Reviewer’s report

Title: Association of common variants in JAK2 gene with reduced risk of Metabolic Syndrome and related disorders

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Reviewer: María Eugenia Sáez

The authors performed a genetic study association for two SNPs at the JAK2 gene for several metabolic syndrome related traits. The authors selected these 2 SNPs based on a previous report by Ge et al. 2008 that found borderline significance for these SNPs with central obesity measures (rs7849191) and lipid traits (rs 3780378). The authors replicate the findings of Ge at all. for triglycerides at rs3780378 but failed to replicate nor the obesity associations at rs7849191 nor the cholesterol associations at rs3780378. In addition, the authors found association with metabolic syndrome for both SNPs

Major limitations

The sample size is relatively small included self-reported European ancestry mainly from Spain and Italy. This implies that some degree of genetic structure can exist within the sample, affecting the genetic association study. Differences in allele frequency by means of ancestry origin should be performed, given that is not possible to perform a principal component analysis. Ancestry origin can also be included as covariable in the study.

It seems that no quality control has been applied to genetic data i.e. duplicated samples or genotyping rates. It appears that only 707 individuals were genotyped for the rs7849191 and 724 for the rs3780378.

It is not mentioned if lipid lowering medication has been taken into account.

No information is provided regarding the distribution of phenotypic data. The authors used ANOVA for normal-distributed and Kruskal-Wallis otherwise. In addition, linear regression analysis was used. It is not clear in table 3 which one has been applied to each analysis. Is the value p=0.001 for the df comparison at rs3780378 derived from and age and bmi adjusted analysis? (it has a b superscript but in the column pb no significance is denoted). For Kruskal-Wallis analyses, median and range should be described rather than mean and SD.

Given the strong dependency of the analyzed traits from age and BMI, I think that is more appropriate the reporting of the adjusted linear regression models with transformed phenotypic values (i.e log transformation) for phenotypes deviating from normality.

For the haplotype analysis, In order to reduce the degree of freedom, the TT haplotype, with a frequency less than 5%, could be removed from the analysis

Minor
Allele frequencies for rs7849191 are badly described: for the TT genotype the frequency is 0.15 are not 0.015.

The paper from Ge et all. (ref. 11) is referred throughout the report as Dongliang GE et all.

Table 1. LAP definition is absent

Using Hapmap rel 28 and haploview 4.2, the selected SNPs capture a 21% of SNPs with MAF > 10 at r2 > 0.8. Rs3780378 captures variability at 19 SNPs.

**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