Pelizaeus-Merzbacher Disease in a Family of Portuguese Origin Caused by a Point Mutation in Exon 5 of the Proteolipid Protein Gene

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Single-strand conformational polymorphism analysis of an affected male with Pelizaeus-Merzbacher disease (PMD) showed a slight change in mobility of amplified exon 5 of the proteolipid protein (PLP) gene. The exon was sequenced and a G→A transition at codon 216 was found. This mutation eliminates a BstNI restriction site and creates a MaeI restriction site. In 1989, Gencic et al. reported a mutation that destroyed the same BstNI site, but resulted in a substitution at codon 215 [Am J Hum Genet 45:435-442]. The mutation we report here is also present in the patient's mother and her male fetus as determined by polymerase chain reaction analysis of amniocytes.

INTRODUCTION

Pelizaeus-Merzbacher disease (PMD) is an early onset, X-linked disorder of the central nervous system (CNS). The clinical signs of classical PMD include nystagmus, progressive psychomotor retardation, involuntary movements, ataxia, titubation, and death within the second decade of life. This rare disorder affects primarily the white matter. To date, the causes of several cases of PMD have been unique mutations in the proteolipid protein gene (PLP). PLP is the major structural protein of CNS myelin. In this report, we present a unique mutation in exon 5 of the PLP gene in a family of Portuguese origin. This codon 216 mutation causes a loss of a BstNI site and a gain of a MaeI site that was used to diagnose prenatally the mutation in a male fetus.

MATERIALS AND METHODS

A child (II-1, Fig. 1) of Portuguese parents had abnormal eye movements at one week and poor head control at 4 months. By 8 months OFC was at the 50th centile, but length and weight at the 5th. Nystagmus was pendular and horizontal. There were poor head and trunk control, and scissoring of legs. He could not sit, roll over, nor grasp. Head computed tomograph (CT), electromyograph (EMG), electroencephalogram (EEG), nerve conduction, and audiogram were normal, but the brain stem auditory evoked response (BAER) was abnormal. Magnetic resonance imaging (MRI) showed diffusely abnormal increase in signals throughout the white matter consistent with a dysmyelinating disease. Somatosensory evoked responses (SER) showed abnormal N13 and N20 responses bilaterally, consistent with abnormal brainstem conduction. At age 4 years, he still could not sit, walk, reach for objects, or speak. There was spastic quadriaparesis with hyperreflexia.

DNA was extracted from peripheral lymphocytes. Single-strand conformation polymorphism (SSCP) analysis [Pratt et al., 1993] and genomic amplification and sequencing [Pratt et al., 1991b] were performed as previously described. Amplification primers for exon 5 were 5′-CTTGCTTTTTGTTCTTCTT-3′ and 5′-TAACCATAAACCCTC-3′. Restriction analyses were done according to manufacturers’ recommendations. Approximately 1 μg of each polymerase chain reaction (PCR)-amplified sample was digested with BstNI (New England Biolabs). To confirm the presence of the mutation a 1 μg sample was digested with MaeI.
DISCUSSION

PMD is a rare X-linked dysmyelinating disorder of the CNS. PLP is the main structural protein of CNS myelin. One fourth to one third of PMD cases have a mutation in the coding portion of the \textit{PLP} gene [Hodes et al., unpublished]. We describe here a G$\rightarrow$A transition in codon 216. Because of present uncertainty about the exact structure of PLP, the substituted serine could be present in either an intracellular or extracellular loop of PLP [Popot et al., 1991]. The change of glycine, an aliphatic side chain amino acid, to serine, an aliphatic hydroxyl side chain amino acid, could change the generally hydrophobic nature of the PLP molecule and thus disrupt the structure of myelin. As more families with the clinical picture of PMD and different amino acid substitutions accumulate, the effect of these changes may become clearer. It is also of interest that each family with a mutation in the coding region of \textit{PLP} reported to date has had a different mutation. The change we report here has not been found in over 80 X chromosomes we have examined by sequencing or SSCP analysis.

Mutations have now been reported in exon 2 [Trofatter et al., 1989; Dlouhy et al., 1993], exon 3 [Pratt et al., 1991a; 1992; Bridge et al., 1992; Doll et al., 1992; Saugier-Veber et al., 1994], exon 4 [Pratt et al., 1991, 1993; Bridge et al., 1992; Doll et al., 1992; Saugier-Veber et al., 1994], exon 5 [Gencic et al., 1989; Pham-Dinh et al., 1991; Strautnieks et al., 1992; Doll et al., 1992], exon 5 [Gencic et al., 1989; Pham-Dinh et al., 1991; Strautnieks et al., 1992; Iwaki et al., 1993], exon 6 [Pratt et al., 1994], and exon 7 [Kurosawa et al., 1993]. In addition, a complete gene deletion has been noted by Raskind et al. [1992], a deletion of parts of exons 3 and 4 [Kleindorfer et al., 1994], and a mutation at a splice site [Strautnieks and Malcolm, 1993].
NOTE ADDED IN PROOF

After this work was finished, we became aware of the article by Otterbach et al., 1993. This reports the same mutation noted by us, but apparently in a different family.

REFERENCES


