Author's response to reviews

Title: De novo SCN2A splice site mutation in a boy with Autism Spectrum Disorder

Authors:

Teresa Tavassoli (teresa.tavassoli@gmail.com)
Alexander Kolevzon (alexander.kolevzon@mssm.edu)
Ting Wang (ting.wang@mssm.edu)
Jocelyn Curchack-Lichtin (jocelyn.curchack-lichtin@mssm.edu)
Danielle Halpern (danielle.halpern@mssm.edu)
Lily Schwartz (lily.schwartz@mssm.edu)
Sarah Soffes (sarah.soffes@mssm.edu)
Lauren Bush (lauren.a.bush@mssm.edu)
David Grodberg (david.grodberg@mssm.edu)
Guiqing Cai (guiqing.cai@mssm.edu)
Joseph D Buxbaum (joseph.buxbaum@mssm.edu)

Version: 2
Date: 3 March 2014

Author's response to reviews: see over
Response to Review 1

Thank you very much for your thoughtful comments, which we addressed in our revision.

1. The article would benefit from a little more detail on which chromosomal microarray analysis (CMA) was used aCGH or SNP and at which density.

We added more details, specifically “Genetic testing included chromosomal microarray analysis (CMA) (Agilent Human CGH 1×244A, Agilent Technologies, Santa Clara, CA)”.

2. The authors obviously have looked at the rest of the exome variants, a statement about other inherited mutations present or not would be of benefit here.

In this study, both unaffected parents and the patient were sequenced and only de novo mutation had been looked at to identify possible pathogenic variants with dominant effects as the priority. Since the genetic etiology of ASD has not been elucidated, we think looking at inherited mutations (from unaffected parents) would not be beneficial to identify possible pathogenic mutations with dominant effects.

3. A possible ‘Typo’ The de novo SCN2A splice site mutation produced a stop codon10 amino acid downstream, possible resulting in a truncated protein and/or a nonsense-mediated mRNA decay. Should this not read possibly?

The spelling mistake was corrected accordingly. Thank you very much for bringing it to our attention.

Response to Review 2

Thank you very much for your comments. We tried to address these in our revised manuscript.

The case is one of three previously reported as having different SCN2A mutations. The case for it as "an identified ASD gene" is circumstantial at best.

Describing SCN2A as an “identified ASD gene” is based on recent literature. Taken from Sanders et al. 2012: “Among a total of 279 identified de novo coding mutations, there is a single instance in probands, and none in siblings, in which two independent
nonsense variants disrupt the same gene, SCN2A (sodium channel, voltage-gated, type II, α subunit), a result that is highly unlikely by chance”. In addition a third de novo SCN2A mutation was reported in an independent cohort (Neale et al., 2013). We therefore think the current wording is appropriate.

_The conclusions that the mutation is "pathogenic" is speculative….The text should reflect the descriptive nature of the work and not describe it as pathogenic in a recently identified ASD gene._

We appreciate the reviewers concern and have refined the language in acknowledgement. For example, in the abstract we changed the wording from pathogenic to “might be contributing to risk”; “This report suggests that a mutation in SCN2A might be contributing to risk for ASD.” And in the discussion we mention: “Although this particular mutation has not been reported before, it could be considered as contributing to risk of ASD by causing abnormal gene splicing, leading to significantly shortened protein product and/or an abnormal message that is subject to nonsense-mediated mRNA decay.”

_Major compulsory revisions_

_The paper should be shortened to about 1/3 its size_

We shortened the manuscript as much as possible without compromising its content.

_Minor essential revisions_

_In the abstract the sentence beginning "to characterise a seven-year old…." is poorly written and should be revised to make better sense._

We appreciate the feedback and have revised the sentence accordingly, and the whole manuscript; “We describe results from clinical and genetic characterizations of a seven-year-old male with ASD.”