1), Croatia(1), Russia(1), Austria(1), Canada(1)
East Asian (52)	China (39), Japan (10), Korea (3)
Arab (4)	Israel (3), Saudi Arabia (1)
African (2)	South Africa (1), African American (1)
Latino (2)	Puerto Rico (1), Columbia (1)
Other (2)	Malaysia (1), Unknown (1)
Sum	287

[a]Only several studies had provided clear ancestries of the families in Europe and America (as is shown in Supplement Table 3). The ancestries of most of the families are assumed based on the countries

Table 2 The 21 genes found in family studies

Function	Genes
Genes with established roles in coagulation	*FII* (coagulation factor II; prothrombin)
	FV (coagulation factor V)
	FXII (coagulation factor XII)
	FGA (fibrinogen, A alpha polypeptide)
	FGB (fibrinogen, B beta polypeptide)
	FGG (fibrinogen, G gamma polypeptide)
	HRG (histidine-rich glycoprotein)
	PROC (protein C)
	PROS1 (protein S)
	SERPINC1 (antithrombin)
	SERPINE1 (plasminogen activator inhibitor-1)
	THBD (thrombomodulin)
Genes with role in metabolism	*CBS* (cystathionine-beta-synthase)
	MTHFR (methylenetetrahydrofolate reductase)
Gene with role in palate disorder	*GP1BA* (glycoprotein Ib, alpha polypeptide)
	PEAR1 (platelet endothelial aggregation receptor 1)
Genes without established role in thrombophilia	*GPR25* (G protein-coupled receptor 25)
	HFE (hemochromatosis)
	SLC4A1 (solute carrier family 4, anion exchanger, member 1)
	LYST (*Homo sapiens* lysosomal trafficking regulator)
	MAST2 (*Homo sapiens* microtubule associated serine/threonine kinase 2)

Table 3 Number of VTE families reported with the five classic genes

Gene	Caucasian	East Asian	China	Others	Sum (%)
F2	28	8	5	4	40 (13.9%)
	G20210A (22)			G20210A (2)	
F5	86	1	1	1	88 (30.7%)
	FVL (85)			FVL (1)	
SERPINC1	54	10	6	3	67 (23.3%)
PROC	52	11	8	2	65 (22.6%)
PROS1	26	21	18	1	48 (16.7%)

(86/225), followed by *SERPNC1* at 24.0% (54/225), while *PROS1* mutations were least commonly reported at 11.6% (26/225; Table 3).

F2

The gene *F2* encodes prothrombin. A total of eight different mutations in six loci of *F2* were reported in 40 VTE families according to our review. The *F2* G20210A mutation (rs1799963, variation in the 3′ UTR region of the gene) is a well characterized mutation associated with a rather strong risk of VTE. In this review, the G20210A mutation was the most frequently reported mutation, with an incidence of 62.5% (25/40); among the families presenting this mutation, 22 families were Caucasian, one family was Colombian [8], one family was Puerto Rican [9] and one family without clear ancestry. Other missense mutations have also been reported in Caucasian families—a substitution of arginine for glutamine (p.Arg596Gln, also called prothrombin Belgrade) in four Serbian families [10–12], a substitution of arginine for tryptophan (p.Arg596Trp) in an Italian family [13] and a substitution of arginine for tryptophan (p.Arg173Trp) in a Dutch family [14]. Arginine at position 596 is an important site for the regulation of enzyme activity, and mutation at this site leads to a decrease in the antithrombin (AT) binding ability, resulting in the risk of thrombosis [15]. Interestingly, only eight Asian families were reported with missense mutations of *F2*, with G20210A has not been reported to date. Three Japanese families presented with variations at position 596; of these, two alterations were the missense mutation of p.Arg596Gln [16, 17] and one was a missense mutation of c.1787G > T, p.Arg596Leu

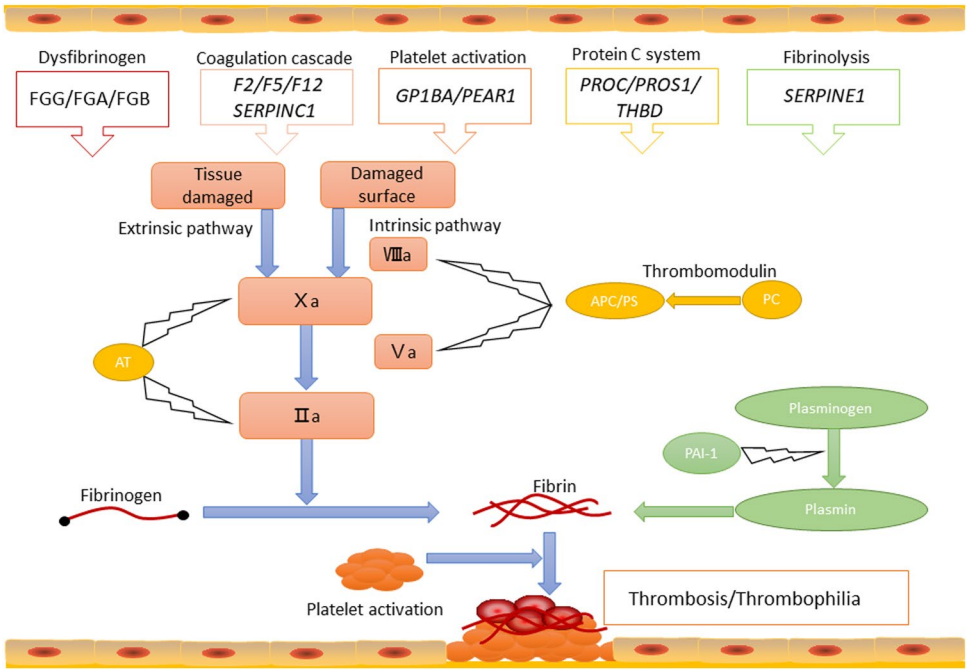

Fig. 2 The genes that reported in the family studies lead to thrombophilia through different pathways. Mutations in *FGG*, *FGA* and *FGB* genes cause dysfibrinogenemia, leading to the development of thrombophilia. Mutations in *F2*, *F5*, *F12,* and *SERPINC1* result in the development of thrombophilia through the activation of the coagulation cascade. Mutations in of *GP1BA* and *PEAR1* affect platelet activation, resulting in the development thrombophilia. Mutations in *PROC*, *PROS,* and *THBD* lead to the development of thrombophilia through the protein C system. Mutations in *SERPINE1* affect fibrinolysis, leading to the development of thrombophilia.

[18]. Two rare *F2* mutations—c.494C > T, p.Thr165Met and c.1274G > A, p.Arg425His—were detected in two Chinese families [19, 20]. In addition, a recent study detected a missense mutation—p.Arg541Trp—in three Chinese families [21].

F5

Factor V Leiden mutation (FVL, R506Q, rs6025) is probably the most well-known gain-of-function variation associated with VTE. It was reported by Leiden team that the majority of the patients with familial activated protein C resistance (APCR) had the same mutation, a guanine to adenine transition at nucleotide 1691 in exon 10 of *F5* [22]. In our review, FVL was the most reported mutation in VTE families, with an incidence of 30.0% (86/287). Among the 86 families with FVL, 85 were of Caucasian origin, and one was of Arab origin [23]. FVL has never been reported in Asian families. Cai et al. has identified a novel mutation—heterozygous G → C transversion at base2172—changing the codon for amino acid 666 from GAG (glutamate, E) to GAC (aspartate, D) in *F5,* which was associated with APCR in a Chinese family with VTE, and was reported for the first time [7]. However, in the following study, the FV E666D mutation was not detectable in any of the 163 VTE patients, including 6 APCR-positive patients [24]. In a Spanish family, FVL was detected in combination with another mutation in *F5* (G1091C, Arg306Thr, FV Cambridge, FVC) [25]. This mutation is rare and is associated with pathological levels of APCR. The association of the mutation with the risk of VTE is still unclear [26]. In an Italian family FVL was detected in combination with two other mutations in *F5* (p.His1299Arg and p.Tyr1702Cys) [27]. FV H1299R is marked by an A → G transition at position 4070, resulting in a transition from histidine to arginine. Carriership of the FV H1299R allele is associated with mild APCR and with a relative excess of the more thrombogenic FV isoform in plasma [28]. Therefore, this mutation increases the risk of venous thrombosis in carriers of the FVL mutation [29]. The newly identified missense mutation, FV Y1702C (changing amino acid 1702 from tyrosine to cysteine), which leads to FV deficiency, may enhance APCR [27].

SERPINC1

The gene *SERPINC1* encodes antithrombin. In the present review, a total of 57 different mutations in *SERPINC1* were found among 67 VTE families, of which 54 were Caucasian and ten were East Asian (six Chinese [10, 30–32], three Japanese [33–35] and one Korean [36]). Among the 57 mutations, 38 are missense mutations, and others are indel, nonsense, or frameshift mutations. AT Cambridge II (p.Ala384Ser) was detected in four Caucasian VTE families, two from England [37–39]. This is a G → T substitution at nucleotide position 13,268 (GCA → TCA), resulting in the replacement of the normal alanine residue at position 384 by serine and the synthesis of a dysfunctional AT with normal heparin affinity but a reduction in anti-IIa activity. In addition, four families were detected with a replacement of arginase at position 393 (p.Arg393His in two families [35, 40], p.Arg393Cys [41] and p.Arg393Pro [42] in one family, respectively).

PROC

PROC encodes protein C (PC). Inherited PC deficiency is transmitted as a dominant autosomal trait. According to our review, 57 different mutations in *PROC* were reported among 65 families (52 Caucasian families, 11 East Asian families). In a Portuguese study, five different *PROC* mutations were identified in eight unrelated VTE families with reported low/borderline PC plasma levels [43]. The most frequent mutation found in this study was a nonsense mutation of p.Arg199X, detected in four families containing patients with higher numbers of VTE episodes. In a Hungarian family study, a nonsense mutation, a rare frameshift deletion, and nine different missense mutations were determined in *PROC* [44]. Furthermore, a Dutch family study reported that over 50% (8/15) of Dutch VTE families with PC deficiency share a founder R272C mutation [45]. Eight Chinese families [31, 46–52], two Japanese families [53, 54], and one Korean family [55] with *PROC* mutations were included in the present review.

In our review, the p.Arg230Cys mutation was found in two Hungarian families [44]. This mutation was reported in the PC mutation database in 1995 and was a common genetic alteration noted among Hungarian patients [44]. The p.Thr298Met mutation was detected in two Caucasian families [56, 57] and an Arab family [23]; this mutation had previously been reported in PC deficiency families. A missense mutation, p.Arp169Trp, has also been reported in two Caucasian families [56, 58] and a Japanese family [53]. This mutation abolishes the site of thrombin cleavage that activates PC [59]. Finally, a Arg → Gln mutation was also detected in the position 169 in an English family [58].

PROS1

PROS1 encodes protein S (PS). Inherited PS deficiency is transmitted as a dominant autosomal trait. According to our review, a total of 46 different mutations in *PROS1* were reported among 48 families (26 Caucasian families, 21 Asian families, and one African American family). A Chinese study identified 53 unrelated families with PS deficiency, but only 14 families with at least two VTE patients were included in the present review. The mutation p.Glu67Ala in *PROS1* was reported in three families [31]. We also included nine families with at least two VTE patients from a Spanish study [60]. Among the nine families, the mutation p.Gln238X was reported in three families. The p.Met570Thr mutation in *PROS1* was also identified in three families [58, 61]. The Met570Thr mutation may possibly be associated with PS deficiency [62]. Additional in vitro experiment may establish whether or not this mutation is associated with VTE. No mutation was found in either the Caucasian or Asian families.

Other genes

MTHFR

The *MTHFR* C677T polymorphism was identified and compounded with other gene defects in 26 Caucasian families.

SERPINE1

In a family with thrombotic disease, an 18-base pair deletion in the PAI-1 gene (*SERPINE1*) promoter region was identified [63]. Of the5of 11 family members experiencing thrombosis, four were heterozygous for the deletion variant. PAI-1 4G/5G polymorphism in combination with other gene defects was identified in nine VTE families.

THBD

A study reported thrombomodulin gene defects in four families from the United States with thromboembolic disease, and four heterozygous point mutations were detected [64].

FGA, FGB, FGG

Eight families were reported with fibrinogen variants [65–72]. In a Kurdish family with dysfibrinogenemia and familial venous and arterial thrombosis, a novel mutation c.221G > T in exon 2 of *FGB* was detected [65]. Another study used exome sequencing to identify a mutation of Arg458Cys in *FGA* in a family with recurrent VTE that remained undiagnosed for many years [66].

F12

F12 C67T was detected in three families with multiple genetic alterations [25, 37, 73].

GP1BA, PEAR1

Two Chinese families were detected with a mutation in *GP1BA* and *PEAR1* respectively [74, 75]. These two genes play a role in platelet disorder, but whether these mutations increase the risk of VTE remains unclear.

Discussion

We reviewed a total of 154 published studies containing 287 VTE families (225 Caucasian families, 52 East Asian families, four Arab families, two Latino families, two African families and others) for gene defects associated with the disease. More Caucasian families (225/287) were reported to have VTE than Asian families (52/287). A reason may be

that the incidence of VTE is much higher in the Caucasian population (75–269 patients per 100,000 individuals in the United States and Europe [2] vs 10–30 patients per 100,000 individuals in China [3]). Another reason may be the lack of awareness and research on VTE in Asia, leading to many Asian families having not been identified and reported in the literature. Although it has been suggested that VTE risk may be five times higher in African families than in Asian-ancestry populations [76], the present review only included two African families as some studies did not provide sufficient information on ethnicities, such as African, Hispanic, or other populations.

The prevalence of thrombophilia in Caucasian and East Asian families is shown in Table 3. FVL was detected in most Caucasian families included in the present review, while *F2* G20210A was also detected in a large proportion, which should be due to the high prevalence of these two common variants in Caucasians [77, 78]. However, *F5* defects were the least reported among the five genes in East Asian families. In contrast, the *PROS1* defects were the most reported in East Asian families (21/52, 40.4%) while being the least identified defects in Caucasian people (26/225, 11.6%) among the five genes (Table 3). Among these genetic variants, there is a clear inverse relationship between prevalence and strength [79]. Deficiencies of natural anticoagulants are rare but increase VTE risk by up to tenfold while common variants, which include FVL and *F2* G20210A, with a prevalence of several percent increasing VTE risk twofold to fivefold [80]. We collected the number of carriers with VTE in every family and calculated the penetrance as carriers with VTE/carriers. We come to a similar conclusion that the strength of natural anticoagulants deficiency (*SERPINC1* [0.709], *PROC* [0.569], *PROS1* [0.706]) is stronger than the two common mutations (FVL [0.46], G20210A [0.417]) (Supplementary Table 3). In brief, our review identifies the type and frequency of gene mutations associated with VTE among different ethnic groups; therefore, it provides useful genetic information for future testing and research on VTE in family pedigrees. Furthermore, it seems that the deficiency of anticoagulant proteins plays an important role in thrombophilia or the etiology of VTE.

There have been a number of Genome Wide Association Studies (GWAS) studies in VTE since 2009. Until now, GWAS conducted in Caucasian patients not only have confirmed known susceptible genes found in previous studies (*F5, F2, ABO, FGG/FGB/FGA, PROCR*), but also identified novel genes such as *TSPAN15, SLC44A2,* and *ZFPM2*. In a recent GWAS study, 14 newly reported associated loci have been found [81]. However, it should be noted that apart from the high VTE-risk SNPs (single nucleotide polymorphisms) identified by candidate gene studies, most of the genetic variants reported by GWAS only show moderate-to-low-effect sizes. Interestingly, some of the novel genes such as *TSPAN15* and ZFPM2 have no role in the coagulation system, which indicates that there may be other mechanisms contributing to VTE pathogenesis.

For most of the family studies, polymerase chain reaction (PCR) gene sequencing was used with clear targets. However, it also means sequencing was solely performed in a single selected gene, which causes other gene polymorphisms to be omitted. Whole exome sequencing (WES) has also proved its utility in VTE genetic research over the years. In WES-family studies, novel genes and novel mutations were easier to find but more difficult to prove to be causative. In WES-family studies, all polymorphisms in exons will be detected, however, introns will still be missed. None of the family studies used whole-genome sequencing. In addition, there is controversy regarding testing for thrombophilia as only some selected patients can benefit from accurate testing and individualized management, which has been well-discussed in recent reviews [82, 83]. However, it is argued that with the increasing availability of direct-to-consumer diagnostics and personalized genomic testing, we may focus on patients with identified thrombophilia rather than on the indications for undertaking tests [83].

Limitations and potential clinical implications

We have firstly made a comparison of the prevalence of five classic genes among Caucasian and East Asian VTE families. The main limitation is the lack of knowledge of ancestry of most families, so we assume ancestry based on the country of origin. Some studies that we assumed as Caucasian could be African, Hispanic, or other population in reality. Another limitation may be the underestimation of *SERPINC1*, *PROC,* and *PROS1*. Many VTE families with these protein deficiencies were not included in our review because of a lack of genetic research or only contain a VTE proband without symptomatic relatives, so the contribution of these three genes may be underestimated, especially in Caucasian families. Although more novel mutations have been discovered, few have undergone in-depth research. In addition, family studies may not have identified the correct mutations. The restriction of technology really limits our knowledge of how fully we have cataloged the causal mutations and their penetrance or segregation in families. In short, our results can provide indications for future VTE genetic research, but they are only based on the sequencing data of family studies. Further, it is important for clinicians to understand the genetic diversity of VTE and improve the individualized management of thrombophilia patients.

Conclusion

This review of 287 families revealed a total of 21 different genes, among which FVL was the most reported mutation in VTE families. *F2*, *F5*, *SERPINC1*, *PROC* and *PROS1* were the most frequently reported genes associated with VTE. Moreover, we found that there are differences in the prevalence of individual gene mutations among different ethnic groups, providing indications for future VTE genetic testing and research. Due to the lack of genetic data from Asian countries for this study, more samples of Asian families with genetic information from increasing the application of next-generation sequencing will be needed for future investigation in order to reach a more accurate conclusion.

Author contributions CW and ZZ conceived and designed the study, having full access to all of the data in the study and taking responsibility for the content of the manuscript. YZ, ZZ and SS analyzed the data, took responsibility for the accuracy of the data analysis and wrote the first draft of the manuscript. WN, WJ and WX contributed to the interpretation of the data and clinical inputs. All authors were involved in the revision of the manuscript for important intellectual content and approved the final version to be published.

Funding This work was supported by the Fund of The National Key Research and Development Program of China (No. 2016YFC0905600), the Fundamental Research Funds for the Central Universities (NO. 3332018184), CAMS Innovation Fund for Medical Sciences (CIFMS) (2018-I2M-1-003).

Compliance with ethical standards

Conflict of interest No conflicts of interest are involved in this manuscript, and manuscript is approved by all authors for publication.

Ethical approval No additional ethical approval needs to be obtained.

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