Reviewer’s report

Title: Factor V Leiden G1691A and Prothrombin G20210A mutations among Palestinian patients with sickle cell disease

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Reviewer: Alejandro Lazo-Langner

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BHM-D-00041

The authors present a study evaluating the association of Factor V Leiden and prothrombin gene variant with clinical manifestation in patient with sickle cell disease. Overall the manuscript is well written. A few points to consider;

1. The risk of thrombosis associated with heterozygous state for either thrombophilic trait seems too high. In general it is acknowledged a 2-4 fold increase in the risk of venous thrombosis but the ABSOLUTE risk is rather low. Please modify and also point out that the thrombosis risk is for venous events, not arterial ones.

2. Not clear if the controls were screened for SCD trait.

3. It is not clear what is the primary objective and outcome of the study. Please clarify this point in a subheading in the methods section. Include an outcome definition. Please include a sample size calculation, or a justification for your sample.

4. The P-values for the OR for the association between FVL with SCD are not very large. One would wonder if this association is indeed real or it is just a result of multiple comparisons. Furthermore, some of the 95%CI do not seem to correspond to the reported p-values (e.g. PGV and SS or AS. Please double check the statistical analysis. Also, the CI are very wide for the OR, which suggests that the sample size is small. How do you explain this?
5. Table 5 shows the prevalence of symptoms comparing wild versus mutant patients. Again, it seems that there are multiple comparisons, albeit the values suggest that there might be a signal. What could be the pathophysiological explanation for such association? One could argue that chest pain may be related, but splenomegaly? Also, the frequency of blood transfusions is a continuous variable and should be analyzed using linear regression, not logistic, as it seems to have been the case. It makes me think that the statistical analysis was conducted with the aim of finding a significant value. Please elaborate

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

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