Reviewer's report

Title: Race-Ethnic Differences in the Association of HbA1c-Associated Genomic Loci with HbA1c Levels and Mortality in U.S. Adults: the Third National Health and Nutrition Examination Survey (NHANES III)

Version: 1 Date: 19 December 2011

Reviewer: Andrew D Paterson

Reviewer's report:

This is a clearly written paper on HbA1c risk allele frequencies across 3 race/ethnic groups in the US and their association with HbA1c and mortality.

Minor Essential Revisions:

The title is a little awkward, perhaps 'Hba1c-associated genomic' could be removed without loss of clarity.

It is not clear whether red cell traits were collected in NHANES. Even if the authors do not analyse them here, i think discussion of whether this would be possible would be useful in the discussion.

In the Methods, the authors say that 704 with diabetes were excluded. It would be helpful to be clear how these were proportionately contribute by each of the 3 major ethnic groups studied.

There is great genetic heterogeneity within each of the populations studied, especially African Americans. It would be useful to state this. Is there other genetic data that could be used to estimate the heterogeneity within each group, and whether that heterogeneity is associated with HbA1c.

In the methods 'SNP genotyping ..' the r2 of proxy SNPs is stated in CEU. Please add the r2 in other relevant HapMap populations.

In general it is not clear what the power is for each SNP in each ethnic group. A simple table describing the power to each locus for HbA1c in each group (based on the prior effect sizes) would be helpful. Are the mostly negative results expected due to universal low power?

Again, some statement about the expected power of the mortality analysis.

Ref # 7 should be updated with the published paper.

Table 2, the SE for some SNPs are specified to too many significant digits - it will help reading to make them consistent.

Table 4. The 3 right-most columns are presumably for the 11SNP score, but the fact that the results occur on the line for the first SNP could potentially be
misleading. Perhaps a separate supplementary table would be the best place for this part of the table. In the same table there’s a strange green triangle in the 4th last column - probably some Excel effect.

Fig 1. It would be helpful to add the name of the risk allele for each SNP.

In supplementary Table 1. in cell 'B4' the SNP name has been removed by error.

What is the cause of the p=0.002 for HWE for HFE in NHW (supplementary Table 2).

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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