Reviewer's report

Title: ANGPTL4 variants E40K and T266M are associated with lower fasting triglyceride levels in Non-Hispanic White Americans from the Look AHEAD Clinical Trial

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Reviewer: Yvonne Böttcher

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ANGPTL4 variants E40K and T266M are associated with lower fasting triglyceride levels in Non-Hispanic White Americans from the Look AHEAD Clinical Trial

The presented article by Melissa C Smart-Halajko describes effects of two ANGPTL4 non-synonymous variants E40K and T266M on triglyceride levels. The authors used for their investigations the Look AHEAD population and included in their study 2708 type 2 diabetes individuals.

Major Compulsory Revisions:

The working hypothesis by the authors is not well designed. Since the authors aim to identify possible association of the ANGPTL4 variants with triglyceride levels (continuous trait), which has been already shown by others in 30,000 non-diabetic individuals, it is not entirely clear why the authors try to correlate in subjects with T2D and what the scientific benefit will be.

Abstract:
- There is no clear objective presented. Please clarify this.
- Please present triglyceride levels as mean ± S.D.
- “We have demonstrated a significant association of the functionally compromised ANGPTL4 E40K variant with lower triglyceride levels.” (in what population??? T2D or non-diabetic subjects) Please clarify.
- “In addition, our findings suggest that in type 2 diabetes, T266M may contribute to effects on triglyceride levels demonstrating the role of Angptl4 as a regulator of triglycerides levels in T2D.” (since this is a conclusion please describe how exactly T266M contributes)

Introduction, last paragraph:
- Please clarify/justify your working hypothesis why the association of the ANGPTL4 variants with lower triglycerides should be assessed in type 2 diabetic individuals.

Materials and Methods:
-Please clarify why the presented numbers of genotyped individuals are different from those presented in the Abstract (2601 vs 2708 individuals).

-Please be more precise with presentation of the variants and use only E40K and T266M. It is not necessary to mention rs numbers (only once).

- Please describe the ethnic sub cohorts your are analysing.

Statistical methods:
-Please add power calculation.

-did the authors stratified analysis for subjects with and without lipid lowering medication?

Results:
-The two variants are not in high LD. The authors explain this, which is correct in the beginning of the first paragraph of the results.

- Then this paragraph does not make sense: “Because of the strong LD between the two cSNPs, we examined whether the association of T266M with triglyceride levels merely reflected the presence of E40K. When the K40 carriers were excluded, the association of T266M with triglycerides remained significant in multivariate linear regression using a general additive model of inheritance, with M266 homozygotes having 22.6 mg/dl lower triglycerides compared to TT individuals (p=0.002).” Please clarify this.

-Table 2: The table present genotype frequencies, not allele frequencies. It is not clear to the reviewer how a minor allele frequency (MAF) can have a 95% CI. Please correct this. Please show an additive model for both variants. This has been mixed in Table 2 (dominant mode for E40K, because of small groups I guess; additive mode for T266M). The authors can present a p-value for the dominant model for E40K and explain this.

-There is a second table 2. Please correct this.

-Table 3: Again, no genetic model is mentioned. Please show also the additive mode.

-There is a second Table 3, please change that.

-Figure 1: What about the genotype EK/TT? Please add these data as well.

Discussion:
-Please re-write the discussion chapter according to the reviewer’s comments (above).

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests