Identification of Three Novel PKU Mutations among Chinese: Evidence for Recombination or Recurrent Mutation at the PAH Locus

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Three novel mutations have been identified in the phenylalanine hydroxylase (PAH) genes of Chinese classical phenylketonuria (PKU) patients. Two of these substitutions (W326X and Y356X) result in the generation of a premature stop codon, while the third (IVS-7nt2) alters an invariant dinucleotide splicing signal. These mutations together account for about 10% of all PKU alleles in the Chinese population. The W326X mutation is associated with PAH RFLP haplotype 4, the most common haplotype in Orientals, while the IVS-7nt2 mutation occurs once on a haplotype 7 chromosome. The Y356X mutation is associated with multiple haplotypes, possibly due to crossover, gene conversion, or recurrent mutation.

Classical phenylketonuria (PKU) is an autosomal recessive metabolic disorder caused by a deficiency of hepatic phenylalanine hydroxylase (PAH). To date, over 60% of all PAH mutations in the Chinese population have been identified, and each mutation is in linkage disequilibrium with a single RFLP haplotype [see (3) for review]. Here we report three additional Chinese PAH mutations. Two are associated with single RFLP haplotypes in Orientals, while the IVS-7nt2 mutation occurs once on a haplotype 7 chromosome. The Y356X mutation is associated with multiple haplotypes, possibly due to crossover, gene conversion, or recurrent mutation. © 1992 Academic Press, Inc.

ASO-hybridization analysis failed to detect these substitutions on 104 normal Chinese alleles. Among mutant alleles, IVS-7nt2 and W326X are rare, accounting for 1 and 2% of all Chinese PKU alleles, respectively (Table 1). Y356X is more prevalent (7%), despite being found primarily on the less common haplotypes 7 and 9 (Table 1). Kindred analyses demonstrated that both IVS-7nt2 and W326X are present on haplotype 4 alleles, while Y356X is linked to four different haplotypes (3, 4, 7, and 9). IVS-7nt2 was found only in Northern Chinese, W326X only in Southern Chinese, but Y356X has a similar frequency in both populations (data not shown).

One hypothesis that could explain the association of Y356X with multiple haplotypes in both Northern and Southern Chinese populations is hypermutability. Several investigations have implicated hypermutable CpG dinucleotides in the occurrence of PAH mutations (1, 4, 6). However, since Y356X does not involve a CpG dinucleotide, this particular mechanism cannot be invoked. In addition, it might be expected that the frequency of a recurring mutation should be highest on chromosomes of the predominant haplotype (i.e., 4) and lower on chro-
TABLE 1

Population Genetics of Three Chinese PKU Mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Haplotypes</th>
<th>Chinese Frequency</th>
<th>Caucasian Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVS-7nt2</td>
<td>7</td>
<td>1/104</td>
<td>0/50</td>
</tr>
<tr>
<td>W326X</td>
<td>4</td>
<td>2/104</td>
<td>0/50</td>
</tr>
<tr>
<td>Y356X</td>
<td>3, 4, 7, 9</td>
<td>7/104</td>
<td>0/50</td>
</tr>
</tbody>
</table>

Allele-specific oligonucleotide probes for these mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Normal probe</th>
<th>Mutant probe</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVS-7nt2</td>
<td>5'-CCGAACCCGTTGAGTACTG-3'</td>
<td>5'-ACGATCTCATCGGTTCCG-3'</td>
</tr>
<tr>
<td>W326X</td>
<td>5'-ATTTACTGGTTTACTGT-3'</td>
<td>5'-ACGATCAACTAGTAATAAT-3'</td>
</tr>
<tr>
<td>Y356X</td>
<td>5'-CTACAGTACTGCTTATC-3'</td>
<td>5'-CTACAGTACTGCTTATC-3'</td>
</tr>
</tbody>
</table>

* Number of mutant alleles bearing the mutation/total number of mutant alleles analyzed by ASO hybridization analysis.

mosomes of rare haplotypes (i.e., 3, 7, and 9). In this instance, Y356X is observed only once on a haplotype 4 background, while it occurs twice and three times on haplotype 9 and 7, respectively. Although these data do not support the recurrent mutation hypothesis, the number of mutant alleles are too few to dismiss this hypothesis.

A second hypothesis that could explain these findings is random mutation in an ancient Asian “founding” population followed by gene conversion or crossover. A comparison of haplotypes 3, 4, 7, and 9 shows that they each differ from the others at two or more RFLP sites, including in some cases those flanking the mutation site.

Transfer of this mutation between alleles of different haplotypes must therefore either involve only a small region of the gene containing the mutation site or possibly predate the divergence of these haplotypes. According to this hypothesis, the present low frequency of this allele must reflect genetic drift. The precise mechanism(s) accounting for Y356X association with multiple haplotypes may become evident as additional alleles of this type are examined.

REFERENCES

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