Reviewer’s report

Title: Association between a rare SNP in the second intron of human Agouti related protein gene and increased BMI

Version: 2 Date: 9 December 2008

Reviewer: Yvon Chagnon

Reviewer’s report:

Compulsory Revisions.
Three SNPs have been detected in this sample, and the authors choose to study the less variable of them for which no variant homozygote was observed. Why they did not analyzed also one of the two other SNP that are in complete linkage disequilibrium with each other?

It would be important to analyze SNPs that have been reported previously to be associated with body composition such as Ala67Thr. Did the authors detect this relatively frequent variant in their sample of 95 patients?

In the Abstract, what is the meaning of “carriers of the rs11575892”? All subjects carried this SNP. Also, the authors could not conclude that they reported for the first time an association of AGRP with BMI, two previous reports made it earlier, Argyropoulos (2002) with late-onset obesity, and Marks (2004) with different body composition phenotypes.

In Methods, it makes no sense to use an ANOVA knowing the importance on BMI of covariate effects such as age and gender.

In Results page 9, stating “…carriers of rs11575892 T allele…” is not appropriate since no TT homozygotes were detected and the effect of this genotype on BMI at this stage is purely speculative, as the statement made in Page 10 (“…homozygous individuals who may have pronounced effect…”). In fact, no effect or even a lower BMI could be eventually observed in TT homozygotes. It would be more indicated to use “…rs11575892 CT heterozygotes…” for example.

In Page 10, splicing could also be positive in contrast to “…truncated or defective AGRP…”, by producing an AGRP isoform with a greater orexigenic effect, for example.

In Page 11, the authors need to sequence more then one KB of the promoter to conclude that no variant could be found there. Usually, five kb are sequenced.

Minor Essential Revisions
In the Abstract, please clarify what are the “other” non-genetic factors.
In Page 10, what the authors mean by “controlled environmental factors”? Did
they mean stratification for age, sex and other factors?

In the Conclusion, the authors speculate on the usefulness of their results as a new diagnostic marker. What are the specificity and the sensitivity of their marker to detect a higher BMI? It is probably very low since the MAF of this SNP and it is doubtful that it can be use as diagnostic.

Discretionary Revisions

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declare that I have no competing interests'