Reviewer's report

Title: 'Fat mass and obesity associated' gene (FTO): no significant association of variant rs9939609 with weight loss in a lifestyle intervention and lipid metabolism markers in German obese children and adolescents

Version: 1 Date: 4 April 2008

Reviewer: Hakon Hakonarson

Reviewer's report:

Dr. Muller and colleagues show that the SNP variant, rs9939609, previously shown to be associated with obesity is not associated with weight loss in a standardized lifestyle intervention program. They also tested for association of rs9939609 alleles with fasting blood parameters indicative of glucose and lipid metabolism using a case-control design and did not detect association to those parameters. The investigators conclude that they have confirmed that the A-allele of the SNP, rs9939609, is a risk factor for early onset obesity whereas its impact on weight loss or on serum levels of glucose, triglycerides and cholesterol could not be detected in their study cohort. While the research question being pursued by the investigators is an important one, there are several problems with this study that have to be addressed.

Major critique:

1. Is this the same study cohort that the investigators recently reported association on in PLoS One – (at least 85 of them that had their ARMS-PCR genotypes confirmed through GWA appear to be); If this is the case this is not an independent replication of association of this FTO SNP with obesity and should be references/clarified as such,

2. The control group examined is small (n=178) so the study in underpowered to conclude on lack of an association; the authors provide power calculations for multiplicative genotype relative risk model (and regression based analysis) which may not be correct model. The OR for association with obesity is 1.24 suggesting the effects they are looking for in relation with the other traits are unlikely to be higher.

3. The author’s state that the degree of overweight was quantified with Cole’s least mean square method, which normalized the BMI skewed distribution in childhood and expressed BMI as a standard deviation score (BMI-SDS). The authors should clarify how this method compares with the perhaps better standardized definition of a z-score by the Center for Disease control (CDC) http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm

4. Are all the study subjects Caucasians? It may be relevant to refer to the recent pediatric study reported on the association of a common tagging SNP in both Caucasians and African-Americans (Grant et al. PLoS ONE, 2008)
Minor critique:

1. The controls used include lean adults mean age 24 years compared to mean age of 10 years for the cases – where they adults overweight as children?

- Accept after discretionary revisions (which the authors can choose to ignore)

Level of interest: Modest

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- An article of importance in its field

Quality of written English: Good

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- Acceptable

Statistical review

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- Yes, and I have assessed the statistics in my report.

Declaration of competing interests: NONE

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