New Glucose-6-Phosphate Dehydrogenase Mutations From Various Ethnic Groups

By E. Beutler, B. Westwood, J.T. Prchal, G. Vaca, C.S. Bartsocas, and L. Baronciani

Seven new mutations that produce glucose 6 phosphate dehydrogenase (G6PD) deficiency are described. Three are in variants that were biochemically characterized and described previously, while four were found in samples that had not been characterized biochemically. Several of the mutations affect the amino acids that are mutated in other G6PD variants. As had been noted previously, variants that are associated with nonspherocytic anemia are located either near the glucose 6 phosphate or the NADP binding sites. Variants more distant from these sites are not associated with chronic hemolysis.

Based on the biochemical characteristics of genetic variants of glucose-6-phosphate dehydrogenase (G6PD), over 400 different mutations were thought to exist.1 As it became possible to identify mutations at the DNA level, it was shown that many variants thought at one time to be distinct were actually identical.2 Nonetheless, analysis of DNA from G6PD-deficient individuals from various populations has continued to show that additional mutations exist.

Materials and Methods

We performed sequence analysis on polymerase chain reaction (PCR)-amplified genomic DNA from G6PD-deficient individuals from various ethnic groups using previously described methods.3 In each case the existence of the mutation was verified either by sequencing the opposite strand, detecting the formation or destruction of a restriction site, or both. G6PD Pawnee,1 Guadalajara,4 and Alhambra3 have been characterized previously. While complete sequence analysis can be performed on a single milliliter of blood, biochemical characterization of deficient variants generally requires 200- or 300-mL samples. Thus, insufficient blood was available for biochemical characterization of the other variants. The residual enzyme activity of G6PD "Santiago" and "Ierapetra" was less than 1% of normal, that of "Mexico City" 35% of normal and electrophoretically rapid, and that of "Japan" 3.3% of normal.

Results and Discussion

Seven mutations that have not been described previously were found. The results of our studies are summarized in Table 1.

Including the seven new variants described here, we know of 40 published and unpublished distinct mutations affecting G6PD.6 All but one, a deletion of a triplet,7 represent point mutations.

So many mutations are now scattered through the coding sequence of G6PD that several of the mutations reported here for the first time involve amino acids, or even nucleotides that are altered in other mutations. Thus, G6PD "Mexico City" is characterized by a G → A transition at nucleotide 680, the same nucleotide that is altered from G to T in one of the types of G6PD A-. In G6PD "Mexico City" the arginine at amino acid 227 is changed to a glutamine, while in one form of G6PD A- it has become a leucine. G6PD Guadalajara is a mutation at nucleotide 1159, which changes the arginine 387 to cysteine. The same amino acid is changed to histidine in G6PD Beverly Hills, a mutation involving the adjacent nucleotide 1160. G6PD "Japan" changes the glycine 410 to aspartic acid, while it is changed to cysteine in G6PD Riverside, a mutation at the adjacent 1228.

The mutations described here continue to follow the pattern that we described previously.2 Mutations producing nonspherocytic hemolytic anemia are located either near

Table 1. G6PD Mutations

<table>
<thead>
<tr>
<th>Ethnic Origin</th>
<th>Previous or Proposed Designation</th>
<th>Reference</th>
<th>Clinical Effect</th>
<th>Nucleotide Substitution</th>
<th>Amino Acid Substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chilean</td>
<td>&quot;Santiago&quot;*</td>
<td>NSHA1</td>
<td>N/A</td>
<td>C</td>
<td>198 Arg → Pro</td>
</tr>
<tr>
<td>Mexican</td>
<td>&quot;Mexico City&quot;*</td>
<td>None</td>
<td>680 G → A</td>
<td>227 Arg → Gin</td>
<td></td>
</tr>
<tr>
<td>Greek</td>
<td>&quot;Ierapetra&quot;*</td>
<td>None</td>
<td>1057 C → T</td>
<td>353 Pro → Ser</td>
<td></td>
</tr>
<tr>
<td>Mexican</td>
<td>Guadalajara*</td>
<td>4</td>
<td>NSHA1</td>
<td>1159 C → T</td>
<td>387 Arg → Cya</td>
</tr>
<tr>
<td>US White</td>
<td>Alhambra*</td>
<td>5</td>
<td>NSHA1</td>
<td>1180 G → C</td>
<td>394 Val → Leu</td>
</tr>
<tr>
<td>Japanese</td>
<td>&quot;Japan&quot;*</td>
<td>4</td>
<td>NSHA1</td>
<td>1229 G → A</td>
<td>410 Gly → Asp</td>
</tr>
<tr>
<td>US White</td>
<td>Pawnee*</td>
<td>1</td>
<td>NSHA1</td>
<td>1316 G → C</td>
<td>439 Arg → Pro</td>
</tr>
</tbody>
</table>

*Proposed designation.
†Previous designation.
‡Nonspherocytic hemolytic anemia.
the glucose 6 phosphate binding site (G6PD Santiago) or near the putative NADP+ binding site G6PD Guadalajara, Alhambra, and Japan. Mutations that are distant from these regions were not associated with chronic hemolysis.

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REFERENCES

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