Comparison of 2 new cases


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SUMMARY Two new cases of $^\gamma$ $\delta$ thalassaemia and $^\gamma$ 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 $\gamma$ $\delta$ gene complex in general.

The structural genes coding for the non-$\alpha$ globin chains in man appear to be closely linked on the same chromosome in the order $^\alpha$ $^\gamma$ $^\delta$ or $^\gamma$ $^\delta$ $^\gamma$ (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 ($^\gamma$ and $^\gamma$) to adult ($\delta$ and $\beta$) chain synthesis which occurs in the perinatal period. Disorders involving this control mechanism, however, may lead to the continued production of $\gamma$ chains in adult life; these conditions can be divided broadly into the $\beta$ and $\delta$ thalassaeasias 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 $^\gamma$ and $^\gamma$ chains or only $^\gamma$ 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); $\delta$ thalassaemia in a Chinese family (Mann et al., 1972) and in a Negro family (Huisman et al., 1975a); and in the recently described $^\gamma$ $\beta^+$ 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 $^\gamma$ $\delta$ 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 $\gamma$ $\delta$ gene complex.

In this report we describe a further case of $^\gamma$ $\delta$ thalassaemia, occurring here in a Negro family in which Hb C is also present, and compare it with a new case of $^\gamma$ 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.

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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 ^3H 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 γ chains of fetal haemoglobin may contain either glycine (γγ) or alanine (αγ) at position 136 (Schroeder et al., 1968). Determination of the Oγ/αγ ratio was carried out in two ways. Purified γ chains obtained from CM cellulose chromatography were digested with trypsin, and peptide γ15, 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 γCB3 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 γ15 or γCB3. Values of 1.00 or 0.00 indicate that only γγ or αγ 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 A2, 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 + A2 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

![Starch gel electrophoresis of haemolysates prepared from (a) the propositus M.K., (b) his mother S.C., and (c) his father W.K.](http://jmg.bmj.com/)

**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.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Relationship</th>
<th>Hb (g/dl)</th>
<th>RBC x 10^6/μl</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 A2 (%)</th>
<th>Hb C + A2 (%)</th>
<th>Hb F (%)</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>
</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>
</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>
</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>38.5</td>
<td>6.8</td>
<td>14.7</td>
<td></td>
<td></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 alkaline 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 $\delta\beta$ thalassaemia and hence that the propositus is a compound heterozygote for Hb C and $\delta\beta$ 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 $\delta\beta$ thalassaemia heterozygote the overall imbalance of $\alpha$/non-$\alpha$ chain production was slight, $\alpha$/non-$\alpha = 1:08$. The specific activity of the $\alpha$ chains was about 1·5 times that of the $\beta$ and $\gamma$ chains. The relative production of $\gamma$ and $\beta$ chains is more difficult to assess accurately because the presence of the pre-$\beta$ peak coincides with the peak of $\gamma$ chains (Fig. 3). Nevertheless, the ratio of the specific activities of $\beta$ and $\gamma$ chains was 1:2. This implies a slower turnover of $\gamma$ chains compared with $\beta$ and, because of the pre-$\beta$ 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 $\gamma$- and $\beta$-chain specific activities, further tending to lower falsely the $\beta/\gamma$ specific activity ratio. Taking these considerations into account it can be estimated that a more realistic value for the relative specific activities of the $\beta$ and $\gamma$ chains would be about 1:5:1 in this patient.

Globin-chain synthesis studies in the propositus showed a complete absence of $\beta^A$ chain production and a greater degree of imbalance than was observed in his heterozygous mother. The presence of a pre-$\alpha$ peak migrating with the $\beta^C$ chains again makes accurate quantification impossible. Ignoring the presence of the pre-$\alpha$ peak altogether we obtain an $\alpha/\gamma, \beta^C$ ratio of 1:40, a minimum estimate of the imbalance. A more realistic value can be obtained by assuming that the proportion of pre-$\alpha$ is the same in the propositus as in his mother, i.e. one-sixth of the total $\alpha$ 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 $\alpha$/non-$\alpha$ ratio of 2:3. The proportion of $\gamma$ chains synthesised relative to $\beta^C$ 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 $\beta^C$ chain peak being $\alpha$ chain. This finding is supported by the specific-activity data which reveal that the $\gamma$-chain specific activity is only about half that of the $\beta^C$ chain.

![Fig. 2](http://jmg.bmj.com/ on June 24, 2017 - Published by group.bmj.com)
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![Graph showing chromatographic separation of globin chains](image)

Fig. 3 Chromatographic separation of the globin chains from whole cell lysates of S.C. (top) and M.K. (bottom) after incubation of the red cells with $^3$H leucine.

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 (f)</th>
<th>MCH (pg)</th>
<th>Retics (%)</th>
<th>Hb A2 (%)</th>
<th>Hb FAD (%)</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>11.9</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 $^{G}_γ$ 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-
Globin-chain synthesis

Globin-chain synthesis was measured in a reticulocyte-rich fraction of the patient’s blood, incubated with ³H leucine for 30 minutes (Fig. 4). The α/α chain synthetic ratio was 0·90 and the proportions of newly synthesised γ, β, and γβ chains were similar to those found in the peripheral blood. The specific activity ratios were a/β 1·3; a/γ 0·95 and a/γ 1·3, indicating, perhaps, a slight degree of chain imbalance.

Discussion

The combined haematological and genetic evidence indicates that the propositus in family K is a compound heterozygote for δβ thalassaemia and Hb C, while his mother is a δβ-thalassaemia heterozygote. The differential diagnosis of heterozygous δβ 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 δβ 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 thalassaemia gene. In the case of his mother, the degree of chain imbalance was only slight, though the specific activity of the α chains was about 1·5 times that of the βα and γ chains. The marginal imbalance observed reflects the milder degree of chain imbalance in δβ thalassaemia as compared with β thalassaemia, presumably resulting from the increased γ-chain production in the former; similar ratios have been observed in a Chinese family with this disorder (Mann et al., 1972). However, in Negro β-thalassaemia heterozygotes, in whom there is no increase in γ-chain production, a/α 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-

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 ³H 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 immunofluorescent 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 δγ type only. The chromosome containing the βc gene presumably carries a normal complement of δγ and βγ 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

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

while in her son it is

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

(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, contain 4.66 pg Hb F per F cell, though in normals both δγ and γ 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 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-thalassaemia heterozygote (see results section). This is further supported by the higher level of Hb F-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 δγ 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 haemoglobinization. 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). 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 βc 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 synthesis ratio, confirm the previous suggestions (Kendall et al., 1973; Smith et al., 1973; Nute et al,
$\gamma \delta \beta$ thalassaemia and $\gamma \beta$ HPFH (Hb Kenya type)

1976) that 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 $\gamma \beta$ 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 (Stamatoyannopoulos 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, $\gamma \beta$+ HPFH, found in two Negro families (Huisman et al., 1975b; Friedman and Schwartz, 1976), and Negro $\gamma \gamma$ 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 $\gamma \gamma$$^+ \gamma$ type found in Mediterranean areas, involves the deletion of part of the $\beta$ and $\delta$ structural genes (Ottolenghi et al., 1976) and it is assumed that in the formation of the $\gamma \delta$ fusion chain of Hb Kenya there has also been a deletion, in this case involving the C terminal end of the $\gamma$ gene, the $\delta$ gene and the N terminal end of the $\beta$ gene (Huisman et al., 1972; Kendall et al., 1973; Smith et al., 1973). If $\gamma \beta$ thalassaemia is also the result of a deletion it can be represented as $\gamma \delta$ and Hb Kenya as $\gamma \delta$, the enclosed areas being deleted. A deletion is also the most likely explanation for $\gamma \beta$+ HPFH, in this case of the $\gamma$ and $\delta$ genes, and, though there is no direct evidence for the involvement of a deletion in $\gamma \gamma$ Negro HPFH, there is evidence that a considerable part of the $\beta$ and $\gamma$ genes are deleted in the $\gamma \gamma$$^+ \gamma$ Negro HPFH (Kan et al., 1975; Forget et al., 1976; Ottolenghi et al., 1976). $\gamma \beta$+ HPFH can thus be represented $\gamma \delta$ and the $\gamma \gamma$ form, assuming it to be a deletion, as $\gamma \delta$ and, i.e. including the same structural genes as $\gamma \delta$ 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.

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