Reviewer's report

**Title:** Serum uric acid correlated polymorphisms were associated with phenotype gout in Han Chinese males: a case-control study

**Version:** 3  **Date:** 31 January 2015

**Reviewer:** Tony Merriman

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This was a straightforward study of 8 SNPs associated with serum urate in Europeans for their association with gout in Chinese. The methodology and analysis is (mostly) sound, however there are issues with rationale and interpretation.

**Major compulsory revisions:**

1. The interpretation (abstract) that there are genetic differences between populations was based on an apparent opposite direction of association at GCKR between Chinese and the Phipps-Green et al study. In fact the direction of association is consistent. In the Zhou et al study the G allele is protective, and the A allele therefore risk. This is the same as Phipps-Green et al (in both Polynesian and European). [Note that 'effect' allele is the one that the OR reported correlates with]

2. Some of these authors have previously published on GCKR in Chinese (Wang et al. Hum Genet 2011). Why was this study not cited? Was there overlap in data sets?

3. The SNPs selected were based on those reported by the Kolz et al 2009 study. In the field this is not a recent study, and has been superceded by Kottgen et al published 2-years in Nature Genetics. This study should be cited, and the authors should explain why they did not study all 28 variants reported by Kottgen et al. The authors should also cite and compare their results to Urano et al (J Rheumatol 2013). Furthermore, why was ABCG2 not analysed?

4. Based on a HWE P of 0.008 rs1183201 (SLC17A1) was excluded from analysis (although association testing was still done). The FDR approach should be applied, or the P Bonferroni corrected by the 8 SNPs tested, whereupon it would be non-significant. I think this variant should be included in the analysis. It is certainly incorrect to claim throughout the manuscript that SLC17A1 was not replicated. In fact it was the strongest association.

5. Discussion of SLC22A12. Flynn et al (2014) (http://www.ncbi.nlm.nih.gov/pubmed/24360580) should be cited, where association of SLC22A12 with gout in European was reported. Thus the conclusion that rs505802 is unique to Chinese is not correct. Also the authors should reconsider the statement that SLC22A12 is a substantial risk factor for
gout/SU.

6. The FDR should be applied to the Table S2 analysis. Reported associations would not be significant. Please also show P values, especially for the serum urate analysis. Association with age does not need be be done.

Minor essential revisions:
1. Please put page numbers in.
2. Background, para 2. Does the 40% heritability refer to hyperuricaemia or gout/ Sulem et al did not calculate any heritability estimates. Please refer to original study.
3. Background, para 2. Using refs 8-12 it is claimed that the variants are consistently replicated across ethnic groups. However the studies cited are (nearly universally) European.
4. Can the authors outline the parameters they used for the power calculations and also reference the software used.
5. SLC2A9 discussion. The low prevalence of rs734553 minor allele in Chinese most likely relates to a population history that differs from Europeans. The variant is old (it is present in multiple populations). The authors should probably delete this extremely speculative discussion.
6. That functional studies weren't done here is not a limitation.

Level of interest: An article whose findings are important to those with closely related research interests

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

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