Reviewer's report

Title: Variants in KCNQ1 increase type II diabetes susceptibility in South Asians
A study of 3,310 subjects from India and the US

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Reviewer: Shiro Maeda

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In this manuscript, Been et al. examined the association of 4 SNPs within KCNQ1, 3 in intron 15 and 1 in intron 11, with type 2 diabetes in populations with Asian Indian ancestry. The authors used two case-control studies, 2,431 subjects living in Northern India (Punjabi cohort) and 879 subjects living in the US (US cohort), and reported significant association of rs231362 in intron 11 of KCNQ1 with type 2 diabetes in the Punjabi cohort. They also identified that rs2237895 in intron 15 showed modest association of type 2 diabetes in combined analysis, and risk allele carriers for the rs2237895 showed decreased beta cell function in both cohorts. Although the authors have provided interesting information, there are several concerns in the present manuscript.

Major Compulsory Revisions

1 Because the US cohort included subjects with different origin, western and southern India, the combined analysis should be performed by a meta-analysis after evaluating heterogeneity, or by a logistic regression analysis including variables accounting for the origin. The former seems better way, since genotype distribution of each SNP in combined control tended to be deviated from HWE proportion, p = 0.0192, 0.0455, 0.0917 for rs2237892, rs2237895 and rs231362 respectively. Combined analysis for quantitative traits also should be performed by a meta-analysis.

2 The results of haplotype analyses added little information. In addition, the presented p values in this analysis seem something wrong (it is strange that haplotype with 95% CI of 0.96 – 1.48 has significant p value of 0.009, and this P value goes smaller after permutation). There are other similar strange results that haplotypes with 95% CI overlaid across 1.0 have significant P values (<0.05).

Minor Essential Revisions

1 Power estimates should be based on ORs in previous reports and risk allele frequencies in the present population.

2 Footnote of table 2 is not match well with actual table 2, e.g. Position of SNPs on chromosome has been taken from NCBI (Genome Build 36.3) in the footnote, but not shown in the table.

3 KCNQ1 stands for potassium voltage-gated channel, KQT-like subfamily,
member 1

4 Line 6 in page 7, [non-Asian Asian] should be [non-Asian].

5 Line 5 – 6 from the bottom of page 13, descriptions, [2% vs. 65%], [1% vs. 65%], are probably wrong.

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.

Declaration of competing interests:

I declare that I have no competing interests