Reviewer's report

Title: TM4SF10 gene sequencing in XLMR patients identifies common polymorphisms but no disease-associated mutation

Version: 1 Date: 30 May 2004

Reviewer: Carsten Bergmann

Reviewer's report:

General

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

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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)

The present study by Christophe-Hobertus et al. nicely describes mutation screening of the TM4SF10 gene in a cohort of patients with XLMR. Overall, the paper is well written and structured. It is well known that XLMR constitutes a largely heterogeneous group. Thus, in a considerable proportion of particularly non-syndromic XLMR patients the underlying gene defect still remains to be unravelled. As none of the patients analysed by the authors carries a mutation in the TM4SF10 gene (even if the promoter region has not been screened so far), TM4SF10 mutations won't be a frequent cause of XLMR. Of course, it cannot be definitely excluded that further studies may reveal alterations in this gene as a rare cause of XLMR.

In total, 16 patients originating from 14 putatively unrelated families and five healthy controls were enrolled in direct sequencing of the TM4SF10 gene. This gene has been recently characterized by the authors and is located on Xp21.1. Its longest open reading frame consists of three exons comprising 543 bp. The 3233-bp long 3'-UTR was also included in this survey due to its evolutionarily conserved character. The TM4SF10 gene is predicted to encode a 181 aa, four-transmembrane domains protein with so far unknown function termed Brain Cell Membrane Protein 1 (BMCP1). A major site of expression is in the brain.

1) Given the X-chromosomal localization of the TM4SF10 gene, high expression levels of the encoded protein BMCP1 in brain tissue, and its putative role in cell junctions prompted the authors to screen males affected by XLMR for mutations in this gene. Furthermore, the structurally similar TM4SF2 gene that is located in the vicinity of the TM4SF10 gene constitutes a known XLMR gene. This gene has been previously excluded as underlying reason of XLMR in the study cohort. However, it remains nebulous how this was done. Thus, the authors should add information on the method applied (direct sequencing?). In case only the coding region of the TM4SF2 has been screened for mutations so far, it may be a reasonable approach to look for mutations within regulatory sites (e.g., promoter region) (of course, the latter is only thought of as a discretionary revision).

2) Information should be added on the patients analysed (including data on degree/severity of MR) even if this was already done in previous works or may appear less important as most individuals merely display impaired cognitive functions without any further features. It is recommended to shortly summarize the main features of each patient in a table that should also include data on family structure (multiplex pedigrees?/mildly affected carrier females known?).

3) What was the reason to screen more than one affected patient in two pedigrees of the current
4) Please provide additional information on linkage analysis of multiplex families included in the present study (extent of interval).
5) Has chromosomal analysis been performed in any patient and did it show normal results in any case? What other genes known to be involved in XLMR were previously excluded (albeit these data were already provided in previous studies, it should be mentioned as it makes the paper more readable).
6) Was there any difference in allele distribution of the SNPs among patients and controls?

Discretionary Revisions (which the author can choose to ignore)

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: Acceptable

Statistical review: No

Declaration of competing interests:
None.