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

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Reviewer: Vincenzo Trischitta

Reviewer’s report:

The authors have conducted a nested case-control study of 718 postmenopausal women aimed at examining the associations between variations at TRPM6 and TRPM7 loci and the risk of type 2 diabetes (T2D). Several tagging SNPs in both genes were analyzed but no significant association was observed. However, among individuals with low magnesium intake was inadequate (<250 mg per day; i.e. in the lowest quintile of the control sample), haplotype analyses showed that carriers of both the rare alleles at two non-synonymous SNPs in TRPM6 (Val1393Ile and Lys1584Glu) were significantly more likely to be affected by T2D (i.e. to be cases, rather than controls). In addition, bioinformatics analyses indicated potential functional relevance of TRPM6 Val1393Ile SNP, thus reinforcing the biological plausibility of the observed association.

The finding is novel, the design is excellent (i.e. a nested case-control based on prospective study with up to 10 years of follow-up, and an effective matching strategy used in a well-characterized population) and the paper is well written. The only severe limitation is the small sample size which does not allow the authors to detect modest genetic effects and which increases dangerously the risk of false results caused by statistical fluctuation. A second limitation is the lack of replication in an independent population. All this is clearly stated by the authors who are, as a matter of fact, very cautious in interpreting and commenting their own data. Although I understand that nowadays studies on the genetics of complex traits are asked to be performed in (multiple) samples, which are large enough to maximally reduce the risk of false results due to chance and/or population stratification, I still believe that “hypothesis generating by a well designed study to be further tested in subsequent attempts” is still one the most effective way to help science progressing. No matter if the hypothesis is further confirmed or not. This is, exactly, what this paper does.

The only minor suggestion I have is to shorten the Discussion.

Level of interest: An article of limited interest

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.