Haemoglobinopathies, Thalassaemias and Enzymopathies in Saudi Arabia

M. A. F. El-Hazmi

Since the first discovery of sickle cell gene in Saudi Arabia in 1963 by Lehmann and coworkers, significant progress has been made in the study of genetic red cell abnormalities that influence the stability and integrity of the red cells. The sickle cell gene, α- and β-thalassaemia and glucose-6-phosphate dehydrogenase deficiency genes have been encountered in almost all regions of Saudi Arabia at a variable frequency. The clinical manifestations of these genes both in homozygous, heterozygous and double heterozygous cases have been investigated and a variable presentation is encountered in the population from different regions. More recently studies at the molecular level have been initiated to investigate the various globin genes using restriction endonucleases and results from the different regions show significant polymorphism in the β-globin gene cluster producing several β-globin gene haplotypes.

In this paper we summarize the studies on haemoglobinopathies, thalassaemias and enzymeopathies reported from different regions of Saudi Arabia and outline the progress made in these fields which constitute a major problem for health authorities in Saudi Arabia and pose a challenge to scientists and physicians alike.

Haemoglobinopathies, due to structural abnormality of the sickle cell haemoglobin, were first

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recognizd in Saudi Arabia in 1963 by Lehmann and coworkers during a screening programme. Thereafter, Gelpi reported the presence of sickle cell gene in Saudis living in the oasis population of Qateef and Al-Hasa and discovered the existence of the gene for glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. The author also observed that the sickle cell anaemia was mild in this population and suggested that coexisting thalassaemias, G-6-PD deficiency and other haemoglobin variants, ameliorated the clinical presentation of sickle cell anaemia thus producing a mild form of the disease. At
about the same time, Weatherall and coworkers described a mild form of sickle cell disease resulting from interaction between Hb S and α-thalassaemia gene and termed it as a ‘new sickling disorder’.\textsuperscript{5} This study showed that α-thalassaemia occurred in a high percentage of the adults from the eastern province and also reported Hb Barts in the newborns.\textsuperscript{6} Subsequently, the benign nature of sickle cell disease in the Saudis from the Qatif and Al-Hasa Oases was confirmed and the presence of a high percentage of haemoglobin F was considered as an ameliorating factor.\textsuperscript{7–10} However, later studies revealed a mild sickle cell anaemia even in the absence of elevated levels of Hb F.\textsuperscript{11–13}

Studies conducted in other regions of Saudi Arabia revealed the presence of Hb S, α- and β-thalassaemia and G-6-PD deficiency genes in several regions of the country.\textsuperscript{11,13} Significant differences in the frequency of the Hb S gene were encountered even within the same region. On the other hand, a close correlation was found between these genes and malaria endemicity.\textsuperscript{14–23}

This paper summarizes studies conducted on the Saudi population and highlights recent developments in the field of haemoglobinopathies, thalassaemias and enzymopathies.

**Sickle Cell Haemoglobinopathies**

Several in-depth studies have been conducted to investigate the prevalence and natural history of sickle cell anaemia in different regions of the country. The frequency of Hb S gene in the different regions of Saudi Arabia are presented in Fig. 1. Investigations carried out to study the clinical manifestations, haematological and biochemical analyte values in sickle cell anaemia patients from the eastern and south-western provinces have shown statistically significant differences.\textsuperscript{4,8,20,24–40} These studies showed that in general the sickle cell disease in the eastern province is ‘mild’ with minimal requirements for blood transfusion, absence of ‘hand and foot syndrome’, reduced incidence of infections, few biochemical abnormalities and longer survival. While in the other provinces a severe form of sickle cell anaemia was encountered with features similar to those commonly reported in Africans and Black Americans.\textsuperscript{25,30,35,38–42} The majority of the patients from these regions suffered from severe and frequent episodes of crises, required blood transfusions frequently, some suffered from ‘hand and foot syndrome’, avascular necrosis of the head of the femur, were more prone to infections and

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*Figure 1. Frequency of sickle cell (Hb S) gene in different regions of Saudi Arabia calculated using: ((2 × HbSS) + Hb AS)/2 × total no. investigated. These results are obtained during our screening studies in different regions of Saudi Arabia. (No. investigated: Qaseem 1015; Qatif 962; Hafouf 1490; Riyadh 840; Sulayl 1362; Najran 1860; Jizan 1466; Qunfuda 823; Al-Baha 1071; Makkah 877; Yanbu 1095; Khaim 1016; Al-Ula 409; Baha 933.) f = 62.5635; df = 27; p < 0.0001 (ANOVA).*
Table 1
The haematological parameter values and clinical manifestations in sickle cell anaemia patients from eastern and south-western provinces of Saudi Arabia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Eastern</th>
<th>South-western</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients investigated</td>
<td>54</td>
<td>75</td>
</tr>
<tr>
<td>Haematological parameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>10.8 ± 2.2</td>
<td>8.4 ± 1.2</td>
</tr>
<tr>
<td>RBC (× 10^12/l)</td>
<td>3.9 ± 1.0</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>PCV (l/l)</td>
<td>0.3 ± 0.05</td>
<td>0.22 ± 0.05</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>78.5 ± 10.5</td>
<td>81.3 ± 12.8</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>28.6 ± 5.1</td>
<td>29.0 ± 5.6</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>36.1 ± 3.6</td>
<td>36.1 ± 5.2</td>
</tr>
<tr>
<td>Hb A₂ (%)</td>
<td>2.8 ± 0.5</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td>Hb F (%)</td>
<td>11.3 ± 6.2</td>
<td>10.3 ± 7.0</td>
</tr>
<tr>
<td>Retic Count (%)</td>
<td>6.5 ± 4.2</td>
<td>21.6 ± 10.3</td>
</tr>
</tbody>
</table>

Clinical manifestations

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallor</td>
<td>42.86</td>
</tr>
<tr>
<td>Jaundice</td>
<td>14.29</td>
</tr>
<tr>
<td>Joint and bone pain</td>
<td>85.7</td>
</tr>
<tr>
<td>Abdominal crises</td>
<td>43.0</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>14.3</td>
</tr>
<tr>
<td>Hand and foot syndrome</td>
<td>Rare</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Skeletal deformity</td>
<td>Rare</td>
</tr>
<tr>
<td>Hospitalization (several)</td>
<td>42.9</td>
</tr>
<tr>
<td>Transfusion requirement (several)</td>
<td>42.9</td>
</tr>
</tbody>
</table>

required frequent hospitalization. However, there were exceptions, where some patients with a 'severe' sickle cell anaemia were encountered in the eastern province while some patients with 'mild' form of the disease were encountered in the south-western province. In a recent study two groups of patients in the eastern province were followed from birth to 4 years of age. A more severe clinical and haematological presentation was encountered in the group of patients originally from the south-western province compared with those from the eastern province. In general, in patients from the south-western province, the clinical picture and haematological findings revealed a higher prevalence and degree of anaemia, a higher frequency of haemolytic and aplastic crises, 'hand and foot syndrome' and required more frequent hospitalizations compared with the eastern province patients. Genetic factors including associated thalassaemia, high Hb F level and G-6-PD deficiency did not produce an ameliorating effect as that encountered in the eastern province population. The haematological and clinical presentation in Saudi sickle cell anaemia patients with a mild and severe disease are summarized in Table 1. These results also suggest the presence of at least two distinct forms of sickle cell disease in Saudi patients.

Rarer haemoglobinopathies
Other abnormal haemoglobins including Hbs C, G, E, D, E, Hb O Arab, Hb Riyadh, Hb Handsworth, Hb F Dammam and Hb Setif have been identified in sporadic cases in different regions of the country. However, homozygosity and/or double heterozygosity for the sickle cell gene and other abnormal variants have been rarely encountered and clinical and laboratory findings in these states have not been reported.

Sickling disorders and infections
Patients with sickle cell disease are highly prone to develop bacterial infections and the latter are considered to be a major cause of morbidity and mortality in children with sickle cell disease. This is believed to be due to defective host defence mechanisms including reduction in immunoglobulin and complement levels, phagocytic activity and impaired splenic function.

Studies conducted on sickle cell disease patients from the eastern province have revealed the presence of Salmonella, Streptococcus and Haemophilus in most cases admitted with infection. Oral penicillin prophylaxis has been recommended in these children. Case control studies on sickle cell disease children from the south-western province of the country with severe form of the sickle cell disease have shown a significant beneficial effect of combined pneumococcal vaccination and penicillin prophylaxis in reducing morbidity in these patients.

Sickle cell haemoglobinopathies and nutritional status
Deficiencies of certain essential nutrients have been reported in patients with sickle cell disease, particularly zinc and copper deficiencies. In Saudi patients no such deficiencies have been reported in the sickle cell disease patients from the eastern province. However, reduced zinc levels have been demonstrated in the sickle cell disease patients from the south-western province (El-Hazmi et al, in preparation). Such deficiencies often aggravate the clinical manifestations of sickle cell disease and may contribute to retarded growth and hypogonadism. In some cases dietary supplementation with soluble vitamins including riboflavin and vitamin E (El-Hazmi et al., in preparation) have frequently been disclosed in these patients. In a few studies on sickle cell disease it has been indicated that the children suffering from the disease have a higher caloric requirement. This is
due to the moderately hypermetabolic state secondary to the increased rate of tissue turnover. In addition, the total body protein turnover is believed to increase due to the increased turnover of haemoglobin molecules and folic acid requirements are higher due to increased haemolysis. However, the data verifying these observations are scanty and further studies are required to ascertain the nutritional requirements and the nutritional status in patients suffering from chronic sickle cell anaemia.

The Thalassaemias

The thalassaemias are a group of genetic disorders caused by decreased biosynthesis of one or more of the globin chains of haemoglobin. The major thalassaemias investigated in Saudi Arabia are those due to decreased $\alpha$-globin chain synthesis i.e. $\alpha$-thalassaemia, and those due to decreased $\beta$-globin chain synthesis i.e. $\beta$-thalassaemia. The former generally result from deletion of one or more of the $\alpha$-globin genes, and are widely distributed in the different regions. Non-deletion types of $\alpha$-thalassaemia are also known and usually result from point mutations in and around the $\alpha$-globin genes.

In Saudi Arabia both $\alpha$- and $\beta$-thalassaemias have been encountered and in this section the studies conducted and results obtained are outlined.

$\alpha$-Thalassaemias

Following the discovery of Hb Barts in the eastern province population, several studies have been conducted in different regions of Saudi Arabia to identify different types of $\alpha$-thalassaemias and to determine the $\alpha$-gene frequency. The results have shown the presence of both deletion and non-deletion type of $\alpha$-thalassaemias, but at variable frequencies in different regions of the country. More recently the frequency of the deletion type of $\alpha$-thalassaemia has been determined using restriction endonuclease Bam HI. The heterozygous ($-/-\alpha\alpha$) and homozygous ($-/-\alpha\alpha$) forms of $\alpha$-thalassaemia have been identified at a high prevalence in some regions of Saudi Arabia. The frequencies in the different regions are presented in Fig. 2. However, heterozygous $\alpha$-thalassaemia ($-/-\alpha\alpha$) has been shown to occur at a very low prevalence, confirming the earlier observations that hydrops faetalis ($-/-\alpha\alpha$) and Hb H disease ($-/-\alpha\alpha$) are rare in Saudis, despite the high frequency of $\alpha$-thalassaemias. Non-deletion types of $\alpha$-thalassaemias
resulting from mutation of one or a few bases have also been reported in Saudis.\textsuperscript{69}

The nature of deletion, i.e. whether leftward or rightward deletions, have also been investigated using the restriction endonuclease Bgl II. As a result of these studies the major cause of \(\alpha\)-thalassaemia in Saudis has been identified as rightward deletion.\textsuperscript{63} However, studies have revealed that leftward deletion does exist in the Saudi population and are thus averting earlier suggestions that leftward deletions were confined to the population of South-east Asia.\textsuperscript{72} In addition, \(\alpha\)-thalassaemia cases who were doubly heterozygous to leftward and rightward deletions were identified amongst Saudis.\textsuperscript{73} Furthermore, using the restriction endonucleases, Hpa I, Hind III, Bgl II, Xba I and Bam HI it was shown that triple \(\alpha\)-gene arrangements i.e. \(\alpha\alpha\alpha\textsuperscript{anti}\)\textsuperscript{3,7} occur in all regions of Saudi Arabia though at a considerably low frequency (<0.05), suggesting that unequal crossing-over of \(\alpha\)-genes could not be the major mechanism in production of deletion types of \(\alpha\)-thalassaemias.\textsuperscript{74} Furthermore, triple \(\alpha\)-genes in association with sickle cell and \(\beta\)-thalassaemia genes have also been identified in the Saudi population.\textsuperscript{75} Recently a case of triple \(\alpha\)-genes, homozygous to HbS was encountered suffering from a severe form of sickle cell disease.

The clinical and haematological presentation in patients with \(\alpha\)-thalassaemia due to one or more \(\alpha\)-gene deletions, show a markedly variable picture.\textsuperscript{76} The values of haematological analytes in patients with one or two \(\alpha\)-gene deletions are presented in Table 2. The studies showed that both the \(\alpha\)-thalassaemia.2 homozygous and heterozygous cases have lower values of total haemoglobin, PCV, MCV and MCH, with the former having values lower than the latter. Reduction in Hb A2 level, an indicator of \(\alpha\)-thalassaemia was not commonly encountered in these patients.\textsuperscript{76}

Interactions between \(\alpha\)-thalassaemias and other red cell genetic abnormalities are a commonly encountered feature in all regions of Saudi Arabia, particularly those where the abnormal genes occur at a high frequency. However, further investigations are required to determine the molecular basis of \(\alpha\)-thalassaemia, frequency of interaction with other abnormal genes and effect of such interactions on the clinical and haematological presentation of each abnormality.

\(\beta\)-Thalassaemia

\(\beta\)-Thalassaemias occur at a variable gene frequency in the different regions of Saudi Arabia.\textsuperscript{16,17,20,32} Both \(\beta^0\) and \(\beta^+\)-thalassaemia have been reported
and frequencies of \( \beta \)-thalassaemia in different regions are presented in Fig. 3. Currently, studies are focused on the study of the clinical presentations and the natural history of \( \beta \)-thalassaemias. Further studies at the gene level, are aimed at identifying the molecular basis of different types of \( \beta \)-thalassaemias.

### \( \beta \)-Globin Gene Polymorphism

DNA polymorphism in the \( \beta \)-globin gene region was first reported by Kan & Dozy using the restriction endonuclease Hpa I.\(^{77}\) It was revealed that the \( \beta^A \)-globin gene was linked mainly to a 7.6 kb fragment generated when DNA was digested with Hpa I, while the \( \beta^B \)-globin gene was mainly associated with 13.0 kb Hpa I fragment.\(^{77}\) However, later studies revealed that both \( \beta^A \) and \( \beta^B \) genes were associated with 7.6 kb and 13.0 kb Hpa I fragments at varying frequencies in different populations.\(^{78–80}\) Studies in Saudi Arabia showed that in individuals from different regions of Saudi Arabia, both \( \beta^A \) and \( \beta^B \) globin genes may be linked to 13.0 kb, 7.6 kb, 7.0 kb and 5.6 kb fragments.\(^{81,82}\) However, significant differences were encountered in the frequency of \( \beta^B \) associated with different Hpa I fragments. In the Eastern province \( \beta^B \) was linked mainly to the 7.6 kb fragment while in the north-western and south-western provinces the \( \beta^B \) was linked mainly to 13.0 kb fragment. The frequency of \( \beta^A \) linked to 7.6 kb and 13.0 kb fragment in different regions did not show any difference. These findings have led us to propose different origins of the sickle cell gene in different regions of Saudi Arabia.\(^{81}\) Furthermore, it appears that the 7.6 kb fragment is frequently present in patients with a mild sickle cell disease while the 13.0 kb Hpa I fragment is found at a higher frequency in patients with a severe disease. Further studies are expected to determine whether there is any association between \( \beta^B \)-globin gene polymorphism and the nature of the sickle cell anaemia.

An interesting finding in Saudis was the presence of triple \( \beta \)-globin genes in a few normal individuals, and in Hb S heterozygous and homozygous cases. Since normally each individual has only one pair of \( \beta \)-globin genes, one on each chromosome, it was suggested that individuals with three \( \beta \)-globin genes could have derived one extra gene by the mechanism of unequal crossing-over.\(^{83}\) A similar mechanism has been shown to result in deletion of the \( \beta \)-genes and producing Hb Lepore and anti-Lepore.

### \( \beta \)-Globin gene haplotypes

The \( \beta \)-globin gene cluster is located on the short arm of chromosome 11 in a 50 kb region and is composed of \( \epsilon, G_{\alpha}, A_{\alpha}, \delta, \psi \beta \) and \( \beta \) globin genes (Fig. 4). The \( \epsilon \)-gene of embryonic globin is the most 5' of all the genes in the \( \beta \)-globin gene cluster, followed by \( G_{\alpha}, A_{\alpha}, \delta, \psi \beta \) and \( \beta \)-globin genes, where, the \( \beta \)-globin gene is most 3' gene in the cluster.

Using different restriction endonucleases, several polymorphic sites have been identified in and around the \( \beta \)-globin gene cluster.\(^{84,85}\) In the conventional nomenclature, the presence of a polymorphic site is indicated by a + ve sign, while its absence is indicated by a – ve sign. The \( \beta \)-globin gene haplotypes in sickle cell anaemia patients from different regions have been investigated. The results at the five sites highlighted in Fig. 4 have shown that the major haplotype in sickle cell anaemia patients from the eastern province is ++ + + +, while in the patients from north-western and south-western provinces the major haplotype
is \(-\ -\ -\ -\) \(^{86}\) Some studies indicated that the haplotype \(+\ +\ -\ +\ +\), in the eastern province population, is associated with elevated Hb F level and hence a mild form of sickle cell anaemia.\(^{87,88}\) However, during our studies no association could be demonstrated between the \(\beta\)-globin gene haplotypes and Hb F level\(^{86}\) thus contradicting the earlier suggestion that the haplotype \(+\ +\ -\ +\ +\) is a genetic marker for elevated Hb F.

**Xmn I polymorphism in the \(\beta\)-globin gene region**

The extension of the restriction endonuclease studies to investigate the Xmn I polymorphism in the \(G_{\alpha}\) cluster on chromosome 11 revealed further differences among Saudi patients from different regions. The endonuclease Xmn I has two restriction sites, one on either side of the \(G_{\gamma}\) cluster. Normally, digestion with Xmn I produces an 8.1 kb fragment containing the two \(\gamma\)-globin genes. An Xmn I polymorphic site caused by mutation, exists at position 158, 5' to the \(G_{\gamma}\), and its presence results in the production of a shorter 7.0 kb fragment. This polymorphic site has been associated with high \(G_{\gamma}\) globin gene expression in sickle cell anaemia and \(\beta\)-thalassaemia patients.\(^{89,90}\)

Investigation of the Xmn I polymorphism in sickle cell anaemia patients from different regions of Saudi Arabia revealed that all patients from the eastern province have the polymorphic site and thus produce a 7.0 kb fragment, though in the normal individuals (Hb AA) the polymorphic site is not identified in any case. On the other hand, sickle cell anaemia patients and normal individuals from the south-western province of Saudi Arabia have a very low frequency (0.033) of association with the Xmn I polymorphic site and produce mainly the 8.1 kb Xmn I fragment. The disease is mild in the former patients and severe in the latter. However, so far no association could be demonstrated between the Xmn I polymorphic site and Hb F level in contrast to association with the clinical presentation.\(^{91}\)

Taken together these findings indicate that the mild sickle cell anaemia in the eastern province population appears to be associated with the \(\beta\)-globin haplotype \(+\ +\ -\ +\ +\), 7.0 kb Xmn I fragment, 7.6 kb Hpa I fragment and high
G. /A. level. The severe sickle cell anaemia, seen in western provinces on the other hand, appears to be associated with the haplotype - - - +, 8.1 kb Xmn I fragment, 13.6 kb Hpa I fragment G. /A., ratio less than 1 (Fig. 4).

**Interaction Between Sickle Cell Haemoglobinopathies and Thalassaemias**

The frequency of coexisting α-thalassaemia and sickle cell haemoglobin in the Saudi population is high due to a high frequency of both genes in the same localities. In Hb S heterozygotes a significant reduction in Hb S level is encountered in patients with coexisting α-thalassaemias and the red cells are hypochromic-microcytic. In Hb S homozygotes, coexisting α-thalassaemia improves the value of haematological parameters, reduces values of red cell indices and has an ameliorating effect on the clinical manifestations of the disease, particularly in the population of the eastern province. Though similar results were encountered in the population from other regions, the degree of disease amelioration was not to the same extent. This suggests that some other, yet unknown factors (possibly genetic as mentioned earlier), also play a significant role in influencing the manifestations of the sickle cell disease in the eastern province.

Coexisting β-thalassaemia was also encountered in association with the Hb S gene. In Hb S heterozygotes, β⁺-thalassaemia produces hypochromic microcytic cells, a variable degree of anaemia and an elevation of Hb S level. Hb S/β⁻-thalassaemia, on the other hand, produces a clinical picture similar to that of sickle cell anaemia. A high prevalence of coexisting Hb S and β-thalassaemia gene is observed in all regions where the two genes exist at a high prevalence. Further detailed studies are required to define the natural history of Hb S/β⁺ and Hb S/β⁻-thalassaemia in the Saudi population from different regions of the Kingdom.

**Enzymopathies**

Since the discovery of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency in the eastern province of Saudi Arabia in the 1960s by Gelpi, considerable interest has been directed towards the investigation of red cell enzyme deficiency in various regions of Saudi Arabia. Consequent studies have shown the presence of G-6-PD deficiency in other regions of Saudi Arabia including Al-Hafouf, Jaizan and Khaiber, Al-Baha, Al-Ula, Al-Qunfuda and in other regions in western Saudi Arabia. The frequency of G-6-PD deficiency in the male and female population in different regions is presented in Fig. 5.

Investigations in Saudi Arabia have shown that a close correlation exists between the frequency
of G-6-PD deficiency and past or present history of malaria endemicity. Phenotyping of G-6-PD has disclosed the presence of extensive polymorphism of G-6-PD variants. The phenotype G-6-PD-B⁺ has been identified as the major phenotype in all regions of Saudi Arabia. The other variants included G-6-PD-A⁺, G-6-PD-Mediterranean, G-6-PD-A⁻, G-6-PD Khartoum and unknown G-6-PD-variants with partial G-6-PD activity but the same electrophoretic mobility as G-6-PD-B⁺.

Other erythrocytic enzyme deficiencies including partial pyruvate kinase, glutathione reductase, hexokinase and 6-phosphogluconate dehydrogenase deficiency have been identified in different regions of the country at a variable frequency.

Interaction between sickle cell and G-6-PD deficiency gene have been frequently identified in most of the regions of Saudi Arabia. In the HB S homozygotes and heterozygotes the frequency of G-6-PD deficiency is significantly higher than in normal individuals in Al-Hafouf, Jaizan, Najran, Khaibar, Jeddah and the surrounding area. However, in other areas including Al-Ula, Al-Baha, Al-Qunfuda, Makkah and Bisha such correlation was not encountered. In some regions an ameliorating effect of coexisting G-6-PD deficiency is encountered. However, in other regions no significant changes are observed in sickle cell disease patients with or without G-6-PD deficiency.

Conclusion
Progress in the study of haemoglobinopathies, thalassaemias and enzymopathies in Saudi Arabia, has been outstanding in the last 25 years. Clinical, haematological, biochemical and genetic studies have revealed a unparalleled wealth of information on Saudi population genetics. However, the molecular bases dictating the clinical manifestations remain largely unresolved. Several aspects are still incomplete and a large number of questions are still unanswered, particularly at the genetic level. It is hoped that further studies will highlight other interesting features of these genetic disorders that appear to be a major cause of chronic anaemias in Arabia.

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References
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