

# Consanguinity and genetic disorders

## *Profile from Jordan*

Hanan A. Hamamy, MD, MSC, Amira T. Masri, MD, Azmy M. Al-Hadidy, MD, FRCR, Kamel M. Ajlouni, MD, FACP

### ABSTRACT

**Objective:** With 20-30% of all marriages occurring between first cousins, increasing attention in Jordan is now given to role of consanguinity in the occurrence of genetic diseases. The objective of this study is to define the specific categories of genetic disorders associated with consanguineous marriages.

**Methods:** Etiological categories and consanguinity rates were studied among 623 families with genetic syndromes, congenital anomalies or mental retardation, or both, seen at the National Center for Diabetes, Endocrinology and Genetics for the period August 2002 to August 2006. Comparisons were made for first cousin marriage rates in the study group and that for the general population.

**Results:** First cousin marriages constituted 69%, 22% and 41.7% of marriages among families with autosomal recessive conditions (group 1), dominant, X-linked and chromosomal conditions (group 2) and sporadic undiagnosed conditions (group 3) respectively. The differences in rates of first cousin matings versus non-consanguineous matings were highly significant when comparing known figures in the general population with group 1 and 3, but not significant with group 2.

**Conclusion:** Two messages to the public and health care personnel regarding consanguinity can be derived from this study. The first message is that among genetic disorders, only autosomal recessive disorders are strongly associated with consanguinity. The second message is that approximately 30% of sporadic undiagnosed cases of mental retardation, congenital anomalies and dysmorphism may have an autosomal recessive etiology with risks of recurrence in future pregnancies.

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*From the National Center for Diabetes (Hamamy, Ajlouni), Endocrinology and Genetics, Department of Pediatrics (Masri), and the Department of Radiology (Al-Hadidy), Jordan University Hospital, Amman, Jordan.*

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*Address correspondence and reprint request to: Prof. Hanan Hamamy, National Center for Diabetes, Endocrinology and Genetics, PO Box 13165, Amman 11942, Jordan. Tel. +962 (6) 5347810. Fax. +962 (6) 5356670. E-mail: hananhamamy@yahoo.com*

Arab countries, including Jordan manifest high consanguinity rates, a relatively high number of mothers over 35 years of age, a large family size and a high frequency of hemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency.<sup>1,2</sup> Consanguinity continues to attract attention among medical and population geneticists, clinicians and social scientists. The decline in infant mortality rates in most Arab countries through the improvement in childhood nutritional status and combating infectious disease means that genetic disorders will be assuming an ever-increasing importance. Consanguineous marriages in Jordan comprise one third to one half of all marriages, with first cousin marriage rates in the range of 20-30%.<sup>3,4</sup> It becomes imperative to verify what the true risks for offspring of consanguineous parents are in a population that favors consanguinity on one hand and condemns consanguinity as the cause of all genetic diseases on the other hand. The risks to offspring of first cousin parents have been confirmed in 2 situations. It has been estimated that the birth defect rate among newborns of first cousin parents is double the baseline population rate for birth defects.<sup>5</sup> There is an increased risk for offspring of consanguineous couples to be affected by an autosomal recessive condition in families harboring such genes.<sup>1</sup> Sometimes autosomal recessive genes are hidden within the family for generations and they only show on the surface in a new consanguineous marriage within the family. With the rising public awareness for genetic disorders in Jordan, more and more consanguineous couples are seeking premarital counseling. To be able to take an informed decision for their future, these couples want to know the risks for their

offspring of having a genetic or congenital disorder or of being physically or mentally retarded. For these couples, the genetic counselor calculates the risks for birth defects that are derived from the literature and the risks for any specific autosomal recessive condition known to be segregating in the family. However, there are still many uncertainties in areas such as physical and mental development of the child and any increased risks of being affected by late onset conditions as diabetes, hypertension and cancer. There is a need to design a wide range of multidisciplinary investigative approaches to assess the advantages and disadvantages of consanguinity on health and social structure in Arab populations. This study presents the consanguinity profile of families seen at the main genetic counseling clinic in Amman and the association of consanguinity with specific categories of genetic disorders. The preliminary information obtained from this study could help in defining the health risks associated with consanguinity as part of the genetic educational guidelines targeted to the public and the health sector.

**Methods.** The study was performed at the Genetic Counseling Clinic of the National Center for Diabetes, Endocrinology and Genetics (NCDEG) in Amman, Jordan for the period August 2002 to August 2006. Families chosen to be included in this study were 623 families who had infants or children with one or more of the conditions of multiple congenital anomalies, dysmorphic features, mental retardation, failure to thrive in infancy or short stature in children, single anomaly, and repeated or unexplained infant deaths. Genetic diseases are generally categorized into unifactorial, chromosomal and multifactorial. Families included in this study are those with either chromosomal etiology confirmed by karyotyping, or of unifactorial etiology confirmed by specific clinical features, or specific laboratory investigations, or a pedigree compatible with a specific mode of inheritance, or both. Families with suspected multifactorial inheritance were excluded

because of the difficulty in confirming this etiological category. Families were placed in 3 etiological groups, where group 1 included families with autosomal recessive conditions, group 2 included families with chromosomal, dominant and X-linked recessive conditions and group 3 included families with sporadic undiagnosed conditions. Consanguineous marriages were classified into first cousins (includes parallel paternal, parallel maternal, cross and double first cousins), and beyond first cousins (includes first cousins once removed and second cousins). Beyond second cousins marriages and those reported as from the tribe were considered non-consanguineous. Consanguinity profile of the families in this study were compared to the consanguinity profile among the general population of the same area retrieved from the study carried out at the NCDEG using figures for marriages contracted after 1980,<sup>3</sup> being comparable to the dates of marriages of families included in this study.

Statistical analysis was carried out using Chi-square test with *p*-value determination (Microsoft Excel 2003).

**Results.** Among 878 families counseled at the NCDEG, autosomal recessive was the underlying etiology in 32% and dominant inheritance in 13% of cases, with 34% remaining without a definite diagnosis, of which 80% were sporadic. First cousin marriages comprised 41.7% among all marriages in these families. Data on 623 families were included in this study. Families were affected by conditions caused by autosomal recessive, dominant and X-linked recessive inheritance, and conditions caused by numerical or structural chromosome abnormalities. Families with offspring with sporadic undiagnosed condition were also included. **Table 1** presents the data on consanguinity profiles and etiological categories of 623 families included in this study retrieved from the Genetic Counseling Clinic, and the consanguinity profile of 2594 families retrieved from general population in the same area.<sup>3</sup>

**Table 1** - Consanguinity profiles and etiological categories of 623 families seen at the genetic clinic and 2594 families retrieved from general population.

Profiles	No. of patients (%)					
	First cousins including double first cousins		First cousins once removed + second cousins		Non-consanguineous	Total
Group 1: Couples with offspring affected by autosomal recessive conditions	167	(69)	41	(16.9)	34 (14)	242
Group 2: Couples with offspring affected by dominant, chromosomal and X-linked conditions	36	(22)	17	(10.4)	113 (69.3)	163
Group 3: Couples with offspring affected by sporadic, undiagnosed conditions	91	(41.7)	39	(17.9)	88 (40.4)	218
Couples from general population in Amman (3)	504	(19.4)	157	(6.1)	1933 (74.5)	2594

First-cousin marriages constituted 69% (autosomal recessive conditions [group 1]), 22% (dominant, X-linked recessive and chromosomal conditions [group 2]), 41.7% (sporadic undiagnosed conditions [group 3]), and 19.4% among the general population. The difference in rates of first cousin matings versus non-consanguineous matings was highly significant ( $p < 0.001$ ) when comparing the general population with families in group 1 and 3, but not significant with families in group 2 ( $p > 0.05$ ). Likewise when consanguineous versus non-consanguineous marriages were compared, the differences were highly significant ( $p < 0.001$ ) when comparing the general population with families in group 1 and 3, but not significant with families in group 2 ( $p > 0.05$ ).

**Discussion.** Jordan is one of the countries in the Middle East where consanguineous marriages are culturally favored. First cousin marriage rate among the general population in Jordan was reported to be 28-32% among marriages contracted before 1980.<sup>3,4</sup> Consanguinity rates seem to be decreasing in frequency among the younger generation, with a rate for first cousin mating of 19% among marriages contracted after 1980 in Amman.<sup>3</sup> The high rate of consanguinity among the general population in Jordan is expected to increase the proportion of autosomal recessive conditions, which encompassed 32% of all presentations to the clinic. In a genetic counseling clinic in Baghdad, where first cousin marriage rate reaches 29%, 31% of all referrals were categorized as autosomal recessive in etiology.<sup>6</sup> Among 200 couples representing all referrals of Middle Eastern origin seen at a large Clinical Genetics Unit in Montreal, autosomal recessive disorders were more than twice as common in the inbred as in the non-inbred families.<sup>7</sup> A lower figure of 17% for single gene disorders was reported from a clinic in the USA.<sup>8</sup> This study revealed a high rate of first cousin marriages of 69% among parents of patients with autosomal recessive conditions (Table 1) as opposed to 22% among parents of patients with chromosomal, dominant and X-linked conditions and to 19.4% among couples in the comparable general population.<sup>3</sup> The rate of first cousin marriages among parents of undiagnosed sporadic cases reached 41.7% (Table 1), being very close to the rate among all cases seen at the clinic, which implies that approximately one third of undiagnosed cases could have an autosomal recessive etiology. This fact should be kept in mind when these families inquire about risks of recurrence in future children. This study shows that only autosomal recessive conditions were strongly associated with

consanguineous marriages, whereas consanguinity rates among families with other etiological categories of single gene or chromosomal disorders were not significantly different from the consanguinity rate among the general population. Consanguineous marriage is an integral part of cultural and social life in Jordan, and attempts to discourage it at the population level may be inappropriate and undesirable.<sup>1</sup> Families with segregating autosomal recessive conditions are usually advised to limit further intermarriages among high at-risk carriers in the family if carrier testing is not available. In a community where selective termination of an affected fetus is restricted, prospective genetic counseling to families with segregating recessive genes and premarital testing and screening whenever feasible remain important measures for prevention and control of genetic diseases.<sup>9,10</sup> It is essential to include education of the public and of health personnel among programs for the prevention and control of genetic and congenital disorders. These educational programs should encompass evidence-based guidelines on counseling for consanguinity.

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