Reviewer's report

**Title:** Failure to replicate an association between common variation in the growth hormone-chorionic somatomammotropin hormone gene cluster and adult fasting insulin in a UK Caucasian population

**Version:** 1  **Date:** 3 August 2006

**Reviewer number:** 1

**Reviewer's report:**

**General**
The authors have attempted to replicate the recently described association between the CSH1. genetic minisatellite in the growth hormone chorionic somatomammotropin hormone gene cluster and adult fasting insulin in a UK Caucasian population. There is wide allelic variation at this locus, and the authors have based their analyses on the same allelic classification used in the original study by Day et al. which reported significant associations with reduced weight at 1y and higher fasting insulin levels in adult Caucasian males.

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

1. The failure to replicate genetic associations is a major current issue and have lead to calls for increased sample size and power not only for the original study, but also the replication studies. While the current study is clearly larger than that of Day et al., it is still relatively small. What are the 95% confidence limits for weight at 1 by genotype, in boys and girls? These are mentioned in the discussion but not shown. Girls with TT appear to have a 500-600 g reduction in weight at 1 consistent with the original study.

2. For purposes of replication it is important to use the same definition of the affected phenotype as the original study. The original study showed several significant associations, suggesting a likely role of the variant on Hyperinsulinaemia-related metabolic syndrome traits: including blood pressure, triglycerides and stimulated insulin and glucose levels. The current study should make clear that they can only test one aspect of this trait, i.e. fasting insulin.

3. The difference in age between the populations (59 to 72 years in Day et al. vs. 27 to 36 in the current study) is an obvious source of heterogeneity as age has a marked effect on these metabolic outcomes. This should be highlighted in the abstract and conclusions.

4. A further association in the original study was with shorter adult height. What was the association in the current study?

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

5. Results: para 3 should clarify that these results are not actually shown.

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**Discretionary Revisions (which the author can choose to ignore)**

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**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.