Reviewer's report

Title: Rheumatic Heart Disease in Uganda: The Association between MHC Class II HLA DRB1 Alleles and Disease: A Case Control Study

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Reviewer: Giuseppina Di Biase

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Commentary by Giuseppina Di Biase

In this research paper the Authors have broached a very interesting issue, i.e. the point that several alleles of the HLA class II genes appear to be the dominant contributors to the development of rheumatic fever and rheumatic heart disease. There are several aspects which need to be better elucidated. They are briefly represented below.

Results
- “HLA-DR1 (OR=0.42, CI 0.21-0.85, P=0.01, Pc=0.09) showed a positive trend towards association with not having RHD”. In my opinion, the term you used here is improper and would need to be corrected. In fact, the word “trend” denotes a non significant relationship, so it is characterized by a nonsignificant p-value, although rather close to statistical significance (e.g. p=0.076). By contrast, in this sentence a significant association (p= 0.01) rather than a true, properly called "trend" is noticeable. Thus the sentence should be amended as follows: "HLA-DR1 was demonstrated to be associated with a decreased risk of RHD (OR=0.42, CI 0.21-0.85, P=0.01 ...)".

-“HLA-DR1 (OR=0.42, CI 0.21-0.85, P=0.01, Pc=0.09) showed a positive trend...” Moreover I don't understand the meaning of the acronym Pc( Pcorrected?). As a rule, full term should be provided before introducing in the text any acronym. Please clarify accordingly. If the interpretation "P corrected “ is right, please specify the sense of this "P correction"

Discussion
-“We found .. a positive trend towards association of HLA-DR1 with healthy controls” The improper use of the word “trend” is re-proposed here. Please correct again, by underscoring the existence of a significant association ( not a trend) between HLA-DR1 and the freedom from RHD.

-According to Guilherme et al.( Ann Pediatr Cardiol. 2011 Jan-Jun; 4(1): 13–21) “The HLA-DR7 allele that was found in Brazilian, Turkish, Egyptian, and Latvian patients could be considered the HLA class II gene that is most consistently associated with rheumatic fever and rheumatic heart disease”. Nevertheless, in the present study the association evidenced by other Authors between this allele and rheumatic disease is lacking. Please illustrate more thoroughly the possible reasons that have led to very different results, when searching for candidate alleles within the chromosoma 6, depending on the ethnic composition of the
analyzed population samples or as a consequence of different genotypical profiles of the involved microbial strains in a given country and time period.

Discussion- “Identification of individuals with susceptibility genes to RHD could potentially provide an opportunity to screen patients with borderline RHD for secondary prophylaxis, and to place such people in a more routine follow up for streptococcal surveillance”. In the opinion of some, secondary prophylaxis with benzathine penicillin, once a week in the first month and subsequently once a month for a few years, should be systematically executed in patients with a history of one or more episodes of rheumatic fever, especially in areas where it is endemic, without relying on the tests of genetic susceptibility. In fact they could be misleading, since a complete agreement has not been reached yet for them among the researchers. In the Discussion please also illustrate this controversial point and related conflicting outlooks concerning possible therapeutic strategies.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests