Reviewer’s report

Title: The MAP2K5-linked SNP rs2241423 is associated with BMI and obesity in two cohorts of Swedish and Greek children

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Reviewer: KONSTANTINOS ROUSKAS

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Title of the manuscript: The MAP2K5-linked SNP rs2241423 is associated with BMI and obesity in two cohorts of Swedish and Greek children.

Authors: Mathias Rask-Andersen
Josefin A. Jacobsson
George Moschonis
Anna E. Ek
George P. Chrousos
Claude Marcus
Yannis Manios
Robert Fredriksson
Helgi B. Schiöth

Date: 04/04/2012

Reviewer: Dr Rouskas Konstantinos

In this article, Rask-Andersen et al attempted to examine genetic variation in gene MAP2K5, involved in growth factor stimulated cell proliferation and muscle cell differentiation, with childhood obesity and BMI in two independent cohorts. Their principal results are a nominal association of the minor allele of the polymorphism rs2241423 with protection against obesity in a case-control study and with lower BMI in a population-based cohort. However, I would like to make the following comments:

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. In the present study, authors attempted to analyze only one locus of the 32 associated with obesity in study of Speliotes et al Nat Genet 2010. Why authors analyzed only one SNP of GIANT consortium and not all the 32 SNPs? According to which criteria and why they selected to study MAP2K5 gene among the 32 obesity-susceptibility loci?
2. Authors do not comment limitations of the study. Did they apply multiple testing such as a Bonferroni correction, for Swedish cohort? Authors should test power calculation of SNP by softwares (QUANTO etc).

3. Authors provided genotype call rates and HWE p-values for both cohorts. Were HWE-testing and genotyping call rate the only criteria used for validating the genotype data?

4. Authors found that rs2241423 is associated with lower risk of obesity in Swedish cohort. Did authors search for association to risk of being obese in the Greek children by dividing them in subgroups (Table 1)?

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Title page: incomplete affiliation no.3. Also, there are no e-mail addresses for all authors.

2. Abstract page: it has no structured format as requested (Background, Methods, Results & Conclusions).
   a. Authors should state that minor allele associated with protection against obesity and lower BMI is allele A.
   b. Authors should include statistics and genotyping methods in brief.
   c. Prefer rs2241423 instead of Rs2241423 inside the text.
   d. Add Ors or b-coefficient and 95%CIs for p-values of association.
   e. Authors must state the number of Swedish controls (n=519) used for comparison with obese Swedish children (n=474)

3. There are no keywords after abstract.

4. Introduction:
   a. Add abbreviation for ERK5 (Extracellular-signal-Regulated Kinase 5) and CNS (Central Nervous System)

5. Methods and Materials:
   a. While in Introduction section authors say that genotyping in Swedish cohort was performed in 476 obese children and 521 controls, in this section they refer to 474 obese and 519 controls. Which number is the correct? Please be more precise.
   b. Abbreviation for BMISDS (standard deviation score).
   c. Add a sentence for written informed consent of Swedish participants.

6. In Results section, 1st paragraph, p-value and 95%CI differ from those in Table 2. Please correct.

7. Titles of Tables must be above the Table and legends can then follow.

8. Table 1. P-values should be included for comparisons among groups.

9. Table 3. List HWE and MAF in the same order as in Table 2.
10. No competing interests and author’s contributions are shown.
11. Change all references according to Journal’s reference style (see instructions for authors)

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. As the authors say, the minor allele of rs2241423 was associated with a protection against obesity in Swedish cohort. Was that result observed under additive model? As in GWAs study of Speliotes et al Nat Genet 2010 evidence of non-additive (dominant or recessive) effects and heterogeneity by gender were examined, did the authors make similar tests?
2. Were related subjects excluded from the study? Please add a sentence or a word in exclusion criteria.

Minor issues not for publication

1. In paragraph ‘Greek child cohort – The ‘Healthy Growth Study’”, there is a mistake in the sentence: Waist and hip circumference….0.1cm….at a standing position.
2. In paragraph ‘Genotyping and linkage disequilibrium analysis’ write Hardy instead of hardy.
3. In Results section, use 95%CI instead of CI95%.

Competing interests: I declare that I have no competing interests.

**Level of interest:** An article of importance in its field

**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.