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:** 8 September 2006

**Reviewer number:** 2

**Reviewer's report:**

General

Firstly, I don't mind my identity (Ian Day) being revealed to the authors. Secondly, I apologise to the authors for the long delay but I have been incapacitated by simultaneity of a house and imminent institutional move, the aftermath of having my car written off by a reckless driver (while I was in it), and a trojan that did del *.doc on my computer while I was off networked virus protection.

To my knowledge, mine is the only group to have characterised and investigated the MVR which we designated CSH1.01, in large scale association studies. The labour undertaken by the present group deserves to be published in its own right, it would not have been a trivial study in the way that a single SNP study can be.

My main points are that the insulin aspect of the study is NOT a replication, as the title would suggest, 30 year olds and 65 year olds are quite different and age dependence/divergence of genotypes is well recognised and traits of metabolic syndrome certainly increase very markedly with age. In single gene disorders, there are numerous examples, and even in insulin resistance this is well recognised (see for example PARL(PSARL). I propose that the title be modified to 'a study of..' rather than its present incorrectly assertive form. A clearer recognition of this point in the discussion with appropriate references should also be made.

Technically, the study of early life weight is not a negative result but an uninformative result through insufficient statistical power and one could then argue destined for a JURB instead of JNRB [where U=uninformative]. The authors do acknowledge this and I do acknowledge that there would have been sufficient power to detect a somewhat larger effect. It would be harsh though to enforce this! On the other hand, there are differences in males which in a larger study could be around 2% magnitude, albeit the opposite way from our original study. In fact (unpublished) we have studied this marker in another study, and a tag for it in a third, and in every study have seen significant differences for boys (but not girls), but not in the same direction. Since the cohorts are from different locations and eras, genotypes of this genomic region may interact with early weight and other traits in a complex fashion and we are currently engaged in a larger scale study. I think the authors should add a couple of lines of discussion about the point that although not reaching any significance, the mean values for each genotype are not equal and furthermore there is a steady trend of values across male T/D1 groups.

-----------------------------------------------------------------------------

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

-----------------------------------------------------------------------------

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

See above

-----------------------------------------------------------------------------

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

**What next?:** Accept after minor essential revisions

**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.