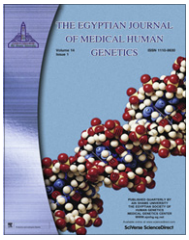
The Egyptian Journal of Medical Human Genetics (2013) **14**, 157–164

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com



ORIGINAL ARTICLE

Consanguinity and its relevance to clinical genetics

Rabah M. Shawky [a,*], Solaf M. Elsayed [a], Mouchira E. Zaki [b], Sahar M. Nour El-Din [c], Ferihan M. Kamal [a]

[a] *Pediatrics Department, Faculty of Medicine, Ain-Shams University, Cairo, Egypt*
[b] *Biological Anthropology Department, Medical Research Division, National Research Center, Cairo, Egypt*
[c] *Medical Genetics Center, Faculty of Medicine, Ain-Shams University, Cairo, Egypt*

Received 16 December 2012; accepted 1 January 2013
Available online 29 January 2013

KEYWORDS

Consanguinity;
Chromosomal abnormality;
Genetic counseling;
Child death;
Homozygosity

Abstract Consanguineous marriages have been practiced since the early existence of modern humans. Until now, consanguinity is widely practiced in several global communities with variable rates. The present study was undertaken to analyze the effect of consanguinity on different types of genetic diseases and child morbidity and mortality. Patients were grouped according to the types of genetic errors into four groups: Group I: Chromosomal and microdeletion syndromes. Group II: Single gene disorders. Group III: Multifactorial disorders. Group IV: Diseases of different etiologies. Consanguineous marriage was highly significant in 54.4% of the studied group compared to 35.3% in the control group ($P < 0.05$). Consanguineous marriages were represented in 31.4%, 7.1%, 0.8%, 6%, 9.1% among first cousins, one and a half cousins, double first cousins, second cousins and remote relatives respectively in the studied group. Comparison between genetic diseases with different modes of inheritance showed that recessive and multifactorial disorders had the highest values of consanguinity (78.8%, 69.8%, respectively), while chromosomal disorders had the lowest one (29.1%). Consanguineous marriage was recorded in 51.5% of our cases with autosomal dominant diseases and in 31% of cases with X linked diseases, all cases of mental retardation (100%) and in 92.6% of patients with limb anomalies ($P < 0.001$). Stillbirths, child deaths and recurrent abortions were significantly increased among consanguineous parents (80.6%, 80%, 67%) respectively than among non consanguineous parents. In conclusion, consanguineous marriage is significantly higher in many genetic diseases which suggests that couples may have deleterious lethal genes, inherited from common ancestor and when transmitted to their offsprings, they can lead to prenatal, neonatal, child morbidity or mortality. So public health education and genetic counseling are highly recommended in our community.

* Corresponding author. Tel.: +20 222585577.
E-mail address: shawkyrabah@yahoo.com (R.M. Shawky).

Peer review under responsibility of Ain Shams University.

ELSEVIER Production and hosting by Elsevier

1. Introduction

The terms inbreeding and consanguinity are used interchangeably to describe unions between couples who share at least one common ancestor. Inbreeding in population genetic terms refers to a departure from nonrandom "mating" in which

1110-8630
http://dx.doi.org/10.1016/j.ejmhg.2013.01.002

individuals "mate" with those more similar (genetically) to them than if they "mated at random" in the population. The offspring of consanguineous unions may be at increased risk to genetic disorders because of the expression of autosomal recessive gene mutations inherited from a common ancestor. The closer the biological relationship between parents, the greater is the probability that their offspring will inherit identical copies of one or more detrimental recessive genes. For example, first cousins are predicted to share 12.5% (1/8) of their genes. Thus, on an average, their progeny will be homozygous (or more precisely, autozygous) at 6.25% (1/16) of gene loci (i.e., they will receive identical gene copies from each parent at these sites in their genome) [1].

Consanguinity is prevalent in many Middle Eastern and Arab cultures and societies [2]. Some studies have shown significant differences in genetic disorders between children born to consanguineous marriage partners and those born to non-consanguineous parents [3], while others have found no significant differences [4]. Marriage between close biological relatives is generally regarded with suspicion and distaste. In many populations there is a strong preference for consanguineous unions, most frequently contracted between first cousins, and marriage outside the family is perceived as a risky and disruptive option. The increasing importance of the genetic contribution to the overall disease profile in both developed and developing countries has highlighted potential problems associated with detrimental recessive gene expression in consanguineous progeny [5].

In fact, single gene disorders are common in Eastern Mediterranean families due to the practice of consanguinity that tends to retain rare mutations within affected families, who may contain a high frequency of mutation carriers. Genetic disorders and congenital abnormalities occur in about 2% - 5% of all live births, account for up to 30% of pediatric hospital admissions and cause about 50% of childhood deaths in industrialized countries [6]. Consanguinity without known genetic disease in the family appears to cause an increase in mortality and malformation rate. First cousin marriages, the most common counseling problem, seem to have an added risk of about 3 percent, so that a total risk of 5 percent for abnormality or death in early childhood, about double the general population risk, is a reasonable though approximate guide [7]. It is possible, but not certain that the risk is less for populations with a long tradition of cousin marriage. It is only recently that genetic disorders are being fully recognized and accurately diagnosed in these populations. By contrast, some immigrant groups of Asian origin in the UK show an unusually high frequency of recessively inherited disorders, some extremely rare. This may well reflect increased consanguinity due to isolation and restriction of marriage partners [8]. Some studies have shown a relationship between consanguinity and some genetic conditions and health problems such as phenylketonuria (PKU), immunodeficiency disorders, children's hypertension, beta-thalassemia, protein-C and protein-S deficiency, low birth weight and Down syndrome [9–11].

The aim of this study was to determine the effect of consanguineous marriage on different types of genetic diseases and child morbidity and mortality.

2. Subjects and methods

This study was a retrospective study, reviewing the files of 8109 patients attending the Genetics clinic, Children's hospital, Ain Shams University, Cairo, Egypt .Their ages ranged between 3 days and 32 years (with a mean of 5.67 ± 11.84 years) .They presented as diseased children, or adults for genetic counseling due to repeated abortions, stillbirths, or diseased offspring. Results were compared with consanguinity among 10,000 healthy couples as controls [12].

Patients were classified according to the types of genetic disorders into four groups:

Group I Chromosomal and microdeletion syndromes e.g. Down syndrome, Cri du Chat, Klienfilter syndrome, Turner syndrome and Prader willi syndrome, etc...

Group II Single gene disorders:

- Autosomal recessive e.g. phenylketonuria and mucopolysaccaridosis.
- Autosomal dominant e.g. Marfan's syndrome and achondroplasia.
- X- linked e.g. Duchenne muscular dystrophy and fragile X syndrome.

Group III Multifactorial disorder e.g. Epilepsy and primary amenorrhea.

Group IV Diseases of different etiologies (Multiple congenital anomalies and blood diseases).

The following data were obtained from our patients:

1. Occurrence of stillbirths, abortions and their frequency.
2. Degree of consanguinity (first cousins, one and half cousins, double first cousins, second cousins and remote relatives).

Statistical methods

- Data entry and analysis were done using a computer with SPSS version 10.0.
- Appropriate statistical methods were applied (descriptive and analytical).
- The individual inbreeding coefficients *(F)* were computed according to Wright's path method [13].

$$F = \sum_{i=1}^{c} \left(\frac{1}{2}\right)^{m_i+n_i+1}$$

where m_i and n_i refer to the number of paths from the ith common ancestor, and c refers to the number of common ancestors. The genealogical inbreeding coefficient for each disease was then computed as the average of all individual F values.

3. Results

Consanguineous marriage was significantly higher in the studied group (54.4%) compared to the control group (35.3%). Consanguineous marriages represented 31.4%, 7.1%, 0.8%, 6%, 9.1% among first cousins, one and a half cousins, double first cousins, second cousins and remote relatives respectively in the studied group compared to 30.4%, 2.2%, 0.8%, 1.9%, 0.0% respectively in the control group, Table 1.

Recessive and multifactorial disorders had the highest values of consanguinity (78.8%, 69.8% respectively), while chromosomal disorders had the lowest one (29.1%), Tables 2 and 3.

Consanguineous marriage was highly significant in autosomal recessive diseases (78.8%). It was detected in 93.4% of cases of sensorineural deafness, 89.4% of cases of Phenylketonuria, 78.1% of epidermolysis bullosa dystrophica patients,

Table 1 Comparison between different degrees of consanguinity in the studied groups.

	1st cousin	One & half cousin	Double 1st cousin	2nd cousin	Remote relative	Total cons.
No. of patients (%)	2544 (31.4%)	575 (7.1%)	63 (0.8%)	486 (6%)	739 (9.1%)	4408 54.4%
No.of Controls (%)	3037 (30.4%)	222 (2.2%)	80 (0.8%)	191 (1.9%)	–	3530 35.3%
P-value	> 0.05	< 0.05*	> 0.05	< 0.05*	< 0.001***	< 0.05*

* *P*-value < 0.05, 0.01 (Significant).
*** *P*-value < 0.001 (Highly significant).

Table 2 Comparison of consanguinity in relation to different modes of inheritance in the studied groups.

	Consanguineous	Non consanguineous	*P*-value
Chromosomal (2563)	744 (29.1%)	1819 (70.9%)	> 0.05
Autosomal recessive (600)	471 (78.8%)	129 (21.2%)	< 0.01*
Autosomal dominant (188)	97 (51.5%)	91 (48.5%)	> 0.05
X-linked (300)	93 (31%)	207 (69%)	> 0.05
Multifactorial (2648)	1849 (69.8%)	799 (30.2%)	< 0.05 *
Others (952)	553 (58%)	399 (42%)	< 0.05 *
Control (10000)	3530 (35.3%)	6470 (64.7%)	< 0.05 *

* *P*-value < 0.05, 0.01 (Significant).

Table 3 Relation between different degrees of consanguinity and chromosomal disorders.

Disease	Degree of consanguinity					Total cons.	Non cons.	*P*-value
	1st cousin	One & half cousin	Double 1st cousin	2nd cousin	R.R			
Down synd. (2465)	435 (17.6%)	45 (1.8%)	–	52 (2.1%)	178 (7.2%)	710 (28.8%)	1755 (71.2%)	*P* > 0.05
Cri-du-chat (5)	3 (60%)	–	–	–	–	3 (60%)	2 (40%)	*P* < 0.05*
Klienfilter (9)	2 (22.2%)	–	–	1 (11.1%)	–	3 (33.3%)	6 (66.7%)	*P* > 0.05
Turner (65)	17 (26.1%)	–	–	–	9 (13.8%)	26 (40%)	39 (60%)	*P* > 0.05
Prader Willi (19)	1 (5.25%)	–	–	1 (5.25%)	–	2 (10.5%)	17 (89.5%)	*P* < 0.05*
Total (2563)	458 (17.9%)	45 (1.8%)	–	54 (2.1%)	187 (7.3%)	744 (29.1%)	1819 (70.9%)	*P* > 0.05

R.R: remote relative; Cons: consanguinity.
* *P*-value < 0.05, 0.01 (Significant).

Table 4 Relation between different degrees of consanguinity and autosomal recessive diseases.

Disease	Degree of consanguinity					Total cons.	Non cons.	*P*-value
	1st cousin	One & half cousin	Double 1st cousin	2nd cousin	R.R			
MPS (150)	44 (29.3%)	2 (1.3%)	1 (0.6%)	21 (14%)	37 (24.6%)	105 (70%)	45 (30%)	*P* < 0.01*
PKU (189)	44 (23.2%)	–	–	–	125 (66.1%)	169 (89.4%)	20 (10.6%)	*P* < 0.001***
Peters anomaly (2)	1 (50%)	–	–	–	–	1 (50%)	1 (50%)	*P* > 0.05
S.N.D (60)	24 (40%)	22 (36.6%)	8 (13.3%)	–	2 (3.3%)	56 (93.4%)	4 (6.6%)	*P* < 0.001***
DystrophicEpi.bullosa (32)	21 (65.6%)	–	–	–	4 (12.5%)	25 (78.1%)	7 (21.9%)	*P* < 0.01*
N.D.D (162)	60 (37%)	28 (17.2%)	–	18 (11.2%)	7 (4.4%)	113 (69.8%)	49 (30.2%)	*P* < 0.01*
Bardet–Biedel (2)	2 (100%)	–	–	–	–	2 (100%)	–	*P* < 0.001***
Total (597)	196 (32.8%)	52 (8.7%)	9 (1.5%)	39 (6.5%)	175 (29.3%)	471 (78.8%)	129 (21.2%)	*P* < 0.01*

Cons: consanguinity; MPS: mucopolysaccaridosis; S.N.D: sensorineural deafness; PKU: phenylketonuria; N.D.D: neurodegenerative disease.
* Significant.
*** *P*-value < 0.001 (Highly significant).

70% of cases of mucopolysaccaridosis, and 69.8% of neurodegenerative disease cases, Table 4.

Consanguineous marriage was recorded among 51.5% of autosomal dominant diseases, Table 5.

In X-linked diseases consanguineous marriage was detected in all cases of mental retardation (100%) and in 28.1% of patients with Duchenne muscular dystrophy, Table 6.

Table 5 Relation between different degrees of consanguinity and autosomal dominant diseases.

Disease	Degree of consanguinity					Total cons.	Non cons.	*P*-value
	1st cousin	One & half cousin	Double 1st cousin	2nd cousin	R.R			
Noonan syndrome (4)	3 (75%)	–	–	–	–	3 (75%)	1 (25%)	$P < 0.05^{*}$
Sticklers syndrome (3)	1 (33.5%)	–	–	–	–	1 (33.5%)	2 (66.5%)	$P > 0.05$
Cerebellar ataxia (64)	12 (18.7%)	–	–	–	17 (26.5%)	29 (45.3%)	35 (54.7%)	$P > 0.05$
Achondro-plasia (29)	6 (20.7%)	–	–	–	9 (31%)	15 (51.7%)	14 (48.3%)	$P < 0.05^{*}$
Osteo-genesis imperfect (56)	13 (23.2%)	–	–	12 (21.5%)	–	25 (44.7%)	31 (55.3%)	$P > 0.05$
Marfan syndrome (32)	10 (31.3%)	5 (15.6%)	–	4 (12.5%)	5 (15.6%)	24 (33.3%)	8 (66.7%)	$P > 0.05$
Total (188)	45 (23.9%)	5 (2.65%)	–	16 (8.5%)	31 (16.5%)	97 (51.5%)	91 (48.5%)	$P > 0.05$

Cons: Consanguinity.
* Significant.

Table 6 Relation between different degrees of consanguinity and X-linked diseases.

Disease	Degree of consanguinity					Total cons.	Non cons.	*P*-value
	1st cousin	One & half cousin	Double 1st cousin	2nd cousin	R.R			
Fragile X (12)	4 (33.3%)	3 (25%)	–	5 (41.7%)	–	12 (100%)	–	$P < 0.001^{***}$
Duchenne muscular dystrophy (288)	1 (0.3%)	29 (10%)	–	20 (6.9%)	31 (11%)	81 (28.1%)	207 (71.9%)	$P > 0.05$
Total (300)	5 (1.6%)	32 (10.6%)	–	25 (8.3%)	31 (10.3%)	93 (31%)	207 (69%)	$P > 0.05$

Cons: consanguinity.
*** Highly Significant.

Table 7 Relation between different degrees of consanguinity and multifactorial and miscellaneous disorders.

Disease	Degree of consanguinity					Total cons.	Non cons.	*P*-value
	1st cousin	One &half cousin	Double 1st cousin	2nd cousin	R.R			
Imp. hymen (9)	2 (22.2%)	–	–	1 (11.1%)	–	3 (33.3%)	6 (66.7%)	$P > 0.05$
Ameno-rrhea (140)	50 (35.7%)	11 (7.8%)	–	–	10 (7.1%)	71 (51.8%)	69 (49.2%)	$P > 0.05$
Azospermia (9)	–	–	–	–	1 (11.1%)	1 (11.1%)	8 (88.9%)	$P > 0.05$
Limb anomaly (257)	218 (84.8%)	3 (1.1%)	2 (0.8%)	–	15 (6%)	238 (92.6%)	19 (7.3%)	$P < 0.001^{***}$
Epilepsy (390)	139 (35.6%)	10 (2.8%)	–	1 (0.2%)	16 (4.1%)	166 (42.5%)	224 (57.4%)	$P > 0.05$
Cleft palate (60)	17 (28.3%)	–	–	–	–	17 (28.4%)	43 (71.6%)	$P > 0.05$
Mental retardation (1763)	813 (46.1%)	263 (14.9%)	3 (0.1%0	144 (8.1%)	118 (6.7%)	1341 (76.1%)	422 (23.9%)	$P < 0.05^{*}$
Hydro-cephalus (20)	11 (55%)	–	–	–	1 (5%)	12 (60%)	8 (40%)	$P < 0.05^{*}$
Total (2648)	1250 (47.2%)	287 (10.8%)	5 (0.18%)	146 (5.5%)	151 (5.7%)	1849 (69.8%)	799 (30.2%)	$P < 0.05^{*}$

Cons: consanguinity; Imp: imperforate.
* Significant.
*** Highly Significant.

Table 8 Relation between different degrees of consanguinity and other diseases.

Disease	Degree of consanguinity					Total cons.	Non cons.	*P*-value
	1st cousin	One & half cousin	Double 1st cousin	2nd cousin	R.R			
Ambigious genetalia (20)	6 (30%)	7 (35%)	–	–	3 (15%)	16 (80%)	4 (20%)	$P < 0.01^{**}$
Undescen. testis (65)	5 (7.7%)	–	–	1 (1.6%)	5 (7.7%)	11 (17%)	54 (83%)	$P > 0.05$
Golden har syndrome (3)	1 (33.3%)	–	–	–	–	1 (33.3%)	2 (66.7%)	$P > 0.05$
CP (519)	180 (34.7%)	100 (19.2%)	–	8 (1.5%)	6 (1.3%)	294 (36.7%)	225 (43.3%)	$P > 0.05$
Cong. Cataract (69)	37 (53.6%)	2 (2.9%0	–	–	1 (1.5%)	40 (58%)	29 (42%)	$P < 0.05^{*}$
MCA (201)	123 (60%)	2 (1%)	9 (4.4%)	5 (2.4%)	5 (2.4%)	144 (72.2%)	57 (27.8%)	$P < 0.05^{*}$
Blood diseases* (75)	47 (62.6%)	–	–	–	–	47 (62.6%)	28 (37.4%)	$P < 0.05^{*}$
Total (952)	399 (42%)	111 (17.5%)	9 0 (94%)	14 (1.5%)	20 (2.1%)	553 (58%)	399 (42%)	$P < 0.05^{*}$

Cons: consanguineous; Undescen: undescended; Cong: congenital; MCA: multiple congenital anomalies; CP: cerebral palsy.
* Blood diseases included thalassemia & sickle cell anemia.

Table 9 Relation between different degrees of consanguinity and recurrent abortions, stillbirths and child deaths.

	Degree of consanguinity					Total cons.	Non cons.	*P*-value
	1st cousin	One& half cousin	Double 1st cousin	2nd cousin	R.R			
R.Ab (1951)	962 (49.3%)	78 (3.9%)	51 (2.6%)	93 (4.7%)	113 (5.8%)	1297 (67%)	644 (33%)	$P < 0.05$*
S.B (1106)	891 (80.6%)	–	–	–	–	891 (80.6%)	215 (19.4%)	$P < 0.01$*
Child death (1327)	650 (49%)	198 (14.9%)	15 (1.1%)	37 (2.8%)	161 (2.2%)	1061 (80%)	226 (20%)	$P < 0.01$*
Total (4384)	2503 (57%)	276 (6.3%)	66 (1.5%)	130 (2.9%)	274 (6.3%)	3249 (74.1%)	1085 (25.9%)	$P < 0.01$*

R.Ab: recurrent abortion; Cons: consanguineous; S.B: still births.
* Significant.

Consanguineous marriage was also more common in multifactorial disorders (69.8%), compared to non consanguineous marriage (30.2%). In multifactorial and miscellaneous disorders, consanguineous marriage was significantly higher in mental retardation (76.1%), hydrocephalus (60%), while it was highly significant in limb anomalies (92.6%), Table 7.

Consanguineous marriage was detected in 80% of cases with ambigious genetalia, 72.2% of patients with multiple congenital anomalies and 62.6% of patients with blood diseases, Table 8.

Stillbirths, child deaths and recurrent abortions were significantly increased among consanguineous parents than among non consanguineous parents. Percentages were 80.6%, 80%, 67% respectively, Table 9.

In autosomal recessive disorders a higher F (0.021) was detected as compared to controls (0.019).

4. Discussion

Consanguineous marriage attracts considerable attention as a causative factor in the prevalence of genetic disorders. It is estimated that globally over 20% of the human population live in communities with a preference for consanguineous marriage, and over 8.5% of all children have consanguineous parents. Consanguinity is widely practiced in countries of Asia and Africa especially in societies where Islam prevails while its prevalence is low in Western countries. It also has high rates in Arab countries [14–17].

In our study, consanguineous marriage was reported in 54.4% of the studied group compared with 35.3% in the controls. Shawky et al., [12] reported that the overall frequency of consanguinity in Egypt is still high, however this frequency varies by region. It was significantly higher in Sohag (42.2%) and great Cairo (36.1%) than in Assuit (21.7%). Also it was higher in rural areas (59.9%) than in semiurban and urban areas (23.5%) and (17.7%), respectively. This increase in consanguinity rate is due to the fact that many families prefer marriage among first cousins to preserve family structure, links and provide social, economical and cultural benefits. Many Egyptians believe that there may be more compatibility and less tendency to divorce between husband and wife from a consanguineous family. This favored the appearance of complex phenotypes of genetic disorders which result in difficulties in phenotype classification [18]. Hashem et al., previously reported that consanguineous marriage prevails among 34.49% of normal Egyptians, 58.08% of those having heredofamilial disease, 65.21% of those having minor congenital anomalies and in 49.19% having major congenital anomalies with normal chromosomal pattern [19]. El-nekhely et al., also reported that studies of parental consanguinity in the general population in Egypt throughout the last 40 years showed an average consanguinity rate above 30% [20].

Our results showed that the most common degree of consanguineous marriages among our patients was first cousins (31.4%). The same was also reported among the general population in Egypt, where first cousin marriage occurred in 86% of studied subjects [12]. In our study, autosomal recessive and multifactorial disorders had the highest rate of consanguinity (78.8% and 69.8% respectively). It was detected in 70% of cases of mucopolysaccharidosis, 89.3% of patients with phenylketonuria, 93.4% of patients with sensorineural deafness and in 69.8% of patients with neurodegenerative disease. Closely similar results were also previously reported for mucopolysaccharidosis [21], neurodegenerative disorders [22] and sensorineural deafness [23].

Comparison between genetic diseases with different modes of inheritance showed that recessive disorders had the highest values of inbreeding coefficients ($F = 0.021$) as compared to controls (0.019), while chromosomal disorders had the lowest one. However in another locality in Egypt (Alexandria), Mokhtar et al., reported that 45.2% of the patients referred to the genetics clinic had genetic disorders, 33.6% of whom had autosomal recessive disorders. The frequency of consanguinity among parents of patients with autosomal recessive disorders was high (60%, with 48% first cousins) and the average inbreeding coefficient was higher (0.03) than that reported for the Egyptian population in general (0.01) [24]. On the other hand Jain et al., in India reported that the common types of consanguineous marriages were between first cousins (50.6%) and uncle and niece (42.4%) and the mean coefficient of inbreeding was 0.056 which was higher than that reported in this study [25].

The association between consanguinity and genetic defects is well demonstrated in previous studies performed on well known autosomal recessive disorders among Egyptian patients such as hearing loss and phenylketonuria [26,27]. Hamamy reported that, rare and novel autosomal recessive disorders have been widely reported from communities with high consanguinity rates, including Arabs, since the main impact of consanguinity is an increase in the prevalence of such disorders [28]. Analysis of data in the catalog for Transmission of Genetic disorders in Arabs (CTGA), a database on genetic disorders in Arab populations maintained by the center for Arab Genomic Studies (CAGS), indicates that among more than 1000 disorders in the CTGA Database, 68% follow a recessive mode of inheritance. Also Hoodfar et al., reported that, inbreeding or consanguineous marriages have an effect on

the rates of reproductive loss, congenital malformations and genetic diseases, mainly autosomal recessive [29]. In our study consanguineous marriage was reported in 78.8% of patients with autosomal recessive disorders compared to 21.2% in non consanguineous patients. In Jordan Hamamy stated that consanguinity rates among parents affected with autosomal recessive diseases were 85% [30]. Also in India Bidhan has shown a high percentage of consanguineous marriage in patients with autosomal recessive disorders [31]. Individuals born of consanguineous union have segments of their genomes that are homozygous as a result of inheriting identical ancestral genomic segments through both parents. These data imply that prolonged parental inbreeding has led to a background level of homozygosity increased ~5% over and above that predicted by simple models of consanguinity [32]. In mathematical terms, consanguinity does not alter the allele frequencies of common disorders, but increases the probability of mating between two individual heterozygotes for the same recessive mutant allele. In this regard, the risk of birth defects in the offspring of first-cousin marriage is expected to increase sharply compared to non-consanguineous marriages particularly for rare autosomal recessive disease genes, because for common recessive conditions, there is a high chance that the abnormal gene may be carried by unrelated spouses and may be expressed in their progeny [33].

In our study consanguineous marriage was detected in 29.1% of patients with chromosomal disorders including 28.8% of Down syndrome patients. Alfi et al., had observed an increased frequency of consanguineous parents among their Down syndrome patients and postulated the existence of a gene that could influence mitotic non-disjunction in the zygote followed by loss of monosomic cells and the formation of a complete trisomic or mosaic embryo [34]. Nevertheless their results, based only on 20 cases and were not confirmed later on by Hamamy et al., [35]. However Amudha et al., demonstrated that the effect of consanguinity on chromosomal abnormalities was almost significant ($P < 0.001$). They added that chromosomal abnormalities, numerical and structural, may occur as de - novo at post-zygotic mitosis or transmitted because of the errors at meiosis in the parental gametogenesis [36]. Muller et al., also observed a significant effect of consanguinity among patients with chromosomal abnormalities. Three malformations/disorders were relatively frequent: Down syndrome, esophageal atresia, and profound deafness. The rate of malformations and significant medical conditions was 7.77% when the parents were first cousins and 3.63% when they were not related ($P = 0.002$), [37].

In our study consanguineous marriage had no significant effect in autosomal dominant disorders, except Noonan syndrome and achondroplasia ($P < 0.05$), or in X-linked diseases except Fragile-X syndrome ($P < 0.001$). In Egypt, Temtamy and Aglan stated that statistical analysis revealed no significant increase in parental consanguinity rates in autosomal dominant, X-linked, or chromosomal disorders [38]. In Jordan, Hamamy et al., also reported that consanguinity rate among parents of patients affected with autosomal dominant diseases was 25%–30% which was not significant compared to controls [39].

Our results also showed that consanguineous marriage was reported in 69.8% of patients with multifactorial diseases, which was significant compared to non consanguineous marriage. Bener and Hussain reported that the occurrence of asthma, mental retardation, epilepsy and diabetes was significantly more common in offspring of all consanguineous than non consanguineous couples [40]. Sayee et al., also emphasized the effect of consanguinity on mental retardation and or congenital abnormalities [41]. In Egypt, Temtamy et al., [42] reported that high rates of consanguinity were found in polygenic disorders. Also Al-Ghazali et al., in UAE reported that consanguinity was identified as a risk factor for several morbid conditions including congenital abnormalities and multifactorial disorders [43]. Also in a study done in Qatar, Bittles et al., reported that there is a significant increase in the prevalence of common adult diseases like mental retardation, hearing defects, heart diseases and others in consanguineous families [5].

Consanguineous marriage was reported in 58% of our patients with diseases of different etiologies (e.g. ambigious genetalia, multiple congenital anomalies) which was significantly higher ($P < 0.05$), compared to the non-consanguineous group (42%). This is in agreement to Amar et al., in India who reported that the rate of most of diseases like multiple congenital anomalies and ambiguious genetalia was significantly higher in offspring of consanguineous than non consanguineous parents [44]. In our study, consanguineous marriage was detected in 80% of cases with ambigious genetalia, 72.2% of patients with multiple congenital anomalies and 62.6% of patients with blood diseases. The frequency of consanguineous marriages was higher among parents of offspring with congenital malformations compared with the figures for the general population in all studies reported among Arabs, including Egypt, [45,42] UAE, Kuwait, Oman [46–48], Iraq, Jordan [49,50], Lebanon [51], Tunisia [52] and Saudi Arabia [53]. Shawky and Sadik reported that consanguineous marriage was significantly increased by 45.8% in the offsprings with congenital malformations compared to that of the general population 38.9% [45]. Pinto [54] reported a twofold increase in the incidence of congenital malformations (CMs) among the clinical effects of parental consanguinity. The mating in consanguinity gives exactly the conditions most likely to enable rare features to show itself [55]. A study done in Egypt on the etiology of congenital malformations, Shawky et al., reported that chromosomal anomalies constituted 21.4%, genetic syndromes represented 31% while 47.6% were due to unknown causes. Most of the genetic syndromes were due to autosomal recessive inheritance and this is due to a high degree of consanguinity [56]. Zlotogora, also reported an increased incidence of congenital malformations in the offsprings of consanguineous couples due to homozygous expression of recessive genes inherited from their common ancestors [57].

However, the results of our study were in contrast to those reported by Mehrabi and Zeyghami who stated that although the consanguinity for malformed patients was high, there was no significant relationship between malformations and the degree of relation of the parents [17]. Also, in a study by Bromiker in Palestine, no statistically significant difference was found in the incidence of congenital malformations with the degrees of parents' relation [58].

Increased mortality among the offspring of consanguineous marriages has been widely reported in human populations from different parts of the world [59]. In our study consanguineous marriages were present in 80.6% of cases with stillbirths, 80% of cases with child mortality and 67% of cases with recurrent abortions, which were significantly higher compared to

those in non consanguineous marriages (19.4%), (20%), and (33%) respectively. This is in agreement to an Indian study which revealed that the frequency of spontaneous abortions and stillbirths was higher in the offspring of consanguineous marriages than in that of non-consanguineous marriages [60]. A similar effect was also observed in the infant mortality rate, which is known to have a genetic component [61–63]. These results indicate the presence of strong recessive elements in the transmission of these lethal genes. In fact, consanguineous marriage increases the risk of recessive hereditary diseases and polygenic one in their offspring by allowing the chance of the detrimental recessive genes to become a homozygous state manifested by biochemical defect or congenital malformation.

5. Conclusion

The future prevalence and status of consanguineous marriage is a matter of conjecture. A rapid decline in its prevalence is improbable in the meantime in Arab countries including Egypt. In many developing countries, strenuous official efforts are being made to lessen the appeal of close-kin unions, although with no apparent appreciation or acknowledgement of the balancing social and economic benefits. To achieve comparable advances in developing countries, extensive community education programes are needed to reduce the burden on health care systems, and to complement the existing diagnostic, counseling and treatment skills of local staff. Also the government should put strict laws for premarital tests.

Conflict of interest

We have no conflict of interest to declare.

References

[1] Robin LB, Arno GM, Alan B, Louanne H, Stefanie U, Debra LD, et al. Genetic counseling and screening of consanguineous couples and their offspring: recommendations of the national society of genetic counselors. J Genet Couns 2002;11(2):97–119.

[2] Bener A, Hussain R. Consanguineous unions and child health in the State of Qatar. Paediatr Perinat Epidemiol 2006;20(5):372–8.

[3] Jaouad IC, Elalaoui SC, Sbiti A, Elkerh F, Belmahi L, Sefiani A. Consanguineous marriages in Morocco and the consequence for the incidence of autosomal recessive disorders. J Biosoc Sci 2009;41(5):575–81.

[4] El Mouzan MI, Al Salloum AA, Al Herbish AS, Qurachi MM, Al Omar AA. Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study. Ann Saudi Med 2008;28(3):169–73.

[5] Bittles AH. Consanguinity and its relevance to clinical genetics. Clin Genet 2001;60(2):89–98.

[6] Emery AEH, Rimoin DL, editors. Principles and practice of medical genetics, 2nd ed., vols. 1–2. Edinburgh: Churchill Livingstone; 1990.

[7] Rahmani SA, Aboualsoltani F, Pourbarghi M, Dolatkhah H, Mirza AA. The frequency of consanguineous marriages and their effects on offsprings in Tabriz city. Shiraz E-Med J 2010;11(1):1–9.

[8] Harper Peter S. Practical genetic counselling. 5th ed. Oxford: Butterworth Heinemann; 1998, vol. 123, pp. 128–29.

[9] Al-Herz W. Primary immunodeficiency disorders in Kuwait: first report from Kuwait national primary immunodeficiency registry (2004–2006). J Clin Immunol 2008;28(2):186–93.

[10] Saleh EA, Mahfouz AA, Tayel KY, Naguib MK, Bin-al-Shaikh NM. Hypertension and its determinants among primary-school children in Kuwait: an epidemiological study. East Mediterr Health J 2000;6(2–3):333–7.

[11] Kanaan ZM, Mahfouz R, Tamim H. The prevalence of consanguineous marriage in an underserved area in Lebanon and its association with congenital anomalies. Genet Test 2008;12(3):367–72.

[12] Shawky RM, El-Awady MY, Elsayed SM. Consanguineous matings among Egyptian population. Egypt J Med Hum Genet 2011;12:157–63.

[13] Wright S. Coefficients of inbreeding and relationship. Am Nat 1992;56:330–8.

[14] Ali A, Zahad S, Masoumeh A, Azar A. Congenital malformations among live births at Arvand Hospital, Ahwaz, Iran – a prospective study. Pak J Med Sci 2008;24(1):33–7.

[15] Al-Ghazali LI, Dawodu AH, Sabarinathan K, Varghese. The profile of major congenital abnormalities in the United Arab Emirates (UAE) population. J Med Genet 1995;32:7–13.

[16] Madi SA, Al-Naggar RL, Al-Awadi SA, Bastaky LA. Profile of major congenital malformations in neonates in Al-Jahra region of Kuwait. East Mediterr Health J 2005;11(4):700–6.

[17] Mehrabi KA, Zeyghami B. The effect of consanguineous marriage on congenital malformation. J Res Med Sci 2005;10(5):298–301.

[18] Shawky RM, Elsayed NS, Sadik DI, Seifeldin NS. Profile of genetic disorders prevalent in northeast region of Cairo, Egypt. Egypt J Med Hum Genet 2012;13:45–62.

[19] Hashem N. Incidence of glucose-6-phosphate dehydrogenase in Egypt. Egypt Clin Genet 1968;46:347–51.

[20] El-Nekhely I, Namaste S, Shriver EK. Analysis of country situation survey: National plane of action. The 2nd conference of the Middle East and Africa newborn screening initiative. Cairo, Egypt, 2008; 12–14.

[21] Shawky RM, Abdel-Monim MT, El-Sebai AA, El-Sayed SM. Cardiac and ocular manifestations in Egyptian patients with mucopolysaccharidosis. East Mediterr Health J 2001;7(6):981–5.

[22] Shawky RM, Fateen EM, Zaghloul MS, Salem AA. Prevalence of some lipidosis among Egyptian children with neurodegenerative disorders. Egypt J Med Hum Genet 2006;7(1):47–73.

[23] Nour El-Din Sahar M, Hamed Lobna. Sensorineural hearing impairment is a common feature of consanguineous marriage. Egypt J Hum Genet 2008;9(1):121–7.

[24] Mokhtar MM, Kotb SM, Ismail SR. Autosomal recessive disorders among patients attending the genetics clinic in Alexandria. East Mediterr Health J 1998;4(3):470–9.

[25] Jain VK, Nalini P, Chandra R, Srinivasan S. Congenital malformations, reproductive wastage and consanguineous mating. Aust N Z J Obstet Gynaecol 1993;33(1):33–6.

[26] Ismail SR, Hashishe MM, Maurad MI, Abdel Kader M. Inheritance of non-syndromal genetic deafness. J Egypt publ. Health associat 1996;LXX1:403–438.

[27] Hashishe MM. Genetic study of phenylketonuria. J Egypt Publ Health Associat LXVII 1992;443–63.

[28] Hamamy H. Consanguinity and novel technology: cracking the code of autosomal. HGM 2011 programme abstract book. From the issue entitled "HUMAN GENOME MEETING 2011". HUGO J 2011;5(1):1–346.

[29] Hoodfar E, Teebi AS. Genetic referrals of middle Eastern origin in a western city: inbreeding and disease profile. J Med Genet 1996;33:212–5.

[30] Hamamy H, Jamhawi L, Al-Darawsheh J, Ajlouni K. Consanguineous marriages in Jordan: why is the rate changing with time? Clin Genet 2005;67:511–6.

[31] Bidhan KD. The effect of inbreeding on mortality and morbidity among telugu-speaking populations of Kharagpur, West Bengal, India. Int J Anthropol 2006;21(2):151–63.

[32] Woods CG, James C, Kelly S, Daniel JH, Moin DM, Martin M, et al. Quantification of homozygosity in consanguineous individ-

uals with autosomal recessive disease. Am J Hum Genet 2006;78(5):889–96.
[33] Al-Gazali L, Hamamy H, Al-Arrayad S. Genetic disorders in the Arab world. BMJ 2006;333:831–4.
[34] Alfi OS, Chang R, Azen SP. Evidence for genetic control of nondisjunction in man. Am J Hum Gent 1980;32:477–83.
[35] Hamamy HA, Masri AT, Al-Hadidy AM, Ajlouni KM. Consanguinity and genetic disorders. Profile from Jordan. Saudi Med J 2007;28(7):1015–7.
[36] Amudha S, Aruna N, Rajangam S. Consanguinity and chromosomal abnormality. Indian J Hum Genet 2005;11(2):108–10.
[37] Mueller RF, Young ID. Elements of medical genetics. 11th ed. Edinburgh: Churchill Livingstone; 2001, p. 100–245.
[38] Temtamy S, Aglan M. Consanguinity and genetic disorders in Egypt. Middle East J Med Genet 2012;1(1):12–7.
[39] Hamamy HA, Masri AT, Al-Hadidy AM, Ajlouni KM. Consanguinity and genetic disorders. Profile from Jordan. Saudi Med J 2007;28:1015–7.
[40] Bener A, Hussain R, Teebi AS. Consanguineous marriages and their effects on common adult diseases: studies from an endogamous population. Med Princ Pract 2007;16:262–7.
[41] Sayee R, Thomas IM. Consanguinity and chromosomal abnormality in mental retardation and or multiple congenital anomaly. J Anat Soc India 2007;56(2):30–3.
[42] Temtamy SA, AbdelMeguid N, Mazen I, Ismail SR, Kassem NS, Bassiouni R. A genetic epidemiological study of malformations at birth in Egypt. East Mediterr Health J 1998;4:252–9.
[43] Al Ghazali LI, Bener A, Abdul Razzak YM, et al. Consanguineous marriages in the United Arab Emirates. J Biosoc Sci 1997;29:491–7.
[44] Amar T, Krishna V, Pushpa C, Manish J. Congenital malformations at birth in central India: a rural medical college hospital based data. Indian J Hum Genet 2010;16(3):159–63.
[45] Shawky RM, Sadik DI. Congenital malformations prevalent among Egyptian children and associated risk factors. Egypt J Med Hum Genet 2011;12:69–78.
[46] Dawodu A, Al-Gazali L, Varady E, Varghese M, Nath K, Rajan V. Genetic contribution to high neonatally lethal malformation rate in the United Arab Emirates. Commun Genet 2005;8:31–4.
[47] Al-Kandari YY, Crews DE. The effect of consanguinity on congenital disabilities in the Kuwaiti population. J Biosoc Sci 2011;43(1):65–73.
[48] Patel PK. Profile of major congenital anomalies in the Dhahira region, Oman. Ann Saudi Med 2007;27:106–11.
[49] Mahdi A. Consanguinity and its effect on major congenital malformations. Iraqi Med J 1992;40–42:170–6.
[50] Khoury SA, Massad DF. Consanguinity, fertility, reproductive wastage, infant mortality and congenital malformations in Jordan. Saudi Med J 2000;21:150–4.
[51] Bittar Z. Major congenital malformations presenting in the first 24 hours of life in 3865 consecutive births in south of Beirut, incidence and pattern. J Med Liban 1998;46:256–60.
[52] Khrouf N, Spang R, Podgorna T, Miled SB, Moussaoui M, Chibani M. Malformations in 10,000 consecutive births in Tunis. Acta Paediatr Scand 1986;75:534–9.
[53] ElMouzan MI, AlSalloum AA, AlHerbish AS, Qurachi MM, AlOmar AA. Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study. Ann Saudi Med 2008;28:169–73.
[54] Pinto Escalante D, Castillo Zapata I, Ruiz Allec D, Ceballos Quintal JM. Spectrum of congenital malformations observed in neonates of consanguineous parents. An Pediatr (Barc) 2006;64(1):5–10.
[55] Jaouad IC, Elalaoui SC, Sbiti A, Elkerh Belmahi L, Sefiani A. Consanguineous marriages in Morocco and the consequence for the incidence of autosomal recessive disorders. J Biosoc Sci 2009;41(5):575–81.
[56] Shawky RM, El-Baz FM, Elsobky ES, Osman A, Elsayed SM. High resolution cytogenetic study of patients with multiple congenital anomalies, M.D. Thesis, Ain Shams University, 2005.
[57] Zlotogora J. Genetic disorders among Palestinian Arabs: effects of consanguinity. Am J Med Genet 1997;68:427–35.
[58] Bromiker R, Glam-Baruch M, Gofin R, Hammerman C, Amitai Y. Association of parental consanguinity with congenital malformations among Arab newborns in Jerusalem. Clin Genet 2004;66(1):63–6.
[59] Bennett R, Motulsky A, Bittles A, Hudgins L, Uhrich S, Doyle D, et al. Genetic counseling and screening of consanguineous couples and their offspring: recommendations of the National Society of genetic Genetic Counselors. J Genet Couns 2002;11:97–119.
[60] Shrikant K, Srinivas G. Revisiting Consanguineous Marriages and their Effect on Pregnancy outcomes in India: Evidences from a Nation-wide Survey. Population Association of America 2012 Annual Meeting Program.
[61] Stoltenberg C, Magnus P, Lie RT, et al. Influence of consanguinity and maternal education on risk of stillbirths and infant death in Norway, 1967–1993. Am J Epidemiol 1998;148(5):452–559.
[62] Saha N, Hamad RE, Mohamed S. Inbreeding effects on reproductive outcome in a Sudanese population. Hum Hered 1990;40:208–12.
[63] Thompson JS, McInnes RR, Willard HF. Consanguinity. In: Genetics in medicine. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: W.B. Saunders Company; 1991. p. 152–5.