Reviewer's report

Title: Common genetic variants and type 2 diabetes in urban Ghana: a hospital-based case-control study

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Reviewer: Michele Ramsay

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This research describes a case-control study in a rural African population from Ghana, to replicate SNPs that have been associated with type 2 diabetes (T2D) in Europeans. One SNP in each of three genes, TCF7L2, KCNJ11 and PPAR#, and three SNPs for CAPN10, were tested for associations with T2D (675 cases; 377 unaffected controls). In addition, association was investigated among the unaffected controls (n=377) for seven phenotypic traits, including anthropometric measurements, blood pressure, fasting plasma glucose and urinary albumin.

Few studies on complex disease associations have been done in non-admixed African populations. This is therefore an important replication study for genetic associations with T2D, a common and complex multifactorial trait with a rising prevalence, even among some African populations. This study supports an association with increased risk for T2D in the presence of the TCF7L2 rs7903146 (T) allele, but the frequency of the two SNPs in KCNJ11 and PPAR# are so low that they are uninformative, given the sample size. Since associated SNPs (either detected by GWAS or candidate gene studies) are rarely the causal allele, but may be in linkage disequilibrium with it, replication of individual SNPs may not hold in different populations. This is particularly the case for African populations that tend to have weaker linkage disequilibrium and smaller haplotype blocks. A different study approach would be needed to explore the role of a specific gene with a disease trait, for example, first identify the common variation in the study population in and around the candidate gene and then test for association with the disease. A replication of a single SNP per locus can therefore not be taken to suggest that variants in those genes are unlikely to be associated with T2D, more extensive studies aimed at fine mapping of the genes would be necessary, preferably in the context of a good understanding of the genomic architecture in that population.

It is well established that many SNPs have different allele frequencies across populations (especially when comparing European and African populations) and therefore are expected to have different potential effects in association studies. It has also been shown that genetic predisposition in complex traits (e.g. rheumatoid arthritis, triglyceride levels) exhibits both universal risk alleles and ethnic-specific genetic associations.

Minor Essential Revisions (some discretionary)

1. The title may be reconsidered – perhaps emphasising the positive result
2. Abstract: Remove reference to hypertension, which allele has a frequency of 0.23 for the CAPN10 -19 (indel)?, CAPN10 haplotypes are in fact haplotype combinations (the equivalent of genotypes as opposed to alleles).

3. The focus should be clear – there are two parts to the study
   a. It is an association study for T2D (and therefore reference to the hypertensive cohort which was not analysed seems out of place in the methods section, though it makes sense to include the prevalence of hypertension in the T2D group)
   b. It examines association with several quantitative traits among the control group using logistic regression

4. The results for the KCNJ11 and PPAR# should be given (even if there were only two observations of the variant allele)

5. Methods: Provide references for DNA extraction, genotyping protocols and explain “mutagenically separated PCR assays”

6. Discussion – some over interpretation should be tempered (e.g. one SNP result suggesting a “worldwide distribution complies with the out-of-Africa migration”). Paragraph 4 – consider clarifying and in last sentence did you mean “predisposes”? Paragraph 6 – not clear what relevance of “positional cloning” is in this context.

7. Conclusions – Last two sentences could be improved

8. Careful editing is required – some examples – BMI is not kg/cm2, inconsistencies in allele frequency notation (0.1%, 0.001; 23%, 0.23 etc.), type 2 diabetes vs diabetes, with first use write out FPG

Major compulsory Revisions

1. Since hypertension is so common among the cases, it should be examined as a confounder and adjusted for
2. Haplotype associations for CAPN10 need to be done (e.g. frequency and role of 112 in T2D – as opposed to 111-112)

Level of interest: An article of importance in its field

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

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.