Reviewer's report

Title: A genome-wide search for common SNP x SNP interactions on the risk of venous thrombosis

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Reviewer: Pantelis Bagos

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The manuscript of Greliche and coworkers describes a genome-wide search for detecting gene-gene interactions that contribute to the susceptibility of Venous Thrombosis. The analysis also includes a replication cohort and the authors analysed the combined sample using meta-analysis methods. Such works are of great importance and I strongly believe that deserve publication. However, there are some important points that need to be addressed, especially regarding the method of analysis. In particular:

Major Compulsory Revisions

1) The statistical method that was chosen by the authors, even though it is a valid one (i.e. the strict Bonferroni criteria were applied) there is no indication that it is the best currently available. Moreover, the authors state that «a two stage interaction analysis». The term «two-stage», even though technically correct, is usually referred to strategies in which the SNPs with the significant marginal effects are retained for further analysis. Finally, there are plenty of statistical and computational methods (some of which are especially designed for GWAS) that allow for fast, accurate and powerful detection of GxG interactions. Having said that, I would suggest that the authors include some kind of introduction to GxG interaction methods, especially for GWAS. Afterwards, they may consider the possibility of applying one or more of the proposed methods in order to evaluate the results. I realise that this may be problematic (i.e. it may require time and resources), but if the authors choose otherwise, they will have to document their approach with theoretical arguments.

2) The statement «this is the first attempt to investigate, at the genome-wide scale...» is obviously false. Perhaps the authors meant that this is the first attempt concerning VT.

3) The overall conclusion «interactive phenomena are unlikely to contribute...» is also philosophically and statistically false. The method used in this study failed to identify such phenomena (lack of power). Absence of evidence is not evidence of absence. The authors should rephrase all the relative passages in the manuscript in order to reflect this. Moreover, the discussion of the relative methods (see point 1 above) could help in this regard.

4) The authors used a fixed effects meta-analysis method for pooling the results of the two cohorts. This approach although common, is rather anti-conservative, especially when heterogeneity is present. The authors, claimed that they used
Mantel-Haenzsel test of homogeneity, but there are no such results (they could be appended in table 1). In case of heterogeneity, random effects methods should be used (personally, I would recommend using random effects in the first place).

5) The statistic used for the interaction, derived from logistic regression, is accurate, but perhaps a better solution in order to increase the power would be to use a case only design (http://www.ncbi.nlm.nih.gov/pubmed/10069253). This quite simple (if SNPs are not in LD) since the calculation involves only summary counts and it may result in reaching genome-wide significance.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests