Letter to the editor

A new proteolipid lipoprotein mutation in Pelizæus-Merzbacher disease

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Dear Sir,

Pelizæus-Merzbacher disease (PMD) is an X-linked disorder caused by abnormalities in the proteolipid protein (PLP) gene which has been mapped to the Xq22 region (Willard and Riordan, 1985). The gene contains 7 exons (Diehl et al., 1986). In 10–25% of the families analysed, mutations have been identified in all exons, but predominantly in exons 3, 4 and 5 (Hudson et al., 1989; Kleindorfer et al., 1995). As yet, more than 30 different exonic mutations have been reported (for review Hodes et al., 1993; Seitelberger, 1995), but no correlation could be found between the nature of the mutation and the severity

Fig. 1. Pedigree of the family. Symbols: +, VOR disinhibition; −, hyporeactive VOR, O, not examined; x, mutation carrier.

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of the disease (Hodes et al., 1993). Duplication of the PLP gene is the cause in about 25–60% of the families, which indicates that PLP gene overdosage might be an important genetic abnormality in PMD (Smeets, 1995; Hodes and Dlouhy, 1996; Inoue et al., 1996).

In 1992, we reported disinhibition of the vestibulo-ocular reflex (VOR) in a PMD family (Huygen et al., 1992). All three obligate carriers exhibited VOR disinhibition, which was also found in one of the seven possible carriers, but in none of the three unaffected males (Fig. 1).

We had reason to believe that a similar finding in the two affected males was prohibited by their ocular motor dysfunction. We speculated that VOR disinhibition might be a discriminating feature between carriers and non-carriers of PMD. Recently, a pathogenic mutation has been identified in exon 2 of the PLP gene in this family, leading to substitution of Phe31 for Val. This mutation has not been reported before. Other amino acid substitutions in exon 2 are Pro14Leu (Trofatter et al., 1989; Hodes et al., 1995) and Thr42Phe (Dlouhy et al., 1993; Pratt et al., 1995); a single base (A or G at the third position of codon 55, Gln) synonymous polymorphism was described by Osaka et al. (1995).

The segregation of the Phe31Val mutation in our family (Fig. 1) showed that the mutation was not only present in the patients and the obligate carriers, but also in four out of the seven possible carriers.

One woman with VOR disinhibition did not carry the mutation, while three carriers of the mutation had normal VOR findings. The fourth carrier of the mutation showed a hyporeactive VOR. We conclude that molecular genetic analysis is necessary for reliable carrier detection in PMD; VOR testing or MRI alone are not useful (Huygen et al., 1992; Hodes et al., 1995).

References


