Reviewer's report

Title: A comprehensive investigation of variants in genes encoding adiponectin (ADIPOQ) and its receptors (ADIPOR1/R2), and their association with serum adiponectin, type 2 diabetes, insulin resistance and the metabolic syndrome.

Version: 1 Date: 16 November 2012

Reviewer: Damien Croteau-Chonka

Reviewer's report:

The authors have performed a tag SNP-based association analysis of three adiponectin-related genes (ADIPOQ, ADIPOR1, and ADIPOR2) with total adiponectin level and risk of type 2 diabetes and metabolic syndrome in three European-Australian populations. They find that associated common variants in ADIPOQ explain a modest proportion of variation in adiponectin level consistent with other studies, but do not find evidence of association of these SNPs with metabolic phenotypes.

- Major Compulsory Revisions

(1) Figure 1 is missing from the submission.

(2) In the eighth paragraph of the discussion, the authors make a claim about "insufficient power" to detect associations with T2D. Formal power calculations for detecting adiponectin and T2D/MetS associations and for the study's replication capability should be included in the results section.

(3) The results of the haplotype analyses need more context in the discussion. How much more collectively informative are these results than merely the single-SNP associations alone, say in terms of percent phenotypic variation explained? How might the findings motivate further genetic or molecular characterizations of the ADIPOQ locus?

(4) Much of the fourth paragraph of the discussion reads as results text and so should be moved to the last section of the results about in silico analyses, which itself should have more detail. In place of this discussion text, the authors might talk about how the specific transcription factors that bind sites overlapping the associated SNPs are related to adiponectin biology.

- Minor Essential Revisions

(1) In the first sentence of the conclusions, the indefinite article is missing before "well phenotyped general population".

(2) Under the "Selection and genotyping of tSNPs" section in the results, it is not specified how the tag SNP selection was actually performed. Was it done manually or using Haploview?
(3) The exact number of control individuals used in the T2D case-control analysis isn't specified. It would be helpful to list in Table 1 the number of non-diabetic subjects for the BHS/CUDAS subjects and list that total in the results section under "Analysis of association between tSNPs and T2D, HOMA-IR and MetS".

(4) In the last paragraph of the results section called "Genotype distribution and linkage disequilibrium", there should either be a comma added between "from each pair" and "i.e." or "i.e." should be replaced with a colon.

(5) In the second paragraph of the discussion, the last two sentences about association results in the additional SNPs tagged don't really belong in the discussion as they aren't mentioned in the results section. The authors also make a point in the results about reporting only the associations of SNPs that were not strongly correlated with each other.

(6) In the second-to-last sentence of the conclusions, the authors state that the "present study shows that circulating adiponectin is affected by gene-environment interactions" when no formal GxE analyses have been performed. This sentence should be re-phrased or dropped.

(7) In the acknowledgements, "principle investigator" should be "principal investigator" and there should be a "the" in "version of manuscript".

- Discretionary Revisions

(1) In the first sentence of the third paragraph of the introduction, points i) and ii) appear redundant. They should be combined and the numbering dropped.

(2) Given the low observed heterogeneity in the meta-analysis results, wouldn't a fixed-effects meta-analysis have had a little more statistical power? Perhaps a sentence stating that association results not shown were consistent using this approach.

(3) In the results, it isn't clear to me whether the three tSNPs showing significant departure from HWE were dropped from later analysis. If so, perhaps it should be explicitly stated in the results.

(4) A citation for Wu et al. (2010) (PMID: 20876611) would be appropriate in the fifth paragraph of the discussion as it is actually the first adiponectin GWAS by a very slim margin to report the CDH13 signal as genome-wide significant (in this case, in an Asian population).

(5) The authors state in the sixth paragraph of the discussion that more complete sequencing of the ADIPOQ region should be performed. A paper by Warren et al. (2012) (PMID: 22403302) describes just such an effort in ~14,000 subjects and would be worth discussing briefly.

**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.

Declaration of competing interests:
I declare that I have no competing interests.