SUMMARY  This report describes a Negro family with the \( G\gamma P^+ \) type of hereditary persistence of fetal hemoglobin. Family members with levels of hemoglobin F of 17 to 23% had normal red cell indices, balanced globin chain synthesis, and a pancellular distribution of the fetal hemoglobin, showing that these subjects have a form of HPFH. The production of Hb A and C in addition to the large amount of Hb F in one family member showed that there was an active \( \beta^A \) gene in cis to the HPFH determinant, while structural analysis of the Hb F revealed the presence of only \( G\gamma \) chains. The criteria for the diagnosis of \( G\gamma P^+ \) HPFH, and the relevance of such conditions to the control of globin gene expression, are discussed.

Hereditary persistence of fetal hemoglobin (HPFH) is a condition in which increased levels of fetal hemoglobin (Hb F, \( \alpha_2\gamma_2 \)) are present in persons who are clinically normal, and who have minimal or no haematological abnormalities (Weatherall and Clegg, 1975). It is a heterogeneous group of disorders which can be divided into pancellular and heterogeneous types according to whether the Hb F is present in all, or only a proportion, of the red blood cells (Boyce et al., 1977). The condition can be further subdivided, depending on the amount and structure of the Hb F. The \( \gamma \) chains of Hb F have either glycine (\( G\gamma \)) or alanine (\( A\gamma \)) at position 136 (Schroeder et al., 1968). The \( G\gamma \) and \( A\gamma \) chains are the product of distinct genetic loci which are believed to be linked to the \( \beta \) and \( \delta \) chain genes in the order \( G\gamma - A\delta - \beta \) (Huisman et al., 1972; Weatherall and Clegg, 1975) on chromosome 11 (Deisseroth et al., 1978).

In the most common pancellular HPFH (Negro HPFH), both \( G\gamma \) and \( A\gamma \) genes are expressed in the absence of \( \beta \) and \( \delta \) chain production in cis to the HPFH determinant (Conley et al., 1963; Ringelhann et al., 1970; Huisman et al., 1974). Recently it has been shown that this condition results from a deletion involving parts of the \( \delta \) and \( \beta \) chain genes (Kan et al., 1975; Forget et al., 1976; Ottolenghi et al., 1976; Ramirez et al., 1976).

Other HPFH cases have been reported in which only \( G\gamma \) chains were present (Sukumaran et al., 1972; Huisman et al., 1975a, b; Altay et al., 1976, 1977). Included among these are two Negro families in which 15% Hb F production was associated with both Hb A and S, indicating the production of \( \beta^A \) chains in cis to the HPFH determinant (Huisman et al., 1975b; Friedman and Schwartz, 1976). This condition has been called \( G\gamma P^+ \) HPFH. In this report, we describe a further Negro family with \( G\gamma P^+ \) HPFH, in this case associated with Hb C.

Methods

HAEMATOLOGICAL STUDIES AND HAEMOGLOBIN ANALYSIS

Peripheral blood samples were collected into heparin or EDTA. Haemoglobin and red cell indices were measured with a Coulter Counter S. Fresh blood smears were made from each family member. Haemoglobin electrophoresis was carried out on starch gel with a tris-EDTA-borate buffer system, pH 8.6 (Weatherall and Clegg, 1972). The proportion of Hb A\(_2\) (or Hb C and A\(_2\)) was measured by elution from cellulose acetate strips (Weatherall and Clegg, 1972).

The Hb F levels were measured by alkali denaturation (Betke et al., 1959) as modified by Pembrey et al. (1972). The intracellular distribution of Hb F was examined by both the acid elution technique (Kleihauer et al., 1957) and by immunofluorescence (Wood et al., 1975). The haemoglobin composition of the red cells from two family members (GT and JaT) were also examined after the cells had been fractionated after centrifugation. The packed cells obtained from 30 ml peripheral blood were centrifuged at 64 000 \( g \) for 60 min at 15°C.
centrifugation, 1.5 to 2.0 ml fractions of cells were removed with a Pasteur pipette (fractions 1 to 7). Separation of the cells by density was confirmed by resuspending the cells in plasma and measuring the red cell indices of each fraction. Subsequently, Hb electrophoresis was performed on each specimen thus obtained (Table 1).

**Globin Chain Synthesis**

The relative rates of α, β, and γ chain synthesis were measured in vitro by the incorporation of 3H leucine into reticulocytes which had been enriched by centrifugation at 3000 g for 30 min (Weatherall et al., 1969). The white blood cells which were present in the sample of enriched reticulocytes were removed by passage through a column of α methyl cellulose and microcrystalline cellulose, according to the method of Beutler et al. (1976), before incubation. After separation of the globin chains by CM cellulose chromatography (Clegg et al., 1966), the total counts/min incorporated into each chain were measured by counting 0.5 ml aliquots in 5 ml of a Triton-toluene-based scintillant. For the determination of the specific activity, the contents of the peak tube of each chain were dialysed against 0.5% formic acid. The OD was then measured at 280 nm and duplicate 0.5 ml samples were counted in the scintillant. The specific radioactivity was expressed as cpm/0.5 ml/OD280.

**Composition of Hb F**

A total of 100 mg globin was incubated with 100 mg cyanogen bromide in 5 ml 70% HCOOH at room temperature for 24 h. CNBr and HCOOH were then removed by freeze drying, and the γCB3 (corresponding to γ chain residues 134 to 146) was isolated by gel-filtration through a 2.5 × 90 cm column of Sephadex G50 in 0.01 N HCl. The peptide was further purified by high voltage electrophoresis at pH 6.5 followed by chromatography in n-butanol, acetic acid, water, and pyridine (15, 3, 12, 10 by vol), eluted from the paper in 6 N HCl containing 2 mg/ml phenol, and hydrolysed for 20 h at 107°C.

**Results**

**Haematological and Haemoglobin Analysis**

The family pedigree is summarised in Fig. 1. The proband was a 20-year-old female who was found to have a raised level of Hb F (17.7%) during routine screening before a minor operation. She had no history of ill health and clinical examination was normal. In particular, she was not anaemic nor jaundiced and had no hepatosplenomegaly. Her Hb was 12.6 g/dl, the MCV was 84 fl, and her MCH was 29 pg. Her peripheral blood film showed no abnormalities.

The haematological data from the proband and her family are summarised in Table 2. Haemoglobin values and red cell indices of both parents were within normal limits. The blood film of the father (GT) showed numerous target cells; haemoglobin analysis showed 21% Hb F and 44.2% Hb C, the remainder being Hb A (Fig. 2). Therefore, the father is a compound heterozygote for Hb C and HPFH, whereas the mother carries neither of these genes and is haematologically normal. Their offspring each received either the Hb C or the HPFH.

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**Table 1** Summary of haematological data on individual fractions of centrifuged blood from GT and JaT.

<table>
<thead>
<tr>
<th>Fraction</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (%)</th>
<th>%HbFAD</th>
<th>%HbC+δE CA</th>
<th>%Hba*</th>
<th>MCHbF (pg)</th>
<th>MCHbA (pg)</th>
<th>MCHbC+δAg (pg)</th>
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*By subtraction. AD, alkali denaturation; CA, cellulose acetate electrophoresis.*
gene. The two sibs with HPFH have 17.7 and 17.4% Hb F, respectively, and low levels of Hb A₂; both are haematologically normal. Two sibs with Hb C trait have approximately 35% Hb C and target cells were seen in the peripheral blood. In the 5-year-old child (MG) of one of these, the presence of abnormal red cell indices, together with anisopoikilocytosis, was noted. He also had a lower than average level of Hb C (28%) and a raised level of Hb F (approximately 4%) unevenly distributed in his red cells. Unfortunately, the child's father was not available for study.

In those patients with the HPFH gene, both acid elution smears and examination of blood films by the immunofluorescence technique showed that Hb F was present in virtually all of the cells. With the acid elution technique there was marked variability in the staining intensity from cell to cell (Fig. 3).

The results of the differential centrifugation of the red cells from the HPFH heterozygote (JaT) and the HPFH/Hb C compound heterozygote (GT) are shown in Table 1. The decreasing MCV and increasing MCHC from top to bottom of the smear cells indicate that a separation of the cells according to their density was achieved. No significant differences in the proportions of the haemoglobins present in these cells were observed between various fractions.

GLOBIN CHAIN SYNTHESIS

The biosynthesis data show that in both the same heterozygote for HPFH and the compound heterozygote for HPFH and Hb C the α/αα ratio is balanced (Table 3). It was not possible to separate the γ peak from the pre-β peak, or the βc peak from the pre-α peak by CMC chromatography (Fig. 4).

Nevertheless, the proportion of βc chain synthesis in GT approximated to the amount of Hb C present in the peripheral blood. Similarly, the proportion of γ chain synthesis was similar to the Hb F level in the peripheral blood. The specific activity of the βc chain was less than that of the βa chain on both of these

<table>
<thead>
<tr>
<th>Subject</th>
<th>RBC (10^12/l)</th>
<th>Hb (g/dl)</th>
<th>PCV (%)</th>
<th>MCV (fl)</th>
<th>MCHC (%)</th>
<th>H</th>
<th>A</th>
<th>P</th>
<th>Po</th>
<th>T</th>
<th>A* (%)</th>
<th>Aα (%)</th>
<th>C (%)</th>
<th>F (%)</th>
<th>F cells (%)</th>
<th>Gly</th>
<th>Hba1</th>
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<td>81</td>
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<tr>
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<td>33.8</td>
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<td>---</td>
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<td>+</td>
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<td>2.35</td>
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<td>84</td>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>+</td>
<td>64.20</td>
<td>35.0</td>
<td>0.80</td>
<td>7.5±0.1</td>
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<td>63</td>
<td>20.8</td>
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<td>+</td>
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<td>±</td>
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<td>1-00</td>
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</tr>
</tbody>
</table>

*By subtraction. H, hypochromia; A, anisocytosis; P, poikilocytosis; Po, polychromasia; T, target cells.
Gγβ⁺ type of hereditary persistence of fetal haemoglobin in association with Hb C

subjects (γ/βA = 0.71 and 0.77). In VT the α/non-α ratio was 0.82. In the absence of further biosynthetic and genetic data the significance of this finding is uncertain.

COMPOSITION OF Hb F
Analysis of the γCB 3 from the γ chain of MT gave values for glycine and alanine of 1.00 and 2.00 residues, respectively. This established that the Hb F was solely of the Gγ type. Analysis of peptide γ9, isolated from a two dimensional peptide map of a tryptic digest of γ chains, showed that position γ75 was occupied by isoleucine.

Discussion

The term 'hereditary persistence of fetal haemoglobin' (HPFH) is given to a group of conditions characterised by persistent fetal haemoglobin synthesis beyond the neonatal period in the absence of any major haematological abnormalities. In the common form found in Negroes, there is abundant...
Table 3 Summary of biosynthetic data

<table>
<thead>
<tr>
<th></th>
<th>Total counts/min/0.5 ml</th>
<th>Specific activities (cpm/OD280)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>γ</td>
<td>β^A</td>
<td>β^C</td>
</tr>
<tr>
<td>Father (GT)</td>
<td>1203</td>
<td>1799</td>
<td>4689</td>
</tr>
<tr>
<td>Mother (VT)</td>
<td>1001</td>
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</tr>
<tr>
<td>Daughter (JaT)</td>
<td>539</td>
<td>1847</td>
<td>2739</td>
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</tbody>
</table>

Fig. 4 Chromatographic separation of ^3H leucine labelled globin chains from (top) VT, (middle) JaT, and (bottom) GT.

Evidence to show the absence of β and δ chain synthesis directed by the chromosome carrying the HPFH gene (Wheeler and Krevans, 1961; Conley et al., 1963). Two families have been reported previously, however, in which an HPFH condition has been found in association with β^A and β^S chains (Huisman et al., 1975b; Friedman and Schwartz, 1976). The Hb F in these subjects contained only Gy chains and this, together with the low level of Hb A2, suggested that the condition arose from a deletion.
the \( \alpha \) and \( \delta \) genes from the \( \gamma \alpha \gamma \delta \beta \) globin gene complex. Hence, this form of HPFH has been called the \( \gamma \beta^+ \) type (Friedman and Schwartz, 1976).

The present studies indicate that the family described here also carry a \( \gamma \beta^+ \) type of HPFH. This is shown by the presence in GT of both Hb A and C, together with the high level of Hb F, in the absence of any haematological abnormalities. Clearly there must be \( \beta \) chain synthesis in cis to the HPFH gene. Among his offspring, those with Hb C had normal adult levels of Hb F, while those with high levels of Hb F had a low-normal level of Hb A, as well as the remainder of their haemoglobin being Hb A. Thus, the \( \beta^A \) gene is in cis to the HPFH gene.

Unlike the two previous families in which the \( \gamma \gamma \beta^+ \) type of HPFH was found together with Hb S, in the present case it was found in association with Hb C. However, there was little if any difference between the Hb C/\( \gamma \beta^+ \) HPFH and the Hb S/\( \gamma \beta^+ \) HPFH compound heterozygotes.

The distribution of Hb F in the \( \gamma \gamma \beta^+ \) HPFH heterozygotes and the Hb C/\( \gamma \gamma \beta^+ \) HPFH compound heterozygote was pancellular by both the acid elution and immunofluorescence techniques. However, by acid elution there appeared to be more variable staining from cell to cell than is seen in \( \gamma \alpha \gamma \) Negro HPFH. This may reflect the slightly lower Hb F level (15 to 20\%) in \( \gamma \gamma \beta^+ \) HPFH than in the more common \( \gamma \alpha \gamma \) HPFH (20 to 30\%), which also shows some heterogeneity in the amount of Hb F per cell.

The \( \alpha / \alpha^* \) synthesis ratios in the \( \gamma \gamma \beta^+ \) HPFH heterozygotes were close to unity. However, in both subjects studied, the specific activity of the \( \gamma \) chain was significantly lower than that of the \( \beta \) chain. This could be explained on the basis of differential survival of the cells with most Hb F, as has been shown to occur in \( \beta \)- and \( \delta \)-thalassaemia (Gabuzda et al., 1963; Loukopoulos and Fessas, 1965; Wood et al., 1977). However, the Hb F was evenly distributed throughout all red cell fractions obtained by differential centrifugation. This method separates cells by virtue of their relative densities, which usually reflect cell age (Borun et al., 1957; Rigas and Koler, 1961), and hence suggests that there is little differential survival of red cells containing variable amounts of Hb F. A possible alternative explanation for the lower \( \gamma \) specific activity is that \( \gamma \) chain mRNA may disappear from reticulocytes at a slightly faster rate than \( \beta \) mRNA (Ringelhann et al., 1977). If this were so, \( \gamma \) chain synthesis in vivo might not be truly representative of in vitro synthesis. This hypothesis could be tested by performing simultaneous bone marrow and peripheral blood incubations from a patient such as GT.

Deletions of various parts of the \( \gamma \alpha \gamma \delta \beta \) complex have been advanced as the most likely explanation of the pancellular HPFH conditions, and in some cases of \( \gamma \gamma \gamma \) HPFH deletions involving the \( \delta \) and \( \beta \) genes have been detected, both by cDNA hybridisation (Kan et al., 1975; Forget et al., 1976; Ottolenghi et al., 1976; Ramirez et al., 1976), and by restriction endonuclease analysis of genomic DNA (Mears et al., 1978). A similar deletion involving the \( \delta \) and \( \beta \) loci is also found in some cases of \( \delta \beta \)-thalassaemia (Ottolenghi et al., 1976; Ramirez et al., 1976). In the case of \( \gamma \gamma \beta^+ \) HPFH, such a deletion would presumably involve the \( \alpha \gamma \) and \( \delta \) genes, the loss of this material allowing the continued expression of the \( \beta \) locus, but removing the normal repression of the \( \gamma \) gene in adult life. Whether the reduced output of the \( \beta \) gene results directly from the deletion, or whether the reduction results from the apparently reciprocal relationship between \( \gamma \) and \( \beta \) chain production (Weatherall et al., 1979) remains to be determined.

In addition to \( \gamma \gamma \beta^+ \) HPFH, increased levels of Hb F containing only \( \gamma \) chain are also found in Hb Kenya (Huisman et al., 1972; Smith et al., 1973; Nute et al., 1976), \( \gamma \delta \)-thalassaemia (Mann et al., 1972; Huisman et al., 1975a; Wood et al., 1977), \( \gamma \gamma \beta^+ \) HPFH (Altay et al., 1977), and the Atlanta type of heterocellular HPFH (Altay et al., 1976). These cases have been reviewed recently by Altay et al. (1977). There is considerable difficulty involved in the differential diagnosis of HPFH and \( \delta \beta \)-thalassaemia, particularly those involving the \( \gamma \gamma \) types (Mann et al., 1972; Sukumaran et al., 1972; Huisman et al., 1975a,b; Altay et al., 1977; Wood et al., 1977). The usual criteria of haematology (normal red cell indices in HPFH versus low MCH and MCV in \( \delta \beta \)-thalassaemia), globin chain synthesis (balanced versus unbalanced), and Hb F distribution (pancellular versus heterocellular) all show considerable overlap in the two conditions and may not all be consistent. The recent report of balanced globin chain synthesis in some \( \delta \beta \)-thalassaemia heterozygotes with abnormal haematology and heterocellular Hb F distribution (Kinney et al., 1978) exemplifies this point. In addition, the existence of HPFH cases with very low proportions of \( \gamma \gamma \) chains makes very careful structural analysis of the Hb F essential (Sukumaran et al., 1972; Boyer et al., 1977).
(1975a) (though the critical family member for the exclusion of Gγβ⁺ HPFH is omitted from the pedigree in the second publication) and family M of Altay et al. (1977) where the remote possibility of a Gγβ⁺⁺ HPFH could not be excluded.

The importance of these probable deletion conditions lies in the information they provide as to the control of gene expression and, in particular, the control of fetal and adult haemoglobins during human development. Only by thorough characterisation of the haematological manifestations of these variants will it be possible to interpret the results of molecular analysis obtained by restriction endonuclease mapping and DNA sequencing. It is hoped that in this way some understanding will be gained as to the variable degree of γ chain compensation in HPFH and δβ-thalassaemia. Gγβ⁺ HPFH would appear to be a particularly suitable candidate for such analysis.

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References


Gγβ+ type of hereditary persistence of fetal haemoglobin in association with Hb C


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Note added in proof

Since this paper was submitted for publication, a further case of Gγβ+ HPFH has been reported in association with Hb S and α-thalassaemia (Tatsis 1978, *Blood*, 52, (Suppl.) 119). In addition we have become aware of two early reports of HPFH in association with Hb S and C and A, which seem very likely to be further examples of this condition (McCormick and Humphreys 1960, *Blood*, 16, 1736–1744; Schneider et al. 1960, *New England Journal of Medicine*, 265, 1278–1283).