The study by McInnes et al. examines the frequency of a novel missense variant in the neuroregulin 1 (NRG1) gene (previously associated with psychosis and schizophrenia) in an isolated population of patients with autism from the Central Valley of Costa Rica. They genotyped the exon 11 variant as well as four microsatellite markers in intron 1 for haplotype analysis in 146 patients and their parents and found no association with autism. The study appears to be well performed and the conclusions are sound but there are several modifications that need to be made in order to improve the manuscript.

1) Background: One of the arguments given to justify the study of the neuroregulin variant in autism is that the reduced expression of oxytocin receptors in reelin-haploinsufficient mice suggests a common pathway that might influence affect and socialization in autism and schizophrenia. This claim is unjustified, since the role of oxytocin in autism has been suggested but not demonstrated. The other arguments are sufficient, so this one can be removed.

2) There is no description of the patients studied in Materials and Methods. The authors should provide detailed information about their patients, including gender, age, number of simplex and multiplex families, inclusion and exclusion criteria, information on IQ, etc. Ethical issues should also be addressed (IRB approval and informed consent from parents).

1) The nucleotide number of the exon 11 missense variant is not mentioned anywhere in the paper. Please give the nucleotide number of this variant in the abstract, Background, Methods and Discussion.

2) Abstract, Results section: in the first sentence, the word “although” is used inappropriately. The sentence should read “The NRG1 exon 11 G>T variant was found in 4/146 cases, including one de novo occurrence” or something similar.

3) Since the references are numbered, there is no need to differentiate the two references by Walss-Bass et al. from 2006 by referring to them as 2006a and 2006b. They should be cited in the text by number only (refs 2 and 9) without the year; when referring to the authors as part of the sentence there is no need to include the year (for instance, the citation at the bottom of page 2 should be “Recently, Walss-Bass et al.2 reported that they had identified...”).

4) Genotyping methods, page 3: the genomic sequence given in the first paragraph should be preceded by a colon (instead of a period) and followed by a period. The primer sequences in the following paragraph should be preceded by a comma instead of a colon to avoid a sentence with three colons.

5) Genotyping methods, page 4, 1st paragraph: replace the letter “u” by the micron symbol.

6) Genotyping methods, page 4, 2nd paragraph: the word “and” is missing before the last microsatellite.

7) Results, page 5, 1st paragraph: There are 12 parents from 11 families carrying the T allele that did not transmit it to the patients. Because no information was given about the patients and the possible inclusion of cousin pairs among the families with more than one affected, the relationship between two of these parents...
is not obvious and should be explained in the text. In Table 1 one can see that there was one family in which both parents carried the T allele.

8) Results, page 6: How many markers were analyzed to assess paternity in the patients carrying the de novo T variant in exon 11 (case 129)? If several markers were analyzed for 5 chromosomes it would be justified to rule out non-paternity.

9) Table 1: The authors appear to have forgotten to finish the legend of Table 1 and left three periods at the end. They should explain the meaning of the numbers in parentheses and of the cells in gray.

10) Figure 1: the legend indicating “exon 11” appears to be pointing to exon 10 instead.

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

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.