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The Effectiveness of Genetic Counseling within the Pre-Marital Screening Program upon Sickle Cell Disease Decline in Saudi Arabia

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INTRODUCTION

The prevalence of diseases is becoming higher nowadays. Some of these diseases can be transmitted genetically from one population to another or passed from parents to their offspring. There are different types of genetic inheritance: 1) Autosomal recessive, 2) Autosomal dominant, in which are carried by the chromosomes other than sex chromosomes. 3) X-linked recessive, 4) X-linked dominant, where the mutant gene is carried by female sex determined chromosomes (X-chromosome). 5) Y-linked diseases, where the disease is only carried by Y-chromosome (the male sex determined chromosome) [1].

The incidence of the carriers due to autosomal recessive hemoglobin mutation (e.g. sickle cell disease and thalassemia disorder) is about 5% of the global population and >2/1000 in Middle Eastern ethnic groups [2]. This was highlighted by Yesilipek [3], when he addressed that sickle cell disease is probably increasing all over the world. According to Al-Gazali et al. [4], the recent data shows that genetic diseases, such as hemoglobinopathies and Glucose-6-phosphate dehydrogenase (G-6-PD), are common in Arab countries. The consanguinity marriages (first cousin) and large family production are the important factors that enhance hemoglobinopathies in the "Arabian Peninsula". Saudi Arabia, the core country of this review, is a big part of that Peninsula, so, the extent of sickle cell and thalassemia diseases are highly evident [4]. Hence that the consanguinity marriages is about 50% of the total marriages as the Saudi population is mostly dependent upon tribes, making this a main contributory factor for boosting up the number of affected newborns with sickle cell disease [5].

In an effort to reduce the prevalence of the above genetic diseases, certain procedures were carried out. One of these procedures is screening tests to detect the carrier status of the individuals, to offer them early genetic counselling or even early treatment [6]. The screening programme can be applied either as prenatal screening tests, neonatal screening tests or adult screening tests such as in Cyprus in 1973 [7,8]. Moreover, adult screening tests can be applied as pre-marital screening tests. Such programmes introduced in Iran in 1996, in Ashkenazi Jewish and then in Saudi Arabia in 2003 [2,4,9].

This essay will discuss the National Pre-marital Screening programme in Saudi Arabia, its procedure and the possibility of its success. Advantages and disadvantages of the programme and the effectiveness of the genetic counseling will be stated. Finally, the recommendations will be applied.

SICKLE CELL DISEASE OVERVIEW

Sickle cell disease epidemiology

Sickle cell disease (SCD) is an autosomal recessive condition that is prevalent in the countries where the consanguinity marriages are common such as the Mediterranean basin and Saudi Arabia (WHO Report. Widely, SCD also threatens huge numbers of human beings healthiness worldwide. Hence, the World Health Organization announced that SCD is significantly prevalence in Africa, approximately 10%-40% of the whole population. However, 7% of the people worldwide have been recognized as carriers for different hemoglobinopathies. Thein and Thein [10] have reported that SCD in the Europe and USA has been obviously elevated due to the continuous significant migration events from the Middle East and African countries. Leading to about 100,000 and 3000 affected adults and newborns, respectively, in the USA. While in the United Kingdome the

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suffered individuals are about 12,500 adults and 300 newborns. Therefore, from the above data, SCD is globally burden illness and serious medical and scientific efforts have to be addressed carefully, precisely and hurriedly toward SCD prevention and tackling.

Molecular pathology of sickle cell

Globin chain synthesis occurs on RBC-specific ribosomes, which are generated from particular structural genes, known as the beta (β), delta (δ), epsilon (ε) and gamma (γ) which are located on the short arm of chromosome 11 at 11p15.5 and alpha (α) and zeta (ζ) which are located on the short arm of chromosome 16 at 16p3.3. These genes can produce α, β, δ, γ, ε and ζ globin chains. During human development different hemoglobin are manufactured depending upon his stage of life **(Table 1)**.

Table 1. Different hemoglobins with the globin chains throughout human development.

Hemoglobin	Globin chain	Stage of life
Gower 1	$\zeta_2 \varepsilon_2$	Embryo
Gower 2	$\alpha_2\varepsilon_2$	
Portland	$\zeta_2\gamma_2$	
F	$\alpha_2 \gamma_2$	Fetus
A	$\alpha_2 \beta_2$	Adult
A_2	$\alpha_2 \delta_2$	

Sickle cell disease (MIM 603903) is one of the hemoglobinopathy disorders. This disease was first defined in 1910. This illness is inherited in an autosomal recessive mode, where the patient is homozygous for the mutant genes and both parents are carriers of the mutation. This disease is prevalent in many parts of the world [11].

The missense point mutation of the β-globin gene considered to be the major causative for SCD. Caused by the transversion substitution of the nucleotide A of the 6th codon to the T, leading to a substitution of glutamic acid by valine [1]. This mutation leads to the production of undesired hemoglobin known as hemoglobin S (HbS) [12]. Hemoglobin S shows less stability at the condition of lower O_2 concentration e.g. <85%, at this level the blood pH will be diminished as well as body dehydration. This causes the RBCs to change their normal round biconcave shape to sickle shape or crescent shape. These cells wouldn't be able to move through thinner blood vessels, due to their abnormal and inflexible shape, leading to blood flow blockage and reducing O_2 that reaches the tissues all over the body, leading to severe crises of **Table 2**. Moreover, chronic hemolytic anemia would be induced due to the RBCs becoming highly fragile, then short-lived [13].

Recently, a study conducted by Steinberg and Sebastiani [14], where several candidate genes (38 single nucleotide polymorphism; SNPs) that have shown a previous association to the stroke with SCD patients, have been genotyped in 2 subsets of children with well-defined stroke phenotypes (130 stroke and 103 non-stroke). Distinctly, 3 polymorphisms (ANXA2, TGFBR3 and TEK) were identified to have linked to increased stroke risk **(Table 2)**.

Table 2. The most candidate genes associated with sickle cell disease crisis, with the most significant SNPs and the mode of inheriting.

Gene	SNP ID	Minor allele	HUSTLE (n=206), %	SWiTCH (n=260), %	Genetic model	*P*	Odds ratio	95% CI
ADCY9	rs 2238432	A	33.0	22/3	Dominant	0.003	0.47	0.28-0.79
ANXA2	rs 11853426	T	34.9	44.6	Recessive	0.007	2.70	1.25-5.84
TEK	rs 489347	G	35.9	46.9	Recessive	0.016	2.16	1.11-4.23
TGFBR3	rs 284875	T	7.8	13.5	Dominant	0.005	2.53	1.28-4.99
HbA2	rs 63751476	Δ3.7	17.0	8.8	Dominant	0.009	0.45	0.24-0.84

Interestingly, the ontology analysis of those defined polymorphisms were linked to some critical biological functions such as neuronal signaling mediators, hematopoietic stem cells proliferation, effecting the

hypercoagulable status of SCD and cerebrovascular disease associations.

Clinical manifestation

The serious problems of SCD are compiled mainly in the medical complications that arise from this illness. Serious microbial infections can lead to frequent mortalities of the child, repeated vaso-occlusive crisis, splenic sequestration, pulmonary hypertension. Cerebral infarction is prevalent in about 30% of SCD patients. Acute chest syndrome, the main causative factor leading to death in adulthood affected with SCD. Renal failure, sickle retinopathy are also related to this disease. In some cases psychosocial dysfunction and chronic disability can be seen with the patient suffered with SCD. Significantly shortened life span of about 25-30 years lower than normal individuals and about 3% mortality rate in children making the situation seriously horrific [15,16].

SICKLE CELL DISEASE IN SAUDI ARABIA

Historically, the first description for SCD in the kingdom of Saudi Arabia was in in the Eastern state in early 1960s [17].

Much effort has been carried out to estimate the prevalence of sickle cell disease in Saudi Arabia [18]. At the same time a researcher reported the prevalence of SCD in the South-Western area of Saudi Arabia [19]. Latterly, in 1994 SDC was reported in about 0.029 of Makkah region population [20]. Whereas, a study has shown that the frequency of SCD in Madinah region in the north-western area was higher than the other in Saudi Arabia [21]. Therefore, a national screening programme to determine the incidence of HbS and identify affected individuals would be extremely beneficial.

Screening programme would be the right choice

The pre-marital screening programme was started by the Ministry of Health (MOH) in Saudi Arabia in 21st February 2004 by royal decree. Based on recent research, it was recommended that a national screening programme be established as a means of tackling the high prevalence of inherited hematological diseases [22].

A network of 123 counseling centers send screening samples to 40 laboratories throughout Saudi Arabia. The negative results are given directly to the couple. Positive results are communicated via the genetic counselor so that advice on the possibility of marriage can be provided.

Whereas, in 2016 A network of around 1800 primary health care centers, 200 hospitals and a subset of related national and private health bodies were engaged in the screening. The well oriented laboratory staff at these centers records all important demographic information for each, then blood samples in the EDTA coated tubes is collected. At the laboratory, several hematological investigations will be carried out on the sample including; complete blood count (hemoglobin, red cell count, hematocrit, mean corpuscular volume, red cell distribution width), peripheral blood film for red blood cell morphology, reticulocyte count and sickling test does not seem necessary. Main hemoglobinopathy diagnosis was depended on hemoglobin electrophoresis, and results were interpreted in accordance with standard laboratory diagnostic protocols [11].

A marital certificate would not be submitted to a couple whose results categorize them to be at high risk (positive for sickle cell trait or disease) until they had received the proper genetic counseling from the candidate clinic. However, couples had the right to complete their marital project regardless of the results. Follow ups of all the high-risk couples were provided with genetic counseling physicians working in the different clinics have been conducted with several difficulties.

National pre-marital screening program outcomes

Although, large numbers of relevant research has yet to be conducted in this field in Saudi Arabia, there is a recent study that deal with this issue a precise scientific procedure was published in 2011 [23]. In this study, the total number of 242000 and 296000 men and women were investigated for sickle cell genotyping in 2004 and 2009, respectively. The prevalence of sickle cell disease has been stated as 4.5% in which still the highest among the other genetic disorders especially hematologically related disorders was stated by authors.

Moreover, ~60% of at-high-risk couples were able to be followed up and ~26% of them have cancelled their marital project. Likely, the frequency of cancellation was higher by the continuity of the programme as it was ~9.2% in 2004 and 51.9% in 2009. In regards to the rates of SCD prevalence within Saudi Arabian different provinces, the Eastern province has recorded ~58% of at-risk couples compared to the others, making it the highest. Also the study reported that the SCD carrier incidence was about 93%. Unfortunately, about >50% of at-risk couples decided to stop their marital project in 2009 compared to ~26% in 2004. The estimation was reported in a previous research where ~52% of at-risk couples decided to terminate their marital project [24]. These results show relatively desired outcomes.

Factors affecting the above success

The above results have shown relatively desired numbers although the number of SC disease and carriers in some provinces in Saudi Arabia. The Eastern and Southern provinces for instance, remains the highest incidence of the disease. This might be referred to the malarial parasitic disease is persistently endemic. Hence, Carriers for hemoglobinopathies are believed to be more resistant to malaria parasite infection and their increased biological strength results in an expansion in the number of carriers within the population.

On the other hands, the consanguinity marriages was and still is the initiative core of an autosomal recessive diseases

and hemoglobinopathies are not excluded [25]. In Saudi Arabia consanguineous marriage is proudly one of the traditional behaviors in most of the tribes. This is refers to the characterized geographical location of Saudi Arabia the biggest country on the Arab peninsula at the connection point of three largest and oldest continents in the world, and those tribes try to keep their own ancestry genes. According to the previous estimation of consanguineous marriage in Saudi Arabia were about 69% in the South as the highest, and 41.5% in the Western area as the lowest [26]. However, these noticeable rates are likely to be kept at arisen points in Saudi Arabia [27]. Unsurprisingly, the consanguineous marriage considered at the significant rates within Arab countries from 20-60% **(Figure 1)** [4].

Figure 1. Shows the prevalence of consanguineous marriages in the world.

The traditional issues could be an important part of hemoglobinopathy increment. The Saudis are similar to most Arabs who are well known for maintaining their traditional practices with respect to marriage and are not easily convinced to change their traditions. This is when a subsets of about 2,375 high-risk couples (Sickle cell and thalassemia), that already have received genetic counseling session; about 89.6% among them have continued with their marriage plans, ignoring their high risk status [28]. Moreover, rejection on the grounds of test incompatibility, creates a very severe conflict between the families specifically in the case of consanguineous marriages, increases the situations complexity. More efforts need to be addressed in regards to decrease the incidence of the disease and population knowledge towards hemoglobinopathies. Although, the screening programme seems to be successful according to the above results as both carriers and cases have significantly decreased in some parts of the country compared to the others, the incidence remains higher. Therefore, genetic counseling programs have to be developed and increased especially by the expert genetics counselors. The careless couples at high risk could be talked through strong law procedures, which guarantee the excision of at high-risk marriage projects to be completed [29].

Up to this end, some recommendations are required to be stated. Firstly, educational program must be introduced, expanded, simplified and evaluated to suit the Saudi population. Secondly, the government has to create effective coordination and cooperation between the involved Ministries, i.e., Health, Justice and Interior to allow more effective follow up of incompatible couples to understand the effect and consequences of screening. Thirdly, the national screening program for inherited disorders has to be established and started as early as from secondary school age to avoid later personal stigmatism and family breakdown. Finally, the number of screening centers should be increased and developed technologically with improved genetic councilors especially in high population and diseases prevalent areas [30].

CONCLUSION

The pre-marital screening program in Saudi Arabia appears to be achieving its objective. There was a significant reduction in incompatible marriage certificates. The carrier incidence was the highest in Eastern area, followed by the Southern area and the incidence has been calculated in each region. Further recommendations were presented. The optimum time for screening setup would be at secondary school. The continuation of this program is highly recommended, as it will apparently decrease the incidence of the screened diseases.

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