Glucose-6-Phosphate Dehydrogenase (G6PD) Mutations Associated With F8C/G6PD Haplotypes in Chinese

To the Editor:

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human disease producing red blood cell enzyme deficiency. Nearly 400 biochemical variants have been described, but less than 70 mutations have been identified at the DNA level. We and others have previously shown that at least nine different types of mutation are responsible for G6PD deficiency in the Chinese population of Taiwan. The finding that several polymorphic sites are located near or within the G6PD gene may provide a haplotype pattern that would enable us to analyze the linkage disequilibrium between mutations and polymorphisms.

The F8C/G6PD (coagulation factor VIIIc/G6PD) haplotype spanning the Xq28 region from coagulation factor VIIIc to the G6PD genes was investigated. We have studied four polymorphic sites from this region in 66 Chinese who carry known G6PD mutations. These polymorphic sites include (1) the HindIII site in intron 19 of the factor VIII gene, (2) the 1311 C→T mutation of the G6PD gene, (3) the polymorphic NlaIII site in intron 11 of the G6PD gene, and (4) the polymorphic EcoRI site located 20 kb downstream of the G6PD gene. Table 1 shows that most mutations found in Chinese are mainly associated with haplotype VI+VII, i.e., -- - + (F8HindIII/1311/NlaIII/EcoRI), except for three types of mutation that occur at nucleotide (nt) positions 95, 487, 493, 1024, 1360, and 1388. For example, 29 of 31 Chinese subjects with the 1376 mutation are mainly associated with haplotype 111, whereas all of the 871 mutation cases are linked to a novel haplotype that we name here haplotype XI that has not been reported before. Interestingly, our unpublished data show that haplotype VI+VII is the dominant haplotype that accounts for nearly 80% of the normal Chinese population in Taiwan (manuscript in preparation). These findings support the hypothesis that mutations occurring at nt positions 95, 487, 493, 1024, 1360, and 1388 could all be derived from an ancient haplotype VI+VII.

The 1376 mutation was found to be not only associated with haplotype III (29 cases) but also linked to two other haplotypes (1 case in haplotype I and 1 case in haplotype VI+VII). This result suggested that the mutation at nt 1376 may have arisen repeatedly or a crossing-over event may have occurred between F8C and the G6PD gene or within the G6PD gene itself. In addition, by comparative analysis of the association between the 871 mutation and the 1311 polymorphic site, we found that Chinese subjects who carry the 871 mutation have T at nt 1311, as was previously found in G6PD Vanghan (a Laotian). In contrast, G6PD Jammu (a variant originally detected in an Indian subject) has a C at nt 1311, suggesting that the 871 mutation may have occurred repeatedly or a crossing-over event may have occurred between F8C and the G6PD gene or within the G6PD gene itself. Furthermore, by comparative analysis of the association between the 871 mutation and the 1311 polymorphic site, we found that Chinese subjects who carry the 871 mutation have T at nt 1311, as was previously found in G6PD Vanghan (a Laotian). In contrast, G6PD Jammu (a variant originally detected in an Indian subject) has a C at nt 1311, suggesting that the 871 mutation may have occurred repeatedly or a crossing-over event may have occurred between F8C and the G6PD gene or within the G6PD gene itself. Furthermore, by comparative analysis of the association between the 871 mutation and the 1311 polymorphic site, we found that Chinese subjects who carry the 871 mutation have T at nt 1311, as was previously found in G6PD Vanghan (a Laotian). In contrast, G6PD Jammu (a variant originally detected in an Indian subject) has a C at nt 1311, suggesting that the 871 mutation may have occurred repeatedly or a crossing-over event may have occurred between F8C and the G6PD gene or within the G6PD gene itself.

Table 1. Linkage Analysis Between Mutations and F8C/G6PD Haplotypes in Chinese Subjects From Taiwan

<table>
<thead>
<tr>
<th>G6PD Mutations</th>
<th>F8HindIII</th>
<th>1311T</th>
<th>NlaIII</th>
<th>EcoRI</th>
<th>Haplotypes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>95 A→G</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>392 G→T</td>
<td>3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>487 G→A</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>493 A→G</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>871 G→A</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>1024 C→T</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>1360 C→T</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>1376 G→T</td>
<td>29</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1388 G→A</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* indicates if restriction site is present or if 1311 C→T mutation is present. n indicates the number of affected male subjects analyzed.

* The F8C/G6PD haplotypes were named as described by Filosa et al. Because we did not analyze the polymorphic XbaI site in F8C gene, haplotypes VI and VII cannot be distinguished in our studies.
mutations may have arisen separately. Our findings are consistent with that reported by Xu et al.\(^6\) who analyzed the G6PD haplotype that carried different polymorphic sites located at intron 5 (Pvu II), nt 1116 (Pst I), nt 1311, and intron 11 (Mst III) of the G6PD gene. Finally, we found that most 1388 mutations were associated with haplotype VI + VII, whereas only 1 case was found to be associated with haplotype III. This particular case could have been generated by a recombination event that took place somewhere between F8C and G6PD genes at a later stage.

In summary, we have analyzed the association between G6PD mutations and F8C/G6PD haplotypes and found a strong linkage disequilibrium between some of the G6PD mutations and F8C/G6PD haplotypes. This information may provide some useful information for tracing the diversity of various ethnic populations in the world.

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CORRESPONDENCE

Glucose-6-phosphate dehydrogenase (G6PD) mutations associated with F8C/G6PD haplotypes in Chinese [letter]

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