Author's response to reviews

Title: The NRG1 exon 11 missense variant is not associated with autism in the Central Valley of Costa Rica

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Author's response to reviews: see over
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We thank the reviewers for their thoughtful comments and have addressed their concerns as detailed below.

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.
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.
PROVIDED

Ethical issues should also be addressed (IRB approval and informed consent from parents).
PROVIDED

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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.
THE AUTHORS THAT FOUND THE EXON 11 MISSENSE VARIANT DID NOT REGISTER THIS SNP IN A PUBLIC DATABASE. WE BLASTED THE TARGET SEQUENCE USING NCBI AND THE UCSC GENOME BROWSER AND DID NOT GET THE SAME RESULT. GIVEN OUR DIFFICULTIES FINDING A NUMERICAL CORRELATE FOR THIS PARTICULAR SNP, WE FEEL IT BEST TO RELY ON THE UNAMBIGUOUS SEQUENCE CONTEXT OF THE SNP AS PROVIDED IN THE METHODS SECTION OF THE PAPER.

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.
CORRECTED

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...”).
CORRECTED

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.
CORRECTED

5) Genotyping methods, page 4, 1st paragraph: replace the letter “u” by the micron symbol.
CORRECTED
6) Genotyping methods, page 4, 2nd paragraph: the word “and” is missing before the last microsatellite. CORRECTED

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. WE CLARIFIED THIS IN THE TEXT

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. 3 OR MORE MARKERS WERE USED ON 5 CHROMOSOMES- THIS IS DEFINITELY NOT A 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. CORRECTED

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

Jim Sutcliffe
I have only one question regarding the case with an apparent de novo instance of this variant. If this is true (i.e. assuming paternity is not a problem), can this be a recurring variant?
The haplotype studies, which seem to suggest that the Val/Leu change is present on at least two haplotypes, are consistent with this idea. Given that there is uncertainty regarding phase in two families with the different haplotype, a similar uncertainty may exist for this idea. Do the SCZ studies support the variant being a recurrent event? If so, it would be worth mentioning the possibility.
Discretionary Revisions (which the author can choose to ignore)
If appropriate, consideration of the possibility of the Val/Leu variant being a recurrent change.

YES THANKS, YOUR SUGGESTION IS POSSIBLE. HOWEVER THERE IS NO SUPPORTING INFO FROM THE SCZ STUDY SO WE SHALL WAIT AND SEE.