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Genetic risk factors in thrombotic primary antiphospholipid syndrome: A systematic review with bioinformatic analyses

Md. Asiful Islam [a,*], Shahad Saif Khandker [b,1], Fahmida Alam [a,1], Mohammad Amjad Kamal [c,d,e], Siew Hua Gan [a,f,*]

[a] Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia
[b] Department of Biochemistry and Molecular Biology, Jahangirnagar University, Savar, Dhaka 1342, Bangladesh
[c] King Fahd Medical Research Center, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[d] Enzymoics, Hebersham, NSW 2770, Australia
[e] Novel Global Community Educational Foundation, Australia
[f] School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, 47500 Bandar Sunway, Selangor, Malaysia

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ABSTRACT

Background: Antiphospholipid Syndrome (APS) is an autoimmune multifactorial disorder. Genetics is believed to play a contributory role in the pathogenesis of APS, especially in thrombosis development and pregnancy morbidity. In the last 20 years, extensive research on genetic contribution on APS indicates that APS is a polygenic disorder, where a number of genes are involved in the development of its clinical manifestations.
Aims: The aim of this systematic review is to evaluate the genetic risk factors in thrombotic primary APS. Additionally, to assess the common molecular functions, biological processes, pathways, interrelations with the gene encoded proteins and RNA-Seq-derived expression patterns over different organs of the associated genes via bioinformatic analyses.
Methods: Without restricting the year, a systematic search of English articles was conducted (up to 4th September 2017) using Web of Science, PubMed, Scopus, ScienceDirect and Google Scholar databases. Eligible studies were selected based on the inclusion criteria. Two researchers independently extracted the data from the included studies. Quality assessment of the included studies was carried out using a modified New-Castle Ottawa scale (NOS).
Results: From an initial search result of 2673 articles, 22 studies were included (1268 primary APS patients and 1649 healthy controls). Twenty-two genes were identified in which 16 were significantly associated with thrombosis in primary APS whereas six genes showed no significant association with thrombosis. Based on the NOS, 14 studies were of high quality while 6 were low quality studies. From the bioinformatic analyses, thrombin-activated receptor activity ($q = 6.77 \times 10^{-7}$), blood coagulation ($q = 2.63 \times 10^{-15}$), formation of fibrin clot ($q = 9.76 \times 10^{-10}$) were the top hit for molecular function, biological process and pathway categories, respectively. With the highest confidence interaction score of 0.900, all of the thrombosis-associated gene encoded proteins of APS were found to be interconnected except for two. Based on the pathway analysis, cumulatively all the genes affect haemostasis [false discovery rate (FDR) $= 1.01 \times 10^{-8}$] and the immune system [FDR $= 9.93 \times 10^{-2}$]. Gene expression analysis from RNA-Seq data revealed that almost all the genes were expressed in 32 different tissues in the human body.
Conclusion: According to our systematic review, 16 genes contribute significantly in patients with thrombotic primary APS when compared with controls. Bioinformatic analyses of these genes revealed their molecular interconnectivity in protein levels largely by affecting blood coagulation and immune system. These genes are expressed in 32 different organs and may pose higher risk of developing thrombosis anywhere in the body of primary APS patients.

Abbreviations: aCL, anticardiolipin; ADP, adenosine diphosphate; APOH, apolipoprotein H; APS, antiphospholipid syndrome; β2GPI, β2-glycoprotein I; DVT, deep vein thrombosis; FDR, false discovery rate; GO, gene ontology; IL, interleukin; IRAK 1, interleukin-1 receptor-associated kinase; ITGA2, integrin subunit alpha-2; LA, lupus anticoagulant; mRNA, messenger RNA; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; PAMPs, pathogen-associated molecular patterns; PAR-1, proteinase-activated receptor-1; PBMCs, peripheral blood mononuclear cells; PE, pulmonary embolism; PF4V1, platelet factor 4 variant 1; SELP, selectin P; SLE, systemic lupus erythematosus; STRING, Search Tool for the Retrieval of Interacting Genes; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TLR, toll like receptor; TNF, tumour necrosis factor; tPA, tissue plasminogen activator; VEGFA, vascular endothelial growth factor A; vWF, Von Willebrand factor.

* Corresponding authors.
E-mail addresses: ayoncx70@yahoo.com (M.A. Islam), shgan@usm.my (S.H. Gan).
[1] Joint second authors.

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1. Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by the presence of circulating antibodies such as lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β2-glycoprotein I (β2GPI) antibodies to phospholipid binding proteins. There are two major clinical features of definite APS 1) thrombosis and 2) pregnancy morbidity [1, 2]. Thrombus can be formed in any organ in the body since it is generated in both arteries and veins [3]. APS is an idiopathic disease and the aetiology of the disease remains unknown. However, APS is a polygenic disorder where different factors contribute in the development of abnormal laboratory and clinical features. There are three major types of APS, 1) primary (clinical and laboratory features of APS are present with the absence of autoimmune disease); 2) APS-associated with other diseases [besides clinical and laboratory features, at least an autoimmune disease [*i.e.*, systemic lupus erythematosus (SLE) is present] and 3) catastrophic APS (the most aggressive mode of APS where multiple organs are affected and patients die due to multiple organ failure) [4]. Genetic aspects - majorly mediated by inappropriate activation of immune system have been believed to play important roles in the development of APS [5–7]. Familial cases of APS also indicate towards the involvement of genetics in the pathogenic development of APS [8, 9].

APS is one of the most common thrombophilic conditions observed in young adults where the presence of both arterial and venous thrombosis is reported [8, 10]. According to the Euro-Phospholipid project, thrombosis is the most frequent clinical manifestations (28.1%) for APS [11]. Approximately 55% of APS patients suffer from venous thrombosis [*i.e.*, deep vein thrombosis (DVT) and pulmonary embolism (PE)] [12], while cerebrovascular accidents and transient ischemic attacks are the most common (50%) arterial thrombotic manifestations [13]. Thrombosis is considered as the major cause of death in catastrophic

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