Author's response to reviews

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

**Authors:**

Alberto Penas-Steinhardt (pufetin@gmail.com)
Mariana L Tellechea (marianatellechea78@hotmail.com)
Leonardo Gomez-Rosso Dr (mulag@hotmail.com)
Fernando Brites Dr. (fbrites@hotmail.com)
Gustavo D Frechtel Dr (gfrechtel@ffyb.uba.ar)
Edgardo Poskus Dr (eposkus@ffyb.uba.ar)

**Version:** 4  **Date:** 21 November 2011

**Author's response to reviews:** see over
Dear Tim Sands

Executive Editor, BMC Medical Genetics

Please find the manuscript entitled "Association of common variants in JAK2 gene with reduced risk of Metabolic Syndrome and related disorders" (MS: 7788175805587496) attached for your reconsideration to be published in BMC Medical Genetics.

We really appreciate that the article has been revised by external referees and editorial staff, and are really grateful for all criticisms. We have modified the article taking into account suggestions of the Associate Editor. We provide a point-by-point response, indicating all the changes made in the manuscript or a rebuttal of each point, which you will find appended below.

We really hope the changes made will meet the expectations of the Associate Editor and that you will reconsider the publication of the revised paper after reevaluation.

Sincerely yours,

Dr Penas-Steinhardt

Corresponding author
Response to Associate Editor

Associate Editor's comment 1. Page 4, line 73, there lacks a subject for the sentence.

Response. The paragraph on Page 4, line 73 was properly rewritten (“After binding to its receptor, leptin induces activation of JAK2 and subsequent phosphorylation of specific tyrosines on the receptor”).

Associate Editor's comment 2. The sentence suggestive associations have been explored lack clarity (p 5, line 83)

Response. The sentence on Page 5, line 83 was properly rewritten (“We rewritte the last paragraph of the Background section: “Recently, although not significant at levels which took account of multiple testing, suggestive associations between two single nucleotide polymorphisms (SNPs) of JAK2 gene and central fat, waist circumference and serum lipid variables have been reported”.

Associate Editor's comment 3. The reference 16 concludes that they fail to find association between SNPS in JAK2 and “relevant” phenotypes. The present study is then rather a new attempt to link the “least negative” SNPs of JAK2 with these phenotypes. Please change the way you present the scope of the study.

Response. Ge et al. stated in the article entitled “Association of common JAK2 variants with body fat, insulin sensitivity and lipid profile” that they found suggestive associations between two tSNPs and phenotypes that could reflect the known involvement of JAK2 in the leptin
signalling pathway. They conclude that common JAK2 variants were not strongly associated with body fat, insulin sensitivity or lipid profile in the sample under study because no associations with either tSNP were significant at levels which took account of multiple testing of the 10 tSNP genotypes versus 19 phenotypes, pragmatically taken as p<0.01.

We stated in the Background section that recently, suggestive associations between two single nucleotide polymorphisms (SNPs) of JAK2 gene and central fat, waist circumference and serum lipid variables have been reported. The aim of our study was to test associations between two SNPs of JAK2 and their predicted haplotypes on MS and related phenotypes and quantitative metabolic traits.

We rewrote the last paragraph of the Background section: “Recently, although not significant at levels which took account of multiple testing, suggestive associations between two single nucleotide polymorphisms (SNPs) of JAK2 gene and central fat, waist circumference and serum lipid variables have been reported. Replication is fundamental for deciding that an observed association is likely not due to chance. Therefore, the aim of this study was to explore associations between these two SNPs of JAK2 and their predicted haplotypes on MS and related phenotypes and quantitative metabolic traits”.

Furthermore, in the discussion section we stated that in our study we genotyped only the most significant variants of a gene wide association study conducted by Ge et al.

Associate Editor's comment 4. More generally, I advise toning down a bit the significance of the results. Most of the p-values are > 0.001.

We rewrote the Discussion section, Page 15, line 308: “Our results show that carrying both protective alleles (haplotype CT), would be associated with MS and TG values under 150 mg/dl
and HW. Furthermore, haplotype analysis of quantitative metabolic traits seemed to reveal significant differences in TG, TG/HDL-C and LAP between haplotypes.”

We also rewrote the Conclusions section: “In conclusion, the present study appears to describe for the first time significant associations of common variants in JAK2 gene with MS and lipid metabolism disorders, such as HW, TG/HDL-C and LAP.”

Associate Editor's comment 5. Please test interaction with age.

We performed the interaction test required, as shown in Statistical Analysis section:

“Furthermore, genotype status and age subgroup (2 subgroups according to the average age: <37 and ≥37 years old) were used as factors in a Multivariate linear regression analysis to determine interaction of age and genotype.”

We also added in the Results section, Page 12, line 231: “The association of rs3780378 genotype with TG, LAP and TG/HDL-C was not age-dependent (p=0.059, p=0.213 and p=0.111 for rs3780378 genotype- by-age interaction respectively).”

Associate Editor's comment 6. Please show the exact p-values. Results like ? < 0.001? do not allow a clear evaluation of the significativity and strength of the results.

The table 3 was properly rewritten by adding the exact p-values

<table>
<thead>
<tr>
<th></th>
<th>TT (n=187)</th>
<th>TC + CC (n=537)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD p</td>
<td>p^a</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>120.61 ± 67.764</td>
<td>146.09 ± 105.233</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>P-value</td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>TG/HDL-C</td>
<td>3.27 ± 2.60</td>
<td>0.001²</td>
</tr>
<tr>
<td></td>
<td>4.13 ± 4.13</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>LAP</td>
<td>44.42 ± 37.72</td>
<td>0.0011</td>
</tr>
<tr>
<td></td>
<td>56.00 ± 49.80</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.006</td>
</tr>
</tbody>
</table>