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SCIENCE AND SOCIETY

Genetic counselling and customary consanguineous marriage

Bernadette Modell and Aamra Darr

Consanguineous marriage is customary in many societies, but leads to an increased birth prevalence of infants with severe recessive disorders. It is therefore often proposed that consanguineous marriage should be discouraged on medical grounds. However, several expert groups have pointed out that this proposal is inconsistent with the ethical principles of genetic counselling, overlooks the social importance of consanguineous marriage and is ineffective. Instead, they suggest that the custom increases the possibilities for effective genetic counselling, and recommend a concerted effort to identify families at increased risk, and to provide them with risk information and carrier testing when feasible.

A consanguineous marriage is usually defined as a marriage between people who are second cousins or closer[1]. Consanguineous marriages occur in most populations, but in some they are rigorously avoided, whereas in others they are positively preferred. Consanguineous marriage is customary in the Middle East and parts of South Asia, among Irish Travellers, Zoroastrians, some Jewish communities and many tribes in sub-Saharan Africa and South East Asia. Although the custom is often perceived to be associated with Islam, in fact it is independent of religion. It is estimated that globally at least 20% of the human population live in communities with a preference for consanguineous marriage, and that at least 8.5% of children have consanguineous parents[2,3].

Consanguineous marriage increases the chance that both members of a couple will carry any recessive variant that is being transmitted in their family, and that this will manifest in the homozygous state in their children. As most recessive characteristics are harmless, the custom brings out the latent genetic diversity in a population (for example, given the same gene frequency, there are more people with blue eyes when consanguineous marriage is common than when it is rare). Conversely, it also increases the birth prevalence of infants with serious recessive disorders.

The high prevalence, global extent and genetic implications of customary consanguineous marriage have attracted attention only recently, partly because migration has brought significant numbers of people from populations that favour consanguineous marriage to the West. Another reason is that falling infant mortality in Middle Eastern and South Asian communities is unveiling the contribution of severe recessive disorders to childhood mortality and morbidity[4]. When the problem is recognized, a common first reaction is that consanguineous marriage should be discouraged for genetic reasons. This approach has been promoted in the Middle East, where limited resources seem to exclude provision of genetic services on a Western model. However, more careful consideration leads to the recognition that a consanguineous kinship pattern is integral to the structure of many societies, and has many social benefits[5]. An appropriate approach for genetic counselling must work within and build on, rather than oppose, such social conventions[6,7].

In 1994 and 1996, the World Health Organization's Regional Office for the Eastern Mediterranean (which covers North Africa and the Middle East, including Pakistan) convened two meetings of experts in medical and social sciences to review the place of genetics in medical services in the region[8]. The participants agreed that consanguineous marriage is an integral part of cultural and social life in many areas, and that attempts to discourage it at the population level are inappropriate and undesirable, even though it is associated with an increased birth prevalence of children with recessive disorders. Instead, they recommended an approach that identifies families at increased risk and provides them with genetic counselling. They pointed out that this approach can be unusually effective in populations that favour consanguineous marriage[9], and concluded that the development of genetics services is a particularly high priority for such communities. Discussions in the United Kingdom have reached similar conclusions[10], and the approach has been further developed at a recent multidisciplinary meeting (B.M. and A.D., unpublished observations). This article summarizes the background to these discussions and the recommendations arising from them.

> "Consanguineous marriage increases the chance that both members of a couple will carry any recessive variant that is being transmitted in their family, and that this will manifest in the homozygous state in their children."

Customary consanguineous marriage

The reasons that people give for preferring consanguineous marriage include: strengthening of family ties; relative ease for both men and women in finding a suitable partner; support for the woman's status, as well as better relationships with her in-laws[1,11–13]; and care for people in old age. Also, in practice, consanguineous marriages are more stable than marriages between unrelated partners[1,12]. An anthropological perspective on kinship patterns can help in understanding these observations[13,14].

In many non-European communities, the family name and property are inherited in the male line, and men and their descendants tend to stay together, especially when the family owns land. In this patrilineal framework, men customarily find a wife in one of two ways, with very different implications for the power position of women, as shown in FIG. 1. The first way, by negotiation with unrelated families (patrilineal exogamy), inherently introduces uncertainty for the woman. She breaks her ties with her birth family and must establish her standing in her husband's family as an outsider: only the birth of a son gives her direct access to the family lines of power. Alternatively, marriages can be arranged within the extended family. This is called patrilineal endogamy but, in reality, it is also partly matrilineal. It strengthens the position of women because it involves rearrangement rather than disruption of existing family ties, and tends to equalize the value of women by creating a requirement for equal numbers of sons and daughters within the kinship group.

For most people worldwide, the family remains the main source of social security. In communities that favour consanguineous marriage, multiple family ties confer strong reciprocal obligations on family members to assist each other when in need. Such ties can seriously restrict individuals' freedom of action, but when times are hard this can seem a small price to pay for security. The large, close family structure offers niches for socially or medically disadvantaged members, and relatively less stigma might be attached to inherited conditions[15] (S. Ahmed, personal communication). Therefore, an effort to alter the marriage pattern on medical grounds could undermine the very support systems that help people to cope with genetic disadvantage. Conversely, the convention can place disproportionate obligations on a few individuals, and family disputes can become particularly embittered.

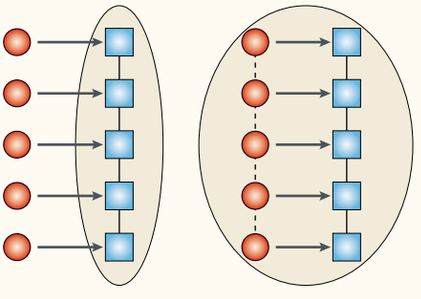

Figure 1 | **Patrilineal kinship patterns can have very different social implications.** The kinship pattern on the left represents patrilineal exogamy, in which wives are selected from outside the extended family or kinship group. The pattern on the right represents patrilineal endogamy, in which wives are usually found within the extended family. The latter situation creates vertical bonds of relationship between the female, as well as the male, members of the family, and strengthens the power position of individual women. Females are indicated by circles and males are indicated by squares. Redrawn with permission from REF. 5 © (1997) Macmillan.

Prosperity and social stability reduce the need for such strong family ties, and economic development might ultimately reduce the frequency of marriage between cousins. However, such changes take place in their own time, and external efforts to accelerate them might be particularly harmful for the less advantaged members of society. Indeed, the loosening of family ties is a recognized social problem of high-resource societies.

Effect on population gene flow. Societies in which consanguineous marriage is customary have a complex social structure. Couples are embedded in an extended family that forms part of a larger related group within which most marriages occur. In Pakistan, this group is the *biradheri* (brotherhood); in the Middle East, it is a tribe[16]. Social structure affects the distribution of gene variants in the population. In 'randomly mating' North European societies, variants become widely distributed, but in endogamous societies they are often 'trapped' in particular kinship groups. In Oman, for example, the population is composed of endogamous tribal units with very limited intermarriage, and inherited disorders are correspondingly unevenly distributed, many being practically restricted to identifiable family and tribal groupings[16]. Strategies for delivering genetics services should take account of such differences.

Prejudices and misunderstandings

In Western societies today, consanguineous marriage is generally viewed as causing physical and mental incapacity, and newspaper articles regularly refer to 'inbreeding' as 'unwholesome'. However, English literature of the nineteenth century contains no trace of these attitudes, and the Oxford English Dictionary locates the first reference to inbreeding as harmful (among cattle) in 1888. Current attitudes therefore seem to be a legacy of the eugenic tendencies of the early twentieth century. Health workers are not immune to the prejudices of their society: many have an exaggerated idea of the genetic disadvantages of consanguineous marriage, and related couples with a child that has any chronic disorder are often told that the child is sick because they are related[10,15,17,18]. The fact that harmful misinformation is being issued daily makes a pressing case for disseminating correct information on the genetic and social implications of consanguineous marriage.

It is often thought that Muslims have little need for genetic counselling as they do not make use of prenatal diagnosis for religious reasons. However, studies have shown a high uptake of prenatal diagnosis in the first trimester for severe disorders, such as thalassaemia, among Muslims in the United Kingdom, Turkey, the Middle East and Pakistan[19–21]. A fatwa (an authoritative ruling on a point of Islamic law) that accepts abortion for genetic reasons in the first trimester has been issued in several Islamic countries, including Pakistan[21] and Iran (A. Samavat, personal communication). Therefore, Muslims need the same genetic counselling services as members of other communities.

Genetic implications

Congenital and genetic disorders fall into two broad categories. In 'multifactorial disorders', a combination of usually neutral variants in one individual can result in their becoming predisposed to the disorder. Multifactorial disorders include most congenital malformations, as well as cardiovascular disease and asthma/eczema, among others. By contrast, 'single-gene disorders' are the classical inherited disorders with a Mendelian dominant, X-linked or recessive inheritance pattern. Consanguineous marriage has a relatively small effect on the prevalence of dominant and X-linked disorders, and its role in multifactorial disorders is still uncertain. Recessive disorders are the only conditions that are clearly more common when parents are related.

Most people carry one or two gene variants that can potentially cause a recessive disorder, but that have no effect on their own health[22]. However, when a carrier's partner happens to carry an equivalent recessive variant, their children have a one in four chance of inheriting it from both parents and suffering from the corresponding recessive disorder. Collectively, people in most populations carry hundreds of different recessive disease variants. A few, such as haemoglobin disorders or cystic fibrosis, are common, but most are rare, and so the random chance of both partners carrying the same variant is small. Nevertheless, a wide range of recessive disorders occurs occasionally and unexpectedly in all populations.

In typical Northern European populations, recessive disorders account for ~4% of all congenital/genetic disorders and for 17% of single-gene disorders[23,24]. However, they

occupy the severe end of the disease spectrum and contribute disproportionately to childhood death and long-term disability.

Consanguineous marriage increases a couple's chance of both carrying the same recessive disease variant and their risk of having affected children. The effect is particularly marked for rare disorders, because a carrier is unlikely to find a partner who carries the same disorder unless they are related. Therefore, in communities in which consanguineous marriage is common, there is an increased birth prevalence of many rare recessive conditions, and a significant increase in the total birth prevalence of congenital and genetic disorders. However, the most common congenital disorders, including Down syndrome, neural-tube defects and cerebral palsy, are not recessively inherited, and so are not more common when parents are related.

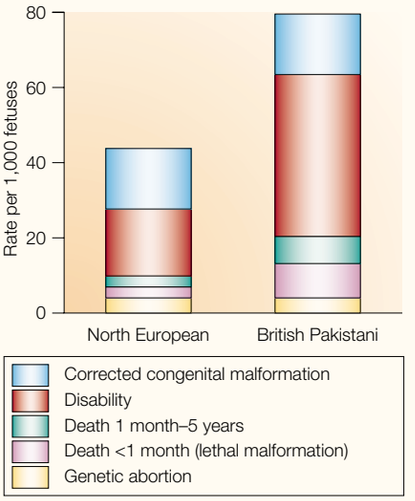

Figure 2 | **Outcomes of viable pregnancies of North European and British Pakistani couples, in which the fetus has a congenital or genetic disorder.** Reported in the 'Birmingham birth study'[28].

Population-level observations

The effect of customary consanguineous marriage at the population level depends on the frequency and nature of all recessive variants in the population, and on the population structure. Documented effects include increased infant mortality and increased birth prevalence of infants with congenital malformations, learning difficulties, blindness, hearing impairment and metabolic disorders. However, there is no measurable increase in the rate of spontaneous abortion or infertility[4]. A meta-analysis — a procedure that rigorously combines existing data in the literature — of 38 studies, mostly from low-resource countries, showed an average 4.4% increase in infant mortality among the offspring of first cousins, compared with unrelated controls[4]. However, congenital disorders that lead to death in lower-resource countries might be successfully treated or lead to disability in higher-resource countries.

Studies in high-resource countries

Data from registers of congenital anomalies give a baseline 2.0–2.5% birth prevalence of serious congenital and genetic disorders for children of unrelated parents, and about twice this figure for children of first cousins[25,26]. However, these registers usually only include disorders that are diagnosed by one year of age. Many serious conditions are diagnosed later in childhood, including less obvious internal malformations, learning difficulties and many single-gene disorders (for example, neurological disorders, thalassaemia and cystic fibrosis). Longer-term studies give an ~4% birth prevalence of genetic and congenital disorders[23,24], and most genetic counsellors give about twice this risk for children of first cousins[27]. However, accurate assessment of the effect of customary consanguineous marriage on childhood morbidity and mortality requires a follow-up study in a country with both a sizeable population that has a preference for consanguineous marriage, and facilities for precise diagnosis and long-term care of affected children.

The 'Birmingham birth study'. There are more than one million residents in groups with a preference for consanguineous marriage in the United Kingdom, where they are particularly concentrated in inner city areas. In Birmingham, where more than 25% of babies born are of British Pakistani, Bangladeshi or Middle Eastern origin[28], a careful prospective study has provided the most detailed information available so far on the relationship between parental consanguinity and the birth prevalence and outcomes of congenital and genetic disorders in a high-resource society.

The researchers enrolled a random sample of 4,886 women who had just given birth, as well as their babies. They established parental ethnicity and consanguinity status, took a full obstetric history, and collected follow-up data on all causes of death and disability to five years of age among study babies. The initial objective was to compare outcomes for the children of non-consanguineous and consanguineous couples, with ethnic group as a factor. However, the numbers in each ethnic group were small and most of the parents of British Pakistani babies were related, leaving too few unrelated couples for a statistically valid comparison within the group. Conversely, the increased genetic risk for related couples seems to be relatively independent of their ethnic origin[4,26]. The most valid and useful comparison was, therefore, between all 2,432 babies of North European origin and all 956 babies of British Pakistani origin.

The genetic implications of a consanguineous marriage are related to the proportion of the children's gene pairs that are identical because they are inherited from a common ancestor. For example, when first cousins marry, their children inherit one-eighth of their genes from their common grandparents, and so one-sixteenth of their genes (6.25%) are identical by descent. This is expressed as a coefficient of consanguinity (F) of 0.0625 (REF. 22).

In the Birmingham study, only 0.4% of the North European couples were related. Among the British Pakistanis, 69% of couples were related and 57% were first cousins. Many couples also had related parents, so the coefficient of consanguinity for the whole British Pakistani group was 0.0431 — equivalent to a population average of 70% first-cousin marriages. Outcomes for the two groups are summarized in FIG. 2.

Among the North European children, the birth prevalence of all congenital and genetic disorders was 4.3%, and that of definite, probable and possible recessive disorders was 0.28% (6.5% of the total). Among British Pakistani children, the birth prevalence of all congenital and genetic disorders was 7.9% — almost twice as high as among North Europeans — whereas the prevalence of definite, probable or possible recessive disorders was 3.0–3.3% — over ten times higher than among North Europeans. Most of these disorders occurred in children of related parents, and most caused early death or chronic disability. There was also an excess of lethal (mainly cardiac) malformations that were apparently unrelated to parental consanguinity, and so recessive disorders accounted for ~75% of the excess over North Europeans. The study amply confirms that populations favouring consanguineous marriage are at increased genetic risk and have a particular need for genetics services.

The recommended approach

In reality, couples of any ethnic origin fall into two groups: a majority who do not both carry the same recessive disorder, and a minority who do and are at 25% risk of an affected child in each pregnancy. A policy orientated to reducing genetic reproductive risk would

Box 1 | **Testing the hypothesis: a Pakistani case study**

A group of large extended families with a history of haemoglobin disorder was compared with a group of control families with no such history[29]. More than 40% of married couples were close relatives, 50% were from the same *biradheri* and only a handful were demonstrably unrelated.

- **The haemoglobin gene variants were very unevenly distributed. Thirty per cent of the members of families with a history of haemoglobin disorder were carriers, but no carriers were found in the control families.**
- **Carriers were at high genetic risk: ~30% of married carriers had a carrier partner.**
- **In most families with a history of haemoglobin disorder, other at-risk couples were identified. Most had already had affected children, but couples could have been identified and informed prospectively if extended family studies had already been routinely done.**
- **One-third of the couples at risk in the families with a history of haemoglobin disorder were not ostensibly consanguineous, but were married within the *biradheri*. It seems that the entire *biradheri* (or branch of it) should be considered as being at risk until proved otherwise.**
- **The study concluded that: first, the proposed approach is valid, and is equally applicable to rare and to common disorders; second, in high-resource countries, it should be integrated into existing health services; and third, in low-resource countries where consanguineous marriage is common, it is a starting point from which to develop more comprehensive genetics services.**

aim to identify and counsel these couples. As the prevalence of couples at risk is four times the affected birth prevalence, the above data indicate that ~1.1% of unrelated couples are at risk and ~13% of British Pakistani couples are at risk. Because the coefficient of consanguinity for the British Pakistani population is equivalent to a 70% frequency of first-cousin marriage, an average first-cousin couple has a 13% × 1.4 = 20% chance of being at risk. The same approximate risk probably applies for first cousins of any ethnic origin[4,26].

The question is how to identify and inform at-risk couples prospectively, before they have had an affected child. In randomly mating populations in which recessive disorders seem to occur sporadically, most at-risk couples can be detected only after the birth of their first affected child. Risk can be detected prospectively only by carrier screening, when this is feasible and the condition is common, as is the case for haemoglobin disorders and cystic fibrosis.

However, expert groups have proposed a 'family orientated' approach for communities in which consanguineous marriage is customary, on the basis of the following argument[8,10]. When families are large with multiple consanguineous marriages, any recessive variant present is likely to manifest in the form of an affected child born into some branch of the family. The diagnosis of this child then signifies that the extended family is at high genetic risk. In addition, because carriers in such families have a high risk of marrying another carrier, taking a genetic family history from any member of such a family should reveal the presence of an affected person and raise the possibility that the consultand (unaffected person) and their relatives are carriers.

The fact that most affected children will be homozygous for the same mutation simplifies the challenge of obtaining a DNA diagnosis and achieving carrier testing. When carrier testing is possible, an organized strategy of offering extended family testing as soon as an affected child is diagnosed will allow carriers to make an informed choice from the widest range of available options for reducing risk. A systematic approach to extended families will ultimately reach the whole population at risk.

"The high prevalence, global extent and genetic implications of customary consanguineous marriage have attracted attention only recently, partly because migration has brought significant numbers of people from populations that favour consanguineous marriage to the West."

An important problem is that, at present, carrier testing is feasible for only a proportion — perhaps 30% — of couples at risk. However, if the Human Genome Project delivers as promised, DNA-based carrier diagnosis should become possible for most genetic diseases in the foreseeable future (some disorders are still diagnosed using enzyme methods; however, as such methods often cannot reliably detect carriers, DNA tests are essential).

The proposed approach has been explored in Pakistan using haemoglobin disorders as a model; because they are common, carriers (5% of the Pakistani population) are easily diagnosed and prenatal diagnosis is available locally[21] (BOX 1). In addition, an approach that works for haemoglobin disorders could be used for any other recessive condition for which carrier testing is feasible. The findings confirmed the hypothesis[29].

Conclusion

The increased health burden of recessive disorders in communities in which consanguineous marriage is common is an important issue for genetics services in high-resource, as well as in lower-resource, countries. In the United Kingdom, for example, minority ethnic groups constitute 7.3% of the population but, when haemoglobin disorders are included, more than 40% of all children with recessive disorders belong to these groups (B.M. and A.D., unpublished data). The uneven distribution of groups at increased risk leads to localized, marked increases in the need for medical genetics and childhood disability services[30]. This article shows that a systematic, long-term family-centred approach to genetic risk and carrier detection might significantly reduce the additional burden of recessive disorders.

At the scientific level, the proposed strategy depends heavily on progress in identifying the mutations that underlie recessive disorders, particularly those leading to mental retardation[28,30]. Molecular geneticists need to appreciate the global health importance of such studies, and develop national and international networks to share precise molecular and pedigree information.

At the service level, we suggest a 'pincer movement' for identifying genetic risk. On the one side, paediatricians, geneticists and other specialists who diagnose affected children need the resources to take extended family histories and provide carrier testing, systematically and on a large scale. On the other side, primary care teams (and maternity services) need to identify prospectively couples at increased risk. Ideally, a careful genetic family history should be taken from every couple before reproduction, but this is a priority for consanguineous couples, including those with no ostensible problem.

However, it is one thing to recognize an appropriate approach and quite a different matter to put it into practice. A multidisciplinary meeting held at the London Royal Society of Medicine in the Autumn of 2001 began the process of spelling out the requirements for the United Kingdom (B.M. and A.D., unpublished observations). The first requirement is for explicit recognition that

the genetic implications of consanguineous marriage constitute an important but complex public health issue, that a national strategy is needed and that, in the absence of planning, the uneven distribution of the risk groups guarantees patchy and inefficient services. The next is for multidisciplinary agreement on a socially and medically appropriate approach, a well-publicized plan and clear definition of the respective roles of primary and maternity care, paediatrics, health promotion, community services, clinical genetics and clinical molecular genetics services.

Once agreed, the recommended approach needs to be implemented and coordinated through public health authorities, to ensure interdisciplinary and inter-regional collaboration. Primary care teams have a crucial role. Fortunately, there is now growing recognition of the importance of genetic approaches in primary care. Training should include a validated method for recording a basic genetic family history, and clear guidance on when to refer consanguineous couples for expert advice. When primary care workers are adequately informed, the community can turn to them for pre-reproductive genetic advice and appropriate specialist referral. The community should also be informed — for example, through teaching in schools about basic inheritance and the importance of the genetic family history.

In fact, the issue of customary consanguineous marriage simply shows the need for a health service infrastructure that is able to deliver the benefits of growing genetic knowledge to a multi-ethnic population, and most of the requirements apply for genetic issues across the board. They call for resources that are not yet generally available in most countries, including community-based and own-language genetic counselling, training programmes, a unified molecular genetics service and expanded clinical genetics services. These will become available only if primary care workers generate demand by referring couples and families who need the service. The benefits to families and communities could be enormous, while the costs of providing the service will certainly be far lower than the long-term costs of maintaining the status quo.

Bernadette Modell is at the Royal Free and University College Medical School, 2nd Floor, Holborn Union Building, Highgate Hill, London N19 5LW, UK, and the Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.

Aamra Darr is at the School of Health and Social Welfare, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK.

Correspondence to B.M. e-mails: b.modell@pcps.ucl.ac.uk; a.r.darr@open.ac.uk.

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Information materials designed for patients and primary care workers in haemoglobin disorders: http://www.chime.ucl.ac.uk/APoGI/
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ERRATUM

THE COMPLEX STRUCTURE AND DYNAMIC EVOLUTION OF HUMAN SUBTELOMERES

Heather C. Mefford and Barbara J. Trask

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On p. 93, the following incorrect sentence was published:
"The finished sequence of 22q (REF. 32) terminates not at the true end, but at an interstitial array of telomere-like repeats within the sequence of a clone that actually derives from 2q13."

It should have read:
"The finished sequence of 22q (REF. 32) does not terminate at the true end, and one might expect a clone that overlaps it and is ascribed to 22q in GenBank to extend the 22q sequence towards the telomere. However, this clone derives from 2q13."