Reviewer's report

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

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Reviewer: Donia Macartney-Coxson

Reviewer's report:

Review of manuscript entitled:
Polymorphisms in GCKR, SLCA9 and SLCA12 were associated with phenotype gout in Han Chinese males: a case control study
Zhou et al

In this study Zhou and co-authors analyse a single polymorphism in each of 8 genes previously associated with serum uric acid comparing 622 Han Chinese individuals with gout to 917 healthy controls. They report associations between gout and 3 SNPs (single nucleotide polymorphisms), one SNP in each of SLCA9, SLCA12 and GCKR. The authors base their SNP selection on a meta-analysis of genome-wide association studies (GWAS) for serum uric acid reported by Koltz et al 2009 for 28,141 individuals. The emphasis of the study is that while elevated serum uric acid is an important indicator and independent risk factor for gout, it is not the same as gout. However, the data do not appear to be consistently explained within this context. There are a number of major concerns with the manuscript (which may or may not relate to this apparent lack of context for the results) which would need to be addressed before publication in BMC Genetics should be considered.

Major concerns:

Abstract:

1. Background (3rd sentence) “…… there is no previous association study of these SNPs in a Han Chinese population”. This sentence is misleading. The 9 SNPs (from Koltz et al 2009) to which this refers are located in 9 different genes; at least some of these 9 genes have previously been associated with gout in Han Chinese. For instance, the current study targets 8/9 of these SNPs but does not explain exclusion of 1/9 (rs2231142 in ABCG2) for which an association with gout in Han Chinese has previously been reported (Wang et al 2010). In addition, the authors cite a previous study of their own (Wang et al 2012, Human Genetics) which reported an association between gout in male Han Chinese and SNPs in GCKR (including rs780094 reported in the current manuscript).

Other studies which report associations between variants in the 9 loci (genes) reported by Koltz et al and gout include:

Zhou et al 2014. Functional polymorphisms of the ABCG2 gene are associated with gout disease in the Chinese Han male population.
Li et al 2014. The hURAT1 rs559946 polymorphism and the incidence of gout in Han Chinese men. (URAT1 is also known as SLC22A12).

Li et al 2012. Polymorphisms in the presumptive promoter region of the SLC2A9 gene are associated with gout in a Chinese male population.

Tu et al 2010. The SLC22A12 gene is associated with gout in Han Chinese and Solomon Islanders.

Tu et al 2010. Associations of a non-synonymous variant in SLCA9 with gouty arthritis and uric acid levels in Han Chinese subjects and Solomon Islanders.

While the exact variants investigated in the current manuscript may not always have been analysed in the studies mentioned above, reference to this work should be made, and the linkage disequilibrium between previously reported variants and those examined in this study reported, and discussed.

Introduction

2. This is a study of Han Chinese and the SNPs selected for analysis were based on previously reported associations with serum uric acid. More mention should be made of previous related studies involving Han Chinese.

Notably, a recent GWAS of serum uric acid in 3473 Chinese with validation analyses of 10 SNPs in a further 8830 Chinese individuals should be referred to in more detail. (Yang et al 2014, reference 11).

Other Han Chinese studies include:

Guan et al 2011. Association of an intronic SNP of SLCA29 gene with serum uric acid levels in the Chinese male Han population by high-resolution melting method.

Li et al 2010. Multiple single nucleotide polymorphisms in the human urate transporter (hURAT1) gene are associated with hyperuricaemia in Han Chinese.

It would also seem appropriate to mention GWAS related to serum uric acid in other Asian populations (Okada et al 2012 and Kamatani et al 2010).

Material and Methods

Statistical Analyses

3. The authors state that Hardy-Weinberg equilibrium analyses was evaluated on the control group. This should have been performed in both cases and controls.

Results

SNP associations with gout risk

4. A clear explanation of why only 8/9 loci reported by Koltz et al were selected for analyses is required.

5. In the section on phenotype details and Table 1 the authors clearly present data showing that the cases were significantly different from controls for a number of phenotypes including gout (i.e. age, BMI, diastolic blood pressure,
blood glucose, triglycerides, creatinine and cholesterol). Table 3 presents the association data with p values adjusted for these covariates. As the study is designed as a case control analysis of gout, association analyses for this trait alone should be performed and presented, and then sequential analyses which consider each of the potential confounding co-variates. Evidence needs to be provided which indicates that gout is (or isn’t) the major contributor to the associations. The authors have attempted to address this by performing an analysis of the clinical data with respect to genotype in the control individuals, arguing that medical treatment of the cases is a confounder. However, only a small number of significant associations were found suggesting that they may have over fitted the model for data presented in Table 3 which is adjusted for the multiple co-variates. Further clarification and detail is required.

Discussion

6. The authors state that the observed association of rs780094 in GCKR with gout is consistent with a New Zealand study (but opposite effect allele) but a German one. They then go on to discuss the possibility that the different population backgrounds may provide an explanation. The recent Han Chinese GWAS of serum uric acid (published in BMC Medical Genomics and therefore I assume that the data is publically available) and the Han Chinese HapMap data provide the authors with the possibility of exploring genomic structure and LD across the region and comparing this with Europeans (HapMap) to generate potentially supportive data for their suggestion at least for these two populations (to my knowledge genomic data for NZ Polynesia populations is not available).

Minor essential Revisions

Introduction

On occasion the translation into English would benefit from editing/refining.

“With the improvement of living conditions, the incidence of hypertension and gout is increasing rapidly…….”

“Gout has imparted a considerable financial burden resulting from severe pain and complications…..”

Material and Methods

Participants and Phenotypes.

• While the title indicates that the study was of males only, this should be stated within the methods section.

• Plink is a “gold standard” for genetic association studies. While it was used for the SNP:SNP interaction analyses it is unclear why SHEsis was selected for the association analyses.

• Plink version 19. Is this correct or should it be 1.9?

**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.

Declaration of competing interests:
I declare that I have no competing interests