Author's response to reviews

Title: Study of the serotonin transporter (SLC6A4) and BDNF genes in French patients with non syndromic mental deficiency

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Author's response to reviews: see over
Dear Editor,

Please find below our answers to reviewers and enclosed the revised manuscript entitled “Study of the serotonin transporter (SLC6A4) and BDNF genes in French patients with non syndromic mental deficiency” by Tabagh et al. for your consideration for BMC Medical Genetics.

Mental deficiency has been linked to abnormalities in cortical neuronal network connectivity and plasticity. The serotonin and brain derived neurotrophic factor (BDNF) signalling systems are directly involved in these mechanisms. Polymorphisms in the SLC6A4 gene determine the neuroanatomical size and functional coupling of the amygdale-frontal cortical circuit in human (Heinz et al., 2005; Pezawas et al., 2005). This circuit has been implicated in several psychiatric disorders including Fragile X and Williams syndrome, two pathologies characterized by mental deficiency (Watson et al., 2008; Meyer-Lindenberg et al., 2005)’’.

We report in this manuscript the first genotyping study on the SLC6A4 gene encoding the serotonin transporter 5-HTT and the BDNF gene in a population of patients with non syndromic mental deficiency.

Thank you for your consideration of our manuscript.

Sincerely yours,

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Response letter:
“Study of the serotonin transporter (SLC6A4) and BDNF genes in French patients with non syndromic mental deficiency”, by Tabagh et al.

To the Editor,
We thank you for giving us the opportunity to submit a revised version of our manuscript. Please find here the reply to the reviewer’s comments.

We included a « competing interests » section and a paragraph concerning authors’ contributions after the “conclusion” as requested. We also make sure that all authors and their e-mail addresses are correctly listed.

Answers to Reviewer 1:
- The 3’UTR SNP of 5HTT was named rs3813034 in the entire manuscript.
- Data for rs25531 (A/G) and 5HTT-LPR (L/S) were associated in table 2 as requested by reviewer 1. Indeed, it is interesting to analyse these polymorphisms based on functionality. We added the following sentences in the Result section (first paragraph): “Hu et al. (2006) reported that GL genotype drive 5HTT expression nearly equivalently as S (AS or GS). Consequently, we grouped the GL, AS and GS haplotypes for analysis. However we did not observe association between NS-MD and a particular haplotype ($\chi^2 = 0.12; p=0.73$) or genotype ($\chi^2 = 1.28; p=0.73$) (Table 2).”
- We removed the following sentence in the Result section (first paragraph): “The AS haplotype (allele A of rs25531/allele S of 5-HTTLPR) was present in 39.3 % and 39.1 % of control individuals and NS-MD patients, respectively.”
- As requested by reviewer 1, we analysed the interaction between AP2-5HTTLPR and BDNF genotypes. These data were added in table 2 and described at the end of the second paragraph of the Result section. “No association was found between NS-MD and a particular combination of AP2-5HTTLPR (AL or others) of SLC6A4 gene and rs6255 (A or G) of BDNF gene.”

Answers to Reviewer 2:
- Several studies reported an association between particular alleles of polymorphisms in SLC6A4 gene and pathologies associating mental deficiency,
such as autistic disorder for example. 70% of autistic patients are mentally retarded. We think our study is of importance because it is the first analysis of the SLC6A4 gene in a population of pure NS-MR patients.

- As mentioned by reviewer 2, the choice of loci is crucial. We chose four loci in the SLC6A4 gene. All of them influence the expression level of serotonin transporter as described in the third paragraph of the Background section. More than 300 studies analyzed the role of 5HTTLPR in diverse neuropsychiatric phenotypes (Glatt et Freimer, 2002). We added the following sentences in the second paragraph of the Background section. “A polymorphism (5HTTLPR) in the promoter of SLC6A4 determines the neuroanatomical size and functional coupling of the amygdale-frontal cortical circuit in human (Heinz et al., 2005; Pezawas et al., 2005). This circuit has been implicated in several psychiatric disorders including Fragile X and Williams syndrome, two pathologies characterized by mental deficiency (Watson et al., 2008; Meyer-Lindenberg et al., 2005).”

- As requested by reviewer 2, we analyzed the patterns of linkage disequilibrium between the two populations studied. We added the following sentences in the first paragraph of the Result section and modified the abstract. “We used pairwise LD measures (D’) between adjacent markers to analyse the patterns of LD in the control and NS-MD populations. Comparison of these unrelated populations revealed a degree of variability which, however, did not reach significativity (Spearman rank correlation, r_s=0.50; p=0.66).”