Consanguineous Marriage: Prevalence, Causes, and Inbreeding Depression

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Abstract

The term consanguineous marriage describes unions between couples known to share at least one common biological ancestor. Although widely permissible under civil legislation, consanguinity is now rare in most Western societies and it has declined markedly in prevalence in Japan during the last two generations. By comparison, in regions such as North Africa, West, Central, and South Asia, 20 percent to over 50 percent of current marriages are between couples related as second cousins or closer, with no evidence of a reduction in popularity. The strengthening of family relationships is of primary importance in the preference for close kin unions, with economic benefits an additional consideration. Consanguinity does not appear to adversely affect human fertility. The unfavorable clinical outcomes associated with inbreeding are caused by the expression of detrimental recessive genes inherited from each parent, giving rise to the phenomenon of inbreeding depression. With the global epidemiological transition from a primarily infectious to a genetic disease profile, it can be predicted that consanguineous marriage will assume much greater prominence as a contributory factor in the prevalence of genetic disease.

Introduction

It can be argued that all humans are to some extent inbred, as evidenced both by the readily identifiable ethnic subdivisions found within our species, and by a simple calculation of the impossibly large number of human ancestors that would be implied if all matings had occurred with non-kin in past generations. From a biological perspective, the term inbreeding is used to describe unions between couples who are known to share genes inherited from one or more common ancestors. In cases where both parents are carriers of the same mutant autosomal (non-sex chromosome) recessive gene, there will be a 1 in 4 chance of its expression in the prenatal period, at birth or later in life depending on the nature and site of the mutation, thus contributing to the phenomenon of inbreeding depression. Although now rare in Western societies, marriages between close biological kin are preferential in many parts of the world, including north and sub-Saharan Africa, the Middle East, Central Asia, and much of the Indian sub-continent (Bittles 1998). For example, in Pakistan over

60 percent of all marital unions in the present generation are contracted between couples related as second cousins or closer (Hussain & Bittles 1998).

In first cousin marriages, the spouses are predicted to have 12.5 percent of their genes in common, and so on average their progeny will be homozygous at 6.25 percent of gene loci, i.e. they will have inherited identical gene copies from each parent at these sites in their genome. This is conventionally expressed as the coefficient of inbreeding (F), which for first cousin offspring is 0.0625, while for uncle-niece or double first cousin progeny $F = 0.125$ and conversely for second cousins $F = 0.0156$. At the population level the mean level of inbreeding (α) can be calculated according to the formula:

$$\alpha = \Sigma\, p_i F_i$$

where (Σ is the sum of the proportion of individuals pi in each consanguinity category F_i. The values of α reported to date can vary from 0.0001 in Western Europe and North America to >0.0570 in some South Asian population isolates which practice preferential consanguineous marriage (Bittles 1998; http://www.consang.net).

In many populations there is a long, unbroken history of consanguineous unions. Under these circumstances the cumulative level of inbreeding may be significantly higher than the value calculated for a single generation. A correction can be applied to account for the effects of ancestral inbreeding using the formula:

$$F = \Sigma\, (1/2)^n\, (1 + F_A)$$

where F_A is the ancestor's inbreeding coefficient, n is the number of individuals in the path connecting the parents of the individual, and the summation (Σ) is taken over each path in the pedigree that goes through a common ancestor.

Religious Attitudes to Consanguineous Marriage

Current Western attitudes towards consanguinity stem largely from the regulations of the early Christian Church, with a ruling on permitted degrees of marriage provided by Pope Gregory I in approximately AD 597 (Bittles 1994). For members of the Latin Church, the effect of this decision was to prohibit marriage with a biological relative, up to and including third cousins. These formal prohibitions on consanguineous unions remained in force until 1917, when they were limited to unions between couples related as first cousins or closer (Goody 1985). As a result, Roman Catholic couples who are related as first cousins and wish to marry in Church must still request and obtain Diocesan dispensation. Similar strict rules governing consanguineous marriage continue to be applied by the Christian Orthodox Church, up to and including third cousins. Among the Reformed Protestant denominations, the detailed Biblical guidelines set out in *Leviticus* 18, 7-18 were widely adopted, although the closest form of approved union usually has been between first cousins.

Within other major world religions, including Buddhism, Islam, and Judaism, and in

smaller religious communities such as the Zoroastrians/Parsis, attitudes to close kin marriage are generally favorable or neutral (Bittles et al. 2001). Likewise, in the Chinese Taoist/Confucian tradition, first cousin marriages of the type mother's brother's daughter (termed 'up the hill') also are permitted. As a result, during the period 1949 to 1967, 1.1 percent to 5.7 percent of marriages in P.R. China were found to be consanguineous in rural Han communities (Du et al. 1981; Wu 1987).

As illustrated in Table 1, there also is a long tradition of consanguineous marriage in Japan that crosses religious boundaries (Imaizumi et al. 1975; Imaizumi 1986a). Comparative studies conducted on Hirado, an island in the prefecture of Nagasaki, indicated that consanguineous unions were most common among the *Kakure Kirishitan*, a syncretic religion embodying elements of Buddhism, Catholicism, and Shintoism, with lesser levels among the Buddhist and Roman Catholic communities respectively (Schull et al. 1968).

Table 1

Consanguineous marriage in Japan

Region	Period	Consanguinity	Mean coefficient of inbreeding (α)	Source
Hiroshima	1948/53	5.9%	0.0027	Schull (1958)
Nagasaki	1948/53	8.0	0.0037	Schull (1958)
Hirado	1964/65	14.7	0.0061	Schull et al. (1970)
Fukuoka	1962/65	7.6	0.0029	Yamaguchi et al. (1970)
All-Japan	1972	5.7	0.0018	Imaizumi et al. (1975)
All-Japan	1983	3.9	0.0013	Imaizumi (1986b)

The situation with respect to consanguinity is somewhat more complicated in Hinduism, in part reflecting the size and immense diversity of the population of India, which encompasses an estimated 50,000 to 60,000 different endogamous groups (Gadgil et al. 1998). All Hindu communities are structured into a number of hierarchical groups, each of which has its own set of rights, duties, and privileges. There are four *varnas*—the Brahmins, Kshatriyas, Vaishyas, and Sudras—and each *varna* is sub-divided into castes (*jati*), with caste membership hereditary and largely inviolable. Castes are further sub-divided into *gotras* that are transmitted through the male line, with marriages prohibited between the children of two brothers. In addition, according to *sapinda* regulations, persons related to each other within a certain number of generations on the paternal and maternal sides of a pedigree are forbidden to marry.

Virtually all Hindu marriages continue to be contracted within caste boundaries, and *gotra* regulations also are observed on a near-universal basis. At the *sapinda* level there are, however, major differences in the preferred marriage practices of the peoples of North and South India. Among the Aryan Hindus of North India, and in Sikhism, pedigrees are examined over an average of seven generations for males and five generations for females to ensure avoidance of a consanguineous union (Kapadia 1958: 117-137). By comparison,

uncle-niece marriage and first cousin unions between a man and his maternal uncle's daughter (mother's brother's daughter) have a long tradition in South India.

No comparable North-South differentiation exists in the Muslim population of India, which now numbers approximately 120 million. (More precise data on the total number of Muslims in India are unavailable because the 1991 Census could not be administered in the strongly Muslim region of Kashmir). However, differences in the levels of consanguineous unions are found between different branches of Islam and between specific communities. While 43.4 percent of marriages in the Shia community of Lucknow in North India were consanguineous (Basu 1975), the comparable figure was less than 10 percent among the *Mappillas* of Kerala, the descendents of Arab traders who settled in the southwest of the country from the eighth century AD (Bittles & Hussain 2000). Within the sub-continent, the clearest division in rates of Muslim consanguineous marriage is between communities in India and their Pakistan co-religionists (Hussain & Bittles 1998; Bittles & Hussain 2000), emphasizing the importance of local and regional marriage customs.

The net result of these various religious preferences and prohibitions within India is shown in Table 2, based on the National Family and Health Survey conducted during 1992-1993 (International Institute for Population Sciences 1995). While consanguineous unions were reported in all religions, at national level the highest rates were observed in the Muslim and Buddhist communities, and the lowest among Sikhs and Jains.

Table 2

Consanguineous marriage by religion, All-India 1992-1993

Religion	Number studied	Consanguinity	Mean coefficient of inbreeding (α)
Hindu	73,648	10.6%	0.0068
Muslim	10,806	23.3	0.0141
Christian	2,142	10.3	0.0068
Sikh	1,673	1.5	0.0009
Buddhist	734	17.2	0.0108
Jain	428	4.2	0.0023
Other	345	9.0	0.0056
All religions	89,777	11.9	0.0076

Source: International Institute for Population Studies (1995)

Civil Legislation on Consanguineous Marriage in Different Societies

Despite Church proscriptions, prior to the mid-nineteenth century first cousin marriages were commonly contracted in many Western societies, including Mediterranean countries such as Spain and Italy, where a large majority of the population was Roman Catholic (Bittles 2000). From the 1850s onward, a major debate was conducted within the scientific

and medical communities of North America and Western Europe regarding the biological effects of close kin marriage and, as part of this process, Charles Darwin attempted to have a question on the prevalence of first cousin marriages included in the 1871 Census of Great Britain and Ireland. The rejection of this proposal by a Parliamentary Select Committee was attacked by Darwin in *The Descent of Man* (1871: 402) and, to overcome the consequent lack of information on consanguinity, his son George Darwin devised an alternative strategy, using surnames as markers of genetic identity. Despite these controversies, there is no civil legislation in Western European countries to restrict first cousin marriage. Indeed, since 1987 half-sibs have been permitted to marry in Sweden.

By comparison, in the U.S.A laws were passed in a majority of states to control, and in many cases to ban, first cousin marriages despite the questionable validity of the information on which these laws were based. Several states subsequently relaxed their prohibition on first cousin marriages, but they remain illegal in twenty-two states and are a criminal offence in eight others. The actual degrees of prohibition differ quite widely between individual states and it is difficult to identify any particular biological rationale behind the proscriptive legislation, other than a general belief that the progeny of consanguineous unions would be of lesser biological fitness. That this suspicion continues to the present day was indicated by the ultimately unsuccessful attempt during 1999/2000 to pass legislation banning first cousin marriages in the state of Maryland.

At the time of its establishment in 1948 there was a generally tolerant approach to marriage between biological relatives in P.R. China. This attitude changed with the introduction of the 1981 Marriage Act under which marriage between first cousins became illegal, with the explanation '*...now that family planning is being promoted and the number of children is reduced, it is even more important to pay attention to the quality of the population*'. Nonetheless, it was stressed that where first cousin unions were customary, the Law should be implemented gradually and '*Crude and summary methods should not be used...*'. In effect, this caveat acknowledged the difficulty of overturning the tradition of first cousin marriage among the rural Han, and the potential sensitivity of the new legislation to the various Muslim minority populations in the country, especially in Xinjiang province. The most extreme current limitations on consanguineous marriage were enacted by the Democratic People's Republic of Korea. Under article 10 of the Family Law adopted by the Standing Committee of the Supreme People's Assembly in 1990, marriages between blood relatives up to and including third cousins are prohibited.

Understanding the Preference for Consanguineous Unions

The preference that exists in many societies for consanguineous marriage is mainly social and to a lesser extent economic in origin, and is based on the strengthening of family relationships. At the same time prenuptial arrangements are greatly simplified, which results in

younger ages at marriage for consanguineous couples, as illustrated for India in Table 3. The implicit security offered by marrying a partner whose entire family background is known is also considered to be of major importance in ensuring the success and the stability of the marital union (Bittles 1994; Hussain 1999).

In all major societies, the most common form of consanguineous marriage is between first cousins. However, the importance of customary influences is apparent from variations in the specific types of first cousin marriage contracted. For example, in Arab Muslim communities, the marriage of a man with his father's brother's daughter is strongly preferred (Khlat 1997), whereas all four types of first cousin union, i.e. father's brother's daughter, father's sister's daughter, mother's brother's daughter, and mother's sister daughter are arranged in South Asian Muslim communities. Mother's brother's daughter marriage is the preferred form of consanguineous union in such disparate populations as the Dravidian Hindus of South India (Rao & Inbaraj 1977), the Han Chinese (Wu 1987), and the Tuareg of North Africa (Degos et al. 1974). Within each of these societies, a union with the groom's father's brother's daughter would be regarded as equivalent to incest.

The highest rates of consanguineous marriage usually are found in poor, rural communities with low levels of literacy (Bittles 1994), but close kin marriage also is widely favored by land-owning families. These contrasts were observed in Japan, with the highest rates of consanguinity among poorer urban families in Hiroshima and Nagasaki (Schull & Neel 1965), but the reverse was true on the island of Hirado where consanguineous marriages were most frequent among land-owning farming families (Schull & Neel 1972). An inverse association between consanguinity and educational status was likewise confirmed across Japan (Imaizumi 1986a), which is the only major population to have recorded a decline in consanguineous marriage within the last two generations (Imaizumi 1986b). A further socio-demographic factor governing the level of consanguineous marriage is the number of potential marriage partners, which may have been an important influence in the very high consanguinity levels observed in some small and remote Japanese communities (Fujiki et al. 1982).

Table 3

Consanguineous marriage by age at marriage, All-India 1992-1993

Marital age in years	Number of women studied	Consanguinity	Mean coefficient of inbreeding (α)
<15	352	17.9%	0.0123
15-19	9,095	13.7	0.0085
20-24	17,983	12.6	0.0081
25-29	17,442	11.5	0.0073
30-34	14,660	10.8	0.0068
35-39	12,461	12.5	0.0080
40-44	9,748	12.0	0.0076
45-49	8,036	11.6	0.0075
Total number	89,777		

Source: International Institute for Population Studies (1995)

The Influence of Consanguinity on Reproductive Behavior and Success

Studies in mice have indicated a significant role for major histocompatibility complex (MHC) haplotypes in the initial stage of mate selection, with a preference for MHC-dissimilar partners and hence inbreeding avoidance. The underlying mechanism appears to be olfactory in nature and could be reversed by cross-fostering, indicating chemosensory imprinting (Penn & Potts 1998). A similar phenomenon has been proposed in humans, with a lower than expected incidence of HLA haplotype matches observed in the Hutterites, a highly endogamous Anabaptist sect resident in South Dakota, U.S.A. (Ober et al. 1997). It has been suggested that this imprinting could be explicable in terms of the influence of the MHC on both male body odors and female body odor preferences (Wedekind et al. 1995). However, other studies have either failed to confirm non-random mating at HLA loci (Pollack et al. 1982; Jin et al. 1995b; Ihara, this volume) or have indicated a greater likelihood of HLA sharing between couples (Rosenberg et al. 1983). In addition, no association could be found between the HLA system and sensitivity to androstenone (Pollack et al. 1982). Thus the current picture with respect to a direct role for the MHC in determining mate choice in humans is unclear.

An overall assessment of the genetic influence on fertility within consanguineous unions also is difficult. Enhanced genetic compatibility would be expected between mother and fetus in consanguineous unions, resulting in an advantageous pregnancy outcome because of decreased rates of ABO incompatibility, and the clinically more severe Rh incompatibility (Stern & Charles 1945) and pre-eclamptic toxaemia (Stevenson et al. 1971). Conversely, according to the fetal allograft concept, a balanced polymorphism for transplantation antigens may be maintained in mammalian species by a selective mechanism in which antigenic disparity between the mother and fetus is beneficial to fetal development (Clarke & Kirby 1966; Ober 1998). This hypothesis has been extensively investigated in human populations, especially among women who have experienced primary recurrent spontaneous abortions, i.e. with all conceptions lost pre-term, but with contradictory findings. In some studies there was a significant positive association between parental allele sharing at HLA loci, principally involving HLA-DR, -DQ and -B alleles, whereas in others no association could be detected (reviewed in Bittles & Matson 2000).

Even if a positive association does exist between infertility and parental HLA allele sharing, it is not absolute, as successful pregnancies have been described in which the HLA haplotypes of the mother and offspring were identical (Oksenberg et al. 1984). Furthermore, in the highly inbred Hutterite community, couples who shared HLA-DR antigens had a median completed family size of 6.5, as opposed to 9.0 among those with no HLA alleles in common (Ober et al. 1988). Therefore it has been proposed that the association between parental HLA compatibility and recurrent spontaneous abortion may best be explained in terms of the expression of deleterious recessive genes located in the HLA-DQ-

DR-B region of the major histocompatibility complex (Jin et al. 1995a). This type of mechanism could cause higher peri-implantation losses and hence explain the somewhat longer birth intervals reported among more inbred Hutterite women (Ober et al. 1999). Similarly, genome-based investigations among highly inbred communities in Pakistan have suggested that there may be selection against homozygosity at specific gene loci involved in embryonic and early fetal development (Wang et al. 2000).

Empirical Studies into the Influence of Consanguinity on Family Size

To determine whether there was evidence of an adverse effect of inbreeding on fertility, published data on family sizes at different levels of consanguineous marriage have been collated (Bittles et al. 2002). Thirty populations in six countries—India, Pakistan, Japan, Kuwait, Turkey, and Nigeria—were examined, representing a total of 576,176 pregnancies to 227,134 women. Five discrete levels of consanguinity were identified in the study: double first cousin or uncle-niece ($F = 0.125$), first cousin ($F = 0.0625$), first cousin once removed/double second cousin ($F = 0.0313$), second cousin ($F = 0.0156$), and nonconsanguineous ($F = 0$). The mean coefficients of inbreeding in the study populations ranged from $\alpha = 0.0027$ (Hiroshima, Japan) to 0.0447 (Pondicherry, India).

The average number of liveborn children per consanguineous category was compared with the corresponding non-consanguineous reference group for each population. In summary, the number of children born to consanguineous couples was higher in 11/17 studies at $F = 0.125$, 27/30 studies at $F = 0.0625$, 15/19 studies at $F = 0.0313$, and 15/20 studies at $F = 0.0156$. Assessed by the non-parametric sign test, the differences failed to attain statistical significance at the 0.05 level for $F = 0.125$, 0.0313 or 0.0156, but the difference was highly significant at $F = 0.0625$ ($p<0.0001$). Obviously simple comparisons of this type can be fraught with problems, in particular a lack of control for factors such as age at marriage, duration of the union, contraceptive usage, and reproductive compensation for early postnatal losses (Hussain & Bittles 1999). Nevertheless, there clearly is no evidence to suggest a systematic consanguinity-associated decline in fertility, which has important implications in terms of the effect of consanguinity on the maintenance of detrimental recessive genes in the gene pool.

Inbreeding Depression in Humans

The phenomenon of inbreeding depression has been well described in the literature across a wide range of species (Charlesworth & Charlesworth 1987), and empirical studies have indicated that inbreeding generally is associated with a shift in the phenotype to reduced biological fitness (Lynch 1991). There also is some evidence of a consanguinity-associated increase in fluctuating asymmetry (Livshits & Kobyliansky 1989).

A regression-based method was devised to rationalize the results of inbreeding surveys in human populations into a meaningful and reproducible format, by calculating the numbers of lethal gene equivalents in a community or population (Morton et al. 1956). Lethal gene equivalents are defined as the numbers of detrimental recessive genes carried by an individual in the heterozygous state which, if homozygous would result in death, and the mean number in a given population can be calculated according to the formula:

$$-\log_e S = A + BF$$

where S is the proportion of survivors in the study population, A measures all deaths that occur under random mating, B represents all deaths caused by the expression of recessive genes via inbreeding, and F is the coefficient of inbreeding. By plotting a weighted regression of the log proportion of survivors (S) at different levels of inbreeding (F), A can be determined from the intercept on the Y-axis at zero inbreeding ($F = 0$), and B (the number of lethal gene equivalents) is given by the slope of the regression. Although a number of limitations have been identified, the regression technique offers a simple and convenient means of assessing and comparing data on the effects of inbreeding in different populations. Through time, estimates of the numbers of lethal gene equivalents per population have gradually been revised downwards, in part reflecting better experimental design and control for non-genetic variables.

An alternative approach was adopted in a meta-analysis based on thirty-eight populations from seven countries, and covering the age range from approximately six months gestation to ten years. A regression was plotted for deaths among first cousin progeny against mortality in the equivalent non-consanguineous offspring. The results indicated 4.4 percent higher mortality in the first cousin progeny, with an estimated 1.4 lethal gene equivalents per zygote (Bittles & Neel 1994). The estimate for the regression line was 1.02 ± 0.09, with a coefficient of determination (R^2) of 0.80 across a wide range of background levels of mortality from 3.3 percent to 39.5 percent, indicating that in these very different populations the overall effect of inbreeding depression appeared to be remarkably constant. Based on the value of 4.4 percent excess mortality at $F = 0.0625$, consanguinity-associated mortality can be calculated for any community or population in which the mean coefficient of inbreeding (α) is available. Once again, however, these estimates may be differentially affected by socio-demographic variables, such as maternal age and education, birth order and birth interval. It also would be difficult to calculate precise cumulative levels of inbreeding, since in most communities pedigree data are only available for 3-5 generations.

Conclusions

Since the classic studies conducted in Japan by Schull and Neel (1965), there has been no comparably detailed investigation into the outcomes of consanguineous marriages, despite the remarkable epidemiological transitions which have taken place during the last two gen-

erations. The situation in Japan is of special interest because of the marked decline in the prevalence of consanguineous unions during the last fifty years (Table 1). While an associated reduction in the prevalence of recessive disorders would be expected, consideration of this topic has remained mostly theoretical (Saito 1988), reflecting the difficulty in collecting comparable data sets across time. In fact, a preliminary study of congenital defects in Japan has shown no change in their relative prevalence during the period 1950 to 1995 (data not shown), but there is a major problem in assessing composite data of this type which may reflect factors such as changes in living standards, maternal pharmacotherapy, the availability of prenatal care, and improved fetal survival.

As noted at the beginning of this paper, it often is overlooked that all humans are to some extent inbred, due to the effects in previous generations of positive assortative mating in groups with small effective population sizes. Where the boundaries between different human groups are long established and rigid, as is the case with caste divisions in India or tribal and clan groupings in the Middle East, over time they could have evolved their own unique profiles of mutations that rapidly expanded in frequency via genetic drift. Under these conditions, random inbreeding and endogamy, as opposed to preferential consanguineous marriage, are probably the primary factors in determining their profiles of genetic disease and hence the patterns of inbreeding depression.

An indication of the degree to which this process can operate was revealed by a genome-based study of three co-resident Muslim communities in Pakistan: the *Awan*, the *Khattar*, and the *Rajpoot* (Wang et al. 2000). Significant differences were observed between the communities at all ten of the autosomal loci tested, and males in two of the three communities had separate, single alleles at the eight Y-chromosome loci examined. As shown in Table 4, the study also emphasized the high residual levels of heterozygosity in the communities despite their shared tradition of preferential consanguinity, and the widely variant patterns of homozygosity at individual microsatellite loci.

Table 4

Homozygosity levels at autosomal microsatellite loci in Pakistan

	Awan	*Khattar*	*Rajpoot*
	n = 80	n = 51	n = 42
Mean	40.9%	28.1%	24.8%
Range	18.6-70.5	4.0-55.0	2.5-40.0

Source: Wang et al. (2000)

Human societies are complex entities, and any judgement as to whether consanguinity is beneficial or disadvantageous must fully consider the effects of socio-economic variables as well as biological influences. This is rather more difficult than it sounds, and the final outcome may be largely dependent on the state of development of a community at a given point in time. Thus in pre-industrial, agrarian communities, the adverse effects of inbreeding manifested as a high rate of one or more genetic disorders may be outweighed by the

social and economic benefits offered by intra-familial marriage, especially when a large proportion of offspring die in childhood of infectious or nutritional disorders. The balance shifts significantly in literate, economically developing, or developed populations in which an ever-increasing proportion of disease is genetic in origin (Bittles 2001). Yet even here, the social cohesion that characterizes consanguineous units may be of benefit, for example in providing support when there is a high risk of inherited malignancies within the family (Savithri et al. 2000).

In effect, what is needed is the compilation of a comprehensive balance sheet that embodies both the realities of biological fitness and the central concepts of kin altruism theory, while acknowledging the social and economic imperatives under which past human populations have existed and present societies flourish. Although daunting, this is a challenge well worthy of acceptance if, as a species, we are to fully comprehend our genetic capacities and limitations.

Acknowledgments

Generous financial support from the Australian Research Council, grant number A09701345, is gratefully acknowledged.

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