Reviewer's report

Title: A polymorphism in the INSIG2 gene is not associated with obesity in a sample of 24,722 individuals from four cohorts

Version: 1 Date: 6 January 2009

Reviewer: Camilla Andreasen

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Comments to the author:
The present study uses four different study populations to access the effect of rs7566605 near INSIG2 on anthropometric measures of obesity. No association is observed with BMI, neither as a dichotomous nor as a quantitative trait, body weight, waist circumference, and waist-to-hip-ratio.

Major revision:

Introduction:
The focus of the introduction needs a change;
The study groups for the present study should not be described in the introduction (page 5 line 14 to page 6 line 5) – it is done in the methods section.
The very detailed description of INSIG2 function (page 6 line 13 to page 7 line 6) is redundant. When the aim of the study is to perform association studies, it would be of much more interesting to describe which association studies have been made on this genetic variant previously. All abbreviations made in the introduction are only used one time and therefore unnecessary.

Methods:
A table summarising all the information given for the four study groups would be preferable.
How is race determined? – selfreported? This should be clearly stated.

Statistical analysis
Sibship = pair of siblings?
Which statistical methods are used when analysing the GENOA study? How is it taken into consideration that siblings, which share much genetics, are analysed
Please state what adjustments that is inferred in the analyses of anthropometric measures – it is perfunctory just to give a reference (24).
Why is the homogeneity between studies analysed – is the combined study material studied at all?
Please perform power analyses – what effect sizes is expected to, are there sufficient statistical power to detect this when the study sample is divided into smaller subsamples?
Consider making meta-analyses between same ethnicities from different study groups if homogeneity allows this – this will increase statistical power.

Results:
Why is only baseline data analysed, it is not exploited at all that you have longitudinal study groups.
Only BMI, weight, waist and waist-to-hip is analysed, are there other phenotypes like total cholesterol, LDL-cholesterol and HDL-cholesterol. Are the endpoint of the different study groups analysed?

Discussion:
Do not start you discussion with a summary of the literature, state your own results an put them into greater context of results in the literature.
How is your racial results compared to previous studies – discuss you references 2,25-27 + 28-36 in more depth than just one line. In page 13 line 2-11 you mention a study of fatty acids, triglyceride and cholesterol but you cannot put you own results into a greater context, why not discuss previous studies on obesity measures instead.

Conclusion:
Skip the summary and state you conclusion.

Tables:
The OR in table 2 does it not refer to the risk of being obese – which is analysed in table 1

Minor revision:
A “6” is missing every time the rs-number is used in the abstract.
It is implicit an rs-number is a genetic variant, so the term rs7566606 SNP is wrong to use, the same for INSIG2 gene – ii is implicit when it is with capital letters and italic that it is a gene.
Spaces are missing in several places.
Use more commas, the text is difficult to read.

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.