Reviewer’s report

Title: XLMR in MRX families 29, 32, 33 and 38 results from the dup24 mutation in the ARX (Aristaless related homeobox) gene

Version: 3  Date: 10 February 2005

Reviewer: Pietro Chiurazzi

Reviewer’s report:

General

This Manuscript reports on the causing mutation and gene for 4 already described MRX families (MRX29, MRX32, MRX33 and MRX38), mapping to Xp22.1. However, some corrections need to be done before it will be suitable for publication. In particular, MRX56 quoted in the paper is actually MRX54 and references 5 and 6 should be switched with each other. Furthermore, the statement made in the abstract and in the Discussion that the dup24 mutation in the ARX gene accounts for 73% (8/11) and 20% (2/10) families with nonspecific (MRX) and specific/syndromic (MRXS) forms of XLMR linked to Xp22.1 is misleading and cannot be simply presented like that. Indeed, as the Authors rightly discuss, Mandel and Chelly pointed out that such overestimates in mutation prevalence were not confirmed by several larger screening studies. Therefore, it is right to be cautious about the actual prevalence of ARX mutations (including the recurrent dup24) as large-scale screening projects may not yield so many results after all.

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

None.

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) My major concern with this manuscript is the strong statement made in the Abstract (conclusion section) and Discussion. I think it is misleading to plainly state "the ARX dup24 mutation .... (accounts) for about 73% of nonsyndromic families linked to Xp22.1". This is true for the particular subset of families studied by the Authors. The Authors may instead rephrase their statement into something like "The ARX dup24 mutation appears to be one of the most common XLMR mutations, being found in several (specific and nonspecific) families linked to Xp22.1".

2) I personally prefer to speak of "specific" and "nonspecific" XLMR, rather than "syndromic" and "nonsyndromic" forms. In fact, some nonsyndromic forms can be considered specific when a metabolic deficit or neuromuscular sign is present.

3) In the Background and Discussion, MRX56 must be changed into MRX54! In fact, it is MRX36, MRX43, MRX54 and MRX76 which were found to have a dup24 in the ARX gene by Bienvenu et al. (2002), which is reference [5]. An extra reference published by Frints et al. (2002) on MRX36 has been quoted by the authors as [6]. This means that the two references should be switched, because reference [5] is quoted after MRX36 (and should be Frints et al.) and reference [6] is quoted after MRX 43, 54 and 76 (and should be Bienvenu et al.).
4) Finally and importantly, the original references describing MRX29 (Hane et al., 1996), MRX32 (Hane et al., 1999), MRX33 (Holinski-Feder et al., 1996) and MRX38 (Schutz et al., 1996) must be quoted, possibly already in the Background, immediately after they are first mentioned! This implies renumbering the last two references (Mandel & Chelly and Gronskov et al.).


Discretionary Revisions (which the author can choose to ignore)

The Authors might add the reference of Kitamura et al. (2004) which reviewed extensively the spectrum of ARX mutations and pointed out the “pleiotropy” also of the dup24 mutation.


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

Declaration of competing interests:

I declare that I have no competing interests.