Author's response to reviews

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.

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Author's response to reviews:

Dr. Erik Alexandersson, PhD
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Dear Dr. Alexandersson,

Please find enclosed our revised manuscript entitled, "Characterization of novel isoforms and evaluation of SNF2L/SMARCA1 as a candidate gene for X-linked mental retardation in 12 families linked to Xq25-26." which we hope has now addressed all the concerns of the reviewers and is ready for an unconditional acceptance for publication in BMC Medical Genetics.

We were very pleased to receive news that the manuscript was accepted in principal pending that we address the minor concerns raised. Two of the three reviewers had no concerns and accepted the manuscript without revision. The third reviewer had some minor essential revisions which we have addressed on the following pages in a point-by-point description. The reviewers¿ comments are summarized in italics followed by the response.

Overall, we believe that the changes have resulted in a much improved contribution.

Thank you for considering our work for publication in BMC Medical Genetics.
1. As agreed in the authors reply, a larger panel would gain more power. In our opinion, the fact that no mutations were identified in this selected population does not rule out the importance of this gene in (XL)MR. The answer, that the pilot needed to be performed first is acceptable. However, what is the follow-up plan and what are the expectations based on these negative results? This should be included in the discussion. In our discussion we discussed our follow-up plan of screening additional families and generating transgenic mice ablated for SNF2L. We have added the following additional sentence to the discussion to highlight our expectations. Together, the analysis of additional samples and the characterization of transgenic mice should define whether the SNF2L gene is a cause of mental retardation.

2. Abstract: The fact that so far no mutations have been identified in SNF2L do not justify the choice of a prime candidate. Please replace prime candidate by candidate. We have made this change to the abstract.

3. Conclusion: Indeed, SNF2L should remain a candidate XLMR gene for other families mapping to this region of the X chromosome including the Shashi syndrome. Indeed, SNF2L should remain a candidate XLMR gene for Xq25-26 linked XLMR families including the Shashi syndrome as well as in sporadic mental retardation cases. We have made the specific change to the text as requested.

4. As previously indicated it still remains unclear if the delta NLS and the NLS variants are found in the transcripts A or B. This is also true for +/- exon 13. Maybe this is not of major relevance, but the authors should discuss this in more detail. We have added the following sentences to the first paragraph on page 10 to highlight the isoform variability that can arise: As such, it will be important to further explore the function of these novel SNF2L isoforms to determine their specific roles, similar to work done with the SNF2L+13 variant. Indeed, with splicing occurring at the 5'-end of the gene (isoforms SNF2LA and B), the 3'-end of the gene (NLS or NLS) and encompassing exon 13 (+exon 13 or exon 13) there are 8 possible isoforms of the SNF2L protein that can impinge on the function/activity of the protein.

5. In the plasmid construct section: The term SNF2L2 variant is used. What is meant the B variant. SNF2L2 is the name given to the cDNA by Okabe et al in the original publication and the reviewer is correct in thinking it is the B variant. For clarity we have added (SNF2LB) after the use of SNF2L2.

6. The name Hans van Bokhoven is misspelled twice. We have corrected the spelling of Dr. Bokhoven's name and thank the reviewer for finding this error.