European Journal of Human Genetics (2015) 23, 1279–1280

www.nature.com/ejhg

LETTERS

'Epistatic interactions between autoimmunity and genetic thrombophilia'

European Journal of Human Genetics (2015) 23, 1279; doi:10.1038/ejhg.2014.287; published online 28 January 2015

In the recent article by Bakir-Gungor *et al*,[1] a novel method of analysis is proposed to elucidate the genetic pathways that are considered essential in the phenotypic expression of complex diseases, such as Behçet's disease (BD). The combined analysis of the data of two genome-wide association studies (GWAS) that were conducted in the Turkish and Japan populations with BD[2,3] reveals a shared pathway between the complement and the coagulation cascade.

On the basis of the epidemiological data and the diagnostic assessment of three patients with major vessel thrombosis who were hospitalized in our department, we have previously formulated the medical hypothesis that the occurrence of genetic thrombophilia and certain features of the complex spectrum of BD in selected patients with thrombosis may not represent a coincidental coexistence, but rather the core features of a genetically based distinct nosological entity.[4] The role of synergistic epistasis is considered the key in this hypothesis, which stems from the observation of three facts with respect to the thrombotic phenomena of BD.[4] The first is that the prevalence of vascular thrombosis in BD is significantly higher in certain populations; the second is that the highest prevalence of certain inherited procoagulant factors are concomitant to the highest prevalence of vasculo-BD in specific ethnic populations; and the third and most important is that only certain reports in the literature confirm a positive association between specific inherited procoagulant factors and thrombotic manifestations in BD patients.

The theoretical background of this hypothesis seems to be supported in a preliminary stage through the scientific work of Bakir-Gungor *et al*,[1] and although its data cannot result in safe and comprehensive conclusions, we are strong advocates of similar future studies. Beside, there is now a body of evidence that imply the epistatic interaction between inherited thrombophilia and autoimmunity. In a recent experimental study by Katzav *et al*,[5] it has been demonstrated that when heterozygous and homozygous factor V-Leiden transgenic mice were immunized with antiphospholipid antibodies there have been various autoimmune responses resulting in neurodegenerative manifestations. Further research in the field of GWAS with the methodology presented by Bakir-Gungor *et al.*[1] seems to be the future direction to elucidate the pathways in complex diseases and therefore individualize the treatments or even re-evaluate the classification of certain diseases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Dimitrios Stoimenis[1], Nikolaos Petridis[1] and Nikos Papaioannou*,[1]
[1]*Department of Internal Medicine, General Hospital "G. Papanikolaou", Thessaloniki, Greece*
E-mail: papaioannou.nikos@gmail.com

1 Bakir-Gungor B, Remmers EF, Meguro A *et al*: Identification of possible pathogenic pathways in Behçet's disease using genome-wide association study data from two different populations. *Eur J Hum Genet* 2015; **23**: 678–687.
2 Remmers EF, Cosan F, Kirino Y *et al*: Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behcet's disease. *Nat Genet* 2010; **42**: 698–U678.
3 Mizuki N, Meguro A, Ota M *et al*: Genome-wide association studies identify IL23R-IL12RB2 and IL10 as Behcet's disease susceptibility loci. *Nat Genet* 2010; **42**: 703–U783.
4 Stoimenis D, Petridis N, Papaioannou N. Behçet's Disease, associated large vessel thrombosis, and coexistent thrombophilia: a distinct nosological entity? *Case Rep Med* 2013; **2013**: 740837.
5 Katzav A, Grigoriadis NC, Ebert T *et al*: Coagulopathy triggered autoimmunity: experimental antiphospholipid syndrome in factor V Leiden mice. *BMC Med* 2013; **11**: 92.

Reply to Stoimenis *et al*

European Journal of Human Genetics (2015) 23, 1279–1280; doi:10.1038/ejhg.2014.288; published online 14 January 2015

We appreciate the comments made by Stoimenis *et al*[1] on our recently published article,[2] describing the application of our novel analysis method to Behçet's disease (BD) genome-wide association study data obtained from the Japanese and Turkish populations. In this study, we analyzed the data in a pathway-related context to identify the disease-related pathways targeted by the single-nucleotide polymorphisms (SNPs).[2] Among the identified pathways, Stoimenis *et al*[1] focus on the complement and coagulation pathway since they identified three BD patients with major vessel thrombosis.

We fully agree with Stoimenis *et al* that in specific ethnic populations there exists a strong prevalence of vascular thrombosis in BD and that there is a positive association between the inherited procoagulant factors and thrombosis in BD.[3] According to our analysis, complement and coagulation pathway ranks as the seventh affected pathway in the Turkish population, whereas it ranks tenth in the Japanese population. Commonly targeted genes in this pathway consist of *PLAT, F5* and *F13A1*. All these genes have been previously identified to be associated with BD and thrombosis.[3] Especially the mutations in *F5* gene in Turkish population have been identified to increase the risk of venous thrombosis.[4] Coagulation factor XIII protein is a crucial protein complex in the final step of blood coagulation process. It is made up of two domains produced by two separate genes, *F13A* and *F13B. F13A* gene is targeted by the SNPs in both populations, whereas *F13B* gene is targeted only in the Turkish population, creating a higher risk of venous thrombi.[5] All the population-specific SNPs targeting this pathway have different functional impacts yielding to different rankings of this pathway in both the populations.