To the Editor:

The level of hemoglobin (Hb) F in patients with sickle cell anemia (SS) or thalassemia (thal) is influenced by numerous factors that include sequence variations in promoters of the globin genes and in the locus control region-2 (LCR-2), the age and sex of the patients, and the number of active \( \alpha \)-globin genes. The latter involves a decrease in Hb F when an \( \alpha \)-chain deficiency (\( \alpha \)-thal) exists because the formation of \( \alpha \beta \) (Hb A) or \( \alpha \beta^s \) (Hb S) dimers is preferred over \( \alpha \gamma \) (Hb F) dimers. Data for SS patients and for \( \delta \beta \)-thal heterozygotes have shown a direct correlation between the severity of the \( \alpha \)-chain deficiency and the decrease in the level of Hb F. Similar results are provided in Table 1, which lists average values for SS patients 10 years or older to exclude any age-related effect. The decrease in Hb F level is most evident in SS patients with a haplotype no. 31 (Asian) homozygosity who are high Hb F producers.

Additional information has come from analysis of blood samples from the so-called SEA-\( \beta \)-thal heterozygotes; this deletion is characterized by a deletion of ~27 kb (including the \( \beta \)-globin gene and the LCR-5, 3' to \( \beta \)) and high Hb F levels. We reevaluated the levels of Hb F and \( \alpha \gamma \) in members of a Vietnamese family and a Cambodian family and in two members of a recently discovered Mongolian family (father and son; both adults); of the seven heterozygotes, one carried 5 \( \alpha \)-, three 4 \( \alpha \)-, two 3 \( \alpha \)-, and one 2 \( \alpha \)-globin genes. Direct correlations between the degree of \( \alpha \)-chain deficiency and the level

### Table 1. Levels of Hb F and \( \alpha \gamma \) in SS Patients, Ages 10 Through 32 Years, With and Without an \( \alpha \)-Thalassemia

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>( \alpha/\alpha )</th>
<th>( -\alpha/\alpha )</th>
<th>( -\alpha/-\alpha )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Hb F</td>
<td>( \alpha \gamma )</td>
</tr>
<tr>
<td>19-19</td>
<td>47</td>
<td>10.0 ± 4.3</td>
<td>37.9 ± 4.4</td>
</tr>
<tr>
<td>20-20</td>
<td>17</td>
<td>8.3 ± 5.8</td>
<td>40.4 ± 4.5</td>
</tr>
<tr>
<td>31-31</td>
<td>5</td>
<td>24.7 ± 3.2</td>
<td>67.3 ± 5.4</td>
</tr>
</tbody>
</table>

Males and females; values are averages plus standard deviations.
of Hb F (highest value 43.5%; lowest value 14.1%), as well as the $\delta\gamma$ value (highest value 68.8%; lowest value 60.4%), were observed (Fig 1). Sequence analysis of $\delta\gamma$ promoters showed that the $\delta\gamma$ gene of the chromosome with the deletion carried a T at position -158 (associated with high $\delta\gamma$ values6), whereas that of the normal chromosome had a C at that position (associated with low $\delta\gamma$ values). Figure 1 also lists the individual data for the 22 SS patients with haplotype no. 31 (Indian; with a T at position -158 of the $\delta\gamma$ promoter and with high $\delta\gamma$ values). A direct correlation is present between the number of $\alpha$-globin genes and the levels of Hb F but not between that number and the level of $\delta\gamma$.

These data support the concept that (severe) $\alpha$-chain deficiencies result in low levels of Hb F in disorders which are, among others, characterized by a (greatly) increased $\delta\gamma$-chain production. The results obtained for the SS patients indicate that the production of both types of $\gamma$ chain ($\delta\gamma$ and $\gamma\gamma$) is decreased equally. The decrease in the $\delta\gamma$ seen in the seven subjects with the SEA-$\beta$-thal (an ~10% decrease from $aalpha$ to $aalpha\delta\gamma\gamma$) is likely caused by a modest increase in $\gamma$-chain production by the two $\gamma$-globin genes on the normal chromosome (in a ratio of ~30% $\delta\gamma$ to 70% $\gamma\gamma$), which may result from the more severe anemia seen in these heterozygotes when an additional $\alpha$-thal-2 condition is present. Apparently the variations in the Hb F and $\delta\gamma$ values result from an interplay of different mechanisms.

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Alpha-Thalassemia and fetal hemoglobin [letter]

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