The Proportion of Hybrid Heterodimers in Homozygous or Doubly Heterozygous \( \beta \) Chain Variant Hemoglobinopathies Associated with \( \alpha \) Chain Hemoglobin Variants

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Abstract. Four \( \alpha \) genes exist on chromosome 16, but one or more of these genes can be deleted in association with Hemoglobin (Hb)G-Philadelphia \textit{in cis} to \( \alpha \)-thalassemia-2 in African-Americans. Therefore, the proportion of HbG-Philadelphia in HbG heterozygotes is trimodal at about 25% for \( \alpha^G_2\alpha^a\), 33% for \( \alpha^G_2\alpha^a\), and 50% for \( \alpha^G_2\alpha^a\) in patients with HbA. Those who are homozygous or doubly heterozygous for \( \alpha \) chain variants (\( \alpha^X_2\) or \( \beta^X_2\)) have neither HbA nor the \( \alpha \) chain variant (\( \alpha^X_2\beta^A_2\)), but have hybrid heterodimers (\( \alpha^X_2\beta^X_2\)). The proportion of hybrid heterodimers here should also be trimodal mirroring \( \alpha \) gene status. Eleven patients were identified: 4 with Hb SSG, 3 with Hb SCG, and 1 each with Hb OCG, HbSSMontgomery, HbSSChicago, and HbSSBourmedes. Heterodimer proportions were: 43.3 ± 1.5, 33.5 ± 2.3, and 15.8 ± 1.1% for 2, 3, and 4 respective \( \alpha \) genes which had been studied in 8/11 of the patients (\( r = 0.98 \)), implying that the prime determinant of the proportion of hybrid heterodimers in this patient group is the number of functional \( \alpha \) genes. (received 7 June 2000, accepted 8 July 2000)

Keywords: Hemoglobinopathy, \( \alpha \)-thalassemia, hemoglobin S, hemoglobin C

Introduction

Rarely, \( \alpha \) chain hemoglobin (Hb) variants occur with \( \beta \) chain variants; this condition most frequently happens when HbG-Philadelphia (\( \alpha^68 \) Asn→Lys) is associated with HbS (\( \beta^6 \) Glu→Lys). This unusual event results in the presence of hybrid heterodimers (\( \alpha^X_2\beta^X_2\)). The proportion of \( \alpha \) chain hemoglobin variant (\( \alpha^X_2\beta^X_2\)) is inversely related to the quantity of functioning \( \alpha \) chain genes on chromosome 16 [1]. Hence, in the case of HbG-Philadelphia, the proportion of HbG present is about 45, 33, or 25% with 2, 3, or 4 \( \alpha \) genes (\( \alpha^a/\alpha^a, \alpha^a/\alpha^a, \text{and } \alpha^a/\alpha^a \)), respectively.

Rarely, \( \alpha \) chain variants occur with homozygous or doubly heterozygous \( \beta \) chain variants, hence, HbA (\( \alpha^A_2\beta^A_2 \)) and the \( \alpha \) Hb variant with normal \( \beta \) chains (\( \alpha^X_2\beta^X_2 \)) are both absent. In this instance the abnormal \( \alpha \) chains bind to the variant \( \beta \) chains to form hybrid heterodimers composed of \( \alpha^X_2\beta^X_2 \). This situation is analogous to homozygous HbA (\( \alpha^A_2\beta^A_2 \)) without a \( \beta \) chain variant. Thus, the proportion of heterodimers in this special case should also reflect the number of \( \alpha \) genes.

Other considerations, such as the relative stability of the hybrid heterodimers in relation to the \( \beta \) chain Hb variant (\( \alpha^A_2\beta^X_2 \)) or the absolute charge difference between the variant \( \alpha \) (\( \alpha^X \)) and variant \( \beta \) (\( \beta^X \)) chain, might also affect the proportion of hybrid heterodimers. Because this rare circumstance might elucidate mechanisms affecting the severity of sickle cell disease, the relevant literature was reviewed to relate the hybrid heterodimer proportion to \( \alpha \) gene quantity.
Review of the Literature

Relevant literature from 1960 until the present was reviewed. *A Syllabus of Human Hemoglobin Variants* [2] was the primary focus of this review. Eleven cases were identified: 4 cases of homozygous HbS with HbG (HbSSG) [3-6]; 3 cases of HbSCG [7,8]; 1 case of HbOOG (HbO-Arab: β121 glu→lys) [7]; 1 case of HbSSChicago (α136 leu→met) [6]; 1 case of HbSSMontgomery (α48 leu→arg) [6,9]; and 1 case of HbSSBourmedes (α37 pro→arg) [10]. Three cases of HbSSMemphis (α23 glu→gln) were also identified, but the αMemphis2βS2 hybrid heterodimers did not separate from HbS and were not accurately quantified [11]. One case of HbSCG was identified in which S-G heterodimers (αG2βS2) were not separated from HbC [12]. The number of α genes was determined for 8 of these cases [6-7,13] (see Table 1).

A trimodal heterodimer proportion was found for the 11 cases: 15.8 ± 1.1, 33.5 ± 2.3, and 43.3 ± 1.5%. Linear regression for the percent heterodimers versus the number of α genes in the 8 patients for whom data were available had a correlation coefficient r of 0.98 (Fig. 1). There was no relationship of the absolute charge difference between α and β chain variants to the normalized heterodimer proportion.

<table>
<thead>
<tr>
<th>Hemoglobins</th>
<th>α genes</th>
<th>% heterodimers</th>
<th>reference</th>
</tr>
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<tbody>
<tr>
<td>SSChicago</td>
<td>4</td>
<td>16.7</td>
<td>[6]</td>
</tr>
<tr>
<td>SSMontgomery</td>
<td>4</td>
<td>14.6</td>
<td>[6,9]</td>
</tr>
<tr>
<td>SSBourmedes</td>
<td>b</td>
<td>16.0^c</td>
<td>[10]</td>
</tr>
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<td>SSG-Philadelphia</td>
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<td>32.9^d</td>
<td>[5]</td>
</tr>
<tr>
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<td>36.0^c</td>
<td>[8]</td>
</tr>
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<td>b</td>
<td>35.7^e</td>
<td>[4]</td>
</tr>
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<td>[7]</td>
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</tr>
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</tr>
<tr>
<td>SSG</td>
<td>2</td>
<td>42.3</td>
<td>[6]</td>
</tr>
</tbody>
</table>

^a determined by HPLC unless otherwise specified
^b not available
^c determined by isoelectric focussing
^d determined by cellulose acetate electrophoresis
^e determined by starch block and agar gel electrophoresis

Fig 1. Graph of a gene number versus percent hybrid heterodimers. Eight patients are included, but there is overlap for HbSCG and HbSSG patients with α-thal-2 homozygosity at 42.5% and 42.3% (see Table 1), so only 7 points are visible on the chart. Note the close correlation (r = 0.98) between gene number and percent heterodimers.
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Discussion

Literature review confirmed the hypothesis that the percent heterodimers in α chain variants associated with either homozygous or doubly heterozygous β chain variants mirrors the trimodal distribution of the α chain variant in the absence of a β chain mutation. This implies that, although the heterodimer proportion might be multifactorially determined, its prime component in these instances is the quantity of functional α chain genes.

For the 3 patients with HbSCG,* the proportions of S-G (αG2βS2) heterodimers (22.8, 15.9, and 18.0%) were virtually equal to the respective proportions of C-G (αG2βC2) heterodimers (19.7, 16.4, and 18.0), [7,8]. Thus, the charge difference between variant α and β chains is relatively insignificant because βS and αG chains have equal charge, whereas, βC and αC chains differ by 1.

Ten of the 11 cases included herein had a sickling hemoglobinopathy (HbSS or HbSC); hence, increased heterodimer proportion is another example of the amelioration of sickle cell disease by α-thalassemia [13] because the presence of 1 or 2 α-thal-2 genes (α/-αα, α/-α-) increases the hybrid heterodimer proportion which will decrease sickling if the hybrid heterodimers are less likely to crystallize than HbS.

Since the only cases here associated with α-thal-2 had the α chain variant HbG, which is linked to the α-thal-2 deletion in cis [1], and since HbG was not identified in the absence of α-thal-2, conclusions here about the influence of α genes on heterodimer proportions might be limited. Cases of HbG associated with 4 α genes (αααα) were not discovered in this study, although 3 other α chain variants (Chicago, Bourmedes, and Montgomery) were found and presumably were associated with a full complement of α genes. Nonetheless, the proportion of hybrid heterodimers was clearly lowest in the absence of α-thal-2 and highest in the presence of homozygous α-thalassemia-2, and the correlation of α gene quantity to hybrid heterodimer proportion was very high (r = 0.98). Hence, the conclusion that the proportion of hybrid heterodimers (αX2 βS2) and α gene quantity are inversely related is justified.

[Added in Proof] Another case of HbSSChicago was reported by Ou and Rognerud [14]. This individual had about 20% hybrid heterodimers (HbS-Chicago). The report [14] does not influence the conclusions or validity of the present article.

References


* In these patients, the % HbS was 29.9, 35.0, and 32.0, respectively; the % HbC was 24.5, 30.1, and 32.0, respectively; the respective values for % HbS-G + % HbC-G heterodimers are listed in Table 1.


