Reviewer's report

Title: First results of the PROSPER/PHASE study, a testing frame for pharmacogenetics of statins in the elderly

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Reviewer: Fotios Drenos

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First results of the PROSPER/PHASE study, a testing frame for pharmacogenetics of statins in the elderly.

Trompet and colleagues present a genome wide association study for calculated LDL in 5,244 subjects from the PROspective Study of Pravastatin in the Elderly at risk for vascular disease. The authors report 42 SNPs in 5 genomic loci as reaching their GWAS significance threshold of 5e-08. All identified loci were previously reported. The authors claim that based on their results, the PROSPER/PHASE study can be a good quality testing frame to study pharmacogenetics in the elderly.

Major comments

• Methods, LDL cholesterol section: As I understand, LDL is the average of two measurements before and after placebo, thus there were no subjects receiving statins treatment at this stage. Can the authors confirm that this is the case and include this in the relevant section clearly?

• Methods, Statistical analysis section: How is the within-study population structure adjustment done? Have the authors used a principal component analysis method, Eigenstrat or something similar?

• Methods, Replication section: Since none of the loci are novel is the replication relevant? Is not the previously reported signals adequate replication? Were the subjects used for replication receiving statins treatment?

• Results: Given the multicentre study used here I believe that a QQ plot and an estimation of the genomic control are essential.

• Discussion: Can the non replication of the LDLR locus be attributed to gene*statins interaction in the replication studies?

• In the conclusion section of the abstract the “Hereby...in the elderly” statement should be changed. The results presented do not really provide proof for the suitability of the study in future pharmacogenetics studies in the elderly. In the current study, the entire cohort was used and showed good statistical power. Suitability for future studies, potentially using other adjustments or splitting of the data is difficult to verify based on the current study.

Overall comments: This is a well conducted study and the methods used are all well established. The main novelty here is the use of an elderly population, which
until now have been under-represented in this kind of studies, and the authors should be commended for this study. Due to this unique feature, replication of results in a comparable population is difficult. In the present study the two replication cohorts used were much younger making the replication of any potential age specific signals difficult which I think is a missed opportunity here.

**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