Co-inheritance of an α Variant Haemoglobin J and β Variant Haemoglobin E

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Summary:
In an attempt to screen the apparently healthy family members of a 13 year boy with haemoglobin (Hb) E trait, his mother and one of his sister shown to have haemoglobin E and first moving haemoglobin J, by capillary electrophoresis. There was normal level of haemoglobin A2 and slight increase in haemoglobin F zone. The haemoglobin J here was an α variant haemoglobin. So, these two were having rare co-inheritance of α and β variant haemoglobin. The major contributor in haemoglobin F zone was most likely haemoglobin JE hybrid. Both of them were almost normal haematologically, except mild microcytosis.

Key Words: Haemoglobin E, haemoglobin J, α variant haemoglobin, β variant haemoglobin, variant α globin, variant β globin, co-inheritance, hybrid haemoglobin.

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Introduction:
Many types of both α variant and β variant haemoglobins or haemoglobinopathies are distributed fairly worldwide. Some are more common like Haemoglobin S, Haemoglobin E, Haemoglobin D, Haemoglobin C etc. Most are less commonly occurring haemoglobin variants like Haemoglobin J. Actually Haemoglobin J is not a single type of variant but a group of variant haemoglobins with same electrophoretic mobility. This group comprises both α variants such as Hb J Sardegna, Hb J Abidjan, Hb J Norfolk etc and β variants such as Hb J Auckland, Hb J Baltimore, Hb J Bangkok etc. So far at least 58 types of Hb J have been detected. Most of these Hb Js are clinically and haematologically silent but some of them result in unstable haemoglobin, high oxygen affinity haemoglobin etc. None of the Hb Js is known to have thalassaemic phenotype like Hb E, which have a mild thalassaemic phenotype as well as structural aberration in β globin. Structural aberration in β globin in Hb E is substitution of an amino acid glutamate at position 26 with another amino acid, lysine. This variant β globin is designated as β26 Glu→Lys or βE 1,2,3. A β variant haemoglobin is a tetramer of two normal α globin chains with two variant β globin chains such as haemoglobin E is a tetramer formed as α2β2 26Glu→Lys. However an α variant haemoglobin is a tetramer of two α variant globin chain with two normal β globin chain such as haemoglobin J Abidjan as α2β2 26Glu→Argβ2.1,2,3 When a person is heterozygous for both α and β variant globin chain then 4 types of tetramer is possible- (1) normal haemoglobin formed by 2 normal α and 2 normal β globin chains, (2) β variant haemoglobin formed by 2 normal α and 2 variant β globin chains, (3) β variant haemoglobin formed by 2 variant α and 2 normal β globin chains and (4) hybrid haemoglobin formed by 2 variant α and 2 variant β globin chains.4

Case Report:
A boy of 13 years, with lower middle class socioeconomic status, diagnosed as a case of haemoglobin E trait, on the basis of haemoglobin (Hb) electrophoresis done in alkaline pH on agarose gel, presented to Haematology out patient department with some non specific complaints like apathy, feeling unwell, reluctance to play or daily performance etc. His electrophoresis was repeated by capillary method and result was haemoglobin A 69.2 %, haemoglobin E 26.9%, haemoglobin F 0.4% and haemoglobin A2 3.5% (figure-1). Haemogram was done and result was haemoglobin 8.7 g/dl, mean corpuscular volume (MCV) 73.7 fl, mean corpuscular haemoglobin (MCH) 22.3 pg, mean corpuscular haemoglobin concentration (MCHC) 30.2% and RBC number 3.91 x 10¹²/L. Peripheral blood...
film (PBF) shown microcytosis and hypochromia with few elongated cells and occasional target cells. The cause of his anaemia was iron deficiency as was evidenced by serum ferritin level 2.63 μg/L. He has no history of blood transfusion. So, the diagnosis of haemoglobin E trait with coexistent iron deficiency was established. He was given oral iron replacement and his anaemia was corrected after 2 months. His mother and two sisters were screened for haemoglobin disorder with haemogram and Hb electrophoresis by capillary method. His father was killed by a road accident, so could not be screened. Haemoglobin electrophoregrams of mother and one sister (sister-1) shown mobilization to E and J zone along with A, A₂ and a significant fraction in haemoglobin F zone (figure-2). His only maternal aunt was also screened. Red cell indices and electrophoretic mobility of the relatives is shown in table-1 and table-2 respectively. Red cell indices, PBF and electrophoretic pattern of other sister (sister-2) and maternal aunt of the concerned boy were quite normal for their age and sex. PBF and red cell indices of mother and sister-1 were almost normal except mild reduction of mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH). Haemoglobin concentration of sister-1 was little below the normal limit (11.5 gm/dl) for her age and that of mother was in lower normal limit. Mother and sister-1 shown almost same electrophoretic pattern, seems to have inherited both α variant haemoglobin-Hb J and β variant haemoglobin-Hb E, which have been explained in discussion section. Major contributor of haemoglobin migrated to F zone is most likely haemoglobin JE hybrid, formed as tetramer of two variant α globin chain α¹ with two β variant globin chain βE.

![Image](image-url)

**Fig.-1:** Electrophoretic pattern of concerned boy of haemoglobin E trait by capillary electrophoresis in alkaline media.

![Image](image-url)

**Fig.-2:** Electrophoretic pattern of haemoglobin of mother by capillary electrophoresis in alkaline media (electrophoretic pattern of sister-1 was very similar to this).

### Table-I

<table>
<thead>
<tr>
<th>Person</th>
<th>Age (year)</th>
<th>Haemoglobin (gm/dl)</th>
<th>RBC x10¹²/L</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (gm/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>42</td>
<td>12.5</td>
<td>4.98</td>
<td>78.3</td>
<td>25.1</td>
<td>32.1</td>
</tr>
<tr>
<td>Sister-1</td>
<td>08</td>
<td>10.8</td>
<td>4.82</td>
<td>70.7</td>
<td>22.4</td>
<td>31.7</td>
</tr>
<tr>
<td>Sister-2</td>
<td>06</td>
<td>11.9</td>
<td>4.39</td>
<td>80.0</td>
<td>27.1</td>
<td>33.9</td>
</tr>
<tr>
<td>Aunt</td>
<td>38</td>
<td>12.4</td>
<td>4.23</td>
<td>94.6</td>
<td>29.3</td>
<td>31.0</td>
</tr>
</tbody>
</table>

### Table-II

<table>
<thead>
<tr>
<th>Person</th>
<th>HbJ zone%</th>
<th>HbA zone%</th>
<th>HbE zone%</th>
<th>HbA₂ zone%</th>
<th>HbF zone%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>15.9</td>
<td>55.5</td>
<td>19.3</td>
<td>2.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Sister-1</td>
<td>16.2</td>
<td>54.6</td>
<td>19.5</td>
<td>3.0</td>
<td>6.7</td>
</tr>
<tr>
<td>Sister-2</td>
<td>-</td>
<td>97.3</td>
<td>-</td>
<td>2.7</td>
<td>-</td>
</tr>
<tr>
<td>Aunt</td>
<td>-</td>
<td>97.3</td>
<td>-</td>
<td>2.7</td>
<td>-</td>
</tr>
</tbody>
</table>

**Discussion:**

In this case report, we have tried to give answer of the following two questions.

*Why the Hb J here is an α variant rather than a β variant?*

Presence of haemoglobin A indicates the presence of normal β as well as normal α globin. So, the presence
of Hb E, a product of β globin variant, in association with Hb A, exclude the existence of another β globin variant as there is only 2 copies β globin gene in human, one in each chromosome 11.5,6 So, the variant haemoglobin migrated in J zone is an α variant rather than a β variant.

There are four copies α globin gene, two in each chromosome 16- one α1 and another α2.5,6 The fraction of Hb J here indicates that most probably there is mutation in only one α gene. When both α and β variants present in same individual then a hybrid haemoglobin, which is a tetramer of two α variant globin with two β variant globin chains; in these cases which should be α1βα2 or haemoglobin JE hybrid.4 If such hybrid is present then the question is where will it be migrated in electrophoresis? In these cases this hybrid haemoglobin most probably contributed the major part in haemoglobin F zone.

Why the major contributor in haemoglobin F zone here is supposed to be JE hybrid rather than haemoglobin F itself?

The causes of raised haemoglobin F are (1) β thalassaemia or haemoglobinopathies with β thalassaemic phenotype e.g. haemoglobin E, haemoglobin Lepore etc. (2) hereditary persistence of haemoglobin F5,6 and (3) some haematological condition other than haemoglobin disorder like aplastic anaemia, paroxysmal nocturnal haemoglobinurea, juvenile myelomonocytic leukaemia, megaloblastic anaemia etc. Haemoglobin F fraction in haemoglobin E trait is usually within normal limit sometimes may be up to 2%.5,6,7 Besides, haemoglobin F was 0.4% in the concerned boy with haemoglobin E trait. Moreover, if there is hereditary persistence of haemoglobin F then the genetic aberration responsible for that should be in the same chromosome which carries the gene for βE as both mother and sister-1 has haemoglobin E trait along with same rise of haemoglobin F. In that case the boy should have inherited the same maternal chromosome 11 provided that his late father was not heterozygous for haemoglobin E and he has not inherited this abnormal gene from his father rather than his mother. But haemoglobin F level of the boy is only 0.4%, so there is no hereditary persistence haemoglobin F here. Most importantly, the negative difference (around 7%) of haemoglobin E level of mother and sister-1 with that of the boy is almost equal to haemoglobin F level of mother and sister-1, which indicate that a fraction of βE globin have been migrated in haemoglobin F zone rather than haemoglobin E zone, due to their tetramerization with α variant globin α1 rather than normal α globin chain. So, it was calculated that major contributor in haemoglobin F zone of both mother and sister-1 was haemoglobin JE hybrid. However, it could be confirmed further by globin chain electrophoresis.8

The electrophoretic mobility of such hybrids of α variant and β variant is difficult to determine as the number of such possible hybrids are enormous but the real occurrence is extremely rare. One such hybrid is haemoglobin GC hybrid formed by coinheritance of α variant haemoglobin G Philadelphia and β variant haemoglobin C, is a slow-moving haemoglobin on cellulose acetate in alkaline pH.9 Another such hybrid is SG hybrid formed by coinheritance β variant haemoglobin S and α variant haemoglobin G, moves to haemoglobin A2, C, E region on cellulose acetate in alkaline pH.4

The coinheritance of α variant haemoglobin J with haemoglobin E in this family seems to be clinically and haematologically insignificant, as there was no significant anaemia or erythrocytosis or features of unstable haemoglobin. There was mild reduction in MCV only which is merely associated with haemoglobin E trait. However biochemical nature of the haemoglobin J here and the genetic aberration responsible for this could not be determined.

References:
haemoglobin and it's interaction with other variant haemoglobins and thalassaemias; p.139-189.


