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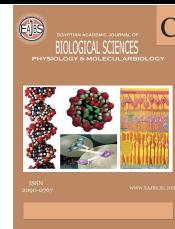
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Prevalence of HbS Gene in Marzouk Region of Southern Libya

Abdelbaset Mohamed Elasbali[1,3], Annour Mohamad Alalem[4], Eyad M A Alshammari[2], Saif Khan[2], Mohd. Adnan[2], Shafiul Haque.[5] [6]*

1- Department of Clinical Laboratory Science, College of Applied Medical Sciences, University of Ha'il, Ha'il-2440, Saudi Arabia
2- Department of Clinical nutrition, College of Applied Medical Sciences, University of Ha'il, Ha'il-2440, Saudi Arabia
3- Molecular Diagnostics and Personalised Therapeutics Unit, University of Ha'il, Ha'il-2440, Saudi Arabia
4- Faculty of Medical Technology, University of Sebha, Sabha- 18758, Libya
5- Research and Scientific Studies Unit, College of Nursing & Applied Health Sciences, Jazan University, Jazan-45142, Saudi Arabia
6- Department of Biosciences, Jamia Millia Islamia (A Central University), New Delhi-110025, India
*Email: shafiul.haque@hotmail.com

ABSTRACT

This study assesses the homozygous and heterozygous status of sickle cell disease (SCD) and evaluates the relationship between consanguinity and the occurrence of HbS gene in families living in Marzouk region of Libya. The study revealed higher frequency (53.34%) of sickle cell trait (HbAS) in Marzouk region; whereas the prevalence of sickle cell anemia (HbSS) was nearly 10%. Out of 210 subjects, two cases of sickle cell with HbC (0.95%) were noticed. High frequency of consanguinity (72%) found in this study suggests that interrelation marriages are very common in Marzouk region and these are one of the major factors for high rate of sickle cell trait. In addition, large family size (average of 6-10 children/family) plays an important role in increasing the frequency of HbS. Surprisingly the carriers of HbAS showed some clinical complications of HbSS like jaundice and joints splenomegaly. Interestingly, one case of aplastic crisis was also detected in HbAS carriers. In the long run these findings will help in deciphering the mechanisms of the disease processes within SCD and management of the disease by implementing effective control measures and prevention strategies (like, genetic counseling, pre-marital screening etc.) along with care and rehabilitation of the affected population.

INTRODUCTION

Genetic diseases, especially hereditary blood disorders such as Sickle cell disease (SCD) and the thalassemia syndromes are a significant problem in many countries (AlArrayed & AlHajeri 2010). SCD comprises a range of pathological conditions resulting from the inheritance of the sickle haemoglobin (HbS) gene either homozygously or as a compound heterozygote with other interacting abnormal hemoglobin genes. SCD is clinically one of the most important haemoglobinopathies and single gene disorders of human beings. Basically SCD refers to a collection of autosomal recessive genetic disorders characterized by the HbS variant of the β-globin gene. Individuals affected with sickle cell anemia have two copies of this variant (HbSS), and the primary haemoglobin present their red blood cells is sickle haemoglobin. Individuals affected with other types of SCD are compound heterozygotes and carry one copy of the HbS variant plus one copy of another β-globin genetic variant, for e.g., HbC or Hbβ-thalassemia. Generally, these individuals produce a mixture of variant haemoglobins. However, carrier individuals have one copy of the normal β-globin gene (HbAS), producing a mixture of sickle haemoglobin and normal haemoglobin. The carrier state for SCD is generally called as sickle cell trait (SCT) and individuals with SCT do not express SCD and protected from malaria infection.

In Africa, more than 200,000 infants are born yearly with SCD (Makani *et al.* 2007). Similarly, in the United States, SCD affects about 72,000 people and 2 million are carriers (Creary *et al.* 2007). Several reports show that the presence of HbS in almost all Arab population at variable frequencies ranging from <1% to almost 20% in some areas (El-Hazmi & Warsy 1997). SCD is widespread in the Middle Eastern Arab countries, although significant inter- and intra- countries differences are encountered in the frequencies of the abnormal genes. The main factors which are believed to play a major role in the increased frequencies of the HbS include consanguinity, large sibship size, migration and environmental factors (El-Hazmi *et al.* 2011). However, only scanty reports are available related to inherent variations of the phenotypic expressions of SCD in geographically distinct populations of the Arab world.

The impact of consanguinity is variable; it depends on the isolation of the population, with rates of 1% to 11% in different regions for first and second cousin marriages (Cruz 2013). There is a high rate of consanguinity in Libya; however, information on its relationship with genetic disorders is limited. The first report of occurrence of sickle cell anemia in a Libyan family was reported by Elfagm *et al.* in 1980 (Elfagm *et al.* 1980). Earlier study indicated that HbS and HbC traits were dominant in Southern Libya while β-thalassemia was more commonly seen in Eastern Libya (Sherrif *et al.* 1989). In the south of Libya, the prevalence of sickle cell trait and sickle cell anemia was reported to be 4.2% and 1.2% respectively, while in eastern part of the country the prevalence of sickle cell anemia was 0.005% (Sherrif *et al.* 1989, El-Mangoush *et al.* 1990). A screening study demonstrated the prevalence of HbS, HbC and thalassaemia genes in Libyan population however the incidence rate of abnormal haemoglobins in the indigenous Libyan was low (Jain 1979). Later findings endorsed that SCD occurs at a low frequency among Libyans (Jain 1985), but the actual burden of the disease is yet not clear due to high consanguinity.

In general the Middle Eastern Arabian region is a set of common factors which comprise the rapid increase

in the population and rich historical, cultural, traditional and religious commonality. The large family size (sibship), high rate of consanguinity in conjunction with tribe/clan endogamy, makes the Arabian region unique from genetic analysis viewpoint. Hence, the present study was undertaken to detect the pattern of sickle cell gene in families living in Marzouk region of southern Libya and to evaluate the relation of consanguinity and the occurrence of HbS gene among these families.

MATERIALS AND METHODS

Patients with sickle cell anemia from Marzouk city of Libya and neighboring villages that undergo a regular blood transfusion in Marzouk Hospital were selected as subjects. Immediate family members and close relatives including brothers, sisters, parents, and both paternal and maternal grandparents were included in this study. A formal written consent was obtained from all the participants and a validated questionnaire was explained, employed and filled-up by the subjects. Personal demographic information such as name, age, sex, home address, number of family members, presence of consanguinity between parents and its degree, family history of anemia and other pertinent health complaints were obtained from the studied subjects. Details of clinical symptoms and signs of sickle cell anemia were collected from the subjects' clinical files and medical reports by accompanied doctor. Venous blood samples were collected from the patients and were divided into two parts. In the first part anticoagulant EDTA was added to be used for hematological tests, like complete blood count (CBC), peripheral blood smear (PBS), reticulocyte count, slide-sickling test and solubility test. Haemoglobin (Hb) electrophoresis was preformed following the method of Bain and Bates (Bain & Bates 2006) and was done only for sickle-positive samples

detected by both slide and solubility sickling tests. While the second part of the blood sample was collected in a plain tube (without adding any anticoagulant) and left to clot and serum was separated by centrifugation for the determination of bilirubin levels of sickle-positive samples.

RESULTS

In this study, 210 native Libyans of twenty different families of Marzouk region were tested for the presence of heterozygous or homozygous form of HbS variant of the β-globin gene. Out of 210 subjects, 118 (56%) were males and 92 (44%) were females. The overall results revealed that participating subjects were distributed as 10, 53.34, 31.71, and 0.95% for patients (HbSS), carriers (HbAS), normal subjects (HbAA), and two patients (HbSC), respectively. The average age of various group of participants was: patients (HbSS) (n = 23) 14±7 years, carriers (HbAS) (n = 112) 32±20, and normal subjects (HbAA) (n = 75) 28±20. Heterozygous individuals (HbAS), who were usually asymptomatic presented with some clinical manifestations such as joint pain, jaundice and eye problems. One case of heterozygous HbAS was presented with aplastic anemia. Sickle cells were seen in all PBS of homozygous subjects, whereas only 77% of heterozygous patients have sickle cells in their PBS. The results of hematological parameters have been shown according to the type of haemoglobin in Table 1. Mean bilirubin levels in patients (HbSS) were noticed as total 5.2±1.9 mg/dl direct 4.1±2.2 mg/dl and indirect 0.9±0.5 mg/dl. However, the mean bilirubin levels for carrier subjects (HbAS) were total 1.0±0.8 mg/dl, direct 0.5±0.3 mg/dl and indirect 0.5±0.4 mg/dl. The mean bilirubin levels present in subjects have been shown in Table 2. Interestingly, consanguinity was found in 72% of the studied cases in both first and

second generation. Table 3 shows the consanguinity among two generation with first, second and third cousin relation. Figure 1 shows HbS positive samples by solubility sickling tests whereas Figure 2 demonstrates HbS positive samples using haemoglobin electrophoresis. At alkaline pH, Hb migrates towards the anode (+) in electrophoresis, as Hb is a negatively charged protein. Structural variants that had a change in the charge on the surface of the molecule at alkaline pH got separated from HbA. Hb variants that have an amino acid substitution, which was internally sited may not separate, and those that have an amino acid substitution but had no effect on overall charge will not get separate by the electrophoresis[12]. In Figure 2, HbA (normal) migrates faster towards the anode than HbS and HbC (abnormal). There are slight differences in the mobility of HbSS and HbSC (HbC is slightly faster than HbS). Control sample (HbAA) was used in all the plate.

Table 1: Hematological parameters (mean±SD) according to the types of haemoglobin

Parameters	HbAA (no = 75)	HbAS (no = 112)	HbSS (no = 21)	HbSC (no = 2)
Hb (gm/dl)	13.7 ± 3.4	13.2 ± 2.4	7.2 ± 1.1	10.2
PCV (%)	40 ± 4.4	40 ± 6.5	25 ± 3.5	32
RBC ($X10^{12}$/L)	4.9 ± 0.5	4.9 ± 0.9	3.3 ± 0.4	4.7
MCV (f.l)	83 ± 6.9	81 ± 9.4	76 ± 9.7	67
MCH (p.g)	28 ± 2.8	27 ± 3.7	25 ± 4.9	20
MCHC (gm/dl)	33 ± 1.9	32 ± 3.2	31 ± 3.7	31
Retic (%)	1 ± 0.4	1.2 ± 0.5	8 ± 3.4	0.9
WBC ($X10^9$/L)	7.0 ± 1.7	7.25 ± 2.4	10.6 ± 4	10
Plate ($X10^9$/L)	352 ± 99	224 ± 121	278 ± 101	483

Table 2: Serum bilirubin levels (mean±SD) in patients and carriers

Bilirubin (mg/dl)	HbSS (no = 21)	HbAS (no = 112)
Total	5.2 ± 1.9	1.0 ± 0.8
Direct	4.1 ± 2.2	0.5 ± 3
Indirect	0.9 ± 0.5	0.5 ± 4

Table 3: Consanguinity among two generations

Consanguinity	First generation		Second generation	
	No	%	No	%
First cousin	0	O	4	18.18
Second cousin	2	14.28	2	9.10
Third cousin	7	50.00	11	50.00
Non Consanguinity	5	35.72	5	22.72

DISCUSSION

Earlier reports demonstrated the presence of HbS in almost all Arab population at variable frequencies ranging from <1% to almost 20% in some areas (El-Hazmi *et al.* 2011). In Saudi Arabia the highest incidence of sickle cell gene has been reported 30 and 25% in Western province and Eastern province, respectively (John 2010). In Egypt, along the Nile Valley, the HbS gene is almost nonexistent, but in the western desert near to Libya border variable rates of 0.38% in the coastal areas (El-Hazmi *et al.* 2011), 9.0% in the New Valley oasis of EL-Kharga and EL-Dakhla (Selim *et al.* 1974), and 22.17% in the Siwa Oasis (Ibrahim *et al.* 1974) have been reported. Earlier studies reported the dominance of HbS and HbC traits in Southern Libya while β-thalassemia has been more commonly

found in Eastern Libya (Sherrif *et al.* 1989, El-Mangoush *et al.* 1990).

The tradition of consanguineous marriage (inbreeding) goes far back in history and has been known in the Arabs from biblical times (Abdalla & Zaher 2013). Earlier report shows high rates (30 to 49%) of consanguinity in in various Arabian countries (El-Hazmi *et al.* 2011, Basson 1979, Khlat 1988, Khoury & Massad 1992). There is a high rate of consanguinity in Libya; however, information pertaining to its relationship with genetic disorders is limited. The present study shows 72% consanguinity in first and second generation with first, second and third cousin marriages. The type of consanguinity in first and second generation with first cousin, second cousin and third cousin relation has been shown in Table 3. We found high incidence of carriers of HbAS (53.34%) in all families from grandparents to parents. Interrelation (consanguineous) marriages are very much practiced among the people of Marzouk region (sampling region) of Libya. The incidence of consanguinity could be a major factor of high rate of sickle cell trait. Also, large sibship size is the second important factor for high rate of sickle cell trait among Arabs in general (El-Hazmi *et al.* 2011). As anticipated, we noticed an average of 6 to 10 children in each family of Marzouk region, which shows that large sibship size is an important factor for high frequency of sickle cell trait in the region. The possible disadvantage of these factors on families with mutant genes is that a large number of family members may have abnormal genotype (El-Hazmi & Warsy 1997).

Earlier report from Algeria found abnormal haemoglobin HbJ α- Mexico in 116 subjects of 8 families having an average of 6 children/family (Trabuchet *et al.* 1978). Here in this study of 20 families with high sibship size (an average of 6-10 children/family), we found 112 HbAS carrier subjects, 21 HbSS patient subjects and 2 HbSC subjects. The mean age of HbSS patient subjects was 14±7 years while for HbAS carrier and normal subjects it was 32±20 and 28±20, respectively. The low mean age of patients (HbSS) was possibly due to the complications associated with the disease that leads to death in early stages of their life. The clinical features and presentation of patients of sickle cell anemia (HbSS) were found similar as reported earlier in other Arab countries, except the absence of leg ulcers. Leg ulcers were not detected in sickle cell anemic patients of Marzouk region presumably because the patients do not survive long enough to develop this complication (John 2010). All patients included in this study were blood transfusion dependent and presented with symptoms of jaundice and joints splenomegaly. These clinical features were similar to those reported previously in all provinces of Saudi Arabia except the eastern province (El-Hazmi 1992). The mean bilirubin levels in patients were recorded high (total 5.2±1.9 mg/dl, direct 4.1±2.2 mg/dl, and indirect 0.9±0.5 mg/dl) in comparison with carrier subjects (total 1.0±0.8 mg/dl, direct 0.5±0.3 mg/dl, and indirect 0.5±0.4 mg/dl). The difference between the levels of serum bilirubin was quite significant for patients and carrier subjects (p> 0.000). In this study we found that most of HbAS carriers were asymptomatic but few of them (10 out of 112) had severe clinical manifestations such as joint pains, jaundice, splenomegaly, eye problems. Also, one subject had symptom of aplastic anemia with HbAS. John (John 2010) exhaustively reviewed the clinical profiles in Sickle cell traits and reported the presence of complications in sickle cell trait under extreme anoxic conditions of vascular occlusive episodes, similar to the symptoms appear in homozygous sickle cell disease. Individuals who are

heterozygous for HbS are usually asymptomatic, but few studies reported that the sickle cell trait patients have tendency towards sickling crisis when exposed to hypoxia (McGarry & Duncan 1973, Pembrey *et al.* 1975). Some workers have postulated the possibility of electrophoretically silent second globin chain mutation with a deleterious effect in individuals with symptomatic sickle cell trait (Roth 1985). Here, in this study we found one case of sickle cell trait with aplastic anemia. The affected subject was a 13 year old male child having history of aplastic anemia and he was admitted to the hospital in unconscious state with high blood pressure, papilloedema and facial palsy. His sickle cell trait was identified by sickling test and the diagnosis was confirmed by haemoglobin electrophoresis that showed two bands of HbA and HbS. This case of HbAS with aplastic anemia is an example of reflecting its morbidity in sickle cell trait and warrants alertness for possible emergence of any unusual complications of HbAS trait (John 2010).

The origin of HbS and its mutation has been seen in several locations within Africa (makani *et al.* 2007). Sickle haemoglobin containing red cells inhibits proliferation of *Plasmodium falciparum*, and likely to become deformed and removed from the circulation. Due to movement of populations *via* trade routes and slave trading, dissemination of sickle mutation in different areas of the world took place (Weatherall 1999). The highest prevalence of HbS has been seen in blacks from tropical Africa who participated in slave trade. HbS has been detected in Mediterranean basin, Saudi Arabia and parts of India in significant amount. Approximately 45% of the population in some parts of Africa has sickle cell trait and 8% of blacks in United States carry the sickle gene. It has been recognized that sickle cell trait is most prevalent in areas that are hyperendemic for malaria. It also suggests that HbS provides a selective protection against lethal forms of malaria (Wang 2009).

Shresta and Karki reported the presence of sickle haemoglobin in majority of *Tharus* (a tribe) from malarial endemic region of Nepal and minority of SCD patients were of other ethnic groups (Shrestha and Karki 2013). Although malarial hypothesis explains sickle haemoglobin in *Tharus*, but failed to explain its prevalence in other ethnic groups (Shrestha and Karki 2013). However, migration of humans from malarial regions into non-malarial regions has been noticed and found one of the major factors responsible for sickle haemoglobin.

The rate of migration of populations between and within the different Middle Eastern Arabian countries is significantly high. Up to certain extent this is caused mainly due to prevailing economic condition, financial opportunities and job prospects. In all the Gulf States, including Saudi Arabia, a large proportion of the population is formed of immigrant workers and majority of them have migrated from high HbS frequency areas. Some have settled in these countries for decades, and as a result of inter-marriages, genetic admixtures have been generated. This gene drift has led to the establishment of abnormal genes in several areas (Baghernajad-Salehi *et al.* 2009).

In the Middle Eastern countries, malaria endemicity played a major role in influencing the HbS gene frequency, like in other parts of the World (Piel *et al.* 2010, Livingstone 1957). The carriers of HbS have a natural resistance against malaria development and this is a major advantage to survival in adverse conditions. Several reports from the Middle Eastern Arab countries corroborated the "malaria hypothesis" by showing a close correlation between the

frequencies or prevalence of the abnormal gene and past and present history of malaria endemicity (El-Hazmi & Warsy 1986, El-Hazmi *et al.* 1994).

The action of natural selection on genetic resistance to malaria has been shown in a multitude of contexts (Allison 1954, Kwiatkowski 2005). Certainly, the sickle-cell variant (i.e., the HbS allele) has been identified in four distinct genetic backgrounds in different African populations, suggesting that the same mutation arose independently several times through convergent evolution (Kwiatkowski 2005). In addition to HbS, other distinct mutations in the β-globin gene have generated the HbC and HbE alleles, which arose and spread in Africa and in Southeast Asia, respectively (Pardis & Sabeti 2008). Although data on genetic and congenital defects are not handy in the Arabian communities and only limited information is available but considering the high rate of consanguinity and other relevant factors, it can be predicted that SCD disorders are more frequent in this population.

Genetic diseases like SCD because of its chronic nature levy heavy medical, financial and emotional burdens. Thus, the efforts to combat complications of the disease are multifaceted and the effective control and prevention strategies are great importance beside treatment, care and rehabilitation of the affected in the population. Keeping high frequency of sickle cell trait in Southern Libyan population, there is an urgent need to initiate systematic epidemiological studies to assess the prevalence rate of SCD in other areas of Libya. Lately, few Arab countries have ongoing pre-marital screening programs for haemoglobinopathies, with success stories of reducing the birth rate of affected with SCD, e.g., Bahrain (AlArrayed 2005). Therefore, it is recommended that such programs for pre-marital screening of haemoglobinopathies must be initiated in Libya, especially in high HbS frequency areas, like Marzouk region, to permit couples to take an informative decision when they are both carriers of sickle cell gene.

In conclusion the sickle cell trait (HbAS) is quite high Marzouk region of southern part of Libya. However, the prevalence rate of sickle cell anemia (HbSS) was found to be 10%. Among the samples, two cases of sickle cell with HbC disease (0.95%) were also detected. Furthermore, high rate of consanguinity (72%) found through this study clarified that interrelation marriages are well practiced in Marzouk region and could be a major factor of high rate of sickle cell trait. Also, large family (sibship) size was found as one of the main factors for high rate of sickle cell trait in this region. Surprisingly, the carriers of HbAS demonstrated some complications which are mostly appear in cases of HbSS; and one case of aplastic crisis was also recorded in HbAS carriers. Due to high frequency of sickle cell trait in southern Libyan (Marzouk) population, there is an urgent need to initiate systematic epidemiological studies to evaluate the prevalence rate of SCD in other areas of Libya and management of the disease through implementation of effective control measures and prevention strategies (e.g., genetic counseling, pre-marital screening etc.) in addition to the care and rehabilitation of the affected population.

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DECLARATION OF INTEREST

responsible for the content and writing of this article.

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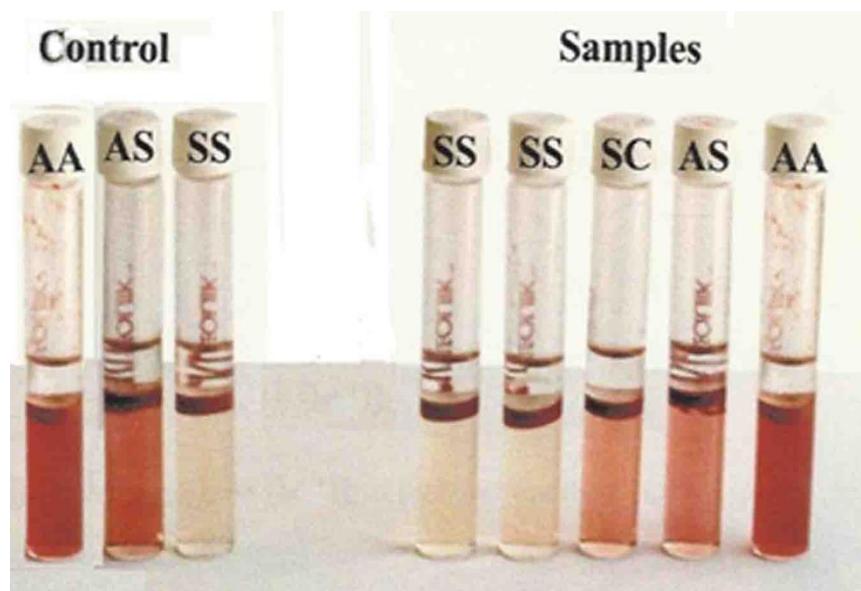
Fig. 1: Demonstration of Sickle-positive samples using solubility sickling test
Where: AA = Normal; AC = Carrier (Heterozygous); SS = Patient (Homozygous); SC = Combined Patients
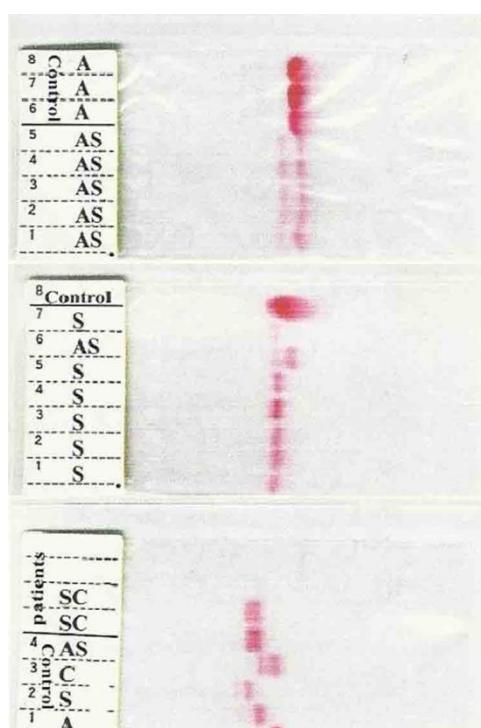

Fig. 2: Haemoglobin electrophoresis for HbSS, HbAS and HbAC

ARABIC SUMMARY

مدى انتشار جينة اليحمور المنجلي (HbS) في منطقة مرزق جنوب ليبيا

عبدالباسط محمد الاسبلي [1,3] . أنور محمد العالم [4]. إياد م أ الشمري [2]. سيف خان [2]. محمد عدنان [2].
شفيع الحق [4,5].

1-   قسم علوم المختبرات السريرية , كلية العلوم الطبية التطبيقية، جامعة حائل، حائل 2440، المملكة
العربية السعودية.

2-   قسم التغذية الإكلينيكية، كلية العلوم الطبية التطبيقية، جامعة حائل، حائل 2440، المملكة العربية
السعودية.

3-   وحدة التشخيصات الجزيئيّة والعلاجات الشخصيه، جامعة حائل، حائل 2440، المملكة العربية
السعودية.

4-   كلية التقنية الطبية , جامعة سبها، سبها 18758, ليبيا.

5-   وحدة الابحاث والدراسات العلمية، كلية التمريض والعلوم الطبية المساعدة، جامعة جازان، جازان
45142، المملكة العربية السعودية.

6-   قسم العلوم الحيوية، جامعة ميليا الاسلامية (الجامعة المركزيه)، نيودلهي 110025، الهند.

أجريت هذه الدراسة لمعرفة مدى انتشار جين فقر الدم المنجلي وعلاقته بزواج الأقارب بين
العائلات التي تعيش بمنطقة مرزق بجنوب ليبيا. حيث أظهرت الدراسة ارتفاعا في نسبة حاملي الجين بلغ
(53.34 %) في حين أن معدل انتشار المرض كان ما يقارب من 10%من أصل 210 عينة مع وجود حالتين
تعانيان من فقردم منجلي مقترن (0.95 %) . وأظهرت الدراسة أيضا أن معدل زواج الأقارب بين العائلات
التي أجريت عليها الدراسة كان مرتفعا بنسبة (72 %) . وهو العامل الرئيسي الذي ساهم في انتشار هذا الجين
بالمنطقة. بالإضافة إلى متوسط حجم الاسر الكبير (يتراوح ما بين 6-10 أطفال / أسرة) الذي يلعب دورا هاما
في زيادة وتيرة انتشار الجين بين الأسرة. كما أظهرت الدراسة وجود بعض المضاعفات السريرية للمرضى،
مثل: اليرقان, آلام ألمفاصل وتضخم الطحال. ومن المثير للاهتمام أنه تم الكشف عن حالة واحدة تعاني من
الأزمة اللانسيجية، مع وجود جين فقر الدم المنجلي. ومن خلال النتائج نوصي بإدارة المرض عن طريق تنفيذ
تدابير الرقابة الفعالة واستراتيجيات الوقاية مثل: (تقديم المشورة الوراثية، فحص ما قبل الزواج، وما إلى ذلك)
جنبا إلى جنب مع الرعاية والتأهيل لجميع السكان المتضررين.