Author’s response to reviews

Title: A null mutation in ANGPTL8 does not associate with either plasma glucose or type 2 diabetes in humans

Authors:

Katharine Clapham (katierose.clapham@gmail.com)
Audrey Chu (AYCHU@PARTNERS.ORG)
Jennifer Wessel (wesselj@iu.edu)
Pradeep Natarajan (PNATARAJAN@mgh.harvard.edu)
Jason Flannick (flannick@broadinstitute.org)
Manuel Rivas (rivas@broadinstitute.org)
Samantha Sartori (samantha.sartori@mountsinai.org)
Roxana Mehran (Roxana.Mehran@mountsinai.org)
Usman Baber (Usman.Baber@mountsinai.org)
Valentin Fuster (valentin.fuster@mountsinai.org)
Robert Scott (Robert.Scott@mrc-epid.cam.ac.uk)
Daniel Rader (rader@mail.med.upenn.edu)
Michael Boehnke (boehnke@umich.edu)
Mark McCarthy (mark.mccarthy@drl.ox.ac.uk)
David Altshuler (altshul@broadinstitute.org)
Sekar Kathiresan (sekar@broadinstitute.org)
Gina Peloso (gpeloso@bu.edu)

Version: 1 Date: 16 Dec 2015
Author’s response to reviews:

Reviewer #1:

This is an interesting study.

Author Reply: Thank you for taking the time to review our manuscript and the positive comment.

Discretionary change:

The Discussion is rather too brief. A more detailed interpretation of findings (e.g. with potential implications for alternative pathophysiologic mechanisms) would be appropriate.

Author Reply: We have added the following text to the Discussion

“While our results do not support the role of ANGPTL8 inhibitors for treatment of type 2 diabetes, there remains evidence that ANGPTL8 inhibition remains a viable anti-triglyceride target [2, 15]. The human genetic analysis presented here provides evidence that an ANGPTL8 inhibitor aimed at lowering plasma triglyceride levels will not have a major effect on glucose tolerance in humans.”

Reviewer #2:

It is a carefully designed and a well written paper.

Although the numbers are big enough for the estimation of the impact of ANGPTL8 p.Q121X on fasting glucose levels, it is difficult to draw any definite conclusions on phenotyping of type 2 diabetes due to the mentioned limitations. Still the results are valuable basis to expand on further research in the future.

Author Reply: Thank you for taking the time to review our manuscript and the positive comment.
Editor comments:

1. Please describe in some more detail the purpose of the study. How was your hypothesis generated? What was the power of your previous report [6] to detect an association between ANGPTL8 p.Q121X and fasting glucose?

Author Reply: Initial experiments performed in mice suggested a role for ANGPTL8 in glucose homeostasis. This lead us to wonder whether ANGPTL8 affected glucose homeostasis in humans. We have modified the Introduction as follows: “allows us to test the hypothesis that carrying ANGPTL8 p.Q121X also perturbs glucose homeostasis in humans.”

The power to detect an association between ANGPTL8 p.Q121X and fasting glucose in the previous report has been added to the Discussion.

“These results are consistent with findings from a preliminary analysis of individuals carrying ANGPTL8 p.Q121X with fasting glucose in Peloso, et al [6], in which no significant association between ANGPTL8 p.Q121X and fasting glucose levels was identified in <15,000 individuals, which only had 45% power to detect a 0.23 mmol/L (1/2-standard deviation; 4.2 mg/dL) effect of p.Q121X on fasting glucose at an alpha level of 0.05. However, the larger sample size utilized in our study allowed for 98% power and a better estimation of the impact of ANGPTL8 p.Q121X on fasting glucose levels.”

2. Was the association between ANGPTL8 p.Q121X and TG/HDL-C replicated in this study population?

Author Reply: We were able to confirm the association between ANGPTL8 p.Q121X and both HDL-C and TG within a subset of individuals with lipid phenotypes readily available. These results do not provide independent evidence of the association between p.Q121X and HDL-C or TG as a proportion of these subjects were included in the AJHG 2014 report.
HDL: n=58,285, beta=0.46, se=0.09, p-val=4.2x10^{-07}

TG: n=51,759, beta=-0.30, se=0.10, p-val=0.002

3. How was T2 diabetes diagnosed in the three cohorts?

Author Reply: We have added the following text to the manuscript to clarify the definition of type 2 diabetes in each of the contributing studies. Two of the contributing studies are large consortiums with multiple definitions of type 2 diabetes and therefore have referenced appropriate papers with phenotype definitions available.

“In the BioImage Study, type 2 diabetes was defined as individuals taking a medication for diabetes, having a fasting glucose > 126 mg/dl or having been told that he/she had diabetes. Type 2 diabetes was defined in the CHARGE Consortium Diabetes Working Group according to Wessel et al[14], and in the T2D-GENES Consortium according to Voight et al [15].”

4. Was there an association between ANGPTL8 p.Q121X and FG in T2D patients and controls separately?

Author Reply: Since treatment of T2D can confound glucose and insulin measurements we only analyzed controls for the association of FG and insulin. The methods state: “Individuals with a diagnosis of diabetes were excluded from the fasting glucose and insulin analyses to avoid the variable effects of diabetes medications on the quantitative traits.”