Reviewer's report

**Title:** Identification of novel isoforms in the assessment of SNF2L as an XLMR (X-linked mental retardation) candidate gene in 12 families linked to Xq25-26.

**Version:** 1 **Date:** 26 November 2007

**Reviewer:** Pietro Chiurazzi

**Reviewer's report:**

**General**

This article provides a detailed characterization of the alternative splicing of the SNF2L/SMARCA1 gene. This gene resides in the Xq25 cytoband, immediately upstream of the OCRL gene involved in the pathogenesis of the Lowe syndrome. The Authors, who are familiar with the SNF2L gene, hypothesized that it may be involved in causing X-linked mental retardation. Indeed, the brain expression profile in the developing mouse, its similarity with the ATRX gene and its involvement in neuronal differentiation make it a likely candidate. Unfortunately no mutation has been found in probands belonging to 12 independent families with mapping intervals overlapping the Xq25 cytoband.

I am not satisfied with the title and would personally suggest that the Authors consider changing it as follows: "Characterization of novel isoforms and evaluation of SNF2L/SMARCA1 as candidate gene for X-linked mental retardation in 12 families linked to Xq25-q26."

**Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)**

1) I could not readily identify the CBP gene quoted in the Abstract (page 2, line 3) as an XLMR genes: please provide me and the readers with appropriate references for this gene as well as for the others quoted in the text. As a matter of fact the "CBP" gene is not mentioned anywhere else in the article!

2) At the end of the Results/Discussion section the Authors mention the Shashi syndrome (MRXS11 %300238) and the Cilliers syndrome, but according to my latest XLMR update there are at least another 1 syndrome and 2 neuromuscular conditions mapping to Xq25 (Wilson/MRXS12 %309545, Gustavson %309555 and CMTX4/Cowchock-Fishbeck %310490). Furthermore, 8 MRX pedigrees (MRX number 27, 35, 42, 62, 70, 71, 75 and 82) also have mapping intervals overlapping Xq25. Maybe some of these are indeed among the tested families (like the Pettigrew syndrome!), but I was not able to recognize them from the codes provided in the Patient material section of the Methods. If this is the case, this should be made explicit.

3) The Authors may want to quote our Review article on XLMR which is in press

4) Finally the Authors suggest that the small size of their sample (12 XLMR pedigrees with linkage intervals including SNF2L/SMARCA1) may explain the failure to detect any mutations in their candidate gene. I agree with them but would also add another explanation, namely the possibility that mutations in SNF2L could cause a more severe phenotype (maybe lethal in males!) associated with mid-/hind-brain malformations.

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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) Page 3, line 5 (Background): change as follows "....patient sequencing projects has increased the identification rate of XLMR disease genes."

2)Reference 7: please write "Rett" with capital "R"!

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Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

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.