Reviewer's report

Title: Microsomal triglyceride transfer protein -164 T>C gene polymorphism and risk of cardiovascular disease: results from the EPIC-Potsdam case-cohort study.

Version: 1 Date: 28 November 2012

Reviewer: Catherine Phillips

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di Giuseppe et al., investigated whether the -164T>C polymorphism in MTTP alters the risk of CVD, depending on the cholesterol levels, in a case-cohort study. While this SNP was not associated with CVD risk, they report interaction between genotype and cholesterol whereby increased CVD risk was observed among individuals with low cholesterol levels, which seemed to be abolished among risk allele carriers with high cholesterol levels. An independent cohort was used to verify findings in the original cohort. Despite OR in the same direction, no significant associations were replicated in the independent cohort, probably due to limited number of CVD cases. The methods are appropriate, data is sound and study limitations have been adequately described.

Minor Essential Revisions

Before the “statistical analysis” section there is a sentence “(I wrote to Susanne Moebus, and I’m waiting for a reply), which should be removed.

Genetic analyses – please clarify whether this was the only SNP determined or whether additional genotyping was performed. Please correct spelling of Qiagen and provide genotyping platforms used in replication cohort (4 platforms are mentioned), also please provide genotyping metrics for the replication cohort (call rate, accuracy etc). Although the 2 SNPs which have been examined are in LD, why was the same SNP not determined in the discovery and validation cohorts?

Given the relationship between MTTP and triglycerides, was their interaction with respect to CVD analysed? Similarly given the link between MTTP and SREBP, and the relationship between SREBP and HDL and LDL cholesterol, it would be worthwhile to examine HDL and LDL modulation of genetic risk to ascertain which particular cholesterol component is driving the observations?

Results page 9, sentence “According to genotype no significant differences in common prevalent diseases and socio-demographic characteristics were observed in subjects with or without CVD (Table 1).” Would read better replacing “common prevalent diseases” with central obesity, obesity and hypertension.

Table 1 - Please clarify abdominal obesity in Table 1 – what criteria and cut-offs were used?

Also no methods for LDL or TG are provided in the methods section, please include.
Although already referenced the discussion in relation to MTP SNPs and circulating lipids would benefit from inclusion of the findings from Phillips et al., (ref 12). While this was a small study there is detailed fasting and postprandial lipoprotein composition data for high CVD risk subjects (T2DM) according to -493 G/T.

Genotype frequencies were not different between CVD and CVD free subjects. This finding should be included in the abstract. Following on from this the conclusions in the abstract and discussion that “the -164T>C polymorphism might have implications for the development of cardiovascular disease” need to be amended, as there is no genetic association but rather an interaction between genotype and total cholesterol levels which predisposes risk allele carriers with low cholesterol levels to increased CVD risk, which seems to be abolished among risk allele carriers with high cholesterol levels.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

No competing interests to declare.