Reviewer’s report

Title: Six sequence variants on chromosome 9p21.3 are associated with a positive family history of myocardial infarction: a multicenter registry

Version: 4 Date: 17 November 2010

Reviewer: Jeffery Anderson

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The present MS genotypes 6 SNPs at the 9p21.3 locus previously shown to be associated with coronary heart disease risk in a cohort of 1065 male ACS patients. Comparison is made with a historical (published) set of controls. The prevalence of all SNPs was increased in MI patients. A stronger association trend was observed in those with a family history of MI, which is highlighted in the title and discussion/conclusion. However, the confidence intervals overlap in each case (Figure 1) and no formal statistical test of a significant difference/heterogeneity is shown. Of course, the association of the SNPs with MI otherwise already is well known, and this represents yet another replication.

Other comments:
1) Throughout the MS, an association of 9p21.3 with "MI" is stressed. Yet, technically, numerous reports actually have shown that the association is with initiation/development of coronary atherosclerosis but not directly with the precipitation of MI (e.g., JACC 2010; 56:479,487). Some recognition of this should be made.

2) The 6 SNPs are in strong linkage disequilibrium. It seems more appropriate to consider them together as constituting a set of haplotypes and assess the haplotype association with premature CHD and also with the question of family history.

3) Multiple other studies have looked at the impact of 9p21 on the contribution of family history to CHD risk prediction, and most have actually found FH not to be significantly attenuated by 9p21. Hence, the discussion should thoroughly review the other literature on 9p21 and see in them to what extent FH indeed is explained by 9p21.

4) It would be of interest to assess the impact does 9p21 have on prognosis of MI would be of interest. Do you have follow-up data to see if those who are 9p21 positive have increased, neutral, or (based on recent reports) slightly lower incident rates of subsequent death/MI?

5) The proportion of STEMI to NSTEMI cases seems high (3:1) compared with the natural distribution of ACS-presenting patients (i.e., 1:3). What is the explanation for this? What might be the impact of this biased distribution of ACS cases?

6) The absence of a validation cohort is problematic. This limitation should be stressed, as is the absence of a parallel control group in the same population.
Level of interest: An article of limited interest

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'