Reviewer's report

Title: High frequency of known copy number abnormalities and maternal duplication 15q11-q13 in patients with combined schizophrenia and epilepsy

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Reviewer: George Kirov

Reviewer's report:

The authors have addressed the legitimate question as to whether patients suffering from schizophrenia and co-morbid epilepsy have a higher rate of certain pathogenic CNVs. Their results seem to support this hypothesis, the analysis and methods used appear sound, so I consider these results real and deserving publication.

There are a number of problems in the presentation of the results, that the authors should address before the paper is published:

1) Have patients from this NIMH sample been included in other publications on CNVs? It is quite important for the field of psychiatric genetics to be aware of such overlaps, as otherwise future reviews and meta-analyses could come to the wrong conclusions. This has been a problem with the AGRE collection of patients with autism, where multiple teams used the available DNAs, making it difficult for researchers to establish the correct frequencies of some CNVs in autism. If the authors are aware of any overlaps, they should point these out in the tables of CNV locations. If not, they should attempt to contact the authors of any papers reporting on these collections and clarify this. I should stress that such overlaps do not invalidate the conclusions of the authors regarding the rate of such CNVs in schizophrenia/epilepsy patients, but the public should know if the findings for certain CNVs are already reported.

2) The authors are unsure which CNVs are accepted as increasing risk for schizophrenia, e.g. NRXN1 is in or out for some of their analyses. In addition they seem unaware of several recent papers of CNVs and schizophrenia, which implicate new loci, and clarify the rate of CNVs in this disorders. I would suggest to change the list of accepted findings to: 1q21.1, NRXN1, 3q29 (Moreno de Luca 2010), 15q11-q13 (maternal duplications, Ingason et al 2011), 15q13.3, 16p11.2(dupl, McCarthy) and 22q11.2. The paper by Levinson et al (2011), which the authors don’t cite, should also give them established frequencies of most of these CNVs in cases and controls. They can then re-calculate their findings, which are likely to get even stronger.

3) The use of bipolars with epilepsy in this paper is a bit confusing. If the authors wanted to include them with the schizophrenics from the start, then they should be reported together, and the calculations done for the two sets. This is probably not a good idea, but if they are reported separately, the sample size is too small. It looks best not report these samples at all.
Minor suggestions:

The "artifact" CNV in Table 5 appears a genuine artifact and should be excluded. Give again the numbers of cases/controls in the Methods. By the way, are the controls useful in the analysis?

The 1st paragraph in the Background section refers to frequencies of CNVs of 0.0021% and others, they are actually 0.21% (correct the decimal points). The authors should be aware that the Stefansson and ISC papers had an overlap, so the true frequencies are a bit lower.

Still in the Background, the authors have to cite the papers by Ingason et al 2011 about the role of maternal duplications at 15q11-q13, accept the established role of 16p11.2 and 3q29.

Table 2 lists "Cus2" and "Cus3", there is a discrepancy with the legend to the table.

Regarding epilepsy and 15q13.3, the authors should cite further papers.

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