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Association between genetic inbreeding and disease mortality and morbidity in Saudi population

Abstract

The demographic and quantitative genetic aspects of consanguineous marriages are reviewed before epidemiologic principles are applied. Consanguineous unions range from cousin-cousin to more distant relatedness, and their prevalence varies by culture. The prevalence is highest in Arab countries. They are most common in groups that are poorly educated, have low socioeconomic status and are conservative, but they are declining with modernization. The prevalence rate of consanguineous marriages in the kingdom of Saudi Arabiais51.3% with an average inbreeding coefficient of 0.02265, which is high compared with many other countries. The most important variables affecting inbreeding are the regional background of the family ($p<0.001$) and the level of education, which is inversely associated with consanguineous marriage ($p<0.001$). The difference in perinatal and postnatal mortalities between consanguineous and non-consanguineous families is not significant. Consanguinity is measured by geneticists using the inbreeding coefficient, the mean consanguinity of a population, and the concept of genetic load. Recessive genes may be deleterious or beneficial if heterozygous in local conditions. Bayesian statistics can predict, by the coefficient of increase, the probability of diseases in an offspring as a function of consanguinity and disease characteristics. Inbreeding generally increases pre-reproductive mortality. Crude mortality increases with inbreeding in proportion to the mortality rate. Morbidity increases significantly with inbreeding in many diseases studies in many countries. Epidemiologic studies usually measure the effects of inbreeding in terms of genetic load, which is not readily translatable into morbidity and mortality. Family study and other methodological study design problems will be used to implement this study. Confounding is the most difficult problem in such studies, because of the difficulty in selecting non-inbred controls. This study will help to understand and develop a better consultation and education for patient and his/her family and their community.

Keywords: consanguinity, inbreeding, morbidity, mortality, SCD, thalassemia, g6pd

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Introduction

Consanguineous marriages have a high prevalence among Muslim-majority countries, and the ratio is increasing in Saudi population.[1] Nowadays, more than half of all the marriages in Saudi Arabia are marriages between cousins.[2] Different types of consanguineous marriages exist, such as marriage between first cousins, which is the most common one, marriage between second cousins, and marriage between third cousins.[2] A number of factors play very critical roles in the consequences of genetic disorders beside relative's marriages, including social, cultural, economic and demographic factors.[3] Also, the age difference between mates is expressed as a factor that increases the chances of getting a genetic disorder due to consanguinity.[4] Consanguinity influences the susceptibility to infectious diseases.[5] This phenomenon is more common in people with low educational level and people who live in urban areas.[1–6] In contrast, it decreases among educated populations.[1] The degree of consanguinity between two individuals is measured by the inbreeding coefficient.[1] It measures the probability that two genes are identical by lineage from the ancestor(s) of the two parents, this proves that two alleles are homozygous (AA or aa), not heterozygous, in an individual.[4] Many studies show that the prevalence of consanguineous marriages among Muslim populations is more than in other populations, worldwide; it is approximately 52%, with an average inbreeding coefficient of 0.0312.[6,7] A comparison of the prevalence of consanguineous marriages between Muslims countries shows a difference in percentage from one country to another. For example, the prevalence of consanguineous marriages in the Saudi Arabia is 57.7% of the 3212 families involved in the study.[2] However, in Pakistan, the percentage reached 60%, with an inbreeding coefficient of 0.0316.[8]

In Qatar, a sample of 1515 Qatari females showed a high rate of consanguinity (54%), with an inbreeding coefficient of 0.02706.[9] The value is equally high in the United Arab Emirates for a sample of 2033 married women. Half of the sample were involved in relative marriages, with a coefficient of inbreeding of 0, 0222.[10] All these studies prove that first cousin marriages are higher than other types of consanguineous marriages.[9–11] Due to the geography of Saudi Arabia, the rate of consanguinity differ from one city to another; the highest rate is 80.6% in Samatah, and the lowest is 34% in Abha in the south west of Saudi Arabia.[2] In Riyadh (the capital city of Saudi Arabia), the rate is 50%.[11] It is important to address this issue in Saudi population, especially in Al-Kharjcity (80 km from the capital city). Consanguineous marriages have a wide range of effects on health. It has been reported that genetic factors due to consanguinity play a significant role in the appearance of inherited diseases.[12] Recently, a link between consanguinity and susceptibility to infectious diseases in humans was reported. Also, it was found that the ratio of TB and hepatitis are high among individuals where consanguineous marriages are common.[12] Further, it has been reported that consanguinity is related to a number of diseases, such as heart disease, multiple sclerosis, depression, asthma, and PID.[12–14] Mortality and morbidity rates are generally increased due to consanguineous unions.[5]

Materials and methods

Population characteristics

The study population comprises patients and families with a history of genetic disease, which was clinically identified or referred to genetic services by the following departments: Women Health, Pediatric, and Internal medicine. Patients' medical information were obtained, including information regarding some significant factors that might increase the frequencies of genetic disease caused by consanguineous marriages, the effect of the level of relationship and severity of disease, and any other factor that might enhance genetic case management and counseling (Table 1). The medical files and/or departmental database of patients were accessed to extract this medical information required for the genetic epidemiology statistical analyses (Table 1). Ethical approval for all studies was awarded by the King Fahad Medical City Research Ethics Committee.

Table 1 The study population comprises patients and families with a history of genetic disease

Factor	Women Health	Pediatric	Internal Medicine
Cases with genetic disorders	Number of cases	Number of cases	Number of cases
Consanguineous marriages	Percentage of consanguinity among the total number of families(drop-in cases or referral cases)	Percentage of consanguinity among the total number of families(drop-in cases or referral cases)	Percentage of consanguinity among the total number of families(drop-in cases or referral cases)
Level of relationship,			
First degree	Percentage of first degree marriages	Percentage of first degree marriages	Percentage of first degree marriages
Second degree	Percentage of second degree marriages	Percentage of second degree marriages	Percentage of second degree marriages
Third degree	Percentage of third degree marriages	Percentage of third degree marriages	Percentage of third degree marriages
Double first cousins	Percentage of double first cousins degree marriages	Percentage of double first cousins degree marriages	Percentage of double first cousins degree marriages
Maternal age (≥35y)	Percentage of mothers with age over 35 years among all mothers in each families	Percentage of mothers with age over 35years among all mothers in each families	Percentage of mothers with age over 35years among all mothers in each families
Affected siblings	Number of affected siblings in each families	Number of affected siblings in each families	Number of affected siblings in each families
Premarital screening	Percentage of families who have been through premarital screening among the total number of families(drop-in cases or referral cases)	Percentage of families who have been through premarital screening among the total number of families(drop-in cases or referral cases)	Percentage of families who have been through premarital screening among the total number of families(drop-in cases or referral cases)
Miscarriages/abortions	Percentage of overall cases	Percentage of overall cases	Percentage of overall cases
Disease severity,			
Mild(1)	Percentage of cases	Percentage of cases	Percentage of cases
Moderate(2)	Percentage of cases	Percentage of cases	Percentage of cases
Severe(3)	Percentage of cases	Percentage of cases	Percentage of cases
Leather(4)	Percentage of cases	Percentage of cases	Percentage of cases
Parents educational level Primarily	Number of individuals	Number of individuals	Number of individuals
Intermediate	Number of individuals	Number of individuals	Number of individuals
High school	Number of individuals	Number of individuals	Number of individuals
College level	Number of individuals	Number of individuals	Number of individuals

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Survey design

Questions were drawn from factors with significant effects on heredity of genetic disease reported from previous studies and genetic knowledge. During the data collection process, the interests of all parties were considered and balanced throughout the process, in consultation with bioethics advisors. Through pilot testing with cognitive interview techniques, the wording of certain questions was refined, and other questions were added or deleted to improve the length and overall flow of the questionnaire. The variables measured four broad domains: personal data (for example, ages of both parents, type of marriage, and premarital examination); personal health (for example, family medical history and medical genetic status); level of education; and social status (for example, personal income).

Field visit

This cross-sectional study was conducted in Al-Kharj city (80km from Riyadh). The aim of this study is to determine the association between consanguinity and disease mortality and morbidity among families who live in Al-Kharj and the surrounded cities, this include King Fahad Medical City in Riyadh and King Khalid Hospital in AL-Kharj.

Bioinformatics

Bioinformatics is the application of computer technology to the management of biological information. Computers are used to gather, store, analyze and integrate biological and genetic information, which can then be applied to gene-based drug discovery and development. The need for bioinformatics capabilities is clearly shown by the explosion of publicly available genomic information, resulting from the Human Genome Project.

Statistical analysis

Descriptive statistics was used, which is the discipline of quantitatively describing the main features of a collection of information,[1] or the quantitative description itself. It is distinguished from inferential statistics (or inductive statistics), in that descriptive statistics aim to summarize a sample, rather than use the data to learn about the population that the sample of data is thought to represent. This generally means that descriptive statistics, unlike inferential statistics, are not developed on the basis of probability theory.[2,3] Even when a data analysis draws its main conclusions using inferential statistics, descriptive statistics are generally also presented. They also provide simple summaries about the sample and about the observations that have been made. Such summaries may be either quantitative, summary statistics, or visual.[7]

Results

Literature review

Previous studies have reported that there is a high percentage of consanguineous marriages in gulf countries (Table 2). Most of these studies investigated the prevalence of consanguinity among individuals who live in these countries directly, and other studies examined the effect of consanguinity on particular diseases.[15–20]

Table 2 Literature review of previous studies reported that there is a high percentage of consanguineous marriages in gulf countries

	KSA[2]	UAE[9]	Qatar[7]	Kuwait[14]	Oman[15]	Pakistan[8]
Consanguinity	57.70%	50.50%	54%	75%	35.90%	60%
Inbreeding Coefficient	0,020-0.030	0,0222	0,02706	0.044067	0.0198	0.0316
Sample	3,212	2,033	1,515	128	60,635	1.011
	Families	Families	Families	Patients	Families	Families
Aim of study,	Investigate the prevalence of consanguineous marriages.	Examine the frequency of consanguineous marriages in United Arab Emirates.	Examine the frequency of consanguineous marriages in the state of Qatar.	The relationship between consanguinity and the risk of PID.	Determine the prevalence of relatives marriage in Oman	Examine the frequency of consanguineous marriages among different districts in Pakistan.

Population characteristics and survey design

Due to the limitation of time and fund for this project, collecting patient's data from local hospitals could not be achieved at the present time. Survey questions were designed to reflect population characteristics (Table 1) and significant factors influencing prevalence and disease prognosis.[21,22]

Bioinformatics

There are a lot of publications about consanguinity. The authors compete to cover all aspects of this subject. A search for previous studies from PubMed was carried out, using several keywords (consanguinity, prevalence, association, Gulf countries, morbidity, and mortality), which yielded 20 articles focused on the prevalence of consanguineous marriages in the Middle East region, especially in gulf countries, because they, in general, share the same customs of marriages with the kingdom of Saudi Arabia and experience the same effects of consanguineous unions on the offspring (Table 3). In this population study that is focused on patients and families with diagnosed genetic diseases, data were collected from the relevant medical records in coordination with the doctors, who are working in different hospitals located in the city of Al-Kharj. According to the surveys performed by previous studies, the most significant factors that influence our hypothesis were identified, and the list contains factors such as level of relationship, gender, level of education, age and economical class. Inbreeding is a social custom handed down through the eastern communities under different justifications, but the development of medicine in the modern era has shown the consequences of this type of marriage, because of its transmission of serious diseases that pose a threat to the lives of newborns.

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Table 3 Prevalence of genetic diseases in gulf and eastern population

Country	No. of Studies	Sample	Hypothesis	Types of Disease	Prevalence of Diseases	Prevalence of Trait	Conclusion
Saudi Arabia	9	Study 1:unknown Study 2: 3212[2] Study 3:1307[3] Study 4:unknown Study 5:38,153[16] Study 6:8918[17] Study 7:488.315[18] Study 8:2100[19] Study 9:1584[20]	Examine the rate of consanguinity and the effect of inbreeding on mortality rate taking into consideration graphic differences of the country.	1- thalassemia (trait and disease) 2-sickle cell anemia (trait and disease) 3-G6PD	Thalassemia: Study 7: 0.07 % SCD: Study 7: 0.26 % G6PD: Study 9: 4.76 % (100/2100) Study 10: 6.9 %	Thalassemia: Study 5: 0.165 % (63/38,153) Study 6: 3.4 % (307/8918) Study 7: 3.27 % SCD: Study 5:0.252 % (96/38,153) Study 7: 4.20 %	Saudi Arabia is among the countries of the world with high rate of consanguinity, especially among first cousins.
United Arab Emirates	3	1: 2033.[9]Females 2: 6.329[24]person 3:22,200.[25]Person	Examine the rate of consanguinity and inbreeding coefficient in United Arab Emirates city population	1- thalassemia (trait and disease) 2-sickle cell anemia (trait and disease) 3-G6PD	Thalassemia: Study 2: 0.9 % SCD: Study 2: 1.6 %	SCD: Study 3: 1.5 %	In one generation, the consanguinity rate changed from 39% to 50.5 %. The rate of consanguinity in Al ain (54.2 %) is more than in Dubai (40 %)
Qatar	1	1515.[7] females	Examine the rate of consanguinity and inbreeding coefficient in Doha city and study the level of relationship between the female and her spouse.				Change in the level of consanguinity from 41.8 % to 54.5% in one generation only.
Kuwait	2	1: 128[14]patients 2: 561[26]Persons	Determine if there is a relationship between consanguinity and PID including performance status and risk of death.	1- thalassemia (trait and disease) 2-sickle cell anemia (trait and disease)	SCD: Study2: 0.9%	Thalassemia: Study 2: 14 % SCD: Study 2:6 %	There is correlation between consanguinity and development of PID.
Oman	2	1:60.635[15]couples 2:6342[21]person	Study the prevalence of consanguineous marriages among the population of Oman.	1- thalassemia (trait and disease) 2-sickle cell anemia (trait and disease) 3-G6PD		Thalassemia: Study2: 2.2 % SCD: Study 2: 5.8% G6PD: Study 2: 38% Thalassemia: Study 3: 13 %	20.4 % of all marriages are contracted among specific tribal grouping which is common behavior in Oman.
Pakistan	3	1:1,011[8] females 2:15,699[22] 3:202,600[23]	Examine the rate of consanguinity and inbreeding coefficient.	1- thalassemia (trait and disease) 2-sickle cell anemia (trait and disease)	Thalassemia: Study 3: 20.6% 2-SCD: Study 2: 1.92 % Study 3: 5.1 %		Consanguineous marriages are common among women who had a primary level of education.

These diseases have become a medical phenomenon and have drawn the attention of researchers in specialized universities and medical centers in many countries. The studies that were conducted dealt with the subject from different angles, and the sizes of these studies reflect the importance of this phenomenon. It can be inferred from these studies that there are high levels of inbreeding in Pakistan and the Gulf states, as shown in Table 1. Most of these studies focused on inbreeding among individuals who live in the abovementioned countries, and they show that inbreeding spreads the impact of diseases such as thalassemia (trait and disease), sickle cell anemia (trait and disease) and G6PD. Many studies, which focused on patients and families of populations that have been diagnosed with

genetic diseases, also highlighted the consequences of inbreeding in the Middle East, especially the Gulf countries. The findings and conclusions are evident, as shown in Table 3. Finally, it was found that the size of the studies conducted in the Gulf countries and Pakistan on this phenomenon, described in Table 4, is a powerful and descriptive indication of the importance and seriousness of inbreeding and the consequent spread of genetic diseases (Figure 1) (Figure 2).

Table 4 Descriptive data including research hypothesis of the population of the study

	Number of studies	Number of studies	Number of studies	Number of studies	Number of studies	Number of studies	Number of studies
	Factor 1	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**	**Factor 6**	**Factor 7**
Hypothesis	Arab	Saudi	United Arab Emirates	Qatar	Kuwait	Oman	Pakistan
Consanguinity	479	431	45	23	27	30	35
Inbreeding	401	339	32	15	20	15	19
Morbidity	177	123	11	10	15	12	18
Mortality	42	29	8	9	7	2	4
SCD + Morbidity	4	3	2	1	7	3	6
SCD + Mortality	0	1	0	0	1	0	0
Thalassemia + Morbidity	11	3	3	2	12	4	10
Thalassemia + Mortality	0	0	1	0	6	1	0
G6PD + Morbidity	5	1	3	0	3	3	6
G6PD + Mortality	0	0	0	0	0	0	0

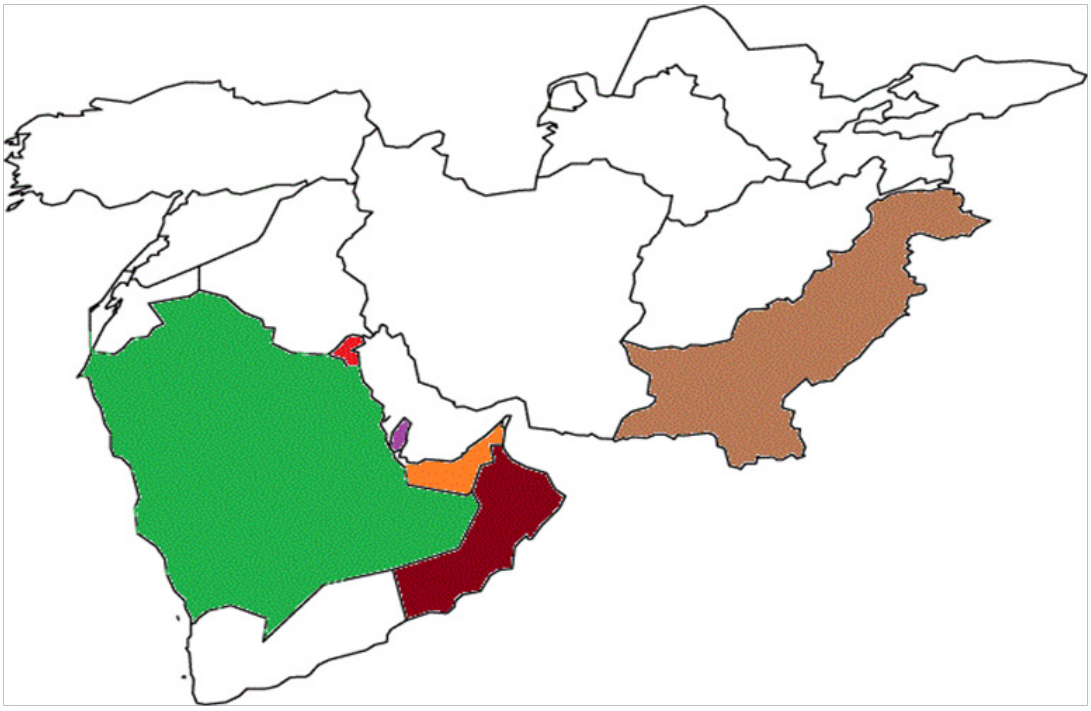

Figure 1 Geographical location colored according to inbreed cutoffs.

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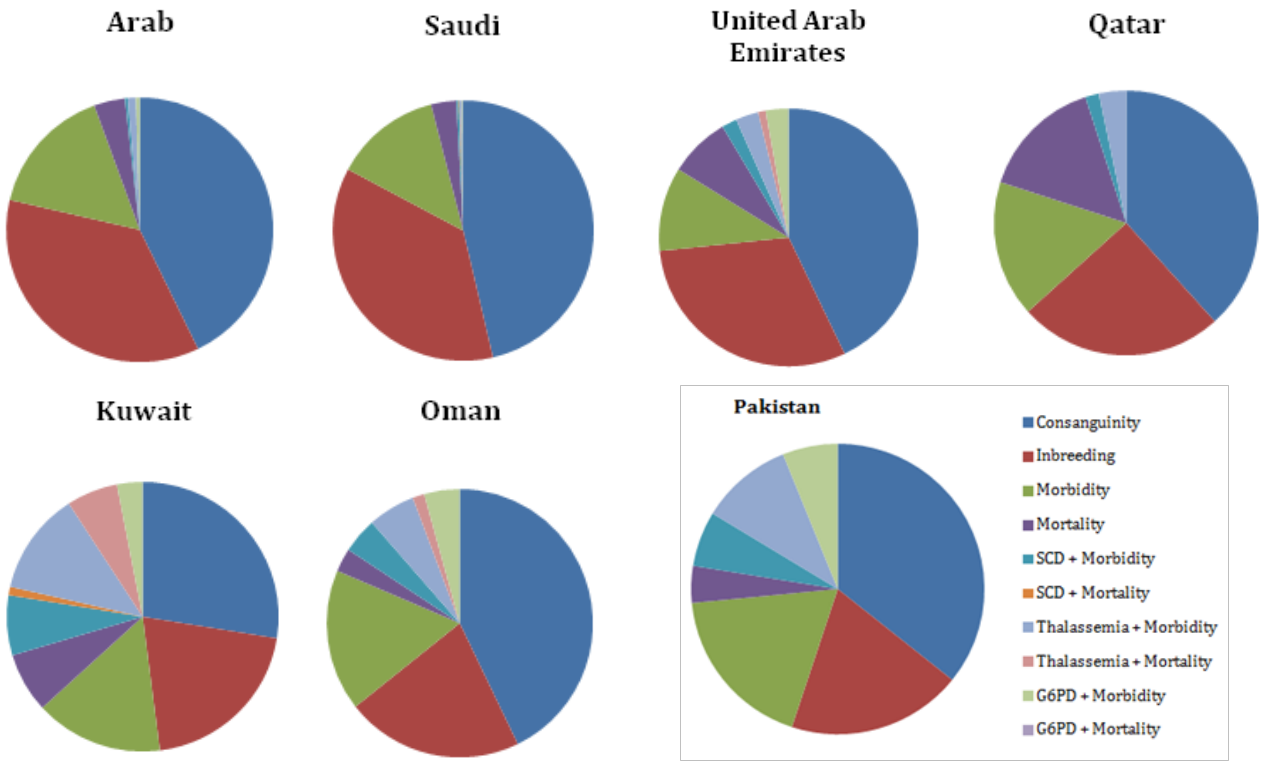

Figure 2 A comparison of the prevalence of consanguineous marriages between Muslims countries shows a difference in percentage from one country to another.

Discussion

Previous studies reported that there is a high percentage of consanguineous marriages in the gulf countries, and the percentage in some of these countries is more than a half of all marriages, such as in Saudi Arabia, Qatar and Kuwait. Generally, the average inbreeding coefficient in the gulf countries is high compared with many other countries, and, specifically, consanguineous unions are more common among first cousins. The most important factors affecting inbreeding are individuals with low-level education and socioeconomic status, and they practice consanguineous marriages more. Low level of education influences one's general understanding and knowledge; therefore, people with low level of education are not well informed about how consanguinity can affect their health, causing genetic mutations that last for many generations if they do not change their marriage practice. However, this does not mean that people with high level of education are free from consanguineous marriages; they also practice it but less than those with low level of education. In spite of the geographical distance between these countries, there is a high prevalence rate of consanguinity with high inbreeding coefficient. This could be due to a common factor, which is shared among the tribes, and it is clear that the common habit of most of these tribes is that marriages are restricted to potential partners from the same tribe only. This means that there is a very high risk of having a specific genetic mutation among many individuals of the same tribe. Genetic diseases with recessive genes are influenced by consanguineous union's more than dominant diseases. The effect of consanguinity is not limited only to genetic diseases, but it is extending to influence the susceptibility of infectious diseases (Table 1).[23–30]

This study aims to identify the frequencies of genetic diseases caused by consanguineous marriages and investigate the role of relationship level between couples and its impact on the severity of diseases. It also determined the effect of consanguinity on mortality and morbidity and found that there are factors that could be useful to manage genetic cases and genetic counseling. Further, this study found effective solutions to control the prevalence of this phenomenon, in order to prevent increase in the ratio of consanguinity. The results will serve as evidence to convince people who do not take this topic seriously and enlighten those who do not have sufficient knowledge about the influence of consanguinity on their health. This study will help to enhance understanding, develop a better consultation strategy and highlight the importance of education, so as to increase the effort of enlightening the population and answering related questions concerning consanguinity. The survey was designed based on significant heredity factors of genetic diseases obtained from literature review and was divided into four categories: personal data, personal health, level of education and social status. Patients and families with previous history of been diagnosed with genetic disease are targeted in this study. The survey covers different aspects, such as the type of inherited disease and if other siblings havethe same type of disease, age of both parents especially the age of the mother, type of marriage (consanguineous or non-consanguineous), relationship degree of parents (first cousins, second cousins, third cousins), and personal income. This information was obtained by accessing patients' files or departmental database.

Several challenges were encountered in the course of this study. King Khalid Hospital in Al-Kharj city was contacted but they couldn't help because they did not have a genetic unit, and all cases were transported to central hospitals in Riyadh city without assigning serial numbers, so they couldn't be followed. After a number of visits to the center of research at King Fahad Medical City in Riyadh, they expressed their willingness to participate in this study. Since, the approval for

the research arrived quite late, the allocated time could not be spent on the survey to accomplish the goals, as planned. However, a plan was proposed that would allow the performance of a comprehensive follow-up study. Multiple visits were then carried out to a number of different hospitals, including King Faisal Specialist Hospital & Research Centre, king Saud Hospital, and king Khalid University Hospital, with the permission of the hospital authorities. Premarital screening and tests for particular diseases, including thalassemia, sickle cell anemia, G6PD, and hepatitis, are mandatory procedures recommended by the health ministry in Saudi Arabia before marriage. These tests have been chosen based on previous studies that measured the most common inherited diseases in the area. Possibly, in the next decades, the list of premarital screening will increase if the effects of genetic factors that cause-inherited diseases are not controlled and if attempts are not made to decrease the prevalence ratio of inherited diseases. Hemoglobinopathies constitutes a big part of premarital screening.

They are important because of their relationship with consanguinity, and the ratio of prevalence in the area is high. It is important to focus on the prevalence ratio of Hemoglobinopathies as a trait not a disease with respect to sickle cell anemia, thalassemia, and G6PD. This is a good idea to control the ratio and decrease the prevalence through development of genetic consultation. Saudi Arabia is among the counties of the world with high rate of consanguinity (57.7%) 2. Qatar and United Arab Emirates experienced a big change in consanguinity rate in one-generation only. This indicates that people who live there are not aware of the effects of consanguinity. Pakistan is not a gulf country, but it shares the same factors with the gulf countries, such as the high prevalence rate of consanguinity (60%) 8 and the fact that consanguineous marriages are more common in women who had a primary level of education. (20.4) 15% of all marriages are contracted among specific tribal grouping, which is common behavior in Oman, also a gulf country. All the above information supports the factors that will build up the hypothesis and the aims of study (Table 3). Consanguineous marriage is clearly a continuous phenomenon. It may be impossible to stop this behavior. However, the prevalence rate of these diseases can be decreased by increasing awareness about the side effects of consanguineous unions on health, especially among regions, cities, and groups of people known to have this custom. Also, genetic consultancy plays a very critical role in the improvement of the general understanding of this important issue.

Limitations and challenges

This study experienced some limitations and challenges. As mentioned before, since a genetic unit was not available at King Khalid hospital in Al-Kharj city or at least a good recording system for the cases was not available, the plan to conduct a cross-sectional study on Al-Kharj population and the surrounding area only was canceled. An additional step was taken and other hospitals with genetic units were visited to accomplish the survey. Another limitation is that some good studies are available as abstract only; payment is required to get access to the whole study. Also, the key words posed a challenge in the preparation of the study and writing the introduction. Finding good studies matching the key words was not easy, because the study is an epidemiological study and the number of related articles is few in the country. Time was another challenge/limitation, since sixteen weeks is insufficient to read, write an introduction, design and accomplish the survey, and conduct statistical analysis of the results. In spite of these few limitations and challenges, the purpose of the study was not greatly affected.

Conclusion

The high rate of consanguineous marriages in Saudi Arabia affects public health, which in turn increases the occurrence of genetic mutation. There is an urgent need to study it and come up with measures to control it in an acceptable manner.

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Conflict of interest

Author declares that there is no conflict of interest.

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