Reviewer's report

Title: The minor C-allele of rs2014355 in ACADS is associated with reduced insulin release after an oral glucose load

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Reviewer: Muhammad A Abdul-Ghani

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In this manuscript, Hornbak et. al examine the hypothesis that single nucleotide polymorphism (SNPs) at two genes encoding short (rs 2014355 at ACADS) and medium chain acylcoenzyme A dehydrogenase (rs 11161510 at ACADM) are associated with impaired beta cell function. The authors genotype subjects from cohorts whom they had available measures of insulin secretion and insulin sensitivity. The authors compare insulin secretion and insulin resistance measure among the three genotypes for each SNP. Their main finding is that subjects with homozygous for the minor allele (cc) at rs 2014355 have impaired insulin secretion compared to the other two genotypes.

This study has two major limitations: (1) the methods utilized to quantitate insulin secretion and insulin sensitivity, and (ii) the interpretation of the results. Neither beta cell function nor insulin sensitivity are directly measured with clamp study even at a subgroup of the subjects. Instead, the assessment is made indirectly with surrogate measures derived from plasma glucose and insulin concentrations during the OGTT. The authors primarily rely on indices that were validated against the IVGTT and do not utilize indices that were validated against the gold standard techniques, like the matsuda and stumvoll indices for insulin sensitivity. Further, the authors miscalculate the insulinogenic index. They divide the increment in plasma insulin concentration during the first 30 minutes of the OGTT by plasma glucose concentration at 30 minutes instead of the increment in plasma glucose concentration during the first 30 minutes (page 7, first paragraph). In addition, the authors have the information about insulin secretion during the entire OGTT 0-120 minutes, #I/#G0-120, but they chose not to present it.

Lastly, and most importantly, the authors misinterpret their data. The beta cell responds to an increment in glucose by an increment in insulin, and this beta cell response should be related to the prevailing level of insulin resistance, because the magnitude of beta cell response to glucose stimulus is larger in insulin resistant individuals compared to insulin sensitive subjects. Thus, to compare beta cell function amongst two groups of individuals, the disposition index should be used, not the absolute plasma insulin concentration nor an index of insulin secretion. Insulin sensitivity indices (HOMA-IR, and BIGTT-Si) indicate (Table 1) that subjects with CC genotype tend to be more insulin sensitive compared to other genotypes. The authors ignore this finding, perhaps because it did not reach statistical significance. But it is important for the interpretation of insulin secretion indices. Because subjects with the CC genotype tend to be
more insulin sensitive, one would anticipate that they have smaller insulin secretion indices, and if one calculates the disposition index for each genotype (BIGTT-si X BIGTT-AIR, or insulinogenic index ÷ HOMA-IR) it is likely that it will be similar among the three genotypes. Thus, the smaller insulin secretion indices in CC subjects, that the authors interpretate as impaired beta cell function, is actually an adaptive response to the improved insulin sensitivity in this group.

**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:**

'I declare that I have no competing interests'