Hemoglobin Lepore Washington in Two Jamaican Families: Interaction With Beta Chain Variants

By E. J. Ahern, V. N. Ahern, G. H. Aarons, R. T. Jones, and B. Brimhall

Hb Lepore Washington was found segregating in two unrelated families. In one family, three subjects doubly heterozygous for Hb Lepore and a beta-chain variant were observed. A woman, aged 76 yr, with the Hb Lepore-Hb S combination had two offspring with Hb Lepore-Hb C combinations. One Hb Lepore-Hb C subject married to a hematologically normal woman had eight offspring: seven living at the time of study, six with Hb Lepore trait, and one with Hb C trait. In the second family, only Hb Lepore trait was found. Interest centers on the first family: the mild symptomatology of the Hb Lepore-Hb S subject, and the absence of crossovers in the seven living offspring of one Hb Lepore-Hb C subject. The latter finding provides further genetic evidence for allelism or close linkage of the locus for Hb Lepore with the beta chain structural locus.

IN THE COURSE of hemoglobin electrophoresis of subjects with erythrocyte morphology suggestive of thalassemia, two unrelated black-white individuals were found to have abnormal bands with mobilities in the Hb S region. In both instances structural studies showed the abnormal hemoglobin to be Hb Lepore Washington. This paper reports the clinical, laboratory, and genetic data on these families.

MATERIAL AND METHODS

Standard methods were employed for routine hematology and for hemoglobin studies. Hemoglobin was estimated by the cyanmethemoglobin method using Pfizer standards. The packed cell volume was measured by the microhematocrit method. Red cell counts were performed on a model F Coulter counter. Serum iron and total binding capacity were measured by the method of Beale et al. The distribution of Hb F in intact red cells was studied by the acid elution technique. Controls consisted of cord blood, normal adult blood, and a 5.0% mixture of cord blood in adult blood (ABO compatible) smeared on the same slide. Routine hemolysates were prepared with carbon tetrachloride and water. Starch gel electrophoresis at pH 8.13 and pH 7.06 was performed on all subjects. Analytical and preparative chromatography of major components was performed using DEAE-Sephadex and CM-Sephadex. Hb Lepore, in the presence of Hb S, was measured on

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Fig. 1. Pedigree diagram of family A. Interrupted lines in generation I indicate that I-10, I-11, and I-12 are half-siblings of I-9. Not indicated is the fact that I-12 is a heterozygote for Hb B2 in addition to having Hb S trait.

RESULTS

Both families were of mixed black-white origins but were predominantly black. The pedigree diagram of family A is shown in Fig. 1 and hematologic data on both families in Table 1.

Family A

Hb Lepore Trait: The propositus (III-3) was admitted to the University Hospital, Jamaica, for a perineal repair following the birth of her hematologically normal son, IV-2. A routine blood film showed hypochromic micro-
Table 1. Hematologic and Chromatographic Data on Families A and B

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Subject</th>
<th>AGE (yr)</th>
<th>Hb (g/100ml)</th>
<th>MCHC (%)</th>
<th>MCV (cuµl)</th>
<th>MCH (µg/dl)</th>
<th>DEAE-Sephadex Chromatography</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hb A&lt;sub&gt;2&lt;/sub&gt; (%)</td>
<td>Hb Lepore (%)</td>
<td>Hb S (%)</td>
<td>Hb C (%)</td>
<td>A.R. Hb (%)</td>
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<tr>
<td>Family A</td>
<td></td>
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<td>74</td>
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<td>24.9</td>
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<td></td>
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<td>2.6 †</td>
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<td>74.0</td>
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<td></td>
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<td>11</td>
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<td>74.0</td>
<td>23.7</td>
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<td></td>
<td>I-20</td>
<td>28</td>
<td>13.0</td>
<td>32.5</td>
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<tr>
<td>Hb Lepore-Hb C</td>
<td>I-11</td>
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<td>27.8</td>
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<td>—</td>
<td>1.5 †</td>
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<tr>
<td>Hb S trait</td>
<td>I-19</td>
<td>76</td>
<td>10.6</td>
<td>35.3</td>
<td>78.0</td>
<td>27.6</td>
<td>3.5</td>
<td>78.3%†</td>
</tr>
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<td>Hb C trait</td>
<td>I-1</td>
<td>65</td>
<td>12.8</td>
<td>35.5</td>
<td>104.0</td>
<td>36.9</td>
<td>1.3</td>
<td>&lt;1.0 Folate deficiency</td>
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<td>I-12</td>
<td>19</td>
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<td>92.0</td>
<td>29.6</td>
<td>1.1</td>
<td>37.4%†</td>
</tr>
<tr>
<td></td>
<td>I-5</td>
<td>53</td>
<td>15.7</td>
<td>35.0</td>
<td>98.0</td>
<td>34.8</td>
<td>0.4</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Hb AS-Hb B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>I-12</td>
<td>66</td>
<td>13.6</td>
<td>34.1</td>
<td>—</td>
<td>—</td>
<td>0.4</td>
<td>37.6% &lt;1.0 Hb B&lt;sub&gt;2&lt;/sub&gt; = 1.8%</td>
</tr>
<tr>
<td>Normal</td>
<td>I-3</td>
<td>48</td>
<td>15.1</td>
<td>34.3</td>
<td>89.0</td>
<td>30.7</td>
<td>1.3</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>

Family B

| Hb Lepore trait | Proetus | 27       | 9.3         | 25.1      | 59.7       | 15.0        | 1.9              | 1.9 11.2 1.0 Iron deficiency |
|                 | Father  | 60       | 12.7         | 31.7      | —          | 1.0         | 1.9              | 2.6 12.6 1.6 Treated       |
|                 | Mother  | 57       | 13.3         | 32.0      | —          | 0.3         | 2.7              | <1.0            |

* Alkaline-resistant hemoglobin.
† Includes Hb A<sub>2</sub>.
‡ Diagnosis based on red cell morphology, electrophoretic pattern, negative sickle test.
§ Includes Hb Lepore.
cytosis and occasional red cells with basophilic stippling. Starch gel electrophoresis (Fig. 2) revealed an abnormal band in the Hb S region measuring 9.8%. Physical examination was unremarkable. Five siblings of the propositus (III-2, -4, -7, -8, -9), two first cousins (III-10, 11), two paternal aunts (II-4, -6), and two half-sisters (I-10, 11) of her paternal grandmother (I-9) also have asymptomatic Hb Lepore trait.

**Hb Lepore-Hb C Combination:** The 57-yr-old father (II-2) of the propositus leads a strenuous outdoor life as a cultivator in hilly rural country, about 2000 ft above sea level. Apart from an episode of chronic left leg ulceration at the age of 50, he has been symptom free. His 60-yr-old sister (II-1), also with Hb Lepore-Hb C combination, has resided at sea level for the past 40 yr leading a sedentary life. She has had no symptomatology relevant to her inherited red cell defects. Physical examination, chest x-ray, and skeletal survey were normal in both. An EKG in II-1 was normal but showed evidence of right ventricular hypertrophy in II-2. Blood films from II-1 and II-2 showed many target forms, occasional microspherocytes, and very occasional nucleated red cells. Starch gel electrophoresis (Fig. 2) showed Hb C with small amounts of Hb Lepore and Hb F but no Hb A (Fig. 3). The $^{51}$Cr red cell survival of II-2 was 22 days, and the red cell mass was 28.0 cc/kg; these studies were not performed on II-1.

**Hb Lepore-Hb S Combination:** The paternal grandmother (I-9) of the propositus, aged 76 yr, has lived for the past 60 yr in a hilly rural community 2000 ft above sea level and still leads a very active life. She has had five successful pregnancies and no abortions. She has never had symptoms suggestive of the acute vascular occlusive or hemolytic crises of sickle cell disease, but at age 70 she was successfully treated for an ulcer over the left lateral malleolus. She has never been transfused. In recent years she has suffered with epigastric discomfort. Physical examination revealed aortic incompetence (BP 200/90) but was otherwise unremarkable. Barium swallow and meal demonstrated a sliding hiatus hernia and chronic duodenal ulcer. There was also x-ray evidence suggestive of an old infarct at the lower end of the...
left humerus; the patient could not recall any symptomatology related to this. Syphilis serology (VDRL) was nonreactive. The electrophoretic pattern (Fig. 2) resembled sickle cell anemia. Her blood film showed 1-2% fixed sickle cells, a few target forms, slight poikilocytosis, and 20 nucleated red blood cells/100 white cells. Liver function tests were within normal limits. $^{51}$Cr red cell survival was 15 days, and red cell mass was 19.1 cc/kg. CM-Sephadex chromatography performed on the whole hemolysate (Fig. 4) and on the Hb Lepore + Hb S fraction, obtained from DEAE-Sephadex chromatography (Fig. 3), gave Hb Lepore values of 11.8% and 10.1% of the total hemoglobin, respec-
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No Hb Bart's was detected on starch gel electrophoresis (pH 7.0) of the concentrated effluent obtained from the CM-cellulose column. Red cell 2, 3-DPG was 20.7 µM/g Hb; the normal range for Jamaican adults is 12.2–16.1 µM/g Hb and for sickle cell anemia subjects 15.5–22.7 µM/g Hb.\textsuperscript{18}

\textit{Hb S Trait:} A paternal uncle (II-5) of the propositus and a half sister (I-12) of her paternal grandmother both have asymptomatic Hb S trait; the latter (I-12) is also heterozygous for Hb B\textsubscript{2}.

\textit{Hb C Trait:} The father (I-8) of four of the children of I-9 died at the age of 35 yr from an unknown cause. Because of the presence of Hb C in his brother I-1 and the findings in his offspring, he is presumed to have had Hb C trait. The high MCV observed in I-1 resulted from folate deficiency, secondary to excessive intake of alcohol, and returned to normal with treatment. III-5, a sibling of the propositus, has asymptomatic Hb C trait.

A sister (III-6) of the propositus died at 6 mo of age from an unknown cause. Nothing is known of the father of II-6.

\textit{Family B}

The propositus, a 27-yr-old woman with Hb Lepore trait, presented at the University Hospital with moderately severe iron deficiency anemia; there were no significant physical findings apart from anemia. The serum iron was 21 µg/100 ml, and total iron-binding capacity was 411 µg/100 ml. Her hemoglobin rose on oral iron therapy, but hypochromic microcytosis persisted. Hb Lepore trait was also found in her father, her mother being normal; no other family members were studied.

No Hb H inclusions were detected in the red cells of any member of family A or family B, nor was any Hb Bart's or Hb H detected on starch gel electrophoresis (pH 7.0). The serum iron, total iron-binding capacity, and transferrin saturation were within the normal range for all subjects, except III-11 in family A and the propositus in family B.

The red cells of III-2 (Hb Lepore trait), II-1 (Hb Lepore-Hb C combination), and I19 (Hb Lepore-Hb S combination) from family A were studied by the acid elution technique; a heterogeneous distribution of Hb F was found in all three.

Hybridization experiments on the isolated Hb Lepore from the propositus in each family and the isolated Hb B\textsubscript{2} from I-12 (family A) confirmed the presence of an abnormality of the nonalpha chains. In subject I-9 (Family A), analytical DEAE-Sephadex chromatography (Fig. 3) revealed a minor peak (less than 0.1% of the total hemolysate) separating before Hb A\textsubscript{2} at pH 8.3. This component was shown to consist of free alpha chains; on mixing with Hb H it disappeared with the formation of Hb A. A similar minor component was also present in II-1, in whom it could not be detected on analytical DEAE-Sephadex chromatography (Fig. 3) but was eluted from a DEAE-Sephadex preparative column. Demonstration of the presence of free alpha chains in subject II-2 was not attempted.

Studies of the amino acid sequences were performed on tryptic hydrolysates of non-\alpha chains isolated from the Hb S from I-9, Hb C from II-2, and Hb
Lepore\textsubscript{Washington} from the propositi of both families. In the case of Hb S, the abnormal $\beta$T-1 peptide was found to have an abnormal valyl residue in place of the glutamyl residue number 6. The two abnormal tryptic peptides characteristic of Hb C, which result from the replacement of the normal glutamyl residue number 6 by a lysyl residue, were isolated from the non-$\alpha$ chain of that hemoglobin and identified by amino acid analysis. All of the other tryptic peptides of these two hemoglobins were normal by chromatography. Tryptic hydrolysis of the non-$\alpha$ chain of the Hb Lepore samples gave rise to an identical set of peptides. On the basis of chromatography, these Lepore peptides appeared to consist of T-2, T-3, T-5, and T-10 of the $\delta$-chain, T-12b and T-13 of the $\beta$-chain, and T-1, T-4, T-6, T-7, T-8, T-9, T-11, T-12a, T-14, and T-15 are common to both $\beta$- and $\delta$-chains. These findings indicate that both Hb Lepore samples are the same as the “Washington” type.\textsuperscript{1}

The results of ABO, Rh, and MN blood grouping on the members of family A were consistent with the stated family relationships.

**DISCUSSION**

Hb Lepore is an abnormal hemoglobin with an electrophoretic mobility in the Hb S region that occurs in low concentration and is associated with thalassemic erythrocyte morphology.\textsuperscript{20} The biochemical difference from normal adult hemoglobin resides in the nonalpha polypeptide chain, the primary structure of which is consistent with origin from a delta-beta fusion gene.\textsuperscript{19} Baglioni\textsuperscript{19} presented evidence that Hb Lepore results from unequal crossing-over between the closely linked\textsuperscript{21} delta and beta hemoglobin genes. Three fusion gene products, Hb Lepore\textsubscript{Washington},\textsuperscript{1} Hb Lepore\textsubscript{Baltimore},\textsuperscript{22} and Hb Lepore\textsubscript{Hollandia},\textsuperscript{1} have been reported; in all of these, the N-terminal portion of the nonalpha chain is deltaike, while the C-terminal portion is betaike. Hb Lepore\textsubscript{Washington}, Hb Lepore\textsubscript{Baltimore}, and Hb Lepore\textsubscript{Hollandia} have areas of delta-beta fusion somewhere between residues 87 and 116, 50 and 86, and 22 and 50, respectively.\textsuperscript{1,22} Although the Lepore-like hemoglobin, Hb Pylos\textsuperscript{23} (Greece), awaits detailed structural study, there is evidence that at least two of the Lepore-like hemoglobins from geographically adjacent Yugoslavia resemble Hb Lepore\textsubscript{Washington}.\textsuperscript{24} The structure of Hb Lepore, together with the absence of Hb A and Hb A2 in the Hb Lepore homozygotes,\textsuperscript{23} is biochemical evidence for allelism of the Lepore locus with the beta and delta structural loci. Further biochemical evidence for allelism with the beta focus is the absence of Hb A in double heterozygotes for Hb Lepore and beta chain variants in this and previous reports.\textsuperscript{25,27} In family A (Fig. 1) of the present study, subject II-2, with the Hb Lepore-Hb C combination, has seven living offspring by his normal wife (II-3), six with Hb Lepore trait and one with Hb C trait. The absence of cross-overs in these offspring provides genetic evidence for allelism or close linkage of the Lepore locus with the beta chain locus. Although the fathers of the five offspring of I-9 are both dead (Fig. 1), the presence of either Hb Lepore or Hb S in these offspring constitutes supportive evidence.

The Hb Lepore-trait subjects in the present study had hemoglobin levels falling within the normal range and, as previously described,\textsuperscript{23} tended to have
milder morphologic changes and derived indices closer to normal values than cases of beta thalassemia trait; the mean corpuscular hemoglobin concentration (MCHC) was frequently above 32.0%. Levels of Hb Lepore (7.0%–13.0%) in trait subjects in the present study were similar to those reported from Greece $^{23}$ and Yugoslavia. $^{28}$ The levels of Hb A$_2$ in the cases from Greece and Yugoslavia ranged from low to normal, while in eight Jamaican, Lepore-trait subjects with normal serum iron studies, the Hb A$_2$ (2.49 ± 0.24%) did not differ significantly from that in 315 adult Jamaicans ascertained by survey $^{28}$ (2.58 ± 0.37%). Hb F in eight Jamaican, Lepore-trait subjects (4.45 ± 2.65%) was not significantly different from that in 18 Pylos-trait subjects $^{23}$ (4.74 ± 3.14%) but was significantly higher ($p < 0.05$) than the Hb F in 40 cases from Yugoslavia $^{28}$ (1.73 ± 1.19%). The method of measurement $^{30}$ in the latter cases, however, is known to give low Hb F values. Compared with the Hb F level in 68 F-thalassemia-trait subjects from Greece $^{31}$ (10.91 ± 3.66%), the Hb F in Lepore trait was significantly lower ($p < 0.001$). However, there appears to be functional similarity in the behavior of the transdelta gene in F-thalassemia trait and Lepore trait. The mean Hb A$_2$ levels per cell in eight Jamaican Lepore-trait subjects (0.58 ± 0.08 μg/cell), 314 Jamaican adults $^{29}$ (0.78 ± 0.15 μg/cell), and seven Jamaican adults with high A$_2$ beta-thalassemia trait $^{29}$ (1.17 ± 0.10 μg/cell) were significantly different ($p < 0.001$) when compared by a one-way analysis of variance. In Jamaican subjects, the mean Hb A$_2$ per cell in the Lepore trait was half that found in beta-thalassemia trait; this is a similar relationship to that found between F-thalassemia trait and Lepore trait. The postulated genetic mechanism for F-thalassemia, deletion of the delta and beta genes in cis, results in a greater stimulation of gamma chain production than does the delta-beta fusion gene of Hb Lepore. $^{31}$ Both, however, stimulate the transdelta gene equally effectively; this is attributed to the absence of beta chain production trans to the functioning delta gene. $^{31}$

The two cases of Hb Lepore-Hb C combination in this study (II-1, II-2, family A) are comparable clinically to the other reported case in the literature (Table 2). The values for the MCHC were consistently at, or above, the normal range in the two cases from the present study (Table 1); this is probably related to the presence of microspherocytes. $^{32}$ Although the subject II-2 has a comparable $^{51}$Cr half life to the high A$_2$-beta thalassemia–Hb C case of Prindle and McCurdy, $^{33}$ his red cell mass was considerably higher. This is probably related to more effective erythropoiesis in the presence of the delta-beta fusion gene, as compared with the beta-thalassemia gene. No explanation is offered for the ECG evidence of right ventricular hypertrophy in II-2.

An interesting facet of the present study is the long, relatively symptom-free life of I-9 (family A) with the Hb Lepore-Hb S combination. The clinical and hematologic data on I-9 place her toward the upper portion of the spectrum of high A$_2$-beta thalassemia-Hb S disease, $^{34}$ but not in a category as mild as F thalassemia-Hb S disease. $^{35}$ A comparison with the four previously described cases of Hb Lepore-Hb S combination, two from Greece and two from Italy (Table 2), reveals that only one of these, the 12-yr-old Greek boy, $^{28}$...
Table 2. A Comparison of the Reported Cases of Hb Lepore-Abnormal Beta Chain Combinations

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr) and Sex</th>
<th>Clinical Severity</th>
<th>Organomegaly</th>
<th>Hb (g/100 ml)</th>
<th>MCHC (%)</th>
<th>MCV (μm³)</th>
<th>MCH (g/l)</th>
<th>Reticulocyte Count (%)</th>
<th>Total Bilirubin (mg/100 ml)</th>
<th>Hb Lepore (%)</th>
<th>Hb S/Hb C (%)</th>
<th>Hb F (%)</th>
<th>A.R. Hb (%)</th>
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<td>Hb Lepore-Hb S combination</td>
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<td>severe</td>
<td>spleen + liver +</td>
<td>8.6</td>
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<td>81.3</td>
<td>26.9</td>
<td>33.0</td>
<td>5.9</td>
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<td>79.3</td>
<td>—</td>
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<td>Family B II-1</td>
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<td>mild</td>
<td>spleen + liver +</td>
<td>12.5</td>
<td>33.8</td>
<td>77.7</td>
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<td>severe</td>
<td>spleen + liver +</td>
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<td>—</td>
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<td>spleen + liver +</td>
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<td>Jamaican</td>
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<tr>
<td>Family A I-9</td>
<td>76 F</td>
<td>mild</td>
<td>spleen — liver —</td>
<td>10.6</td>
<td>35.3</td>
<td>78.0</td>
<td>27.6</td>
<td>3.5</td>
<td>0.1</td>
<td>2.6</td>
<td>10.1</td>
<td>78.3</td>
<td>19.0</td>
</tr>
<tr>
<td>Hb Lepore-Hb C combination</td>
<td></td>
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<tr>
<td>American (Negro)27</td>
<td>17 F</td>
<td>mild</td>
<td>spleen —</td>
<td>10.7</td>
<td>—</td>
<td>20.2</td>
<td>2.2</td>
<td>—</td>
<td>14.0</td>
<td>80.0</td>
<td>6.0</td>
<td>—</td>
<td>6.0</td>
</tr>
<tr>
<td>Jamaican</td>
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<tr>
<td>Family A II-1</td>
<td>60 F</td>
<td>mild</td>
<td>spleen — liver +</td>
<td>12.1</td>
<td>37.5</td>
<td>68.0</td>
<td>25.2</td>
<td>2.0</td>
<td>1.7</td>
<td>10.3</td>
<td>77.8</td>
<td>12.1</td>
<td>6.2</td>
</tr>
<tr>
<td>Family A II-2</td>
<td>57 M</td>
<td>mild</td>
<td>spleen — liver —</td>
<td>13.2</td>
<td>36.2</td>
<td>64.0</td>
<td>22.8</td>
<td>1.3</td>
<td>0.0</td>
<td>10.6</td>
<td>80.2</td>
<td>9.2</td>
<td>4.4</td>
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</table>

* Jamaican cases quantitated by DEAE-Sephadex chromatography, except for Hb Lepore fraction in I-9 that was measured by CM-Sephadex chromatography. All other cases quantitated by starch block.
had a milder condition than I-9. The other Greek case, a 13-yr-old girl, exhibited a hemolytic component as a major problem. In comparison with I-9, the adult Italian siblings had a life-long record of bone and joint pain and hepatosplenomegaly, and one had a poor obstetric history. Levels of Hb Lepore in all cases were similar (Table 2). It was suggested that the higher level of Hb F (25.0% by alkali denaturation) in the 12-yr-old Greek boy might be the reason for his mild disease, as compared to the other Greek case (Hb F = 9.6%). Comparable levels of Hb F (9%-10%) were found by a similar alkali denaturation technique in the Greek girl, the two Italian cases, and I-9 of family A (Table 2). There is no evidence that a significant deficit in alpha chain synthesis was present in any member of family A. The apparent increase in the normal pool of free alpha chains detected in I-9 can be related to the shortened red cell survival, in addition to the presence of Hb S. While the raised Hb F level in the Greek boy with Hb Lepore–Hb S combination provides an explanation for the mildness of his case, reasons for the variability in the clinical expression of the other reported cases of Hb Lepore–Hb S combinations are not apparent.

ACKNOWLEDGMENT

We thank Miss M. Deurst for technical help, Dr. W. N. Gibbs for estimation of red cell 2, 3-DPG, and Mr. A. V. Swan and Mrs. P. Desai for statistical advice.

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Hemoglobin Lepore in Two Jamaican Families: Interaction With Beta Chain Variants

E. J. Ahern, V. N. Ahern, G. H. Aarons, R. T. Jones and B. Brimhall

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