Author's response to reviews

Title: ATA homozigosity in the IL-10 gene promoter is a risk factor for schizophrenia in Spanish females: a case control study.

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Author's response to reviews: see over
Dear Sir or Madam,

I enclose the reviewed version of the manuscript entitled “ATA homozigosity in the IL-10 gene promoter is a risk factor for schizophrenia in Spanish females: A case control study” for being considered for publication in “BMC Medical Genetics” and a point-by-point response to the referee comments.

Thank you very much in advance.

Yours sincerely,

Berta Almoguera
Comments to the Author

Almoguera et al. report the ATA homozigosity in the IL-10 gene promoter is a risk factor for schizophrenia in Spanish females: a case control study. The main subject of the article appears to be interesting. This manuscript is worth for publication in “BMC Medical Genetics” with major revision.

Comments:

1- Abbreviations should be written in full at first mention such as Th1, Th2, TNF.

Abbreviations have been fully explained according to your suggestion (Background, first paragraph, highlighted in yellow).

2- The expression of healty control is synonym with control group. Therefore, “healty” word should be removed.

It has been removed all along the manuscript.

3- The mean age of the patient and control groups with standard deviation should be added to part of the subject.

We have referred to the patient and control’s age in the material and methods section as mean and standard deviation. The comparison between ages in all groups, with the p-value of comparison, is described in the result section (highlighted in yellow).

Alternatively, demographic characteristics of the patient and control groups making a distinction between female and male can be shown in the table.

Age of patients and controls and the comparison has been added to table 1.

4- The mean age of patients and controls as males and females separately should be compared in statistically and should be indicated statistically significant difference whether or not.

Comparison between ages has been included in the results section (page 8, highlighted in yellow) and also the p-value of the comparison.

5- Page2, line 20, “-819 C>T was deducted” should be removed.

It has been removed (“DNA extraction and genotyping” highlighted in yellow)
6- Page 7, line 8, the sequence of primer should be written without spaces.

It has been modified (highlighted in yellow)

7- Page 7, the section of data analysis should be developed. Analysis of genotypic variants should be given more detailed information. How are the -1082 G>A, -592 C>A alleles interpreted such as product size.

More detailed information about the SNPs genotyping has been added to this section (Data Analysis section, page 7, highlighted in yellow)

8- The statistically analysis should be removed from data analysis section and it should be given as a separate section.

We have separated data analysis in two sections as suggested (materials and methods, page 7, highlighted in yellow)

9- Page 8, line 2, in the results section, “-592 G>A” may be incorrect spelling. Need to be reviewed.

It has been changed to the correct form (results, page 8, 2nd line, highlighted in yellow)

10- Two SNPs were investigated in this study. The first polymorphism at position -1082 is a G to A substitution and the second at position -592 a A to C substitution. Therefore, the frequencies of the AA, AG and GG genotypes of -1082 G/A and the frequencies of the CC, CA and AA genotypes of -592 C/A could be given. But, the substitution of -819 C>T was not been studied in this work. In the genotypic frequencies section of Table 2, it didn’t understand how was indicated the genotype consist of -819 C>T allele. The haplotype should be constituted according to -1082 G>A, -592 C>A alleles which is studied.

11- Reasons mentioned in the previous, the data of -819 C>T allele should be removed from Table 3.

Answer for 10 and 11 questions: According to the evidence, those three variants are in linkage disequilibrium and define only three haplotypes in Caucasians which are GCC, ACC, ATA. Because of this strong linkage disequilibrium, if one genotypes two of three positions, the third can be deducted. This has also been supported by the methods used by Ortiz et al referred to in this manuscript (Ortiz, 2006): “There are only three IL-
10 promoter haplotypes (GGC, ATA, ACC) described [21,26,27] in our population. That is why we have only analyzed the first (-1082) and the third (-592) position in the IgAD patients and we then obtained the second position (-819) by a simple deduction”.

Thus, we consider that we might keep the haplotypes with the three positions instead of two.

12- Is the level of IL-10 investigated? The comparison of the level of IL-10 in subjects carrying the variant allele as a homozygote or heterozygote will strengthen further.

Levels of IL-10 have not been investigated but there is wide evidence in the literature of the association of each haplotype with the lower or higher production of IL-10 which has been referred in the text.

13- The genotyping was finished in more than one departments which participated in this study. Therefore, the data analysis should be written more detailed and standardized.

We have included more details about the genotyping in the genotyping and data analysis sections (in yellow). Although the genotyping was performed in two separate departments, both methods have been previously validated (Almoguera, 2010) (Cuyás, 2010) (Applied Biosystems). Additionally, we have confirmed both genotyping results by sequencing and the concordance yielded was very high as stated in the manuscript (results section).

14- Writting of the references should be revised according to guidance for authors.

Reference section has been carefully reviewed to fit with BMC journals style