Reviewer's report

Title: Association of the RYR3 gene polymorphisms with atherosclerosis in elderly Japanese population

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Reviewer: Aya Kawasaki

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In this manuscript, Zhao et al. conducted an association study of RYR3, which was identified in the GWAS of atherosclerotic diseases in Caucasians, with atherosclerosis in Japanese autopsy cases. They reported that RYR3 SNPs, rs877087 and rs2229116, were associated with atherosclerosis severity in Japanese.

I have the following comments:

Major Compulsory Revisions

1. The authors concluded that rs877087 is associated with atherosclerosis severity. However, P value of rs877087 for Hardy-Weinberg equilibrium test was 6.8 X 10^-45. This could be due to, as the authors stated in the limitation, the selection bias related to the nature of the study on the autopsy cases, and/or genotyping problems. In either case, the association data are not convincing as they now stand. I would suggest that the authors should genotype rs877087 by another method, or exclude this SNP from this analysis.

2. The authors selected tag SNPs with r^2 threshold # 0.1, and only two tag SNPs were analyzed in this study. Generally, tag SNPs are selected with a threshold of r^2 > 0.8. If they want to examine the association of the entire 31 kb region between rs877087 and rs2229116, 44 tag SNPs, selected with a threshold of r^2 > 0.8 by the HapMap database, need to be analyzed.

3. Although the authors mentioned that “Four major haplotypes (TGGA, TAGA, TAAA and TAGG) from the 4 SNPs could explain near 90% of the overall genetic diversity observed in this region” (Page 6), the four major haplotypes only explain 90% of haplotypes constituted by these 4 SNPs, and not of “the overall genetic diversity”.

4. The authors should indicate the results of the association study of the rs2132207 and rs658750. Actually, in its current form, it is difficult to understand why the authors genotyped these two SNPs. If the authors intended a trans-ethnic fine mapping by taking advantage of difference in the LD status between populations, they should discuss whether the association of the opposite alleles of rs2229116 between Caucasian and Japanese populations could be explained by the same allele of another “causal” SNP in both populations.
Minor Essential Revisions

1. It is a little difficult to understand Figure 1. It is better to show a heatmap, which can be obtained using Haploview software, to indicate LD status of the 31.1 kb region.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare that I have no competing interests.