Gγ δβ thalassaemia and Gγ HPFH (Hb Kenya type)

Comparison of 2 new cases

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SUMMARY Two new cases of Gγ δβ thalassaemia and Gγ HPFH (Hb Kenya type) have been characterised in detail and compared with regard to haematological data, globin chain biosynthesis, and intracellular distribution of Hb F. The similarities and differences between these two conditions are discussed in relation to the possible underlying defects at the molecular level and to the control of the γδβ gene complex in general.

The structural genes coding for the non-α globin chains in man appear to be closely linked on the same chromosome in the order Gγ Aγ δβ or Aγ δβ Gγ (Huisman et al., 1972; Weatherall and Clegg, 1975). Little is known of the control of this gene complex and particularly of the 'switch' from fetal (Gγ and Aγ) to adult (δ and β) chain synthesis which occurs in the perinatal period. Disorders involving this control mechanism, however, may lead to the continued production of γ chains in adult life; these conditions can be divided broadly into the β and δβ thalassaemias and hereditary persistence of fetal haemoglobin (HPFH) (Weatherall and Clegg, 1975). At the molecular level, these disorders can be subdivided according to the amount of Hb F produced and whether it contains both Gγ and Aγ chains or only Gγ chains. The latter condition has been reported in the Negro type of HPFH (Huisman et al., 1969; Sukumaran et al., 1972; Huisman et al., 1975a, b); the heterozygous state for Hb Kenya found in Negroes (Huisman et al., 1972; Smith et al., 1973); δβ thalassaemia in a Chinese family (Mann et al., 1972) and in a Negro family (Huisman et al., 1975a); and in the recently described Gγ β HPFH, also found in Negroes (Huisman et al., 1975b; Friedman and Schwartz, 1976). Correct identification of these conditions can be difficult (Mann et al., 1972) and cases of Gγ δβ thalassaemia have been misdiagnosed (see Huisman et al., 1975b). Thorough characterisation of these disorders is essential, however, if they are to be of value in understanding the control of the γδβ gene complex.

In this report we describe a further case of Gγ δβ thalassaemia, occurring here in a Negro family in which Hb C is also present, and compare it with a new case of Gγ HPFH associated with Hb Kenya, in which haematological studies on fresh blood and globin chain synthesis have been measured for the first time.

Methods

Haematological data on the family members were determined using a Coulter electronic cell counter. Haemoglobin electrophoresis was carried out in starch gel with a tris-EDTA-borate buffer system, pH 8.6 (Weatherall and Clegg, 1972) and in agar gel at pH 6.0. The proportion of Hb A2 (or Hbs C + A2) was measured by elution after cellulose acetate electrophoresis and the percentage Hb F was determined by alkali denaturation (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).

To determine the age distribution of Hb F-containing cells 10 ml packed red cells were centrifuged at 25 000 g for 45 minutes. The 'top' and 'bottom' 10% of the cells were removed and re-suspended in autologous serum to a normal packed cell volume, for measurement of red cell indices and the proportion of Hb F in each fraction.
Globin-chain synthesis studies were carried out either on whole blood or on the reticulocyte-rich ‘top’ layer described above. 0-5 ml washed cells were incubated as described by Lingrel and Borsook (1963) with 50 μCi $^3$H leucine (50 Ci/mmol) for 1 hour. The cells were then washed three times in saline at 4°C, and the whole cell lysate, including membranes, was converted to ‘globin’ by acid acetone precipitation. Globin chains were separated by CM cellulose chromatography (Clegg et al., 1966) and the incorporated radioactivity determined. Full details of all these methods can be found in Weatherall et al. (1969).

The $\gamma$ chains of fetal haemoglobin may contain either glycine ($^{Gy}$) or alanine ($^{A\gamma}$) at position 136 (Schroeder et al., 1968). Determination of the $^{Gy}/^{A\gamma}$ ratio was carried out in two ways. Purified $\gamma$ chains obtained from CM cellulose chromatography were digested with trypsin, and peptide $\gamma_{15}$, containing residue 136, was eluted from a fingerprint and subjected to amino-acid analysis (Clegg et al., 1966). Alternatively, globin prepared from the whole haemolysate was cleaved with cyanogen bromide (Weatherall et al., 1975) and the $\gamma$CB3 fragment was isolated by paper electrophoresis and chromatography (Kamuzora et al., 1975). In each case the result is expressed as the number of glycine residues in $\gamma_{15}$ or $\gamma$CB3. Values of 1-00 or 0-00 indicate that only $^{Gy}$ or $^{A\gamma}$ chains are present, respectively. Intermediate values show the relative proportions of the two chains when both are present.

**Results**

**Family K**

The propositus is a previously healthy 20-month-old boy of West Indian origin who presented with tonsillitis followed by pain and swelling of his right foot. Clinical examination was otherwise normal and his spleen was not palpable. There were no x-ray changes in his bones.

**Haematological investigation**

The haematological indices of the propositus and his parents are listed in Table 1. Peripheral blood smears of the propositus showed distinct hypochromia and microcytosis with many target cells and microspherocytes. The blood film of his mother showed mild hypochromia with a few target cells, while that of his father was normal.

**Haemoglobin analysis**

A haemolysate prepared from the propositus showed two major haemoglobins, one migrating with Hb $A_2$, which, because of his origin, is presumably Hb C, and the other Hb F (Fig. 1). No Hb A could be detected. Quantification of the haemoglobins after cellulose acetate electrophoresis gave values for Hbs C + $A_2$ of 65-5% and Hb F of 34-5%, whereas the proportion of Hb F measured by alkali denaturation was 23-9%. The intracellular distribution of the Hb F was heterogeneous as judged by the acid elution method. By the more sensitive immunofluorescent technique virtually all the cells were

![Fig. 1 Starch gel electrophoresis of haemolysates prepared from (a) the propositus M.K., (b) his mother S.C., and (c) his father W.K.](image-url)

**Table 1 Haematological indices and haemoglobin analysis on patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Relationship</th>
<th>Hb (g/dl)</th>
<th>RBC x 10$^6$ (fl)</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (%)</th>
<th>Serum iron (μmol/l)</th>
<th>TIBC (μmol/l)</th>
<th>Hb $A_2$ (%)</th>
<th>Hbs C + $A_2$ (%)</th>
<th>Hb F (%)</th>
<th>Hb Kenya (%)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.K</td>
<td>Propositus</td>
<td>8-4</td>
<td>4-34</td>
<td>67</td>
<td>19-4</td>
<td>30-0</td>
<td>4-5</td>
<td>92</td>
<td>65-5</td>
<td>23-9</td>
<td></td>
<td></td>
<td>Hb C/δβ thalassaemia</td>
</tr>
<tr>
<td>S.C.</td>
<td>Mother</td>
<td>13-0</td>
<td>5-07</td>
<td>81</td>
<td>25-5</td>
<td>31-4</td>
<td>22-9</td>
<td>57</td>
<td>2-5</td>
<td>11-3</td>
<td></td>
<td></td>
<td>δβ thalassaemia heterozygote</td>
</tr>
<tr>
<td>W.K.</td>
<td>Father</td>
<td>15-8</td>
<td>5-52</td>
<td>85</td>
<td>28-7</td>
<td>33-3</td>
<td>28-3</td>
<td>71</td>
<td>38-5</td>
<td>0-52</td>
<td></td>
<td></td>
<td>Hb C heterozygote</td>
</tr>
<tr>
<td>P.O.</td>
<td>Propositus</td>
<td>15-8</td>
<td>5-0</td>
<td>90</td>
<td>30-5</td>
<td>35-6</td>
<td>1-0</td>
<td>71</td>
<td>38-5</td>
<td>6-8</td>
<td>14-7</td>
<td></td>
<td>Hb Kenya heterozygote</td>
</tr>
</tbody>
</table>

AD, alkali denaturation.
shown to contain Hb F though there was considerable variation in the intensity of fluorescence from cell to cell (Fig. 2a).

The father of the propositus is a heterozygote for Hb C while the mother has about 11% Hb F (by alkali denaturation), a normal amount of Hb A2, and the remainder, Hb A. Again the intracellular distribution of the fetal haemoglobin was heterogeneous both by acid elution and immunofluorescent techniques, the latter showing 63% Hb F-containing cells (F cells, Fig. 2b). These results, coupled with the haematological data and haemoglobin analysis indicate that the mother is heterozygous for δβ thalassaemia and hence that the propositus is a compound heterozygote for Hb C and δβ thalassaemia.

Globin-chain synthesis

Measurements of globin synthesis ratios were carried out on the whole blood of the propositus and on a reticulocyte-rich population of the mother's red cells.

The elution profiles following CM cellulose chromatography of globin prepared from these incubations are shown in Fig. 3. In the case of the δβ thalassaemia heterozygote the overall imbalance of α/non-α chain production was slight, α/non-α = 1.08. The specific activity of the α chains was about 1.5 times that of the β and γ chains. The relative production of γ and β chains is more difficult to assess accurately because the presence of the pre-β peak coincides with the peak of γ chains (Fig. 3). Nevertheless, the ratio of the specific activities of β and γ chains was 1.2. This implies a slower turnover of γ chains compared with β and, because of the pre-β contamination, this represents a minimum estimate. Since the proportion of Hb F as compared with Hb A in this reticulocyte-rich fraction was reduced as compared with the whole blood value this will also affect the γ and β-chain specific activities, further tending to lower falsely the β/γ specific activity ratio. Taking these considerations into account it can be estimated that a more realistic value for the relative specific activities of the β and γ chains would be about 1:5:1 in this patient.

Globin-chain synthesis studies in the propositus showed a complete absence of βA chain production and a greater degree of imbalance than was observed in his heterozygous mother. The presence of a pre-α peak migrating with the βC chains again makes accurate quantification impossible. Ignoring the presence of the pre-α peak altogether we obtain an α/γ,βC ratio of 1:40, a minimum estimate of the imbalance. A more realistic value can be obtained by assuming that the proportion of pre-α is the same in the propositus as in his mother, i.e. one-sixth of the total α chain radioactivity. (This assumption is probably valid because the incubations were carried out at the same time, under the same conditions, and with the same reagents.) This results in an α/non-α ratio of 2:3. The proportion of γ chains synthesised relative to βC chains is considerably lower than the relative proportions of Hbs F and C in the peripheral blood, even allowing for some of the radioactivity in the βC chain peak being α chain. This finding is supported by the specific-activity data which reveal that the γ-chain specific activity is only about half that of the βC chain.

Fig. 2 Peripheral blood smears from (a) the propositus M.K. and (b) his mother S.C., stained with FITC labelled anti Hb F antibodies, demonstrating in the former that virtually all the cells are stained, but with considerable intercellular heterogeneity, while in the latter, two distinct populations are evident.
Table 2 Red cell indices and haemoglobin data on blood of δβ thalassaemia heterozygote, S.C., after centrifugation

<table>
<thead>
<tr>
<th>Sample</th>
<th>MCV (fL)</th>
<th>MCH (pg)</th>
<th>Retic (Y%)</th>
<th>Hb A2 (%)</th>
<th>Hb Fαβ (%)</th>
<th>F cells (%)</th>
<th>Hb F/F cell (pg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top</td>
<td>78</td>
<td>24.3</td>
<td>4.8</td>
<td>3.34</td>
<td>8.1</td>
<td>52.6</td>
<td>3.79</td>
</tr>
<tr>
<td>Whole blood</td>
<td>80</td>
<td>26.2</td>
<td>1.2</td>
<td>3.44</td>
<td>11.0</td>
<td>63.6</td>
<td>4.56</td>
</tr>
<tr>
<td>Bottom</td>
<td>80</td>
<td>26.8</td>
<td>0</td>
<td>3.00</td>
<td>14.2</td>
<td>88.7</td>
<td>4.30</td>
</tr>
</tbody>
</table>

Differential centrifugation analysis
The results of haemoglobin analysis of the top and bottom 10% of the red cells of the δβ-thalassaemia heterozygote after centrifugation are given in Table 2. The bottom population contains cells with a higher MCH, a greater proportion of Hb F, as measured by alkali denaturation, and also a higher proportion of F cells. If this is the older cell population, as it is generally assumed, the results suggest that those cells containing Hb F have a longer survival than cells containing only Hb A, further evidence to support the results from the globin-chain synthesis studies which indicated a differential turnover of γ and β chains in this patient. Similar results from a Hb S/δβ thalassaemia case were reported by Zelkowitz et al. (1972).

Structural analysis of Hb F
Structural analysis of the γ15 or γ CB3 fragments obtained from the Hb F of the propositus and his mother produced glycine values extremely close to 1.0 (Table 3). This indicates that the fetal haemoglobin in these individuals contains γ chains of the Gγ type only.

FAMILY P.O.
The propositus, a 20-year-old man from the Jaluo tribe of Kenya, currently studying in Britain, was detected during the screening of blood donors.

Haematological and haemoglobin analysis
Haematological examination of fresh blood samples showed that he had normochromic, normocytic cells, and no evidence of iron deficiency (Table 1). Haemoglobin analysis showed the presence of an abnormal band, comprising 15% of the total haemoglobin, migrating just ahead of the Hb A2 on starch gel electrophoresis. This fraction was shown by peptide mapping and amino acid analysis to be Hb Kenya. The Hb F level was raised to 7.1% and the Hb A2 level was reduced to 1.0%. A homogeneous dis-
Table 3  Analysis of glycine/alanine composition of \(^{\gamma_1}\) or \(^{\gamma_C}\) fragments obtained from Hb F of propositus and his mother in family K

| Individual | Diagnosis         | %Hb F | Residues in \(^{\gamma_1}\) or \(^{\gamma_C}\)  \\
<table>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glycine</td>
</tr>
<tr>
<td>S.C</td>
<td>(\delta) thalassaemia</td>
<td>11.3</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.07</td>
<td>1.93</td>
</tr>
<tr>
<td>M.K.</td>
<td>Hb C/(\delta) thalassaemia</td>
<td>23.9</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Discussion

The combined haematological and genetic evidence indicates that the propositus in family K is a compound heterozygote for \(\delta\) thalassaemia and Hb C, while his mother is a \(\delta\)-thalassaemia heterozygote. The differential diagnosis of heterozygous \(\delta\) thalassaemia and hereditary persistence of fetal haemoglobin (HPFH) has previously caused problems (Mann et al., 1972; Sukumaran et al., 1972; Huisman et al., 1974, 1975b); therefore the reasons for considering the present abnormality to be \(\delta\) thalassaemia must be listed.

(1) The red cell morphology and indices of the propositus were abnormal, as, to a lesser degree, were those of his mother. Peripheral blood films showed a microcytic, hypochromic anaemia with the presence of target cells and microspherocytes, findings confirmed by the low MCH and MCV of both affected individuals. These findings are typical of thalassaemia, though in the case of the propositus they are accentuated by iron deficiency (Table 1). No morphological abnormalities are found in Negro HPFH heterozygotes, and red cell indices have usually been reported as being within the normal range (Wheeler and Krevans, 1961; Conley et al., 1963) though in one study there was evidence of slight microcytosis (Natta et al., 1974).

(2) Globin synthesis studies showed imbalanced chain production in the propositus, indicating the presence of a \(\beta\) thalassaemia gene. In the case of his mother, the degree of chain imbalance was only slight, though the specific activity of the \(\alpha\) chains was about 1.5 times that of the \(\beta^A\) and \(\gamma\) chains. The marginal imbalance observed reflects the milder degree of chain imbalance in \(\delta\) thalassaemia as compared with \(\beta\) thalassaemia, presumably resulting from the increased \(\gamma\) chain production in the former; similar ratios have been observed in a Chinese family with this disorder (Mann et al., 1972). However, in Negro \(\beta\)-thalassaemia heterozygotes, in whom there is no increase in \(\gamma\) chain production, \(\alpha/\beta\) ratios of 1.0 to 1.5 are not uncommon (Braverman et al., 1973; Friedman et al., 1973).

Globin-synthesis studies in Negro HPFH hetero-

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**Fig. 4 Chromatographic separation of the globin chains from whole cell lysates of the Hb Kenya heterozygote P.O. after incubation of his red cells with \(^3\)H leucine.**
zygotes have usually shown balanced chain synthesis 
(Natta et al., 1974; Friedman and Schwartz, 1976) 
though 3 cases out of 18 showed an α/non-α ratio 
greater than 1:10. In combination with Hb S however, 
3 out of 6 cases showed a deficit of non-α chain 
synthesis (Natta et al., 1974; Friedman and Schwartz, 
1976) indicating that in conditions where the degree 
of compensation from the β gene in trans to the 
HPFH determinant is limited, chain imbalance can 
be detected. Similarly, in two Negroes homozygous for 
HPFH α-chain/non-α-chain ratios of 1:4 and 2:0 have been obtained (Charache et al., 1976; 
Forget et al., 1976; Ottolenghi et al., 1976).

(3) The intracellular distribution of fetal haemoglobin in both the propositus and his mother was 
clearly heterogeneous by the acid elution method. 
Heterogeneity of Hb F distribution was also observed 
in both individuals by the more sensitive immuno-
fluorescent technique and though virtually all the 
cells of the propositus contained some Hb F, the 
variation in fluorescence from cell to cell was much 
greater than that observed in HPFH heterozygotes, 
using this technique.

By all these criteria, therefore, the disorder in 
family K must be classified as δβ thalassaemia. The proportion of Hb F in the δβ heterozygote, 11%, is 
somewhat lower than in many previously reported δβ 
thalassaemias of Negro origin, who normally have 
20 to 25% Hb F (Weatherall, 1964; Zelkowitz et al., 
1972). This may reflect a difference in the number of 
functioning γ-chain genes in these cases but no details 
of the structure of the Hb F are given in the earlier 
studies. It is interesting, however, that in combination 
with Hb C, the δβ-thalassaemia gene results in a more 
than twofold increase in the proportion of fetal 
haemoglobin produced. This higher proportion of 
Hb F in the compound heterozygote cannot be the 
result of the delayed disappearance of his fetal 
haemoglobin after the changeover from fetal to 
adult haemoglobin after birth, since all his Hb F is of 
the Gγ type only. The chromosome containing the 
βc gene presumably carries a normal complement of 
Gγ and Aγ genes, both of which would be expressed 
during fetal development. Consideration of the MCH, 
the amount of Hb F, and the proportion of F cells, 
however, shows that the mean Hb F/F cell in the mother 
is

\[
4.53 \text{ pg} \left(25.5 \times \frac{11.3}{100} \times \frac{100}{63.6}\right)
\]

while in her son it is

\[
4.64 \text{ pg} \left(19.4 \times \frac{23.9}{100} \times \frac{100}{100}\right).
\]

(Normal adults with a mean Hb F level of 0.45% 
(Pembrey et al., 1972) distributed in 2.8% of the cells 
(Wood et al., 1975) and an MCH of 29 pg, containing 
4.66 pg Hb F per F cell, though in normals both Gγ 
and Aγ chains are produced.) This suggests that the 
greater proportion of Hb F observed in the propositus 
is a result of a relative increase in the number of those 
cells making Hb F and not a result of increased γ-chain 
production in each F cell. Increased numbers of Hb 
F cells may result from their increased proliferation or 
preferential survival in the peripheral blood. That the 
latter situation may obtain in the present case is 
indicated by the greater specific activities of the α 
and βc chains compared with the γ chains in both the 
propositus and, to a lesser extent, in the δβ-thalassa-
emia heterozygote (see results section). This is 
further supported by the higher level of Hb F in 
containing cells at the bottom of the column of cells 
after centrifugation, i.e. presumably the older cell 
population. No significant difference was observed 
in the amount of Hb F/F cell between the young 
and old cell populations.

Hb Kenya heterozygotes also have persistent 
synthesis of Hb F, the γ chains of which are solely of 
the Gγ type (Huisman et al., 1972; Kendall et al., 
1973; Smith et al., 1973; Nute et al., 1976). The 
present case conforms to this pattern and for the 
first time it has been possible to carry out haematological 
examination on fresh blood samples and to 
measure globin-chain synthesis. The red cell indices 
of the present case are absolutely normal and show no evidence of microcytosis or reduced haemoglobin 
zation. Previously reported red cell indices in 
heterozygotes were measured only after several days 
in transit (Kendall et al., 1973; Smith et al., 1973; 
Nute et al., 1976). The MCVs in the 13 published 
cases varied from 71 to 95 fl (mean 81.7 ± 7.5 fl) and 
the MCHs from 22 to 28 pg (mean 25.5 ± 2.1 pg). 
Normal values for this population are not available, 
and iron deficiency caused by hookworm infestation 
is common (Kendall et al., 1973), possibly accounting 
for these low values.

Globin-chain synthesis experiments indicate that 
the overall α/non-α chain synthesis in the present case 
is close to unity, though the specific activity data 
suggest that there is possibly a slight deficit in non-α 
chain production. Clearly the γβ fusion chains are 
synthesised in reticulocytes in approximately the same 
proportion as they appear in the peripheral blood. 
This contrasts with the δβ and βδ fusion chains of 
HbS Lepore and Miyada, which are synthesised only 
in more immature erythroid cells, a pattern of 
synthesis which also holds for normal δ chains 
(Roberts et al., 1972, 1973).

The normal red cell indices, together with the 
approximately balanced α/non-α chain globin syn-
thesis ratio, confirm the previous suggestions 
(Kendall et al., 1973; Smith et al., 1973; Nute et al.,
The continued Hb F production in Hb Kenya heterozygotes is the result of an HPFH type disorder rather than a thalassaemia disorder. The conditions in which there are increased amounts of Hb F containing only $G\gamma$ chains in adult life are $\delta\beta$ thalassaemia, found in Chinese (Mann et al., 1972) and Negro patients (Huisman et al., 1975a and this paper) but not in those of Mediterranean origin (Stamatyannopoulos et al., 1971; Ottolenghi et al., 1976); Hb Kenya (Huisman et al., 1972; Kendall et al., 1973; Smith et al., 1973; Nute et al., 1976) occurring in Negroes, $G\gamma\beta^+$ HPFH, found in two Negro families (Huisman et al., 1975b; Friedman and Schwartz, 1976), and Negro $G\gamma$ HPFH (Sukumaran et al., 1972; Huisman et al., 1975a).

The two cases described here are clearly quite different with regard to red cell morphology, red cell indices, and intracellular distribution of Hb F but similar in respect to globin-chain synthesis ratios. There is good evidence that $\delta\beta$ thalassaemia, at least the $G\alpha G\beta\gamma$ type found in Mediterranean areas, involves the deletion of part of the $\beta$ and $\delta$ structural genes (Ottolenghi et al., 1976) and it is assumed that in the formation of the $G\delta$ fusion chain of Hb Kenya there has also been a deletion, in this case involving the C terminal end of the $G\gamma$ gene, the $\delta$ gene and the N terminal end of the $G\beta$ gene (Huisman et al., 1972; Kendall et al., 1973; Smith et al., 1973). If $G\gamma\delta$ thalassaemia is also the result of a deletion it can be represented as $G\gamma G\gamma G\delta G\beta$, the enclosed areas being deleted. A deletion is also the most likely explanation for $G\gamma\beta^+$ HPFH, in this case of the $G\alpha G\beta\gamma$ and $G\delta$ genes, and, though there is no direct evidence for the involvement of a deletion in $G\gamma$ Negro HPFH, there is evidence that a considerable part of the $G\beta$ and $G\delta$ genes are deleted in the $G\gamma G\gamma$ Negro HPFH (Kan et al., 1975; Forget et al., 1976; Ottolenghi et al., 1976). $G\gamma\beta^+$ HPFH can thus be represented as $G\gamma G\gamma G\delta G\beta$ and the $G\gamma$ Negro form, assuming it to be a deletion, as $G\gamma G\gamma G\delta G\beta$, i.e. including the same structural genes as $G\gamma\delta$ thalassaemia, though not necessarily the same non-structural areas.

The question thus remains as to why the latter condition should present as a typical thalassaemia disorder with hypochromia, microcytosis, and a heterogeneous distribution of Hb F while the other three result in asymptomatic disorders with a minimal decrease in red cell haemoglobinisation and a homogeneous Hb F distribution. The heterogeneous distribution of Hb F in $\delta\beta$ thalassaemia is similar to that observed in heterocellular HPFH, a group of inherited conditions in which the proportion of F cells is increased in otherwise haematologically normal adults (Boyer et al., 1977). The deletion (or other lesion) in $\delta\beta$ thalassaemia may act in a similar manner to the heterocellular HPFH lesion, producing an enlarged F cell population but which is combined, in the case of $\delta\beta$ thalassaemia, with the absence of $\beta$ or $\delta$ chain synthesis in cis (Weatherall et al., 1976). This would result in the observed chain imbalance and microcytosis together with the increased level of Hb F. The mechanism by which this can be brought about at the molecular level is still unclear and further information is required, particularly about the non-coding regions between the structural genes, before a fuller understanding of these conditions is achieved.

References


Friedman, S., and Schwartz, E. (1976). Hereditary persistence of foetal haemoglobin with $\beta$ chain synthesis in cis position ($G\gamma G\gamma$-HPFH) in a Negro family. Nature, 259, 139-140.


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