Reviewer's report

Title: MAOA Promoter Methylation and Susceptibility to Carotid Atherosclerosis: Role of Familial Factors in a Monozygotic Twin Sample

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Reviewer: qing song

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Overall comments:
This is an interesting study that evaluates the methylation of the MAO-A gene in relation to carotid intima media thickness (IMT), taken as an early measure of atherosclerosis. The study is based on 84 monozygotic male-male twin pairs, thus ensuring that the association between methylation and IMT is independent of genetic influences. The use of a monozygotic co-twin control design for epigenetic analysis is superb. The statistical analyses by first treating twins as correlated individuals (GEE analysis), then as two members within a pair (matched pair analysis) provide a useful model to elucidate the potential impact of familial factors (both genetic and non-genetic) on complex traits. The authors show that, when twins were analyzed as individuals, increased methylation level was associated with decreased IMT, but this association substantially reduced in the matched pair analyses, indicating that the observed association was largely confounded by genetic and/or environmental factors shared by the twins. Findings from this study provide guidance on the study design and interpretation of future epigenetic research for complex disorders.

General points:
DNA methylation influence disease process through changing gene expression. Are fresh blood samples available to examine how MAO expression or lack of thereof in blood leukocytes is relevant to IMT?

Minor comments:
1. Pyrosequencing has relevant plate effect. How did the authors control for it? Were the twin pairs analyzed on the same plate?
2. Are differential blood counts available in the study? If so, is % leukocytes, monocytes, neutrophils, basophils, or eosinophils associated with DNA methylation?
3. Table 1. “L density lipoprotein cholesterol” should be “Low density lipoprotein cholesterol”.

Level of interest: An article of outstanding merit and interest 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