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LETTER TO THE EDITOR

A Novel Missense Mutation in the Exon Containing the Putative Ornithine-Binding Domain of the OTC Enzyme in a Female

Communicated by William S. Sly

To the Editors:

We have identified a novel nonsense mutation in genomic DNA from leukocytes of a symptomatic female with ornithine transcarbamylase (OTC) deficiency. The patient, KK, was referred at age 3 years and 10 months with her second episode of intermittent alterations of mental status over a 10-month period. Laboratory studies revealed hyperammonemia (>240 μmol/liter), increased hepatic transaminase concentrations, and elevated concentrations of serum glycine, glutamine, and alanine. Excess orotic acid excretion was documented in the urine and residual enzymatic activity of OTC on needle biopsy samples of the liver from two locations revealed activities of 10 and 15%, respectively.

By Southern blot analysis using a human OTC cDNA probe (Horwich et al., 1984), decreased intensity of the 2.6-kb *Taq*I fragment representing exon 9-containing sequences was evident and was accompanied by an extra 4.5-kb fragment not apparent in the samples from either parent. *Taq*I digestion of PCR amplified products from both parents revealed complete cleavage, whereas in the affected patient, the mutant allele was recognized as an uncleaved fragment upon *Taq*I digestion. Nucleotide sequence analysis of the mutant exon 9 sequence revealed a C→T substitution at codon 320 converting an arginine to a premature stop codon. Figures documenting the southern blot findings, as well as those of the *Taq*I digestion and the sequence analysis, were submitted for review, but are not shown.

Mutations in *Taq*I recognition sites have been identified in other exons of the human OTC gene (exons 1,3 and 5) (Maddalena et al., 1988; Spence et al., 1989; Grompe et al., 1991). The only known alteration of the exon 9 *Taq*I site is a missense mutation (R320L) (Grompe et al., 1991). The exon 9 nonsense mutation in KK probably results in production of a truncated transcript deleted of the last third of exon 9, a functionally important region encoding a putative binding site for ornithine (Horwich et al., 1984).

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