Consanguinity and child health

Anand K Saggar
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Abstract
Marriage between close biological kin is widely regarded as genetically disadvantageous in contemporary Western societies, but consanguineous unions remain preferential in North Africa, the Middle East and large parts of Asia, with marriage between first cousins particularly popular. Many major populations also are subdivided into endogamous communities that have distinctive breeding pools. It is in these populations that intra-community marriage principally governs the spectrum of observed diseases. Because of population subdivision, and because the poorest sections of all populations are most disadvantaged in terms of health and health care provision, there are difficulties in assessing the effects of consanguinity alone on morbidity and mortality. A positive association has been repeatedly shown between consanguinity and childhood morbidity due to the expression of detrimental recessive genes. Examples include deafness, retinal dystrophies, intellectual and developmental disability and complex congenital heart disease. Increased incidences of thalassaemia and other haematological disorders also are reported in many populations. Given the recent patterns of immigration, many Western countries have continued exposure to consanguineous unions, which necessitates the provision of more focused resources to improve the delivery of prospective genetic counselling, prenatal testing, treatment and community care. In communities where consanguineous marriage forms an integral and valued part of the cultural tradition, external attempts to discourage close-kin unions at the population level are inappropriate and unlikely to be successful.

Keywords birth defects; child health; consanguinity; endogamy; morbidity; mortality

The choice of a marriage partner is strongly influenced by geography, ethnicity, religion, education, social status, and political beliefs. Virtually all traditional societies are divided into long-established communities, with limited inter-community marriage. Genome-based association studies from industrialized Western societies have shown similar, although less pronounced, subdivisions. Even in societies with large immigrant communities (e.g. the Americas, Australia), recent arrivals typically marry within their ethnic and/or religious community during the first- and second-post-migration generations. Although offering strong social advantages, intra-community marriage has important medical genetic implications because it is probable that couples from the same ethnic or religious sub-community will have a proportion of their genes in common, with their progeny more likely to be homozygous for a detrimental recessive disorder.¹

Cosanguineous union: basic concepts

Definitions: the term ‘consanguineous’ is from the Latin consanguineus, meaning ‘of the same blood’.

In human genetics, a couple are said to be consanguineous if they share one or more common ancestors. Because most pairs of individuals living in the same location have a common ancestor somewhere in their family tree, for practical purposes the search for a shared ancestor usually does not extend back more than three or four generations.

In medical genetics, consanguineous marriage is commonly defined as a union between couples related as second cousins or closer. Second cousins share 1/32 of their genes from a common ancestor and, on average, their children will be homozygous across 1/64 loci (i.e. equivalent to a coefficient of inbreeding (F) of 0.0156; Table 1).

History: guidelines detailing the permissible types of consanguineous marriage are given in the Biblical Book of Leviticus, chapter 18. First-cousin unions were popular and valued in most Western countries up to the mid-nineteenth century.²

• Charles Darwin married his first cousin Emma Wedgwood.
• Charles Darwin’s sister Caroline married Emma Wedgwood’s brother Josiah after inter-marriage between the Darwin and Wedgwood families in the previous generation.
• Albert Einstein married his cousin Elsa.
• Queen Elizabeth II married her third cousin, Prince Phillip.

There was a marked decline in the prevalence of consanguineous marriage in the UK and other parts of Western Europe during the twentieth century because of a belief that the offspring would be subject to major physical and intellectual problems. Excluding China and Japan, this perspective is not reflected in the rest of the world, where the numerous social and economic advantages to the arrangement of first- and second-cousin marriages are commonly acknowledged (Table 2).

Genetic drift: besides preferential consanguinity, inbreeding can also result from genetic drift. Genetic drift is the influence of chance on gene frequencies in successive generations, with the probability of genetic drift greatest in communities with small effective population sizes (i.e. populations with restricted numbers of potential mating couples). In evolutionary terms, this situation can variously arise:

• through founder effect (when a subgroup of a population establishes a new breeding colony)
• via a demographic bottleneck after major disease- or disaster-related mortality
• in populations comprising multiple subcommunities who avoid inter-marriage.

Small breeding pools: in some regions of the world and among migrant communities originating from those regions, endogamous communities have evolved distinctive breeding pools (e.g. the

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Human genetic relationships$^{23,24}$

<table>
<thead>
<tr>
<th>Biological relationship</th>
<th>Genetic relationships (degree)</th>
<th>Coefficient of relationship ($r$)</th>
<th>Coefficient of inbreeding ($F$)</th>
<th>Empirical risk of AR disorder in offspring$^{23,24,**}$ (%)</th>
</tr>
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<tbody>
<tr>
<td>Incest</td>
<td>First</td>
<td>0.5</td>
<td>0.25</td>
<td>30</td>
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<td>Second</td>
<td>0.25</td>
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<td>Second</td>
<td>0.25</td>
<td>0.125</td>
<td>8–10</td>
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<tr>
<td>Double first cousin</td>
<td>Third</td>
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<td>3–6</td>
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<td>First cousin</td>
<td>Fourth</td>
<td>0.0625</td>
<td>0.0313</td>
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<tr>
<td>First cousin once removed</td>
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<tr>
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<td>Seventh</td>
<td>0.0078</td>
<td>0.0039</td>
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**Empirical risks when it is not known if each partner is an obligate carrier of a deleterious autosomal recessive (AR) gene. The coefficient of relationship ($r$) is the proportion of genes shared by the individuals who are biological relatives. The coefficient of inbreeding ($F$) indicates the probability that a child born to consanguineous parents will be homozygous for a specific gene derived from a common ancestor.

Table 1

UK Ashkenazi Jewish community). The strict concept of random mating does not apply under these circumstances. The net effect is similar to consanguineous marriage, with a higher probability of homozygosity at some gene loci, resulting in an increased probability of expression of recessive genes. Even without recognized consanguineous marriage, genetic isolation can result in an increase in the frequency of community-specific inherited disorders. Under these circumstances, a recessive founder or de novo mutation can rapidly increase in frequency, resulting in the birth of an affected child whether the parents are known to be consanguineous or believe themselves to be non-relatives.$^3$

Homzygosity mapping: the excess risk that an autosomal recessive disorder will be expressed in the children of consanguineous or endogamous unions is inversely proportional to the frequency of the disease alleles in the gene pool.$^9$ Many rare disease genes have been identified by studying highly inbred families with multiple affected members (homozygosity mapping).

Global prevalence of consanguinity

Data on the global distribution of consanguineous marriages are summarized in Figure 1.

Differences between regions: the lowest rates of consanguinity are found in Western Europe, North America and Oceania, where less than 1% of marriages are consanguineous (i.e. unions between couples related as second cousins or closer ($F$ ≥ 0.0156)).

In some parts of Southern Europe, South America and Japan, ~1–5% of marriages are consanguineous, depending on local geography and social customs.

The highest rates of consanguineous marriage have been observed in North Africa, Middle East and much of Central and South Asia, where more than 25% of the world’s population lives and unions between couples related as second cousins or closer can account for ≥ 50% of all marriages.$^3$

A recent decline in the prevalence of consanguineous marriage has been reported in Middle Eastern countries such as Jordan and Saudi Arabia, but increases have been reported in the neighboring Arab states of Qatar and the United Arab Emirates. Little change appears to have occurred in the prevalence of consanguinity during the latter half of the twentieth century in the major South Asian countries of India, Pakistan and Iran.$^4$ The Quran does not offer specific guidance encouraging consanguinity, but marriage between first cousins is a longstanding tradition in the Gulf States, particularly between the children of brothers.

Though consanguinity has been rare in Western societies since the early twentieth century, most Western countries are home to large migrant communities which traditionally have contracted consanguineous unions. Evidence points to continued preference for consanguinity in their newly adopted countries in these communities. The British Pakistani community is estimated to have

Social and economic advantages of consanguineous marriage

Assurance of marrying within the family and the strengthening of family and societal ties
Assurance of knowing one’s spouse before marriage
Reduced chances of maltreatment or desertion
Simplified premarital negotiations, with conditions and arrangement agreed in late childhood or early teens
Greater social compatibility of the bride with her husband’s family, in particular her mother-in-law who also is a relative
Reduced requirement for dowry or bride wealth payments, with maintenance of the family goods and monies
For land-owning families, maintenance of family land-holdings which otherwise may be subdivided by inheritance

Table 2
Occasional review

Pediatrics and Child Health 18:5

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50–60% cousin marriage, and contributes >40% of all births in the northern English city of Bradford.\(^5\)

Civil legislation on consanguineous marriage

Consanguineous unions are largely avoided in Western Europe and Oceania, but first-cousin marriage is permissible under civil law in virtually all countries; half-sibs (\(F = 0.125\)) also have been permitted to marry under specific circumstances in Sweden since 1987.

The situation is quite different in the USA where, until 1861, first-cousin marriage was legal. Legislation to ban different types of consanguineous marriage was gradually introduced, the most recent example being a ban on first-cousin marriage adopted by the state of Texas in 2005. First-cousin unions are a criminal offence in 10 states, and are illegal in a further 22 states, despite a Federal recommendation in 1970 that state laws on first-cousin marriage should be rescinded.\(^2\)

Cousin marriages are not prohibited under English law; most forms of consanguineous union are legal in the UK. The only exceptions are relationships between certain second-degree relatives (e.g. uncle–niece, half-siblings) and incestuous relationships (parent–child, brother–sister).

Social and economic factors associated with consanguinity

The preference for consanguineous marriage is primarily social, but economic considerations are an important part of partner choice (Table 2).

Premarital arrangements are simplified in a consanguineous union, and the relationship of a couple and their in-laws is expected to be more congenial and thus beneficial to female autonomy in patriarchal societies. It is also believed that family ties will be strengthened, and health or financial uncertainties with a partner from another family or community avoided.\(^6\) Marriages within the family reduce the potential financial costs where dowry or bride-wealth payments are the norm.\(^7,8\) Problems arising from marriage to a close relative have been cited if there is a large age gap between spouses, but divorce is uncommon, possibly reflecting the family disunity that could arise if a marriage between cousins was to fail.\(^9\)

Turkey showcases the influence of social and economic factors on consanguinity. First-cousin marriage is showing a steady decline,\(^10\) and the underlying reasons include:

- the higher educational levels of women (hence more time spent in education programmes)
- the increased nuclear nature of the family system
- internal migration from rural to urban settings
- improving socioeconomic status of families
- increasing participation of females in the labour force (which in turn leads to smaller family sizes and fewer numbers of cousins eligible for marriage).

The improved overall educational status of the population means that there is a greater awareness of the potential adverse effects of consanguineous unions on child health in families with a history of recessive disease.

Figure 1 Global distribution of consanguineous marriages. The numbers are lower-bound estimates of the overall global prevalence of consanguineous marriage. Detailed global estimates of consanguineous marriage in the current generation are available by continent, country, region and population at www.consang.net.
Effects of inbreeding on society

The prevailing suspicion about consanguineous unions in Western societies centres on the belief that the offspring of a close kin marriage will be physically and/or mentally disadvantaged. This perception has been used by many in the medical community and in public life to suggest that consanguinity should be discouraged on the grounds of medical expense and/or morality.

Congenital defects with complex causes appear to be more common in consanguineous families and, in gauging the influence of consanguinity and endogamy on health, this increased propensity to bearing a child with some form of disability can be examined in several ways.

Consanguinity and rates of fetal loss

Opinions differ on the association between consanguinity and fetal losses or stillbirths. Enhanced genetic compatibility would be expected between mother and fetus in consanguineous unions due to their greater proportion of shared maternal and paternal genes. For that reason, it is claimed that intrauterine mortality is lower in the pregnancies of consanguineous couples, with lower rates of conditions such as rhesus incompatibility and pre-eclampsia. Conversely, the fetal allograft hypothesis proposes that antigenic disparity between the mother and fetus is beneficial to fetal development, suggesting higher losses in consanguineous pregnancies.

A positive association between parental human leucocyte antigen (HLA) sharing at HLA loci and recurrent abortion was reported in a USA religious isolate, with negative selection against individuals homozygous at HLA loci.11 Retrospective data on pregnancies and prenatal losses may be subject to significant levels of recall bias, resulting in data of dubious reliability and with significant underestimation of the levels of prenatal losses. It is therefore unsurprising that contradictory results have been reported in a number of studies conducted in other populations.12

Comparative fecundity in consanguineous and non-consanguineous couples

Data obtained by a meta-analysis of 30 studies conducted in Asian and African countries showed a higher mean number of children born in all categories of consanguineous marriage when compared with non-consanguineous couples.12 The observed differences may be primarily social in origin because maternal age at marriage is typically negatively associated with consanguinity, resulting in a younger maternal age at first birth and thus an extended reproductive span.13

The uptake of contraception may be lower in consanguineous couples.14 Reproductive compensation has been advanced as an additional explanation for the positive association between consanguinity and fecundity, with infants dying at an early age rapidly replaced. Reproductive compensation may involve a conscious decision by parents to achieve their desired family size. Irrespective of cause or motivation, reproductive compensation effectively reduces the rate at which deleterious genes are eliminated from the gene pool.

Consanguinity and inherited disease

Much attention has focused on consanguinity in recessive disorders. A significant positive association has been repeatedly shown between consanguinity and early mortality, with disorders expressed by detrimental recessive genes particularly involved. In the general population, the risk of having a child with a severe or lethal medical condition is ~2% if there is no known recessive family history of disease, and the couple has not had a previous abnormal child. This risk increases to ~5–6% for a first-cousin couple. The excess risk associated with a first-cousin union is frequently overestimated by doctors and the lay population. This may be because the expected risk of occurrence/recurrence would be 25% if there is a clear family history of a recessive condition.

Consanguineous unions have been most frequently reported within the ruling classes and land-owning families in Western societies. This differs in other parts of the world, where the highest rates of consanguineous marriage are reported among poor, rural and largely illiterate communities and societies throughout Asia and North Africa.6 The poorest sections of populations are most disadvantaged in terms of health and health care provision, so over-representation of poorer and less educated families among consanguineous couples creates problems in assessing consanguinity on morbidity and mortality. A report from Saudi Arabia identified many modifiable maternal risk factors affecting child health (e.g. early and late age of marriage and childbearing, low education, unemployment, multiparity) in addition to consanguineous marriage.15

Table 1 gives the coefficients of relationship and inbreeding plus the risk of an autosomal recessive disorder in the offspring of consanguineous unions. A detailed listing of genetic disorders that have been diagnosed in the children of consanguineous couples is available at www.consang.net.

Consanguinity and deaths in infancy and childhood

Birth weight is an important indicator of short- and longer-term health. Information on the relationship between consanguinity and birth measurements has been mixed. Some studies have suggested that babies born to consanguineous parents are smaller and lighter and therefore less likely to survive; others have failed to detect a significant difference. A study of 10,289 consecutive live-born singleton newborns admitted to eight hospitals in Beirut, Lebanon, showed a negative association between consanguinity and birth weight at each gestational age. But no significant difference was observed in the decreasing birth weight between first- and second-cousin marriages, and at each gestational age consanguinity resulted in a decrease in birth weight of only 1.8%, with the largest adverse effects on foetal growth exerted by lower parity and smoking during pregnancy.16

Estimates of the overall adverse effects of consanguinity on survival have been highly variable because many earlier surveys produced spuriously high values due to inadequate controls for important non-genetic variables influencing childhood health, including maternal age and education, birth order and birth intervals. In ‘developing’ countries, excess consanguinity-associated deaths are largely concentrated during the first year of life, but in most cases a specific cause of death is not available due to inadequate diagnostic facilities, with parental reluctance to sanction prenatal diagnosis or autopsy examinations an additional factor. If a diagnosis has been made, a clear link between consanguinity and autosomal recessive disorders is apparent, with multiple deaths reported in a proportion of consanguineous
families, the effect being proportional to the level of parental genetic relatedness.  

Consanguinity and childhood morbidity

Studies into the prevalence of birth defects are dependent on accurate diagnoses, and the variable timing and clinical settings of investigations often means that genetic diagnoses overlap with and reflect late fetal and neonatal survival rates. First-cousin progeny had 3.8% excess major malformations in an Arab community in Israel, and a 26-year study based on the Medical Birth Registry of Norway reported 1.9% excess birth defects in Norwegian first-cousin couples and 2.4% among Pakistani migrant couples.  

According to the Latin America Collaborative Study of Congenital Malformations, based on 34,102 newborn infants with one of 47 types of congenital anomaly, a significant association with consanguinity was detected only for hydrocephalus, postaxial polydactyly, and bilateral cleft lip ± cleft palate.  

Identifying major categories of disease specifically overrepresented in consanguineous progeny from these data is difficult, but some single gene disorders are present in increased prevalence, including:

- autosomal recessive syndromic hearing loss
- blindness caused by early onset retinal dystrophies
- childhood onset of glaucoma, anophthalmos and microphthalmos.

In Saudi Arabia, bilateral retinoblastoma also has been reported to be more common in consanguineous offspring. More generally, a significant excess of major congenital defects has been diagnosed, particularly disorders with a complex cause and a higher rate of recurrence, possibly reflecting rare (or even unique) recessive mutations.  

Mild and severe intellectual and developmental disability are present at higher frequency in consanguineous families, although poor social conditions may play a significant causative role, particularly in cases of mild disability. In Bradford, with a population of 370,000, the high level of consanguineous marriage in the resident Pakistani community may have contributed to the more than 300 children referred annually to the Child Development Centre, with a disproportionately large number of cases of major neurodevelopmental disorders by national standards.

Increased prevalences of α- and β-thalassaemia, rare complex haemoglobinopathies and other haematological disorders (including coagulation deficiencies and acute lymphocytic leukaemia in childhood) have been reported for consanguineous offspring in different countries. A wide range of inborn errors of metabolism have been reported in indigenous and migrant populations, including lysosomal storage disorders and cerebral lipidoses.  

Living with consanguinity within society

Childhood disability is a major health problem in developing countries. Endogamy principally governs the spectrum of observed diseases in a community and can lead to the higher overall levels of homozygosity frequently observed in genetically subdivided populations. The greater the genetic isolation of a community and the longer its historical separation, the greater the probability that unique mutations will have occurred and attained high frequency.  

Within the UK and many Western countries, the high levels of continued consanguinity, with some evidence that the proportion of consanguineous unions has been rising, requires greater resources to be provided to improve the delivery of prospective genetic counselling and, where appropriate, prenatal testing, treatment and community care. This strategy tallies with the recommendations of the recent WHO Report on Medical Genetic Services in Developing Countries, which also emphasizes ensuring minimal disruption of community traditions and social norms.

A non-judgemental attitude towards consanguineous marriage is central to fostering good working relationships between the medical profession in communities where consanguinity is prevalent, and in enabling people to understand the risks. Attempts to discourage consanguineous unions at the population level are inappropriate and undesirable, particularly in populations and communities where consanguineous unions remain an integral part of cultural and social life. One way of decreasing child mortality within consanguineous unions has been to encourage consanguineous couples and their families to access premarital advice, and make an informed decision on health risks to their offspring.

Since publication of the results of a large cohort study of children born to a largely Muslim Pakistani population in Birmingham, UK, conducted in the late 1980s, much of the interest in migrant health in the UK has centred around the claims of deleterious outcomes of consanguinity and the expense to the taxpayer in Western medical services. There is growing evidence that as societies become more economically advanced, the disadvantages of the excess childhood morbidity associated with consanguinity become more apparent and of greater community concern. In an advanced, industrialized country such as the UK, the ready availability of paediatric intensive care procedures and sophisticated diagnostic protocols have heightened the adverse biological effects of consanguinity.

Summary

The future prevalence and status of consanguineous marriage is a matter of conjecture. It could be argued that the ongoing widespread popularity of consanguinity makes a rapid decline in its prevalence improbable. 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.  

The situation for migrant communities in Western societies is different because there is an attraction to continue with a form of marriage that has beenfavoured for many generations in their countries of origin, but a simultaneous desire among the younger generation to adapt to the different social customs of their adopted homeland. Ultimately, declining family sizes and a consequent reduction in the availability of potential marriage partners within the immediate family may prove to be the major factor in determining the future prevalence of consanguineous unions.

Improved medical and scientific knowledge has decreased the overall burden of care and health costs in Western societies. Specific attention has been paid to meeting the particular genetic counselling and diagnostic needs of couples in consanguineous unions. To achieve comparable advances in developing countries, extensive community education programmes are needed to reduce the burden on health care systems, and to complement
the existing diagnostic, counselling and treatment skills of local staff.

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Acknowledgement

AHB is funded by National Science Foundation Grant 0527751.