Reviewer's report

Title: Common Genetic Variants of the Ion Channel Transient Receptor Potential Membrane Melastatin 6 and 7 (TRPM6 and TRPM7), Magnesium Intake, and Risk of Type 2 Diabetes in Women

Version: 2 Date: 3 December 2008

Reviewer: Ching-Ti Liu

Reviewer's report:

The authors conducted a nested case-control study among postmenopausal women in the Women’s Health Study. They analyzed 25 SNPs either in TRPM6 or TRPM7 for their association with diabetes risk. Although there wasn’t any significant association between any single SNP with diabetes risk, their sliding window haplotype analyses suggested that two non-synonymous TRPM6 variants might be the susceptibility to type 2 diabetes in women with low magnesium intake.

Major Comment

1. The authors claimed that they only consider SNP with minor allele frequency (MAF) greater than 5% in their text. However, in their result, such as table 2, they included the SNP with MAF less than 5%. For example, please explain why the SNP rs944857 was included in the study.

2. On page 8, 19 window frames were used for Bonferroni correction. Please explain how to get this number with 25 (20+5) SNPs in your consideration. Shouldn’t it have 23 (19+4)? Did authors only conduct sliding window to TRPM6? If so, why not TRPM7 as well?

3. In sliding window haplotype-based analyses, the samples are stratified based on the magnesium intake. It would be better to know the results for single SNP and haplotype analyses under such stratification.

4. Cross-species comparison of the protein sequences was performed among different species for TRPM6 and TRPM7. Why select different species for TRPM6 and TRPM7? Did the authors conduct the comparison over many species but only find the conserved result among the listed species?

5. In cross-species comparison of the protein sequences, three segments were selected. Please explain the motivation to select these three segments rather than others.

6. In discussion, authors mentioned their limitations on population stratification issue and claimed that majority (>92.5%) of subjects were white. Since the majority of subjects share the same ethnicity background and hence it won’t loss too many subject if exclude those non-white subjects. So it would be more convincing if authors can present the result obtained from those white subjects only too.
7. In table 3, why did authors only list haplotype 0-0, 1-1, and 0-1? Where is the case for 1-0?

8. In table 3, I wonder why 9.31% was presented in the text on page 10 but 9.30% was presented in the table 3?

9. From table 3, it seems to me, authors only consider dominant model, which is not the same as what they did for single SNP analysis, but they didn’t spell it out in this manuscript.

Minor Comment

10. page 4, the 5th line on the first paragraph, “28345 (71%)……. Of these 27962…” How come these two numbers are different?

11. In the legend of Figure 2, authors placed dash line but there is not any explanation for it.

12. On page 11, please put the rs number for SNP K1584E too.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

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