NUCLEIC ACID SEQUENCE ANALYSIS OF THE PROTEOLIPID PROTEIN GENE IN PELIZAEUS-MERZBACHER DISEASE FAMILIES

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Abstract

The proteolipid protein (PLP) is the major protein species of the myelin sheath of the central nervous system (CNS). One of PLP's functions is to maintain integrity of the sheath by anchoring adjacent extracellular membranes to each other. The *PLP* gene is localized to the X chromosome in mammals. In humans, *PLP* has been localized subchromosomally to the Xq22 region.

Animal models, the *jimpy* mouse and the *md* rat, indicate that defects in the *plp* gene can cause extensive disruption of nerve conduction within the CNS. Pelizaeus-Merzbacher disease (PMD) is a human X-linked recessive disorder that displays myelin deficiency within the CNS. The similarity between the animal models and PMD has implicated *PLP* as a PMD-causing gene.

The seven *PLP* exons have been examined by DNA sequence analysis in eight families presenting with PMD. The polymerase chain reaction allowed amplification of the exons directly from genomic DNA of PMD-affected males. The goal of this research was to find *PLP* sequence polymorphisms that could be used in linkage analysis, thus defining *PLP*'s involvement in PMD.

A variety of changes were found in *PLP*. Family 2 had a C->T transition in exon 2 causing a substitution of leucine (CTC) for proline (CCC) at amino acid 14. Segregation of the exon 2 variant and the PMD gene was completely concordant in this family (lod=4.61, Θ=0). This places the PMD gene for family 2 in or near the Xq22 region and supports the conclusion that PMD is caused by the variant *PLP* gene. Family 3 had a C->T transition in exon 4 that caused a

substitution of isoleucine (ATC) for threonine (ACC) at amino acid 155. Families 4 and 8 had neutral mutations in the codon third-base "wobble" position creating restriction endonuclease polymorphisms that may aid in future PMD research. Family 6 may have a deletion of *PLP* exons 2 through 4; however, the exact nucleotide defect was not defined. Families 1, 5 and 7 had no *PLP* nucleic acid changes.

These results indicate that some forms of PMD may be caused by mutations at the *PLP* locus. However, those families showing an X-linked recessive mode of inheritance, but no *PLP* changes, suggest that either other PMD-causing loci exist on the X chromosome or their defects occur in regulatory regions of the *PLP* gene.

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