Two Independent Genetic Factors in the β-Globin Gene Cluster Are Associated With High $^g_\gamma$-Levels in the HbF of SS Patients

By J.G. Gilman and T.H.J. Huisman

The γ-chains of fetal hemoglobin (HbF) of newborn babies are composed of about 70% $^g_\gamma$ and 30% $^\alpha_\gamma$. In most babies, the $^\gamma$ value declines postnatally to 40%, but in about 20% of black SS patients from Georgia, 5 years and older, the $^\gamma$ level remains high at 60%. Moreover, some 3% to 4% of black newborns have high $^\gamma$ values of 85%. PstI digestion of DNA of one such high $^\gamma$ baby and of one normal newborn showed the former to be heterozygous for the $-^{\alpha_\gamma}-^{\gamma_\gamma}-$ and $-^{\gamma_\gamma}-^{\alpha_\gamma}-$ chromosomes. Only about one fourth of high $^\gamma$ SS patients were such heterozygotes, while three fourths were $-^{\alpha_\gamma}-^{\gamma_\gamma}-/-^{\gamma_\gamma}-^{\alpha_\gamma}-$ homozygotes. Analysis of DNA of 38 SS patients without the $^-\alpha_\gamma$-$^-\gamma_\gamma$ chromosome showed a correlation of $^g_\gamma$ values with genotype at one polymorphic restriction site: at the HincII site in the $^\psi_\beta$ gene, all $-^{\gamma_\gamma}-^{\alpha_\gamma}-/-^{\gamma_\gamma}-^{\alpha_\gamma}-$ homozygotes with high $^g_\gamma$ were +/+ or +/+, while low $^\gamma$ individuals were all −/−. Family studies, involving analyses at four polymorphic sites (HincII sites in the $^\alpha_\gamma$ and $^\gamma_\gamma$ genes and HincII sites in the $^\psi_\beta$ gene and 3' to it), suggested the association of an unidentified high $^g_\gamma$ genetic determinant with haplotype ++−++. This indicates that a genetic factor causing high $^\gamma$ levels in SS patients is closely linked to the $-^{\alpha_\gamma}-^{\gamma_\gamma}-^{\psi_\beta}$ region of the β-globin gene cluster.

Unusual $^g_\gamma$ values are more frequent in adults than in newborns. Approximately 20% of adult SS patients from Georgia have HbF with about 60% $^g_\gamma$ and 40% $^\alpha_\gamma$, values that approach those of newborn babies. High $^g_\gamma$ values have also been observed for cases of $^\alpha_\gamma^\psi_\gamma$-HPFH10 and $\beta$-thalassemia.11-14 We report that at least two genetic determinants are responsible for high $^\gamma$ values in the SS adults. A minority of high $^\gamma$ SS patients are heterozygous for the variant $-^{\gamma_\gamma}-^{\alpha_\gamma}-^{\gamma_\gamma}$ and normal $-^{\gamma_\gamma}-^{\alpha_\gamma}-^{\gamma_\gamma}$ chromosomes. Most high $^\gamma$ SS patients are heterozygous for the normal chromosome and one with an unidentified variant genetic factor that is closely linked to the β-globin gene cluster. Some of the data have been published in abstract form in this journal.15

MATERIALS AND METHODS

Blood Samples

SS patients of this study were 5 years or older, by which age the delayed switch of the $^\gamma_\gamma$-$^\alpha_\gamma$ ratio from newborn to adult values is considered complete.16 Samples from 41 patients and from several members of some families, all living in the state of Georgia, were obtained through the services of the outpatient clinic of the Comprehensive Sickle Cell Center in Augusta. Cord blood samples were submitted to the reference laboratory of the center as part of a statewide testing program for hemoglobinopathies in newborns. Sickle cell anemia and Hbs trait were diagnosed as described previously.9 Amounts of blood collected were: 10 mL for SS patients; 20 mL for AS subjects; and 5 mL for cord blood. All samples were collected in vacutainers with EDTA as anticoagulant after informed consent was obtained.

Analysis of HbF

The composition of the γ-chains of newborn HbF (percentages of $^\gamma_\gamma$ and $^\alpha_\gamma$) was determined by high-pressure liquid chromatography (HPLC) as described previously.16 In general, the HbF from blood samples was isolated by DEAE-cellulose chromatography17 and $^\alpha_\gamma$ and $^\gamma_\gamma$ values determined by the same HPLC method. For data of Fig 3 below, γ-chain compositions were determined by amino acid analysis of CNBr peptide fragments; these data have been published before.18
GENETIC DETERMINANTS FOR HIGH Gy OF HbF

Restriction Endonuclease Analysis of Genomic DNA

Procedures for DNA isolation, blot hybridization, and probes have been described previously.6,12

RESULTS

Detection of Restriction Endonuclease Polymorphisms and the $-\gamma^G$-$\gamma^G$ Chromosome in High and Low $\gamma^G$ SS Patients

A number of polymorphisms for restriction enzyme DNA cleavage sites have been identified in or near the $\beta$-globin gene cluster.19 These sites are genetic markers for different locations in the $\beta$-globin gene cluster and have been used to show linkage of other genetic determinants to that cluster.20,21 In our initial studies, we endeavored to determine the degree of correlation of $\gamma$ levels with the presence or absence of DNA cleavage at each of the four polymorphic sites shown in Fig 1A: HindIII sites in the $\gamma^G$ and $\gamma^A$ genes, and HincII sites in and near the $\psi\beta$-gene. We also identified those individuals with $\beta$-globin gene clusters containing two $\gamma^G$ genes in the $-\gamma^G-\gamma^G$ arrangement, as illustrated in Fig 1B.

Figure 2 shows our results of 41 SS patients from 31 families. In 12 families, the SS offspring (16 in all) had relatively high $\gamma^G$ levels, while in 19 families, the 25 SS offspring had low $\gamma^G$ levels. The data are plotted as $\gamma^G$ value vs "genotype" at each cleavage site: for each site, the minus sign (−) denotes lack of digestion of DNA of a given chromosome and the plus sign (+) denotes digestion, so that an individual can have one of three genotypes (−/−, −/+ or +/+). In addition, unfilled symbols indicate heterozygosity for $-\gamma^G-\gamma^G$ and $-\gamma^A-\gamma^A$ chromosomes, while filled symbols denote normal $-\gamma^G-\gamma^A$ homozygotes. One readily sees from Fig 2 that only three high $\gamma^G$ patients (from three families) had the $-\gamma^G-\gamma^G$ chromosome and that the remaining 13 high $\gamma^G$ individuals (from nine families) had only the normal $-\gamma^G-\gamma^A$ chromosome.

If one examines the distribution of $\gamma^G$ level vs genotype for the HindIII sites in the $\gamma$-genes, little or no correlation is seen. For example, at the HindIII site in the $\gamma^G$-gene, the few −/− genotypes are associated with low $\gamma^G$ levels, but the −/+ and +/+ genotypes are both associated with high and low $\gamma^G$ values. However, the HincII sites show a much greater degree of correlation. In particular, for the HincII site in the $\psi\beta$-gene, all −/− genotypes have $\gamma^G$ values below 48% (except for those individuals with the $-\gamma^G-\gamma^A$ chromosome), for an average low $\gamma^G$ value of 39.3% ± 5.4% (SD). All −/+ genotypes have $\gamma^G$ values above 49% (60.5% ± 6.3% for 12 cases from eight families), while the one +/+ genotype had 71% $\gamma^G$. For comparison, the three heterozygotes for $-\gamma^G-\gamma^G$ and $-\gamma^A-\gamma^A$ chromosomes had 69.5% ± 6.0% $\gamma^G$.

These data show that two genetic factors cause high $\gamma^G$ values in SS patients. One factor is the $-\gamma^G-\gamma^G$ chromosome, in which an $\alpha$-gene codes for a $\gamma$-chain7 as illustrated in Fig 1. Heterozygotes for the $-\gamma^G-\gamma^G$ and normal $-\gamma^G-\gamma^A$ chromosomes accounted for about 25% of families with high $\gamma^G$ SS offspring. The remaining 75% of families with high $\gamma^G$ SS children have a different genetic determinant, closely linked to the $\beta$-globin gene cluster, as indicated by the close association of $\gamma^G$ values and genotype at the polymorphic HincII restriction site in the $\psi\beta$-gene. This factor is not associated with any significant
deletion of DNA at the \( \gamma \)-gene loci, as \( Bg\text{II} \) digestion showed no unusual fragments after \( \gamma IVSII \) probe hybridization (data not shown).

**DNA Polymorphism Haplotypes of SS Patients**

The next stage of this study was to determine chromosomal haplotypes, i.e., the pattern of polymorphic restriction sites,\(^{16}\) for some of the high and low \( G\gamma \) SS patients. Figure 3 shows the predigree of one particularly interesting family and illustrates how one can establish haplotypes from genotype data. In this family, the AS mother (B.W.) was homozygous at all restriction sites studied, so that her haplotypes are \(- - - - \) on both \( \beta^A \) and \( \beta^S \) chromosomes. From this knowledge, one deduces the haplotype of the \( \beta^S \) chromosome transmitted by the father (B.W., Jr) to the SS son (B.W., Jr) or daughter (C.W.). This haplotype is \(- - - + \), which is \( + \) for the \( Hinc\text{II} \) restriction site in the \( \psi\beta \)-gene and associated with high \( G\gamma \) values. Next, because the haplotype of the father’s \( \beta^S \) chromosome is known, that of his \( \beta^A \) chromosome is readily deduced. A similar approach allows the determination of the haplotypes in the remaining family members.

In this family, all but one member had high \( G\gamma \) values. The father’s value was high (64%) because he had the genetic factor associated with the presence of the \( Hinc\text{II} \) restriction site in the \( \psi\beta \)-gene on the \( \beta^S \) chromosome. The mother and one AS daughter (B.A.W.) and one AS child (D.W.) had the genetic factor associated with the presence of the \( \psi\beta \)-gene and associated with high \( G\gamma \) values. Next, because the haplotype of the father’s \( \beta^S \) chromosome is known, that of his \( \beta^A \) chromosome is readily deduced. A similar approach allows the determination of the haplotypes in the remaining family members.

In this family, all but one member had high \( G\gamma \) values. The father’s value was high (64%) because he had the genetic factor associated with the presence of the \( Hinc\text{II} \) restriction site in the \( \psi\beta \)-gene on the \( \beta^S \) chromosome with haplotype \(- - - + \). His two living SS children had high \( G\gamma \) values for the same reason. The mother and one AS daughter (B.A.W.) and her son (E.W.) had high \( G\gamma \) values because of the \(- - - - \) arrangement on their \( \beta^S \) chromosomes. In addition, the AS daughter had the \( \beta^S \) chromosome with the \(- - - - \) haplotype, which contributed to her high \( G\gamma \) value of 81%. The only person in the pedigree known to have a low \( G\gamma \) value (38%) was an AS grandchild (D.W.) with the \(- - - + \) haplotype on both her \(- G\gamma - \gamma - \) chromosomes.

We have determined haplotypes for ten additional families of SS patients and for nine individual SS patients who were homozygous for at least three of the four polymorphic sites that were analyzed. All of the SS patients were also characterized for \( G\gamma \) values and for the \(- G\gamma - G\gamma - \gamma - \gamma - \) chromosomal arrangements. The haplotype data are summarized in Table 1. These data show that the \(- G\gamma - \gamma - \gamma - \) chromosome was found in two haplotypes in SS patients, \(- - - - \) (also seen for \(- G\gamma - G\gamma - \) on the \( \beta^A \) chromosome) and \(+ - - - \). The other high \( G\gamma \) genetic determinant, which is associated with \(+ \) at the \( Hinc\text{II} \) site in the \( \psi\beta \)-gene, was found in only one haplotype on the \( \beta^S \) chromosome, \(+ - - - \). All of the SS patients with at least one chromosome with this haplotype had high \( G\gamma \) values (\( > 56\% \)). In SS patients, low \( G\gamma \) phenotypes (\( < 48\% \)) were associated with three haplotypes on \(- \gamma - \gamma - \gamma - \) chromosomes, \(- - - - + + \), \(- - - - + - \), and \(- - - - + + \). The family studies also yielded data on frequencies of the various \( \beta^A \) chromosome haplotypes, which are shown in Table 1. However, no reliable data on \( G\gamma \) levels are available for the AS individuals of this study, with the exception of the family whose pedigree is shown in Fig 3 (see Discussion).

**Newborn High \( G\gamma \) Values and the \(- G\gamma - \gamma - \gamma - \) Chromosome**

Previous estimates indicated that 3% to 8% of black newborns have high \( G\gamma \) levels of 80% to 85%, compared to the typical newborn value of 70%.\(^{48}\) Figure 4 shows data on the frequencies of \( G\gamma \) levels in over 900 black newborns. Two distributions are clearly present. One,

### Table 1. Haplotypes for Polymorphic Restriction Sites 5' to the \( \delta \)-Globin Gene

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>( - G\gamma - \gamma - \beta^S )</th>
<th>( - G\gamma - \gamma - \beta^A )</th>
<th>( - G\gamma - \gamma - \gamma^S )</th>
<th>( - G\gamma - \gamma - \gamma^A )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(- - - +)</td>
<td>20</td>
<td>1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>(+ - - -)</td>
<td>11</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
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<td>3</td>
<td>-</td>
<td>3</td>
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<td>(+ + + +)</td>
<td>5</td>
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<td>4</td>
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<td>(- - - -)</td>
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<td>(- - - +)</td>
<td>-</td>
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<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>2</td>
<td>22</td>
<td>1</td>
</tr>
</tbody>
</table>

The data on \( \beta^S \) chromosomes are from 20 SS patients from 20 different families, and from one AS (E.W. of Fig 3). The data on \( \beta^A \) chromosomes are from 11 pairs of AS parents of SS children, and from one AS child (D.W. of Fig 3). Haplotypes were determined from family studies and from data on individuals, as described in the text. Note that this is not an unbiased sample, because greater than random representation was given to those with high \( G\gamma \) levels and because the procedure of haplotype determination in single individuals is biased in favor of the most common haplotypes. Thus, these data may give only a rough measure of haplotype frequencies in the population.
accounting for over 96% of all newborns, has a mean $\gamma$ value of about 70%, and the other, in 3.4% of all newborns, has a mean $\gamma$ of about 85%. For SS newborn, two of 118 have $\gamma$ values greater than 80%, which is not significantly different from the overall proportion.

It was previously shown that one baby with nearly 100% $\gamma$ was homozygous for the $-\gamma-\gamma$ chromosome. The value of 85% $\gamma$ seen for the high $\gamma$ newborn subpopulation is exactly that expected for babies heterozygous for the normal $-\gamma-\gamma$ chromosome (producing 70% $\gamma$) and the $-\gamma-\gamma$ chromosome (producing 100% $\gamma$). Thus, it is likely that high $\gamma$ black newborns are such $-\gamma-\gamma-/-\gamma-\gamma$ heterozygotes.

To test this hypothesis, two SS newborn, one with 85% $\gamma$ and the other with 73% $\gamma$, were followed for 10 months after birth. An SC newborn with 87% $\gamma$ at birth was also followed. The $\gamma$ values in the two babies with the high percentages fell to 73% by 8 to 10 months of age, while that in one baby, initially near 70%, decreased to 43% in the same time period. PstI digestion showed that the high $\gamma$ SS baby was indeed a $-\gamma-\gamma-/-\gamma-\gamma$ heterozygote, while the SS baby with the typical newborn $\gamma$ value was homozygous for the $-\gamma-\gamma$ chromosome. The SC baby was not analyzed.

**DISCUSSION**

In patients with sickle cell anemia who are over 5 years of age, there are two different categories with respect to the $\gamma$ level of their HbF: about 80% have HbF with 40% $\gamma$ and 60% $\lambda$, while the remaining patients have high $\gamma$ of about 60%. We have shown here that two types of genetic determinants lead to high $\gamma$ values in adult SS patients. About one fourth of the high $\gamma$ SS patients were heterozygous for the $-\gamma-\gamma-\gamma$ and $-\gamma-\gamma-\gamma$ chromosomes. Their average $\gamma$ value of about 70% agreed with expectation, on the assumption of equal $\gamma$-chain production by both chromosomes (the former producing 100% $\gamma$, the latter 40% $\gamma$). The other three fourths of the high $\gamma$ SS patients had, on at least one chromosome, an unidentified high $\gamma$ genetic factor that is closely linked to the $\beta$-globin gene cluster.

This high $\gamma$ factor was demonstrated by the strong correlation of high and low $\gamma$ levels with genotype at the HincII restriction site in the $\psi$-$\beta$-gene (Fig 2): all high $\gamma$ SS patients who were $-\gamma-\gamma-\gamma-/\gamma-\gamma-\gamma-$ homozygotes had genotypes $+/+$ or $++$ at the HincII site in the $\psi$-$\beta$-gene; the average $\gamma$ value for $+/-$ was about 60%, while the one $+/+$ had 71% $\gamma$. All low $\gamma$ SS patients had genotype $-/-$, with an average $\gamma$ value of about 40%. In a limited number of family studies, all high $\gamma$ SS patients studied were found to have at least one chromosome with haplotype $+/-$. The strong association of high $\gamma$ with $+$/ at the HincII site in the $\psi$-$\beta$-gene could thus reflect an association of high $\gamma$ with the particular haplotype $+/-$. The association of high $\gamma$ with the HincII site was not analyzed.

There are two interpretations of the correlation of $\gamma$ levels with genotype at the HincII site in the $\psi$-$\beta$-gene: (1) this genetic determinant for high $\gamma$ is situated very close to the $\psi$-$\beta$-gene; and (2) this genetic determinant for high $\gamma$ is associated with only one haplotype, $+/-$. These interpretations can be tested by finding persons with other haplotypes that have $+$/ at the HincII site in the $\psi$-$\beta$-gene and by determining their $\gamma$ values.

Such a haplotype has already been observed for the A$^s$ chromosome: $+/-$. There are two interpretations of the correlation of $\gamma$ levels with genotype at the HincII site in the $\psi$-$\beta$-gene: (1) this genetic determinant for high $\gamma$ is situated very close to the $\psi$-$\beta$-gene; and (2) this genetic determinant for high $\gamma$ is associated with only one haplotype, $+/-$. There are two interpretations of the correlation of $\gamma$ levels with genotype at the HincII site in the $\psi$-$\beta$-gene: (1) this genetic determinant for high $\gamma$ is situated very close to the $\psi$-$\beta$-gene; and (2) this genetic determinant for high $\gamma$ is associated with only one haplotype, $+/-$. These interpretations can be tested by finding persons with other haplotypes that have $+$/ at the HincII site in the $\psi$-$\beta$-gene and by determining their $\gamma$ values.

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involved in controlling the postnatal switch in $G\gamma$ values, from 70% in newborn to 40% in adults. Chromosomes that are $+$ for the HincII site in the $\psi\beta$-gene would then contain a defective version of this switching mechanism and maintain high $G\gamma$ values as adults. Several pieces of evidence favor this hypothesis: the one SS individual homozygous for the $- + + +$ haplotype had a $G\gamma$ value similar to that of newborn babies (although a $G\gamma$ value of about 70% was also found in one of 12 heterozygotes). In addition, the one adult high $G\gamma$ compound heterozygote with both $-G\gamma-G\gamma$ and $+ + + +$ chromosomes (B.A.W. of Fig 3) had 81% $G\gamma$, which is similar to the value seen in newborn babies with one $-G\gamma-G\gamma$ and one normal $-G\gamma-A\gamma$ chromosome. This hypothesis also accounts for our data suggesting that high $G\gamma$ values in newborns are due solely to the $-G\gamma-G\gamma$ chromosome. Indeed, the frequency of high $G\gamma$ values in newborns (3.4%) is similar to the estimated frequency of $-G\gamma-G\gamma- / -G\gamma-A\gamma-$ heterozygotes in SS patients (5%, or one fourth of the 20% of high $G\gamma$ SS).

This hypothesis suggests that the $- + + +$ haplotype may be associated with high $G\gamma$ levels in diverse ethnic groups and in conditions other than sickle cell anemia. Data of Orkin and colleagues on homozygous $\beta$-thalassemia patients in the Mediterranean region show that about 12% of haplotypes had this $- + + +$ arrangement (haplotypes III, IV, and IX). In one reported case, an individual with the $\beta$-thalassemia mutation that is usually associated with haplotype III was shown to have high $G\gamma$ levels. In another case, Dutch $\beta$-thalassemia, a high $G\gamma$ level is associated with homozygosity for the $- + + +$ haplotype (unpublished observations). Furthermore, early studies on whites showed high $G\gamma$ levels in adults but not in newborns, which could suggest a significant frequency of the $- + + +$ haplotype in whites, but a very low frequency of the $-G\gamma-G\gamma-$ chromosome. Further study will be necessary to determine the nature of the high $G\gamma$ factor linked to the $- + + +$ haplotype and to test the hypothesis that it may be the same factor responsible for the postnatal developmental switch in $G\gamma$ values.

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