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Hereditary Persistence of Fetal Hemoglobin, β Thalassemia, and the Hemoglobin δ-β Locus: Further Family Data and Genetic Interpretations

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Hereditary persistence of fetal hemoglobin (HPFH) was first documented in 1955 in Ghana [1] and has also been described in non-African populations [2–7]. The association of HPFH with β thalassemia [8–12] and with Hb S and C [9, 13–15] has been amply documented, but heterozygosity for both HPFH and the δ chain variant Hb B_2 has been reported only once [9, 16]. Weatherall and Clegg [17] summarize all these cases. The γ-β fusion gene Hb Kenya was first reported in a family where both Hb B_2 and Hb Kenya were segregating [18]. In this paper one black kindred from the United States and two from Ghana are described which add further to linkage information on HPFH and the linked structural loci for Hb δ and Hb β.

MATERIALS AND METHODS

Standard hematologic methods were used for red cell count, hemoglobin, hematocrit, and osmotic fragility determinations. To demonstrate fetal hemoglobin in red cells, the method of Kleihauer et al. [19] was followed using brilliant cresyl blue–treated blood to eliminate false positive staining of young red cells due to diffuse ribonucleoprotein [20]. The Hb A_2 and B_2 levels were determined on starch block according to Gerald and Diamond [21]. For best separation of these fractions, electrophoresis was carried

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out at pH 8.6 at a constant current of 50 mA for 24 hr. Starch gel electrophoresis on hemolysates was performed according to Smithies [22] using Tris-EDTA-borate buffer at pH 8.6. Hemoglobin F was measured by the 1-min denaturation method of Singer et al. [23]. Red cell survival was determined with the ^{51}chromium technique. Amino acid analysis of CB-3 peptides of γ chains of Hb F has been reported elsewhere (family S) as consisting of the $^{G}\gamma$ and $^{A}\gamma$ types [24]. The various studies on kindred A were carried out in the United States, while kindreds B and C were studied in both Ghana and England.

RESULTS

Kindred A

The index case (III-1; fig. 1, tables 1 and 2), a 22-year-old Negro woman, came to attention when she was referred to the hematology clinic at Colorado

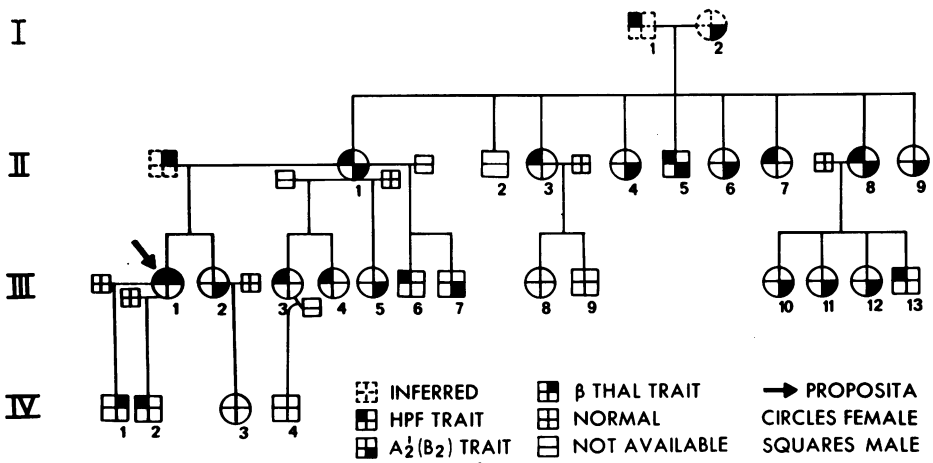

FIG. 1.—Pedigree of kindred A

General Hospital for evaluation of mild anemia. There was no other history of illness. The tip of the spleen was palpable. There were no bony deformities or roentgenographic signs of thalassemia. Her hematologic findings (table 1) were: hemoglobin, 12.1 g/100 ml; red cells, 5.0 million/mm^3; hematocrit, 36%; MCV, 72 μm^3; MCH, 24 pg; MCHC, 33%; reticulocytes, 4%; total bilirubin, 0.95 mg/100 ml; direct bilirubin, 0.18 mg/100 ml; serum iron, 174 μg/100 ml; total iron-binding capacity, 405 μg/100 ml; haptoglobin, 22 mg hemoglobin bound. Her red cells were hypochromic, microcytic, and many were target cells (fig. 2*a*). The acid elution pattern for fetal hemoglobin of the blood smear showed homogeneous staining of all cells (fig. 2*b*). The osmotic fragility curve revealed the presence of a markedly resistant cell population. Oxygen dissociation (Dr. J. V. Weil, Univ. of Colorado, Denver) of whole blood was normal.* The bone marrow

* See NAPS document no. 02545 for data on oxygen dissociation. Order from ASIS/NAPS, c/o Microfiche Publications, 305 East 46th Street, New York, New York 10017.

TABLE 1

HEMATOLOGIC DATA ON KINDRED A

Subject	Age (Yr)	Hematocrit (%)	Hemoglobin (g/100 ml)	Red Cell Morphology
II-1	42	52	14.5	Occasional target cells
II-3	43	47	14.0	Occasional target cells
II-4	44	46	14.5	Normal
II-5	56	56	14.8	Mild anisocytosis
II-6	58	43	14.0	Normal
II-7	50	47	14.2	Rare target cells
II-8	46	46	14.6	Normal
II-9	49	43	14.0	Normal
III-1*	22	36	12.1	Hypochromia, target cells, microcytosis, anisocytosis, poikilocytosis
III-2	20	40	13.6	Normal
III-3	17	45	13.9	Rare target cells
III-4	15	42	13.8	Normal
III-5	8	41	13.8	Normal
III-6	14	40	13.7	Normal
III-7	10	42	13.8	Normal
III-8	15	43	14.9	Normal
III-9	13	50	15.2	Normal
III-10	10	48	14.5	Normal
III-11	13	47	14.0	Normal
III-12	15	46	14.3	Normal
III-13	18	49	14.9	Rare target cells
IV-1*	2	34	9.0	Anisocytosis, poikilocytosis, hypodhromia, occasional basophilic stippling
IV-2	10/12	31	11.9	Moderate anisocytosis, poikilocytosis, hypochromia
IV-3	1	33	12.0	Normal
IV-4	2	34	13.5	Mild anisocytosis

* See text for further details.

showed erythroid hyperplasia with normal maturation of all cell lineages. Stainable iron was present in normal amounts. Her red cell survival time (^{51}Cr) was shortened (half-life, 16 days; normal, 29–34 days). Blood samples were obtained from available family members. The pedigree of the family is shown in figure 1 and the relevant hematologic data in table 1.

Her children (IV-1, IV-2) both appeared healthy. The spleen of subject IV-1 was palpable. This child's alkali-resistant hemoglobin was mildly elevated; Hb A_2 was increased (table 2). His red cells were hypochromic and microcytic (fig. 2*c*), some with basophilic stippling. Distribution of Hb F was heterogeneous in erythrocytes (fig. 2*d*). The following hematologic findings were noted: hemoglobin, 11.5 g/100 ml; red cells, 4.5 million/mm^3; hematocrit, 39%; reticulocytes, 2%; total bilirubin, 1.1 mg/100 ml; direct bilirubin, 0.1 mg/100 ml; serum iron, 90 μg/100 ml; total iron-binding capacity, 280 μg/100 ml; haptoglobin, 45 mg

TABLE 2

HEMOGLOBIN DATA AND KLEIHAUER ELUTION RESULTS ON KINDRED A

Subject	Age (Yr)	Hb F (%)	Hb A_2 (%)	Hb B_2 (%)	Hemoglobin Type	Distribution of Hb F in Red Cells
II-1	42	25	0	1.2	A, F, B_2	Even
II-3	43	19	1.7	0	A, F	Even
II-4	44	1.1	0.9	1.1	A, A_2, B_2	Uneven
II-5	56	24	0	1.4	A, F, B_2	Even
II-6	58	1.2	1.7	1.0	A, A_2, B_2	Uneven
II-7	50	20	2.0	0	A, F	Even
II-8	46	21	0	1.6	A, F, B_2	Even
II-9	49	1.5	1.2	1.3	A, A_2, B_2	Uneven
III-1	22	60	3.5	0	F, A, A_2*	Even
III-2	20	2	1.3	1.6	A, A_2, B_2	Uneven
III-3	17	21	1.9	0	A, F	Even
III-4	15	20	1.6	0	A, F	Even
III-5	8	1.3	1.3	1.2	A, A_2, B_2	Uneven
III-6	14	22	1.5	0	A, F	Even
III-7	10	0.6	1.4	1.3	A, A_2, B_2	Uneven
III-8	15	1.2	2.5	0	A	Uneven
III-9	13	1.4	2.9	0	A	Uneven
III-10	10	1.7	1.0	1.6	A, A_2, B_2	Uneven
III-11	13	1.1	1.5	1.3	A, A_2, B_2	Uneven
III-12	15	1.5	1.0	1.6	A, A_2, B_2	Uneven
III-13	18	20	2.0	0	A, F	Even
IV-1	2	2.3	5.6	0	A, A_2†	Uneven
IV-2	10/12	23	1.8	0	A, F	Even
IV-3	1	3	2.0	0	A	Uneven
IV-4	2	1.3	2.2	0	A	Uneven

* HPFH-thalassemia.
† Thalassemia trait.

hemoglobin bound. The Hb A_2 of subject IV-2 was low, and a high alkali-resistant fraction was found (table 2). The acid elution pattern showed homogeneous distribution of stainable hemoglobin in all cells.

There was no consanguinity in this family nor was there any history of anemia or other illness. With the exception of subjects III-1, IV-1, and IV-2, physical examinations were not permitted. Starch gel electrophoresis of hemoglobin from the other available members of this kindred revealed 10 individuals with elevated Hb F. Three of these also had Hb B_2 but not Hb A_2 (II-1, II-5, II-8), and nine had both Hb B_2 and Hb A_2 and normal Hb F. The hemoglobin data and results of Kleihauer elution tests are detailed in table 2.

Summary. A 22-year-old mildly anemic woman (III-1) was heterozygous for both HPFH and β thalassemia. One of her two children had HPFH and the other had β thalassemia. (The elevated Hb A_2 of the thalassemic child [IV-1] clearly ruled out $\delta\beta$ thalassemia.) Her mother (II-1) and two other maternal

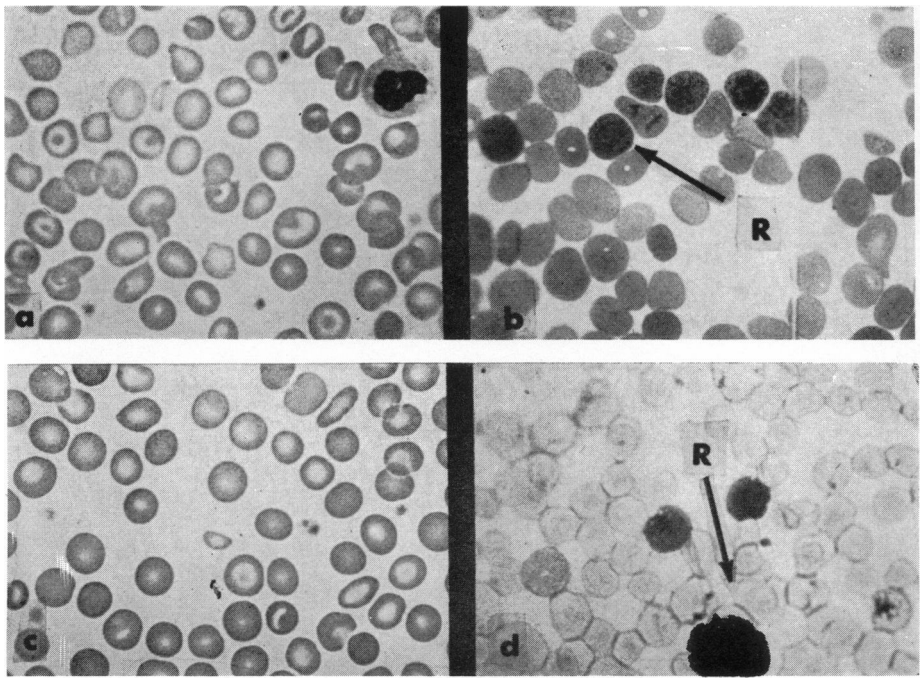

FIG. 2.—*a, b,* Blood films of the proposita (III-1) from kindred A; *c, d,* blood films from her son (IV-1). *a,* Wright-stained smear showing anisopoikilocytosis and targeting. *b,* Hematoxylin-erythrosin stain after acid elution according to Kleihauer et al. [19]. Note homogeneous distribution of Hb F in all erythrocytes. Arrow points to reticulocyte (*R*). *c,* Wright-stained smear showing anisopoikilocytosis, microcytosis, and hypochromia. *d,* Hematoxylin-erythrosin stain after acid elution. Note heterogeneous distribution of Hb F in red cells. Arrow points to reticulocyte, whose Hb A was eluted in the process.

sibs (II-5 and II-8) carried the genes for HPFH and for Hb B_2 and were hematologically normal. These individuals had 11 offspring: five had HPFH and six had Hb B_2. None were normal and none had both abnormalities.

Kindred B

The index case (II-5, fig. 3), a 19-year-old healthy Ghanian girl, was discovered during the course of a school survey. She was found to have 27% Hb F. She had Hb B_2, and Hb A_2 was absent on electrophoresis (table 3). A family study was carried out on her mother, three sisters, and two brothers (fig. 2) who were perfectly well. The father had died some years previously. The children's hemoglobin patterns indicated that the deceased father had carried the gene for Hb C as well as the gene for HPFH. The mother (I-2) had the gene for Hb B_2 which she transmitted to two of her six children (II-5 and II-6). No Hb A_2 was seen in these girls (table 3). None of the six children showed the combination of Hb C with Hb B_2, and none were normal. The Hb C trait was seen in three children

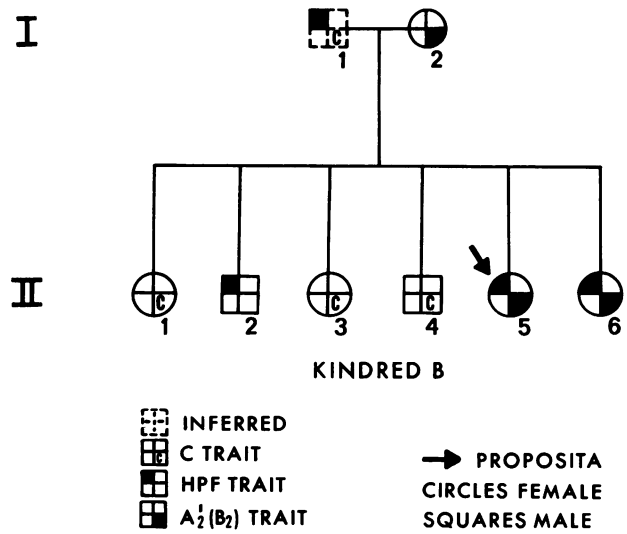

FIG. 3.—Pedigree of kindred B

TABLE 3

HEMOGLOBIN RESULTS ON KINDREDS B AND C

Kindred and Subject	Age (Yr)	Hb F (%)	Hb A_2 (%)	Hb B_2 (%)	Hemoglobin Type	Distribution of Hb F in Red Cells
Kindred B:						
I-2	53	0.6	1.6	< 1.0	A, A_2, B_2	Uneven
II-1	28	1.2	Present	Absent	A, C	Uneven
II-2	27	27	Present	Absent	A, F	Even
II-3	23	0.8	Present	Absent	A, C	Uneven
II-4	21	0.7	Present	Absent	A, C	Uneven
II-5	19	27	Absent	Present	A, F, B_2	Even
II-6	15	27	Absent	Present	A, F, B_2	Even
Kindred C:						
I-1	66	3.3	Present	Absent	A, S	Uneven
I-2	55	22	Present	Absent	A, F	Even
II-1	37	4.0	4.2	Absent	A	Not Done
II-2	39	25	1.8	Absent	S, F*	Even
II-3	30	3.9	Present	Absent	A	Uneven
II-4	22	1.8	1.8	Absent	A	Uneven
II-5	20	24	2.2	Absent	A, F	Even
III-1	10	61	4.7	Absent	F, A, A_2†	Even
III-2	8	28	5.6	Absent	S, F, A, A_2‡	Uneven
III-3	12	3.4	Present	Absent	A, S	Uneven

* Hb S was the preponderant component; interpreted as Hb S–HPFH.
† Interpreted as HPFH–β thalassemia (Hb F > Hb A, even distribution of Hb F, increased Hb A_2).
‡ Interpreted as sickle cell–β thalassemia (Hb S, 56%; Hb A, 10%; Hb F, 28%; Hb A_2, 5.6%).

and the HPFH trait in three children. Two children with HPFH trait also had Hb B_2.

Summary. A woman with Hb B_2 trait had married a man who was inferred to be heterozygous for Hb C and for HPFH in the trans configuration. Three of her six children were Hb C trait carriers and three were HPFH carriers. Two children with HPFH trait also had Hb B_2.

Kindred C

The propositus (II-1; fig. 4, table 3) was a 39-year-old surveyor who reported to the sickle cell clinic in Accra with severe pains of the right hip and a positive

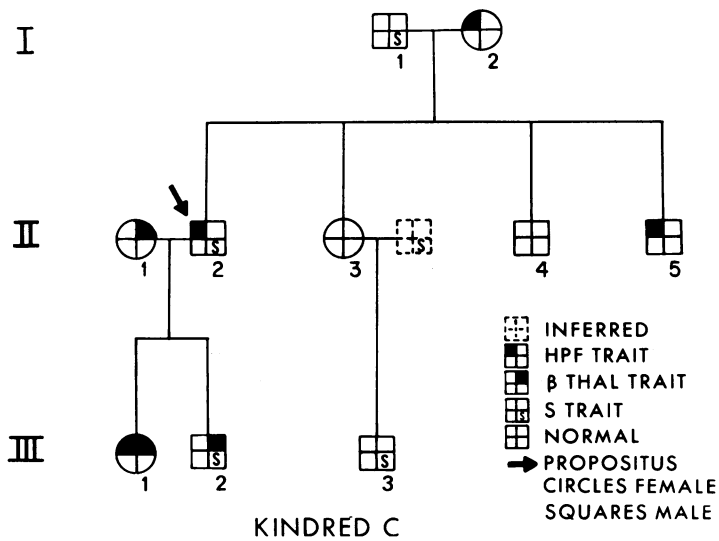

FIG. 4.—Pedigree of kindred C

sickling test. He was found to be healthy apart from a 1½-inch shortening of the right leg with considerable limitation of movement of the affected hip. He was neither anemic nor jaundiced, and the spleen was not palpable. His blood picture was essentially normal: hemoglobin, 16.4 g/100 ml; white blood cells, 5,400 with a normal differential count; and normal red cell morphology. A roentgenogram revealed aseptic necrosis of the right hip. He was found to carry the gene for Hb S and for HPFH (table 3).

The two children of the propositus (III-1, 10 years old; III-2, 8 years old) were mildly anemic: hemoglobin, 10 g/100 ml and 11.1 g/100 ml, respectively. The osmotic fragility of erythrocytes was decreased in both cases. Blood smears showed target cells in both cases. One child (III-1) had a phenotype compatible with HPFH and β thalassemia because of the 61% Hb F level with even distribution of Hb F in the red cells; the other (III-2) had sickle cell thalassemia because of the high Hb S level (56%) and uneven distribution of Hb F in red

cells. The mother of the two children had an elevated Hb A_2 level (4.2%) as well as the characteristic red cell morphologic changes consistent with β thalassemia trait.

Subjects II-2 and II-3, aged 30 and 22, respectively, were healthy individuals with no apparent abnormal hemoglobin. Subject II-4 (20 years old) had HPFH.

The father of the propositus (I-1) is 66 years old and is a sickle cell trait carrier; the mother (I-2) is 55 years old and is heterozygous for HPFH trait.

Summary. A nonanemic man with aseptic necrosis of the hip was found to carry the genes for both Hb S and HPFH. Of his two children, one inherited his HPFH gene and the other his sickling gene. Both children also had β thalassemia transmitted from the mother.

DISCUSSION

The diagnosis of simple heterozygosity for HPFH in members II-3, II-7, III-3, III-4, III-6, III-13, and IV-2 of kindred A, II-2 of kindred B, and I-2 and II-4 of kindred C was based on the following: (1) the absence of anemia and nearly normal red cell morphology in face of an elevated Hb F (tables 1–3); (2) homogeneous distribution of Hb F in red cells after acid elution; and (3) the low Hb A_2 levels where available (tables 2 and 3). Subject IV-2 of kindred A was mildly anemic, possibly due to iron deficiency. In agreement with the concept that HPFH is a benign abnormality, simple HPFH heterozygotes in these three kindreds had no demonstrable hematologic disease.

Ceppellini [25] described the first δ chain variant of human Hb B_2 in American Negroes. Heterozygotes for Hb B_2 were normal hematologically [26]. A search of the literature revealed only one family with a member heterozygous for both HPFH and Hb B_2 [9, 16]. Subjects II-1, II-5, and II-8 of kindred A and II-5 and II-6 of kindred B can be added to the description of this phenotype. These five individuals had no demonstrable Hb A_2, their Hb F was in the range found among simple HPFH heterozygotes, and Hb B_2 levels were depressed in kindred A but not quantitated in kindred B. No normal Hb A_2 was produced in any of these individuals since the HPFH gene completely suppresses normal δ chain production in the cis position. The depression of Hb B_2 levels is consistent with the synthetic activity of only a single Hb B_2 gene. As expected, carriers of both HPFH and Hb B_2 were hematologically normal (table 1).

Among 11 offspring of two individuals heterozygous for both HPFH and Hb B_2 (II-1 and II-8 of kindred A), all children either carried the HPFH gene or the Hb B_2 gene. No children were normal or carried both genes. Subject I-1 of kindred B was an inferred heterozygote for both Hb C and HPFH, and similar findings were noted in his six children; they either carried the Hb C gene or the HPFH gene.

Transmission of the various hemoglobin genes in kindred B was complicated in that the wife of the heterozygote for both Hb C and HPFH also carried the Hb B_2 gene. Two of three children with the HPFH trait obtained the Hb B_2 gene from their mother and thus were heterozygous for both Hb B_2 and HPFH.

In kindred C (fig. 4), a man heterozygous for both Hb S and HPFH married a woman with β thalassemia trait. One of the two children inherited the Hb S gene and the other the HPFH gene, but each of these children also obtained the β thalassemia gene from their mother. Thus these children expressed with Hb S–β thalassemia (III-2) and with HPFH–β thalassemia (III-1). The mild hematologic manifestations in III-1 presumably were accounted for by the high level of Hb F occasionally seen in this disorder.

In view of the β thalassemic phenotype (characteristic morphology and elevated Hb A_2) of subject IV-1 of kindred A (fig. 2, tables 1 and 2), whose father was found to be normal hematologically, the proposita (III-1) must have inherited the β thalassemia gene from *her* father, who unfortunately was not available for study. She therefore was heterozygous for both HPFH and β thalassemia. Both she and subject III-1 from kindred C who also had this combination had about 60% Hb F and decreased osmotic fragility. Normoblastic hyperplasia of the bone marrow of III-1 (kindred A) with presence of stainable iron and a low haptoglobin were consistent with the presence of a thalassemia gene. The absence of Hb H and Hb Bart's on electrophoresis [3, 27] militate against the diagnosis of α thalassemia trait in subject IV-1 of kindred A. Elevated Hb A_2 levels appear to rule out $\delta\beta$ thalassemia in subject IV-1 of kindred A and in II-1 and III-2 of the kindred C.

With the exception of a mild, compensated hemolytic process, individuals heterozygous for both HPFH and β thalassemia minor do not, as a rule, have an increased morbidity when compared to patients with simple thalassemia minor. The shortened ^{51}Cr red cell survival of patient III-1 of kindred A is in agreement with studies demonstrating increased hemolysis in other HPFH–β thalassemia heterozygotes [9, 10, 12]. The oxygen dissociation of hemoglobin in whole blood from this individual was normal despite the large amount of Hb F which approximates that seen in cord blood. This finding is consistent with the observation of normal oxygen affinity of the blood of another HPFH-thalassemia heterozygote so studied [28].

Genetic Considerations

Extensive data exist supporting linkage between the gene for HPFH and the structural Hb β gene [4, 6, 7, 9, 10, 11, 13–15, 17, 23]. These data are derived from offspring of individuals carrying both a structural variant of the Hb β gene (i.e., Hb S or Hb C) and the gene for HPFH. Children of such matings either exhibited the gene for HPFH or that for the abnormal β chain, and at least 39 such offspring have been studied [17]. The interpretation of "linkage" was based on the postulated existence of the HPFH gene as a discrete chromosomal entity. If a parent (particularly the mother, since paternity may be uncertain) carrying the genes for both HPFH and Hb S (or Hb C) would have a normal child without any hemoglobin abnormalities, crossover between the HPFH gene and the Hb β structural locus would be proven. Such an event never has been observed. An additional eight (six from kindred B and two from kindred C) of

such "noncrossovers" are added with this material. It should be recalled that the location of an HPFH gene of the African type alongside one for Hb β^S or Hb β^C on the same chromosome should result in complete suppression of Hb β^S or Hb β^C chain production. The phenotype of such crossovers (β^S or β^C adjacent to HPFH) would be indistinguishable from HPFH trait. Therefore, only one-half of all possible crossover products (i.e., normals) would theoretically be recognizable. Since the γ loci are linked to the Hb δ-β locus [18], and assuming that HPFH is caused by a deletion of the β and δ genes with preservation of the Hb $^A\gamma$ and Hb $^G\gamma$ locus [24] (see below), crossover between the deleted segment and γ genes could not generate any new chromosomal arrangements (fig. 5). Consequently, no normal or double abnormal offspring would ever be theoretically expected. Hence, the absence of recognizable crossovers (i.e., normal offspring of heterozygotes for both HPFH and Hb β structural variants) in the African type of HPFH is compatible with deletion of the β and δ genes. However, arguing from formal genetics alone, close linkage of the Hb β locus to a postulated regulatory gene cannot be ruled out. It should be emphasized that the postulated deletion in the Greek type of HPFH presumes deletion of $^G\gamma$ only with preservation of Hb $^A\gamma$, Hb β, and Hb δ. In this type of HPFH, a crossover between $^A\gamma$ and Hb β could yield a normal chromosome and children with a normal phenotype for hemoglobins.

These data also provide further information on the formal linkage relation between the δ locus and HPFH. Among 11 offspring of two women (II-1 and II-8 of kindred A) with both HPFH and a structural variant of the δ chain (Hb B_2), no crossovers between the δ locus and HPFH were found. The interpretation of these findings is identical with that given for the β locus, since there is excellent evidence from both biochemical and formal genetics that the β and δ structural loci are closely linked and presumably contiguous. Failure to find recombinants between Hb B_2 and HPFH must therefore be interpreted in a manner similar to the lack of recombinants between Hb S (or Hb C) and HPFH. Additional formal genetic data bearing on the linkage relationship of the γ locus and Hb B_2 come from the family of Kendall et al. [18] which included the mating of a man heterozygous for both the β-γ fusion gene (Hb Kenya) and Hb B_2 with a woman having neither of these traits. Of his nine children, four had Hb B_2 and five carried Hb Kenya. None were normal and none had both defects.

The finding of a recombinant chromosome producing a normal hemoglobin pattern in offspring of a heterozygote for *both* HPFH of the African variety and either a β or δ structural variant would be of greatest importance since it would provide evidence *against* the deletion hypothesis. Thus further search for families of this type is important. For instance, Pearson and Moore's [29] finding of a crossover between the δ locus and β thalassemia creating a doubly abnormal offspring (with the δ and β thalassemia locus on the same chromosome) indicates that the type of β thalassemia (with no Hb A synthesis) in that particular family cannot be caused by a deletion. By using nucleic acid hybridization, some types of α thalassemia have been shown to be caused by deletion of the Hb α gene

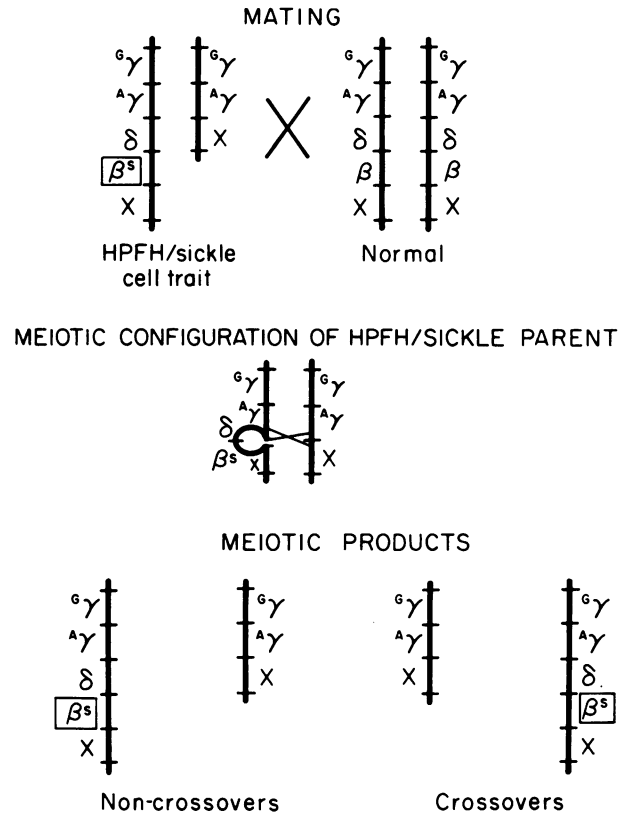

FIG. 5.—Deletion model of HPFH. The γ loci are drawn as linked to the Hb δ-β complex. The $^{A}\gamma$ and $^{G}\gamma$ are separate loci and refer to the presence of alanine (A) and glycine (G) at position 136 of the respective γ chains. The X refers to unspecified genes contiguous to the Hb δ-β locus. In HPFH the Hb δ-β locus is deleted and X is located contiguous to $^{A}\gamma$ and $^{G}\gamma$. Gene order is based on the findings with Hb Kenya.

Upper diagram refers to the genotypes of a mating between a heterozygote for both HPFH and Hb β^{S} and a normal individual. The meiotic configuration of such a compound heterozygote is shown with pairing of both γ loci and both X loci producing a loop consisting of the Hb δ and Hb β^{S} loci. This loop would be too small to be visible in meiotic preparations.

The expected meiotic products in gametes of the compound heterozygous parent are shown as noncrossovers and as crossovers. Note that a crossover between the $^{A}\gamma$ locus and the Hb β^{S} locus leads to no new chromosomal configurations. Consequently all offspring, regardless of crossover, will either have sickle cell trait or HPFH trait. No normal offspring can ever be generated if HPFH is caused by a deletion of this type.

[30, 31]. It is therefore conceivable that some cases of β thalassemia can be caused by deletions, and critical families providing information regarding a deletion model need to be collected.

The exact genetic origin of HPFH is not certain. Several investigators in the early 1960s suggested a regulatory type of mutation with failure to turn on Hb β and Hb δ synthesis [32, 33]. When it became known that the human γ locus is duplicated so that some γ chains have alanine at position 136 ($^{A}\gamma$) while others

have glycine at that position ($^{G}\gamma$) [34], extensive studies on γ chains in various disorders were undertaken [35]. It was shown that a few patients with HPFH had fetal hemoglobin of $^{G}\gamma$ type exclusively [36] while the largest group of Negro patients with HPFH had both $^{A}\gamma$ and $^{G}\gamma$ chains [24, 35], such as in kindred A of this report. These various findings led to the hypothesis that the African variety of HPFH was caused by a deletion of the Hb β and Hb δ loci and occasionally by an additional deletion of the Hb $^{A}\gamma$ locus as well. This hypothesis was strengthened by the discovery of Hb Kenya [18]. The existence of this Hb $^{A}\gamma$-β fusion gene showed clearly that the Hb γ locus is linked to the Hb δ and Hb β loci, as had been suspected. Furthermore, all heterozygotes for Hb Kenya have had increased amounts of Hb F of the $^{G}\gamma$ variety (5%–11%) evenly distributed in the red cells [37]. It appears, therefore, that deletional events in the Hb γ-δ-β gene complex, whether associated with complete deletion of whole structural loci (HPFH) or with γ-β fusion genes (Hb Kenya), may interfere with the regulation of γ chain production and lead to HPFH phenotypes. Kendall et al. [18] postulate a specific regulatory factor located between the Hb $^{A}\gamma$ and Hb δ loci to explain the phenotypic differences between Hb Lepore (a δ-β fusion gene) and Hb Kenya (a $^{A}\gamma$-β fusion gene). Hb Lepore presents as a thalassemic phenotype with uneven distribution of Hb F in red cells, while Hb Kenya has even distribution of Hb F and resembles the phenotype of HPFH. Sophroniadou et al. [38] studied hemoglobin synthesis in the Greek type of HPFH characterized by $^{A}\gamma$ production and some synthesis of β and δ chains. Their data tended to rule out an Hb $^{G}\gamma$-β fusion gene as explaining the Greek type of HPFH and showed subnormal Hb $^{A}\gamma$ and Hb β synthesis preset at fixed levels suggesting a regulatory transcription defect.

Current data therefore suggest that the deletion hypothesis is the primary event leading to HPFH. However, it is becoming clear that deletional events alone cannot explain the various phenotypic findings in HPFH. An additional interference with regulation of transcription is required. Future elucidation of the precise defect in these disorders may be helpful for our understanding of the normal control of fetal and adult hemoglobin synthesis.

SUMMARY

Three Negro kindreds with hereditary persistence of fetal hemoglobin (HPFH) alone and in combination with various other hemoglobin abnormalities including β thalassemia are presented. Among 11 offspring of two women heterozygous for both HPFH and the δ chain mutation Hb B_2, five inherited the HPFH gene and six inherited the Hb B_2 gene. In another kindred, a man inferred to be heterozygous for both HPFH and Hb C had six children; three offspring obtained the Hb C gene and three the HPFH gene. Similarly, a woman heterozygous for both Hb S and HPFH transmitted the Hb S gene to one of her two children and the HPFH gene to the other. Thus among 19 offspring, no crossovers between the HPFH locus or the Hb δ-β locus were observed.

These and earlier data are compatible with deletion of the Hb β and δ loci

as the primary event to explain the genetic origin of HPFH. Genetic considerations indicate that the finding of a single person with a hematologically normal phenotype among offspring of heterozygotes for both the African type of HPFH and a Hb β or Hb δ structural abnormality would invalidate the deletion model.

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