Reviewer's report

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

Version: 1 Date: 25 July 2010

Reviewer: Anna Jonsson

Reviewer's report:

The authors have investigated whether two variants, suggested to impair fatty acid #-oxidation in a recent genome wide association study using metabolite concentrations as proxies for enzymatic activity, associates with altered insulin release following an oral glucose load or with type 2 diabetes. They have been using a population-based cohort of 6,162 middle-aged individuals with available data from an oral glucose tolerance test (OGTT) as well as a case-control cohort including a total of 10,196 individuals. They report that one of the tested variants associate with reduced glucose-stimulated insulin release during an OGTT and suggest that this may in part be mediated through an impaired #-oxidation of fatty acids, while the other tested variant showed no association to reduced insulin secretion or to type 2 diabetes. The manuscript is well written, the study is well powered and the conclusions are sane in relation to results.

Major Compulsory Revisions

No major compulsory revisions needed.

Minor Essential Revisions

In the aim you state that you will investigate indices of insulin release in relation to genotype in 6,162 individuals. According to your table you have analyzed 4,324 and 4,337 glucose-tolerant individuals, respectively, and in Methods, Study population, last paragraph you have stated that the Inter99 cohort has 4,567 glucose-tolerant individuals. You also state that you have a genotyping success rate of >97%, but only 94.7% and 95.0%, respectively, of the glucose-tolerant individuals have been analyzed. Which other phenotypes were you missing from these individuals? It should be stated in the abstract and aim how many of the individuals you have been analyzing for indices of insulin release in relation to genotype, tentatively: Abstract, Methods, first sentence: “[...] and investigated for associations with serum insulin levels following an oral glucose tolerance test (OGTT) in a population-based sample of 4,567 glucose-tolerant, middle-aged individuals”. And: Background, last paragraph (aim): “The aim of the present study was to investigate rs2014355 of ACADS and rs11161510 of ACADM in relation to indices of insulin release in a large population-based study of glucose-tolerant, middle-aged individuals (n=4,567) [...].

As above, the number of investigated individuals for type 2 diabetes association is not consistent between text and tables. According to the text you have
analyzed 10,196 individuals for association between the genotypes and type 2 diabetes, but according to the tables the numbers are 8,313 and 8,344, respectively, which translates into 81.5% and 81.8%, respectively. This is not consistent with a genotyping success rate of >97%. Update the number of individuals with available phenotypes needed for each study, so that it is consistent with the tables.

Discretionary Revisions

Why was not study group 3 included in the analysis of indices of insulin release in relation to genotype, since these individuals also underwent an OGTT. Is this because of missing phenotypes such as insulin measurements?

I would suggest to combine the four tables into one for easier overview, and also to make a figure describing the results for rs2014355, that is, a figure over glucose and insulin measurements per genotype during the OGTT.

Minor issues not for publication

Methods, Biochemical and anthropometric measures, first sentence: Misplaced parentheses: “Height (without shoes) and weight were measured in light indoor clothing, and BMI was calculated as weight (kg/height2 (m2))”. Change to: “[…] and BMI was calculated as weight (kg) / height2 (m2)”.

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

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