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Association between fibrinogen receptor (Glycoprotein IIb) polymorphism and the risk of venous thromboembolism: a systematic review

Zahra Rezaei Dezaki[1], Raihaneh Bagheri[2] and Batoul Pourgheysari[3,4*]

Abstract

Background: The fibrinogen receptor is an integrin on the platelet surface and is shaped from two types of glycoprotein (GP) subunits, GPIIb and GPIIIa. Membrane glycoprotein IIb/IIIa plays an important role in platelet function. The gene encoding the glycoprotein IIIa shows a common polymorphism, PLA2 that increases the binding of the receptor to fibrinogen and enhances the platelet aggregation. The clinical impact of PLA2 polymorphism has been studied in some diseases, but the definition of its exact role on venous thromboembolism complications has been challenging. The present systematic review aimed to clarify the association of PLA2 polymorphism and venous thromboembolism.

Main text: In this study, Electronic databases including PubMed, Embase, Scopus, Web of Science, and Cochrane Library were searched. All the assessed studies focused on the relationship between PLA2 polymorphism and venous thromboembolism. Five studies were eligible for systematic review. One study revealed a significant correlation between PLA2 polymorphism and venous thromboembolism. PLA2 polymorphism was associated with deep vein thrombosis in one study and pulmonary thromboembolism in another one.

Conclusion: The published data supported the hypothesis that having the PLA2 polymorphism of GPIIIa may be a risk factor for venous thromboembolism, but the association cannot be concluded; it needs more clinical investigation.

Keywords: Venous thromboembolism, Deep vein thrombosis, Pulmonary embolism, PLA2 polymorphism

Background

The platelet fibrinogen receptor is essential for preliminary hemostasis, as it regulates platelet aggregation and binds to a combination of fibrinogen, von Willebrand factor (vWF), and fibronectin for the formation of a stable thrombus following vascular injury [1–3].

The mature fibrinogen receptor is an integrin on the platelet surface [4] and is formed from two types of glycoprotein (GP) subunits, GPIIb and GPIIIa [5]. The GP IIIa subunit is a great polymorphic protein with platelet antigen 1 (PLA1) and 2 (PLA2) as the utmost stable allelic variants [6]. The PLA2 polymorphism of GP IIIa results from the substitution of leucine by proline at position 33 [7].

Previous studies demonstrated that the PLA2 isoform increases the binding of the GP IIb/IIIa receptor to fibrinogen and enhances the platelet aggregation, thus it is a possible factor for thrombotic tendency with other prevalent recognized inherited thrombophilic factors such as factor V Leiden (FVL), mutation G20210A in prothrombin gene, and factor XIII polymorphism [8–11].

The clinical impact of PLA2 polymorphism (formed from GP IIIa) has been associated with an increased risk of several diseases where thrombus formation is a crucial pathogenic factor for their development such as

* Correspondence: Zahra.rzi69@gmail.com; bat238@yahoo.com
[3]Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran
[4]Department of Pathology and Hematology, Shahrekord University of Medical Sciences, Shahrekord, Iran
Full list of author information is available at the end of the article

myocardial infarction and stroke, and was suggested as a risk factor for venous thromboembolism (VTE) [2, 12–15]. VTE, including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a major public health problem [16], mostly for hospitalized patients [17] and is among the utmost ordinary preventable reasons of hospital death [18]. VTE appears to be triggered by acquired and hereditary risk factors including mutations in genes encoding hemostatic proteins such as coagulation factors, coagulations inhibitors, and platelet glycoproteins.

Some studies investigated the role of the PLA2 polymorphism in DVT, PE, or VTE, but this is still controversial.

To the best of our knowledge, the association between PLA2 polymorphism and VTE has not been systematically assessed. Therefore, this systematic review aimed to evaluate the prognostic significance of PLA2 polymorphism in DVT, PE, and VTE patients to explore the relationship between this polymorphism and venous thrombotic events.

Main text

Search strategy

Search strategy and selection of articles for this systematic review were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Fig. 1).

We searched the different databases including Pub Med, Scopus, Web of Science, Embase, and Cochrane library databases up to January 2018. Electronic searches were performed combining some keywords that were planned to proper match to MeSH terms.

"PLA2 polymorphism" and "Deep vein thrombosis," "PLA2 polymorphism" and "Pulmonary embolism," "PLA2 polymorphism" and "Venous thromboembolism" or "VTE," "PLA2 polymorphism" and "Deep vein thrombosis" or "DVT," or "Pulmonary Embolism" or "Venous thromboembolism."

We also manually searched the reference lists of primary studies and reviews, in order to find the studies which cannot be found via an electronic search.

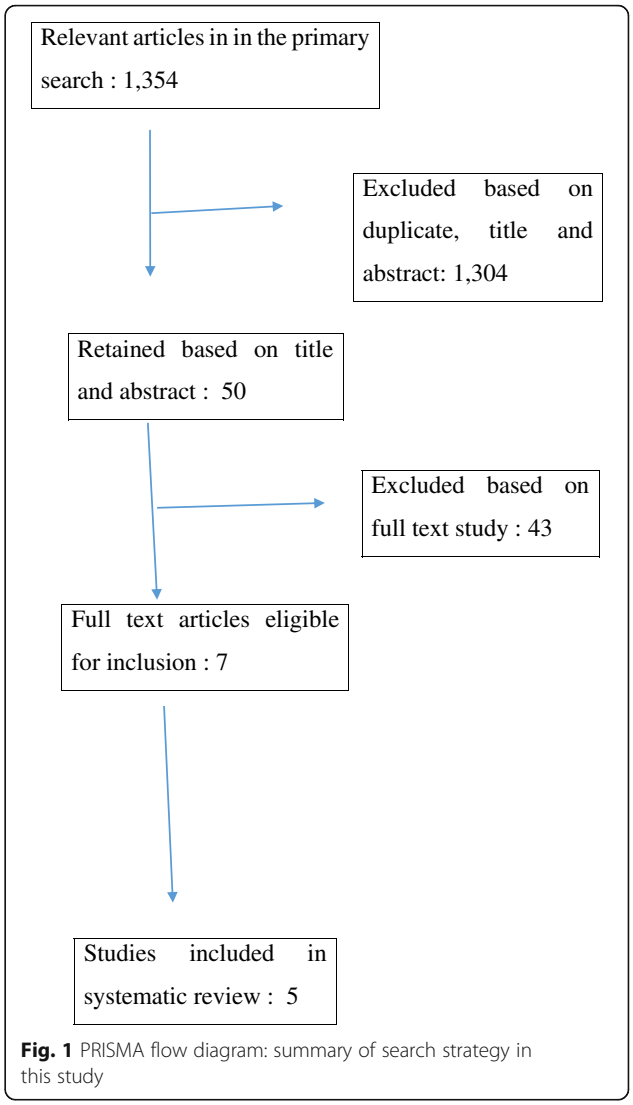

Fig. 1 PRISMA flow diagram: summary of search strategy in this study

Selection criteria

Duplicates were initially removed from the search result. The remaining articles were then screened by scanning titles and abstracts for the inclusion criteria: articles studying the relationship between having the PLA2 polymorphism and risk of DVT, PE, and VTE (at least one of these); studies calculated odds ratio; and published articles in English language.

The exclusion criteria of this review study were as follows: not original articles including commentaries, review articles, case reports, and letters; papers in any language except English; articles with less than ten patients; articles that do not contain full text, including articles presented at congresses and conferences and symposiums.

Article selection was conducted by authors independently. Any disagreement among reviewers was resolved by discussion and reached consensus finally.

Data extraction and quality assessment

One of the reviewers thoroughly investigated the article titles and abstracts to determine the competency of selected articles.

The following data were obtained from each article: first author, year of publication, study population, number of patients, patient characteristics including: age, gender, etc. and odd ratio with 95% confidence interval (Table 1).

Results

The initial search generated 1354 articles, five of which were identified as being strongly relevant following

Table 1 Extracted data from included studies investigating the correlation between PLA2 polymorphism and VTE

Author	Country	Patients number	Median age	OR	95% CI	Type of disease	Frequency of PLA2 polymorphism (%)	*p* value
Ridker et al 1997	USA	121	61	1.07	0.7–1.6	VTE	28.1	0.5
Ivanov et al 2008	Bulgaria	51	48.7/45.47	3.27	1.36–7.93	PE	35.3	0.003
Atzeni et al 2011	Italy	36	34	2.2	1.1–4.5	Behcet's diseases with DVT	41.7	0.04
Pourgheysari et al 2012	Iran	72	52.12	3.4	1.8–6.44	VTE	27.8	< 0.001
Karimi et al 2015	Iran	23	NR	1.33	0.37–4.71	PE/DVT	13	NS
		37		1.37	0.5–3.82	PE	13.5	
		35		6.65	3.09-14.30	DVT	42.9	< 0.001

NR data not reported, *NS* not significant, *N* number, *OR* odds ratio, *CI* confidence interval, *VTE* venous thromboembolism, *PE* pulmonary embolism, *DVT* deep vein thrombosis

review of title and abstract. The detailed selection process is presented in Fig. 1 and a detailed review of coherent data is collected in Table 1. The included articles were studies about the association between PLA2 polymorphism and DVT, PE, or VTE.

The patient populations of the selected papers were from various nationalities.

All patients contributing in these studies were diagnosed with venous thrombotic events with or without PE. The patient populations ranged between 23 and 121 cases.

In all evaluated studies, PLA2 polymorphism was evaluated via restricted fragment length polymorphism (RFLP) PCR.

In all studies, DVT was diagnosed and confirmed using standard methods including ultrasonography, Doppler ultrasonography, D-dimer, and clinical symptoms. Various techniques were also used for PE diagnosis such as clinical presentation, chest X-ray, ventilation perfusion lung scan, electrocardiogram, determination of blood gases, and D-dimer test. PLA2 polymorphism prevalence was reported 13–42.9% in patients (mean = 27.95%).

The median age was within the range of 34–61 years. One of five papers compared age between cases with thrombosis risk concomitant with PLA2 allele and without it [15].

PLA2 polymorphism was associated with VTE in one study [14], but not in another one [15] (Table 1). One of the studies found no correlation between PLA2 polymorphism and thrombotic events in patients with age 60 years or older ($P = 0.5$) [15]. In two of the selected studies, the correlation between PE and PLA2 polymorphism was investigated; one of them showed no association [19], whereas the other one reported the correlation ($P = 0.003$) [20]. In the latter, the prevalence of PLA2 in patients with recurrent PE events was 37% (OR 3.52, CI 1.21–10.3) and one patient was homozygous genotype for this polymorphism.

The association between PLA2 polymorphism and DVT was reported in one of the articles. According to the findings, the frequency of PLA2 polymorphism was significantly higher in DVT, compared to control group ($P < 0.001$) [19]; however, no significant difference was found in the frequency of this polymorphism between PE/DVT or PE patients and control group.

One of the studies investigated the association between PLA2 polymorphism and thrombotic events in Behcet's disease [21]. In this study, the frequency of PLA2 polymorphism was compared between the Behcet patients with DVT and control group. No significant difference was observed between Behcet's disease (BD) and control in the frequency of PLA2 polymorphism, but was found between these patients with DVT and control (OR 2, CI 1.1–3.7) (21). Carriage rate was also significantly higher in BD patients with DVT than control ($P = 0.044$, OR 2.2, CI 1.1–4.5).

The association between recurrent events and PLA2 polymorphism was found in another study [14]. Carriage of this polymorphism had more recurrent VTE events than other patients.

In one of the studies, the effect of aspirin consumption was studied on the association between PLA2 polymorphism and thrombosis. The exclusion of these patients from the cohort had no effect on final output [15].

The prognostic value of PLA2 polymorphism and its correlation with DVT, PE, or VTE has not been thoroughly evaluated. Nevertheless, the predictive value of this genetic marker has been mostly evaluated in cases with stroke or coronary thrombosis [12, 13, 22].

In 1996, Weiss et al. reported a relationship between the PLA2 allele and elevated risk of premature coronary thrombosis [12]. Some years later, in 1999, Feng et al. suggested that PLA2 allotype in GP IIb/IIIa could be a risk factor in patients with VTE. The PLA1/PLA2 polymorphism is characterized by increased affinity of the GP IIb/IIIa platelet receptor for fibrinogen and enhances platelet aggregation as a baseline for thrombosis [22]. Despite this, in 2008, Ivanov et al. declared no association between PLA2 polymorphism and risk of VTE, but

it could be a potential risk factor for developing PE [20]. Their data showed comparable OR to other known thrombophilic mutations, FVL and FII G20210A. They reported that dual carriers of FVL/PLA2 along with early manifestation and unusual position of thrombosis had recurrent PE.

In another study in 2012, Pourgheysari et al. reported that PLA2 polymorphism is highly associated with VTE [14].This was the only inherited thrombophilic risk factor that was correlated with VTE among investigated polymorphisms, FVL, FIIG20210A and HTHFR. The PLA2 polymorphism also played a role in recurrent events in spite of the other polymorphisms. This finding demonstrated the importance of population-based studies.

According to the results of this systematic review, PLA2 polymorphism increased the thrombotic tendency, but no consistency was found between different studies. While Ivanove et al. demonstrated the association of the polymorphism with PE, Karimi et al. found no relationship. Instead, they found the association with DVT [20, 19].

A main limitation of the present review was the lack of enough comparable reports and paucity of research in this study. Due to the low number of publications, the study is not adequately powered to identify the importance of this polymorphism. Because of the limited accessibility of data, it was not possible to perform univariate or multivariate analyses of individual markers in all studies.

Conclusion

It was concluded that PLA2 polymorphism is a risk factor for VTE in some patients. Whether this marker can be used as an important factor in the diagnosis and treatment of patients with DVT or PE needs more investigation. The predictive value of the polymorphism is not clear from the existing publications. As the data were little and somehow incompatible, it cannot be concluded that PLA2 polymorphism is associated with an increased risk of VTE and this hypothesis needs more trainings.

Abbreviations

BD: Behcet's disease; DVT: Deep vein thrombosis; FVL: Factor V Leiden; GP: Glycoprotein; PE: Pulmonary embolism; PLA1: Platelet antigen 1; PLA2: Platelet antigen 2; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; RFLP PCR: Restricted fragment length polymorphism PCR; VTE: Venous thromboembolism; VWF: Von Willebrand Factor

Authors' contributions

BP: Final checking of information, participating in essay writing and submission of article. RB: Searching and gathering articles and extracting information and participating in essay writing. ZR: Searching and gathering articles and extracting information and participating in essay writing. All authors have read and approved the manuscript.

Availability of data and materials

This article is a review article and does not require any materials.

Ethics approval and consent to participate

Since the type of article is review and we have not directly studied human beings, we did not need ethics approval and consent to participate.

Consent for publication

All authors agree to publish the article.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran. [2]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. [3]Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran. [4]Department of Pathology and Hematology, Shahrekord University of Medical Sciences, Shahrekord, Iran.

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