Novel Mutation in Exon 7 of Phenylalanine Hydroxylase Gene in a Chinese Patient with Phenylketonuria

To the Editor:

We recently found a new homozygous R158W mutation in exon 5 of the phenylalanine hydroxylase (PAH; EC 1.1.4.16) gene in a Chinese patient with phenylketonuria (PKU) (1). Polymerase chain reaction (PCR)-amplified DNA fragments were sequenced directly to detect the mutations of the PAH gene by using solid phase technology (2). Another novel mutation (R241C) in exon 7 of the PAH gene in the Chinese patient with PKU is presented here.

Amplification primers and optimal protocols were selected (3) and prepared as before (1). Amplification primers for exon 7 were: 7A, 5'-CTCCTAGTGCCCCTGACTCA-3' and 7B, 5'-XGTGTCGCTGCAAATCTTAGC-3', where X is biotin conjugated to the 5' end of the antisense primer. After initial denaturation for 5 min at 94°C, thermal cycling was carried out for 30 cycles under the following conditions: denaturation for 60 s at 94°C, 120 s annealing at 62°C, and 90 s primer extension at 75°C.

Sequencing revealed a heterozygous C-to-T transition at the first base of codon 241, resulting in a substitution of Arg for Cys. The result was confirmed by use of allele-specific oligonucleotide probes as before (1). A second mutation in the PKU alleles has not yet been identified in other exons of the gene; however, more than 75% of PKU patients are known to be heterozygous for a particular mutation. The biochemical and clinical phenotype of the patient indicated classical PKU with severe hyperphenylalaninemia (pretreatment serum phenylalanine 365 mg/L). It has been reported that a large number of PKU mutations may occur in exon 7 of the gene in Caucasians and Orientals (3-5). In particular, substitutions of Arg for certain amino acids in PKU have been observed at numerous other positions of the PAH gene, and, through both genetic and expression analyses, most of these substitutions have been shown to be the cause of PKU (6). Thus, the effects of a given amino acid substitution may differ significantly depending on its position in the protein (7, 8).

According to genetic and biochemical findings, we consider the R241C substitution in exon 7 a disease-causing mutation.

References

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