Reviewer’s report

Title: Common Genetic Variants on Chromosome 9p21 Are Associated with Myocardial Infarction and Type 2 Diabetes in an Italian Population.

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Reviewer: Rector Arya

Reviewer’s report:

In this manuscript titled “Common genetic variants on chromosome 9p21 are associated with myocardial infarction (MI) and type 2 diabetes (T2D) in an Italian population” the authors have performed a case-control association study in an Italian population to replicate the association of two single nucleotide polymorphisms (SNPs): rs2891168 and rs10811661 from a genomic region on 9p21 that were previously reported to be associated with MI and T2D respectively in PROCARDIS study. They also tested if these SNPs show independent effects on susceptibility to these two diseases.

They analyzed 2407 DNA samples consisting of both cases (1802) and controls (605) and found that rs2891168 was associated with MI, while rs10811661 was associated with T2D. They also performed a pooled analysis combining this study and PROCARDIS study and found confirmatory association findings. This manuscript is well written and the results are interesting. They have used appropriate methods. The sample size was reasonable though the cases and controls were not matched. However, I have some specific comments:

Major Compulsory Revisions

In this study, although all subjects were drawn from Italian population, subjects with T2D were collected randomly from IGLOO and subjects with MI and MI and T2D were collected from GISSI-Prevenzione study (GISSI-P), and control subjects (unmatched non-diabetics with no CAD) were collected from AVIS study, and that the cases and controls were not matched. It is possible to have some impact of population (group/sex) stratification on the observed associations. Therefore, it would be useful, if authors can comment on potential stratification effects, if any, in this study.

Although they provided power calculations for the combined sample, it is not clear if there is adequate statistical power for just the present sample not pooling with PROCARDIS data.

It would also be helpful to see if there is any impact of multiple comparisons on the observed associations.

It is not clear if authors have tested for any residual association in Italians with diabetes after correcting for MI and vice versa.
Minor Essential Revisions:

In the abstract: last sentence in the background section “to verify whether their effects… with these two diseases” may be rephrased for clarity.

Second sentence in abstract conclusions and in the discussion, “We were also able to integrate and complete the PROCARDIS group analysis...” is not clear and it may be rephrased.

In the discussion, paragraph 4, second sentence “We considered that this approach...” is not clear, please clarify.

In the discussion, paragraph 5, on line 1, the phrase “are unexpectedly unable” may be replaced by “fail”

In the discussion, paragraph 6, first sentence, it is not clear what authors are referring to “so far nobody knows the correlations between genotype and phenotype”. Please elaborate or clarify.

Discretionary Revisions

One of the major problems of association studies is that only a few reported associations replicate consistently because initial published associations are often times overestimate the true genetic effect size. As such results from an initial study may be viewed with a caution and it could be due to chance, bias, and/or problems in analysis, interpretation or due to publication bias. So to avoid such false positive associations, it would be ideal to look at or replicate more SNPs (literature SNPs) shown to be associated with CAD/type 2 diabetes across the 9p21 region.

Level of interest: An article of importance in its field

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