Reviewer's report

Title: Mutation screening of melatonin-related genes in patients with autism spectrum disorders

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Reviewer: Erik J Mulder

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Review report for paper: Mutation screening of melatonin-related genes in patients with autism spectrum disorders, Jonsson et al for BMC Medical Genomics

This study reports a screening of mutations in several genes related to the production and function of melatonin in a group of patients with Autism Spectrum Disorders (ASDs). Several mutations were found. Subsequently the authors studied the frequency of appearance of their found mutations in a control group from the general population. Finally they examined functional consequences of the mutations and looked into characteristics of the patients carrying the mutations.

Five rare variants were observed in several different genes, among which the earlier reported splice site mutation in the ASMT gene. None but one variant were found in the control group. None of the new found variants appeared to result in significant changes in the gene products, thus function.

The study was carefully conducted and the report cautiously follows the data. The authors seem to have been alert for “overstatements” in the discussion and conclusion. This paper will be a relevant contribution to science concerning insight in the role of melatonin in ASDs.

I have a few general remarks, which can be considered Discretionary Revisions:

1. It is a pity that the authors did not have data on melatonin or melatoninmetabolites in blood or urine or data on sleep. This would have made the data even more interesting.

2. Although of interest the conservation analysis does not seem to add anything to the results. The authors do not refer to it in the discussion. Unless they choose to discuss it in the discussion, I think it can be omitted from the paper.

At some points I encountered some difficulty following the train-of-thought of the authors, which resulted in the remarks below, all of which are Minor Essential Revisions. Also I noticed some typo’s.

Abstract

The abstract is too condensed en the conclusion of the abstract too bold to be able to appreciate the content of the paper.
3. In the methods the control group should be mentioned.
4. In the results in the first sentence the control group should be mentioned also.
5. In the present wording the 2nd and 3rd sentence of the abstract causes confusion. Only after reading the paper, I could easily follow this part.
6. The sentence in the conclusion: “Our findings provide further support for the notion that the splice site mutation, IVS5+2T>C, in ASMT may infer an increased risk for ASD.” is too bold, this is not what has been studied here, and should be rewritten more like the conclusion of the paper.
7. Typo: 5th sentence – ‘...mutations...has been...’ – should be – ‘...mutations...have been...’

Introduction

8. Page 3; 3rd paragraph; 5th sentence: “Moreover, several monogenic causes of autism are well known, such as fragile X syndrome, Rett syndrome and tuberous sclerosis, and recently rare mutations and copy number variations have been found to be causative or contributory factors for autism spectrum disorders [6-9].” – Since the term autism is generally used to indicate idiopathic autism, the authors should reword this sentence to something like: “Moreover, several monogenic disorders, such as fragile X syndrome, Rett syndrome and tuberous sclerosis, are well known causes of autism like behavior patterns, and recently rare mutations and copy number variations have been found to be causative or contributory factors for autism spectrum disorders [6-9].”
9. Page 4; 8th sentence: I would say that the data on the effect of melatonin on sleep disturbances in ASD are not yet that strong, that one should use ‘greatly improved’ here. Just ‘improved’ would be enough at this point.
10. Typo’s: Page 6; 2nd sentence – ‘raging’ – should be ‘ranging’; 3rd sentence – ‘pateints’ – should be ‘patients’

Methods

11. The ‘patient recruitment and clinical assessment’ paragraph needs a table with patient characteristics. The percentages of patients in the different diagnostic groups of the second group are odd; i.e. 10% of 44 subjects is 4.4 subjects – 4 subjects = 9.1%; 5 = 11.4%. A table with actual numbers and percentages will be more clear.
12. Although no statistical analyses were done, a paragraph with the ‘analytic plan’ and the considerations for the choices made is needed. Some is there in the ‘recruitment’ part, some in the ‘DNA analysis’, some in the ‘Results’.

Results

13. Page 7; 1e paragraph of Results; 4th sentence: “Of the three missense variants identified, S493N in GPR50 and V124I and K243R in MTNR1B, only the V124I variant MTNR1B was absent in controls (Table 1).” The wording is unclear. It would help to first report that of the found rare variant three were missense mutations and after that elaborate the of those three two were found in patient as
well as controls.

Discussion and conclusion

14. Typo: Page 10; 2nd paragraph; 1st sentence: ‘...support the notion...’ – should be ‘supports the notion’

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'