Author’s response to reviews

Title: The prevalence of heterozygous F12 mutations in Chinese population and its relevance to incidents of thrombosis

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Author’s response to reviews:

Dear Dr. Zhang,

The authors are thankful to the reviewers’ insightful comments and suggestions, and have addressed all the questions raised by reviewers point by point. We hope our answers will satisfy the critiques of the reviewers and our manuscript be considered as suitable for publication in BMC Medical Genetics.

Sincerely yours,

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Point-by-point responses to the Reviewer(s)’ comments

Yi Wang (Reviewer 1):

1. Why did you choose the prevalence of F12 C46T variant in patients with VTE and healthy control?

The SNP C46T of F12 gene has been suggested to be associated with incidents of thrombosis events in certain population, which we have briefly described in the discussion section. We therefore include this particular F12 gene variation in our study to explore its prevalence in Chinese and probe its relationship with incidents of thrombosis.

2. In the fourth paragraph, why did you refer to the different criteria for the diagnosis of moderate FXII deficiency?

It is a great question and that is also one of the reasons to perform current study using F12 genetic variances instead of FXII clotting activity in probing the relationship between FXII and thrombosis. Due to reagents used and population studied, the normal FXII clotting activity reference range determined by each lab varies from each other and the criteria for diagnosis of moderate FXII deficiency are different. The genetic variances of F12 gene thus provide an alternative index of FXII deficit, which could be used to establish the relationship of moderate FXII changes and incidents of thrombosis events more accurately, just as we have presented in current study.
Golo Ahlenstiel, MD (Reviewer 2):

- All reviewer comments have been answered.

- I could not find evidence of controlling for multiple comparison. This should be considered.

The authors are very grateful for the suggestion. Multiple comparison control is of great importance and lack thereof is thus indeed a valid concern for the study summarized in the paper submitted. However, from the empirical research conducted with limited sample size, our analysis of multiple F12 variants failed to establish significant correlation with incidents of thrombosis and the risk of having false negative results has instead become the major concern. The control for multiple comparisons is thus of less significance for the current study, however, just as you suggested, it will be an essential consideration in our future study on the topic with expanded population and more F12 gene variances.