Consanguinity, Genetic Drift, and Genetic Diseases in Populations with Reduced Numbers of Founders

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Abstract In western countries, consanguineous marriage often arouses curiosity and prejudice in approximately equally measure, despite the fact that until the mid-nineteenth century cousin marriages were quite common in Europe and North America. Attitudes to consanguinity remain very different in other parts of the world, in particular north and sub-Saharan Africa, the Middle East, Turkey and central Asia, and south Asia, where between 20% and over 50% of current marriages are contracted between biological relatives, with first-cousin unions especially common. Besides intra-familial marriage, in these regions a large majority of marriages also occur within long-established male lineages, e.g., clans and tribes in Arab societies and castes in India. Through time these lineages effectively become separate breeding pools, with founder effect, mutation, genetic drift and bottle-necking separately and collectively influencing gene pool composition. The present chapter first considers the concepts of random and assortative mating and then examines demographic, social, economic, and religious variables that influence the prevalence of preferred types of consanguineous marriage. The effects of consanguinity on human mate choice, reproductive success, and reproductive compensation are identified, and the impact of consanguinity on morbidity and mortality in infancy, childhood and adulthood are discussed and quantified. Three detailed case studies are then used to illustrate the influence of endogamy and consanguinity on human genetic variation and genetic disease: the Finnish Disease Heritage; inter- and intra-population genetic differentiation in India; and the distribution of specific disease alleles in Arab Israeli communities. The scale of global migration during the last two generations, with many millions of individuals, families, and occasionally entire communities moving within and between continents, has created an entirely new scenario in human population genetics. Against this background, consanguinity has re-emerged both as an important feature of community and public health genetics, and as a topic of general interest.

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17.1 Genetic Variation in Human Populations

The concepts of race and ethnicity often are highly controversial topics, and the use of supposed racial characteristics in differentiating between human populations has been strongly censured. At the same time, genomic microarray studies have convincingly demonstrated significant differences between major human populations living in different parts of the world, with common genetic variants playing an important role in inter-ethnic gene expression [86]. However, microarray studies also have shown that 93–95% of the total genetic variation was intrapopulation rather than interpopulation in origin [75]. While the proportionally minor genetic differences between populations and the attendant race/ethnicity/ancestry controversy are widely discussed and argued, an obvious and potentially more significant question arises with respect to the origins and causes of the very high level of intra-population genetic variation. How and why did this variation arise, how and why is it maintained, and what, if any, are the consequences in terms of biological fitness, and more especially genetic disease?

Throughout recorded human history, marriage between a male and female has been the predominant institution within which procreation occurred and genes were transmitted. Therefore a key initial step in investigating intra- and inter-population genetic differences is to examine how and why marriage partners are chosen in different societies. Virtually all traditional societies are divided into long-established communities, with limited inter-community marriage. Indeed, genome-based association studies conducted in industrialized Western societies have revealed similar, if less pronounced sub-divisions, and even in countries with large immigrant communities, such as the USA, Canada and Australia, recent arrivals typically marry within their own ethnic and/or religious community during the first and second post-migration generations. Although offering strong social advantages, this tradi-

tion has important genetic implications, since it is probable that couples from the same national, ethnic or religious sub-community will have a significant proportion of their genes in common, and therefore that their progeny are more likely to be homozygous for a detrimental recessive disorder [14].

17.1.1 Random Mating and Assortative Mating

One of the theoretical cornerstones of human population genetics, the Hardy–Weinberg principle, incorporates the provisos of infinite population size and random mating. Even cursory consideration of the growth rate of the global human population through time would indicate that blanket assumptions of this nature are seriously flawed. Thus it has been estimated that the total global population in 1,000 AD was some 310 million, increasing approximately 20-fold during the course of the second millennium to 6,070 million, with an additional 4,420 million humans in the twentieth century alone.

Likewise, rather than random mating, in many Western countries first cousin unions were both popular and highly prized up to the mid-nineteenth century and, for example, not only did Charles Darwin marry his first cousin Emma Wedgewood, Darwin's sister Caroline married Emma Wedgwood's brother Josiah, following intermarriage between the Darwin and Wedgwood families in the previous generation. However, in modern Western societies there is a strong belief that marriage between close biological kin is genetically disadvantageous, which has led to a marked decline in the prevalence of consanguineous marriage in these populations.

This does not mean that marriage partner choice has become an essentially random process, and even in societies where consanguinity is regarded with disfavor, positive assortative mating is the rule rather than the exception. Thus despite greater personal mobility, the choice of a marriage partner remains strongly influenced by geography and ethnicity, and by essentially social factors, such as religion, education, economic status, and political beliefs. Under these circumstances the strict concept of random mating does not apply, since it is probable that the marriage partners will have inherited identical alleles at a proportion of gene loci.

17.1.2 Genetic Drift and Founder Effect

The phenomenon of genetic drift is most simply defined as the influence of chance on gene frequencies in successive generations, and the probability of genetic drift is greatest in communities with small effective population sizes, i.e., with restricted numbers of potential mating couples. In evolutionary terms this situation can arise in several ways, for example, through founder effect, when a subgroup of a population establishes a new breeding colony; via a demographic bottleneck following major disease- or disaster-related mortality; and in subdivided populations with multiple, strictly endogamous subcommunities.

Where there is restricted marriage partner choice, genetic drift can lead to random inbreeding, with unions contracted between individuals not known to be biological relatives but drawn from the same confined gene pool. The net effect is similar to positive assortative mating, and the main outcome is a higher probability of homozygosity at some gene loci, resulting in an increased likelihood of recessive gene expression. This is important from a medical genetics perspective, since a recessive founder or de novo mutation can rapidly increase in frequency within a small community by chance alone, resulting in the birth of an affected child whether the parents are known to be consanguineous or believe themselves to be nonrelatives [104].

17.2 Consanguineous Matings

The origin of the term consanguineous is the Latin *consanguineus*, meaning 'of the same blood.' In a human genetics context, a couple are said to be consanguineous if they share one or more common ancestors. Since most pairs of individuals living in the same location will have a common ancestor somewhere in their family trees, for practical purposes the search for a shared ancestor generally does not extend back more than three or four generations. In medical genetics, the definition of consanguinity is usually restricted to a preferential union between a couple related as second cousins or closer, although as discussed in Sects. 17.2.1 and 17.4, important exceptions can and do arise.

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17.2.1 Coefficient of Relationship and Coefficient of Inbreeding

Two basic measures are employed to quantify genetic relationships. The first is the coefficient of relationship (r), which is the proportion of genes identical by descent (IBD) shared by two individuals. The coefficient of relationship is calculated from the formula:

$r = \{(1/2)^n\}$

where n is the number of steps apart on a pedigree for these two individuals via their common ancestor. Thus for two persons related as first cousins:

$r = \{(1/2)^4\} + \{(1/2)^4\} = 1/8$

The coefficient of inbreeding (F) is the proportion of gene loci at which an individual is homozygous by descent (Table 17.1). Incestuous relationships, i.e., between father–daughter, mother–son or brother–sister are the closest form of human mating, with the partners sharing half of their genes ($r=0.5$), and so any offspring would be homozygous at 1/4 of gene loci ($F=0.25$). The closest legally permissible consanguineous unions are between an uncle and niece, which occur mainly in South Indian Hindu communities, or between double-first cousins, as in Muslim populations in the Middle East and Pakistan. In both of these types of marriage the partners share one fourth of their genes ($r=0.25$) and the coefficient of inbreeding in their progeny is $F=0.125$. Double-first cousins have both sets of grandparents in common, whereas in first-cousin marriage the couple shares two common grandparents (Fig. 17.1).

Table 17.1 Human genetic relationships

Biological relationship	Genetic relationships	Coefficient of relationship	Coefficient of inbreeding
Incest[a]	First degree	0.5	0.25
Uncle-niece Double first cousin	Second degree	0.25	0.125
First cousin	Third degree	0.125	0.0625
First cousin once removed Double second cousin	Fourth degree	0.0625	0.0313
Second cousin	Fifth degree	0.0313	0.0156
Second cousin once removed Double third cousin	Sixth degree	0.0156	0.0078
Third cousin	Seventh degree	0.0078	0.0039

[a]Incest is defined as a sexual relationship between father–daughter, mother–son or brother–sister

Second cousins have inherited 1/32 of their genes from a common ancestor ($r=0.0313$), and so the offspring of a second-cousin union would be expected to be homozygous (or more strictly autozygous) at 1/64 of their gene loci, i.e., $F=0.0156$. In populations with restricted marriage partner choice, couples who are not second cousins may be related through multiple pathways involving more remote ancestors. Under such circumstances the coefficient of inbreeding for an individual is calculated by summing each of the known pathways of inheritance. Thus, for an individual whose parents are third, fourth and fifth cousins ($r=0.0078$, 0.0039 and 0.00195), the corresponding coefficient of inbreeding is ($F=0.0039+0.00195+0.00098$), i.e., a composite coefficient of inbreeding of $F=0.00683$.

In many societies, specific subcommunities or families have a long and unbroken tradition of consanguineous marriage, resulting in a cumulative coefficient of inbreeding that can greatly exceed the genetic influence of consanguinity in a single generation. To quantify this situation a correction term can be applied using the formula:

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

where F_A is the ancestor's coefficient of inbreeding, n is the number of individuals in the path connecting the parents of the individual, and the summation ($\sum$) is taken over each path in the pedigree that goes through a common ancestor. In small endogamous communities with limited numbers of marriage partners, cumulative inbreeding via multiple consanguineous pathways can result in a significant build-up of homozygosity, even within a few generations.

17.2.2 Global Prevalence of Consanguinity

From a global perspective the lowest rates of consanguinity are found in Western Europe, North America and Oceania, where less than 1% of marriages are consanguineous, i.e., they are contracted between couples related as second cousins or closer ($F \geq 0.0156$). In some parts of Southern Europe, South America and Japan approximately 1–5% of current marriages are consanguineous, depending on local geography and

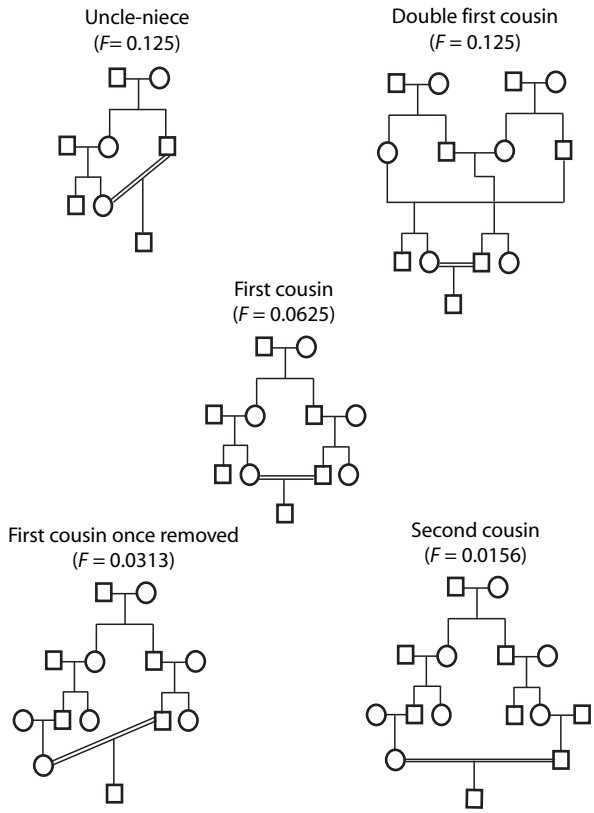

Fig. 17.1 Consanguineous pedigrees

social customs. The highest recorded rates of consanguinity are in North and sub-Saharan Africa, the Middle East, Turkey and Central Asia, and parts of South Asia, where unions between couples related as second cousins or closer account for 20% to over 50% of all marriages (www.consang.net). While a recent decline in the prevalence of consanguineous marriage has been reported in some Middle Eastern countries, such as Jordan [40], increases have been reported in the neighboring Arab states of Qatar [10], and the United Arab Emirates [5]. In the major South Asian countries of India [22], Pakistan [4], and Iran [78] little change appears to have occurred in the prevalence of consanguinity during the latter half of the twentieth century, although there is some evidence that attitudes towards consanguineous marriage are influenced by contemporary political regimes.

Data on consanguinity remains at best partial for many populous countries in Asia, including Bangladesh and Indonesia. Anthropological research in Africa has indicated that cousin marriage is common in many specific communities, but there is little information on its prevalence or the particular types of cousin union that are favored. Although consanguinity has been rare in Western societies since the early twentieth century, most Western countries are now home to large migrant communities which traditionally have contracted consanguineous unions, with all evidence pointing to continued preference for intrafamilial marriage in their newly adopted countries [11, 68]. For this reason, the summary country and regional data on consanguineous marriage presented in Fig. 17.2 are best considered as lower bound estimates of the overall global picture.

If the specific types and frequencies of consanguineous marriage are known, the mean coefficient of inbreeding (α) can be calculated to provide a measure of the intensity of inbreeding in the population, according to the formula:

$$\alpha = \sum p_i F_i$$

where Σ is the summation of the proportion of individuals *pi* in each consanguinity category *Fi*. As indicated in Table 17.2, the values for α vary widely between

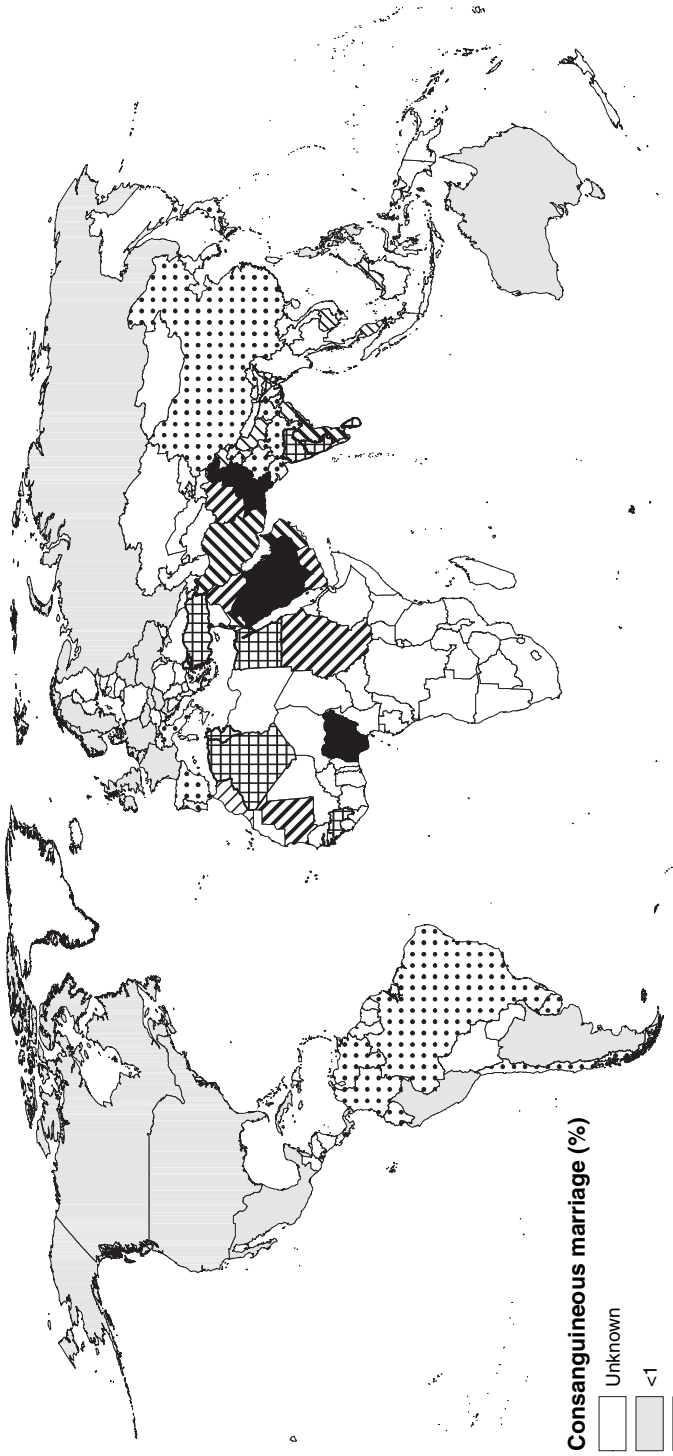

Fig. 17.2 Global distribution of consanguineous marriages

Table 17.2 Prevalence (%) and types of consanguineous marriage in different regions and populations

Region	Study setting	Participants	Number	%	Relationships[a]	Inbreeding (α)	Reference
Western Europe							
Great Britain	Birmingham	Obstetric inpatients	2,431	0.2	1C,2C	0.0001	[23]
Norway	All-Norway	Civil registration	893,941	0.7	1C,2C	0.0002	[56]
Spain	Sigüenza-Guadalajara	RC dispensation	5,315	12.6	1C,$1^{1/2}$C,2C	0.0029	[24]
North America							
Canada	Québec	RC dispensation	21,874	1.3	UN,1C,$1^{1/2}$C,2C	0.0003	[31]
USA	National	RC dispensation	133,228	0.2	1C,$1^{1/2}$C,2C	0.0001	[36]
South America							
Argentina	All-Argentina	Civil registration	212,320	0.4	1C	0.0002	[26]
Brazil	Rio Janeiro	RC dispensation	4,070	1.5	UN/AN,1C,$1^{1/2}$C,2C	0.0008	[30]
	Paraiba	RC dispensation	9,521	12.8	UN/AN,1C,$1^{1/2}$C,2C	0.0058	[30]
Northern Africa							
Tunisia	North	Obstetric inpatients	5,767	26.9	>1C,1C,$1^{1/2}$C,2C	0.0213	[73]
Egypt	National	Household/school/school/workplace	26,554	29.0	D1C,1C,$1^{1/2}$C,2C	0.0101	[39]
Sudan	Khartoum	Blood donors	4,833	52.0	1C,2C	0.0302	[79]
West Asia							
Saudi Arabia	National	Household survey	3,212	40.6	IC,2C	0.0241	[34]
UAE	Al Ain	Health centre	1,502	37.4	D1C,1C,$1^{1/2}$C,2C	0.0245	[5]
Turkey	National	Household survey	5,257	21.1	1C,2C	0.0096	[92]
South Asia							
India North	Lucknow (Hindu)	Obstetric inpatients	7,955	0.1	UN,1C	0.0001	[2]
- South	Karnataka (Hindu)	Obstetric inpatients	86,448	33.5	UN,1C,2C	0.0333	[22]
Pakistan	National	Household survey	6,611	61.2	1C,2C	0.0332	[4]
East Asia							
China - *Han*	Zejiang	Household survey	15,762	1.1	UN,1C,$1^{1/2}$C,2C	0.0006	[100]
Kirgiz	Xinjiang	Household survey	2,863	45.2	D1C,1C,$1^{1/2}$C,2C	0.0274	[99]
Japan	National	Household survey	9,225	3.9	1C,$1^{1/2}$C,2C	0.0013	[45]
Oceania							
Australia	Western Australia	Civil marriages	62,376	0.2	1C,$1^{1/2}$C,2C	0.0001	[67]

[a]Categories of consanguineous marriage: *UN* Uncle-niece, *AN* Aunt-nephew, *D1C* Double first cousin, $F = 0.125$; *1C* first cousin, $F = 0.0625$; $1^{1/2}C$ first cousin once removed, $F = 0.0313$; *2C* second cousin, $F = 0.0156$

populations and regions, from 0.0001 in Western Europe and North America to 0.0241 in Saudi Arabia, 0.0332 in Pakistan and 0.0333 in South India, where consanguineous marriage is widely preferential. In the two latter countries the average level of inbreeding is thus equivalent to all marriages being contracted at the level of first cousin once removed ($F=0.0313$).

Detailed global estimates of consanguineous marriage in the current generation are available by continent, country, region and population at www.consang.net. However, as indicated in Table 17.2, interpopulation comparability is difficult to achieve because of differences in the numbers of subjects recruited and in the types of study population, e.g., whether based on dispensations granted by the Roman Catholic church for consanguineous couples to marry, compulsory civil marriage registration, or records relating to obstetric inpatients. Likewise, the levels at which data have been collected vary, with some studies counting only first- or second-cousin marriages, while in other populations uncle-niece and aunt-nephew, double-first-cousin, and first-cousin once removed marriages also were recorded. What is, however, clearly apparent from Fig. 17.2 is that consanguineous marriage is not restricted to geographically remote communities or to specific religious, ethnic, or social isolates, as has been popularly believed.

17.2.3 Specific Types of Consanguineous Marriage

The specific patterns of consanguineous marriage contracted in different populations largely reflect their traditional customs and beliefs. The highest levels of consanguineous marriage so far reported in a single generation are from the former French colony of Pondicherry in South India, with 54.9% consanguinity (mean coefficient of inbreeding, α, 0.0449) [70], and among army recruits in the province of Punjab, Pakistan with 77.1% consanguinity ($\alpha=0.0414$) [41]. The fact that the mean coefficient of inbreeding was actually higher in Pondicherry than Punjab despite a lower total percentage consanguinity is explained by the fact that most consanguineous marriages in Punjab were between first cousins ($F=0.0625$), whereas in Pondicherry uncle-niece marriages ($F=0.125$) predominated.

Local custom also dictates the specific types of first-cousin unions, so that in Arab Muslim communities a marriage between a man and his father's brother's daughter (FBD) is preferred, as opposed to the mother's brother's daughter (MBD) pattern of first-cousin marriage found in such disparate populations as Dravidian Hindus of South India, Han Chinese, and the Tuareg of North Africa [13]. A further factor to be considered is that in communities where consanguinity is preferential, couples in marriages categorized as nonconsanguineous very probably have inherited a significant proportion of their genes from one or more common ancestor, even though they themselves are unaware of any close genetic relationship.

Although the coefficient of inbreeding for FBD and MBD offspring is the same at autosomal loci ($F=0.0625$), at X-chromosome loci $Fx=0$ for FBD progeny but 0.125 for children born to MBD couples. Therefore, the specific forms of first cousin union favored and contracted within particular populations can have an important influence on the expression of X-linked disease genes.

17.2.4 The Influence of Religion on Consanguineous Marriage

The major world religions exert a strong influence on consanguineous marriage, both directly in terms of the types of marriages permitted and via the enactment of civil legislation. As indicated in Table 17.3, most of

Table 17.3 Religious attitudes towards consanguineous marriages

Religion	Subcommunity	Attitude
Judaism	Sephardi	Permissive
	Ashkenazi	Permissive
Christianity	Greek and Russian Orthodox	Proscribed
	Roman Catholic	Diocesan approval required
	Protestant	Permissive
Islam	Sunni	Permissive
	Shia	Permissive
Hinduism	Indo-European	Proscribed
	Dravidian	Permissive
Buddhism		Permissive
Sikhism		Proscribed
Confucianism/ Taoism		Partially permissive
Zoroastrian/Parsi		Permissive

the major religions sanction consanguineous unions, although there are quite marked differences within each religious tradition. Judaism and Islam largely follow the guidelines provided in Leviticus 18:7–18, but there is a Quranic prohibition on uncle-niece marriages, which are permitted within Judaism. Despite the Judaic core of Christianity, the Orthodox and Roman Catholic Churches restrict close-kin marriage. However, the strictures requiring dispensation for consanguineous unions were substantially relaxed by the Roman Catholic Church in the early twentieth century and now apply only to couples related as first cousins or closer [12]. By comparison, as part of the sixteenth century Reformation, the Protestant denominations basically reverted to the Levitical proscriptions on marriage, with first-cousin unions permissible. A similar divergence occurs within Hinduism, and while many Dravidian South Indians regard consanguineous marriage as preferential, in North India consanguinity is prohibited under the Indo-European Hindu tradition. A further detailed description of Hindu marriage practices and prohibitions is given in Sect. 17.8.2.

17.2.5 Civil Legislation on Consanguineous Marriage

While consanguineous unions are largely avoided in regions such as Western Europe and Oceania, first-cousin marriage is permissible under civil law in virtually all countries, and since 1987 marriage between half-sibs ($F=0.125$) may be permitted in Sweden under specific circumstances. The situation is quite different in the USA. Until 1861 first-cousin marriage was legal, but through time legislation to ban different types of consanguineous marriage was gradually introduced at state level, the most recent example being a ban on first-cousin marriage adopted by the state of Texas in 2005. This means that first-cousin unions are a criminal offense in 10 states, and are illegal in a further 22 states, despite a Federal recommendation in 1970 that all state laws on first-cousin marriage should be rescinded [15]. The USA is one of the few countries to have enacted legislation of this type, alongside the People's Republic of China and the Democratic People's Republic of Korea.

17.2.6 Social and Economic Factors Associated with Consanguinity

Consanguineous unions have been most frequently reported within the ruling classes and land-owning families of Western societies, and also within powerful mercantile dynasties, such as the Rothschilds, whose family members have worked cohesively across national boundaries for many generations. The picture is quite different in other less economically developed parts of the world, with the highest rates of consanguineous marriage commonly reported among poor, rural, and largely illiterate communities in societies throughout Asia and North Africa [12, 43].

As indicated in Table 17.4, the preference for consanguineous marriage is primarily social in nature, since it is believed that family ties will be strengthened, family honor will be optimally maintained, and health or financial uncertainties that may be encountered following marriage with a partner from another family or community are avoided [15]. Also, in societies where males and females are segregated from late childhood, potential marriage partners are more likely to know each other if they are biological relatives, since they would have been able to meet at family social functions. Premarital arrangements are simplified in a consanguineous union, and the relationship of a couple and their in-laws is expected to be more congenial, which is particularly important for female autonomy in the patrilocal societies typical of most Asian countries (Table 17.4).

As in Western societies, economic considerations are an important facet of marriage partner choice, and in

Table 17.4 Social and economic advantages of consanguineous marriage

The assurance of marrying within the family and the strengthening of family ties
The assurance of knowing one's spouse prior to marriage
Simplified premarital negotiations, with conditions and marriage arrangements agreed in the partners' early or late teens
Greater social compatibility of the bride with her husband's family, in particular her mother-in-law, who also is a relative
Lower risk of undeclared health problems in the intended spouse
Reduced requirement for dowry or bridewealth payments, with consequent maintenance of the family goods and monies
For land-owning families, maintenance of the integrity of family land-holdings, which otherwise might be subdivided by inheritance

countries in which dowry payments are the norm, marriages within the family reduce or even negate the potential financial costs to the bride's family [12, 57]. Problems arising from marriage to a close relative have been cited in a minority of cases, especially where there is a large age gap between spouses. But in most instances marital stability appears strong and divorce is uncommon, possibly reflecting the family disunity that could arise if a marriage between cousins were to fail [13].

17.3 Inbreeding and Fertility

The prevailing suspicion of consanguineous unions in Western societies is centered on the belief that the offspring of a close-kin marriage will be physically and/or mentally disadvantaged. However, it also has been suggested that consanguineous relationships are less fertile than unions between nonrelatives. An influential early example of spiritual guidance on the inadvisability of consanguineous marriage was provided by Pope Gregory I in the late sixth century. Besides rather dubiously citing Leviticus 18:6 as the basis in Holy Scripture for the avoidance of cousin marriage, 'None of you shall approach to any that is near of kin to him, to uncover their nakedness,' and thus avoiding the specific guidelines provided in Leviticus 18:7–18, the Pope also claimed that unions between consanguineous spouses were infertile [38]. Where empirical information has been collected in human populations, the studies often have relied on small sample numbers, a shortcoming that makes the results difficult to assess [21]. However, in general, reduced levels of pathologic sterility have been reported among consanguineous couples [33, 72] with no evidence of an increase in fetal loss rates [21, 48], and indirect indicators of fetal survival, such as multiple birth rates and the secondary sex ratio, also failed to show an adverse inbreeding effect.

17.3.1 Genetically Determined Factors Influencing Human Mate Choice

It has been proposed that an olefactory mate-choice system operates in humans and other mammals. For example, in studies on the Hutterites, a highly endogamous Anabaptist sect resident in the USA, there was a lower than expected incidence of HLA haplotype matches between spouses, which was interpreted as evidence for the instinctive avoidance of partners with similar human leukocyte antigen (HLA) haplotypes [64].

The phenomenon of mate choice also was investigated in Swiss university students, with female students asked to conduct blind smell-testing of cotton T-shirts previously worn by male students and score the resultant body odors in terms of pleasantness and 'sexiness.' It was claimed that level of attractiveness of the male body odors was proportional to the degree of major histocompatibility complex (MHC) dissimilarity between the male subjects and the female testers, although follow-up studies indicated a high level of scoring variance [94]. Quite different results were obtained when a similar experiment was conducted with unmarried Hutterite women. In this case, the women were more likely to favor the odor of a 'donor' with whom they shared an intermediate number of HLA alleles. Furthermore, the positive preference appeared to be based on HLA alleles inherited from the subject's father but not her mother [49].

From the viewpoint of actual marriage partner choice, it can be convincingly argued that the findings of each of these studies have limited relevance in communities where consanguineous unions are strongly preferential, since in these more traditional societies marriage contracts are generally subject to parental decision-making [21].

17.3.2 Inbreeding and Fetal Loss Rates

Enhanced genetic compatibility would be expected between mother and fetus in consanguineous unions owing to their greater proportion of shared maternal and paternal genes. In keeping with this premise it has been claimed that intrauterine mortality is reduced in the pregnancies of consanguineous couples, with lower rates of conditions such as Rhesus (Rh) incompatibility [87] and pre-eclamptic toxemia [88]. Conversely, the fetal allograft hypothesis proposes that antigenic disparity between mother and fetus is beneficial to fetal development [29, 62], which would suggest higher losses in consanguineous pregnancies.

Table 17.5 Average number of live-born children by coefficient of inbreeding (F) (from [21])

	Coefficient of inbreeding (F)[a]				
	Uncle-niece/ double first cousin	First cousin	First cousin once removed	Second cousin	Nonconsanguineous
	$F=0.125$	0.0625	0.0313	0.0156	0
Mean number of live-born children	3.26	3.43	3.18	2.96	2.57
Number of studies	17/30	30/30	19/30	20/30	30/30

[a]The patterns of consanguineous marriage assessed varied between individual studies, with comparative data on fertility in first-cousin and nonconsanguineous matings available for all 30 studies analyzed, for uncle-niece/double first cousin unions in 17 studies, for first cousins once removed in 19 studies, and for second cousins in 20 studies

A positive association between parental HLA sharing at allele loci and recurrent abortion has been reported, with negative selection against individuals homozygous at HLA loci [51]. Unfortunately, retrospective data on pregnancies and prenatal losses may be subject to significant levels of recall bias, resulting in data of dubious reliability and significant underestimation of the levels of prenatal losses [95, 96].

Studies based on sequential human chorionic gonadotrophin (hCG) assays are more reliable, with on average some 40+% of all post-implantation conceptions lost. This figure rises with advancing maternal age, and in a hCG-based study in Bangladesh, while 45% of the pregnancies detected among women at 18 years of age spontaneously miscarried, among women aged 38 years fetal losses increased to 92% [65]. Since these levels of spontaneous abortion/miscarriage are very much higher than generally reported in inbreeding studies, there must be a strong suspicion that early pregnancy losses have been undetected or were underreported in investigations that relied solely on women's recall.

17.3.3 Comparative Fertility in Consanguineous and Nonconsanguineous Couples

A majority of comparative studies into fertility have shown a positive correlation between consanguinity and the number of live-born children. Data analyzed in a meta-analysis of 30 studies conducted in Asian and African countries are summarized in Table 17.5, with a higher mean number of children born in all categories of consanguineous marriage when compared with nonconsanguineous couples. Since the structure of each study varied according to the locally preferred types of consanguineous marriage, complete data were available only for first-cousin and nonconsanguineous couples, with first cousins showing the highest mean number of children ($n=3.43$). But even among the uncle-niece and double-first-cousin marriages ($F=0.125$), information on the numbers of live-born children had been published for 17 of the 30 populations, with mean fertility ($n=3.26$) higher than among nonconsanguineous spouses ($n=2.57$).

Typically, maternal age at marriage is negatively associated with consanguinity, resulting in a younger maternal age at first birth [22]. In addition, a higher mean age of motherhood has been reported among consanguineous couples [91], which supports the belief that early marriage, the earlier commencement of reproduction, and maximization of the maternal reproductive span by consanguineous couples are critical biosocial factors in determining family size.

The uptake of contraception may be lower in consanguineous couples [44], and reproductive compensation has been advanced as an additional explanation for the positive association between consanguinity and fertility, with infants dying at an early age rapidly replaced [63, 83]. Reproductive compensation could involve a conscious decision by parents to achieve their desired family size, but at the same time a further pregnancy following the death of a breast-fed infant may mainly be a consequence of the cessation of maternal lactational amenorrhea. The relationship between consanguinity, fertility, and reproductive compensation is however complicated, since the greater the number of children born to parents who are carriers of one or more detrimental recessive alleles, the higher the expectation that at least some of their progeny will be affected and so could die in early childhood.

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17.4 Inbreeding and Inherited Disease

A significant positive association has been repeatedly demonstrated between consanguinity and early mortality, with disorders involving the expression of detrimental recessive genes especially involved. But since the poorest sections of all populations are most disadvantaged in terms of health and health care provision, overrepresentation of poorer and less educated families among consanguineous couples creates problems in assessing the effects of consanguinity on morbidity and mortality.

The first structured study into the medical effects of inbreeding was organized by Dr. Samuel Bemiss of Louisville, Kentucky [9], who in 1858 examined reports forwarded by medical colleagues on the health outcomes of unions ranging from incest ($F=0.25$) to third-cousin marriages ($F=0.0039$). Hundreds of further studies have been undertaken since that time, based on a variety of sampling techniques including pedigree analysis, household surveys and questionnaires administered to hospital in- and outpatients. In populations where uncle-niece or double-first-cousin and first-cousin marriages are preferential, unions beyond second cousins ($F<0.0156$) are of limited medical significance [13]. By comparison, where consanguineous unions generally are rare, biologically remote relationships in the present generation, such as third cousins and beyond ($F\leq0.0039$) may nevertheless be of clinical importance in families where cumulative inbreeding at differing levels of consanguinity has occurred through time, with a consequent build-up of homozygosity. A similar phenomenon can arise in communities in which close-cousin unions have been proscribed on religious grounds but marriages between couples who are related to a lesser degree are permissible.

17.4.1 Consanguinity and Deaths in Infancy and Childhood

Data on the relationship between consanguinity and birth measurements have been mixed, with some studies suggesting that babies born to consanguineous parents are smaller and lighter, and therefore less likely to survive, whereas others have failed to detect any significant difference. By comparison, there is a general consensus that postnatal mortality and morbidity are higher among the progeny of consanguineous unions, and the rarer the frequency of a deleterious recessive gene in a population, the greater the proportional disadvantageous effect of inbreeding on its expression [13]. Estimates of the overall adverse effects of consanguinity have been highly variable, and it is generally accepted that earlier surveys may have produced spuriously high values due to inadequate control for important non-genetic variables that are known to influence childhood health, including maternal age and education, birth order, and birth intervals.

In developing countries, excess consanguinity-associated deaths are largely concentrated during the 1st year of life, but in many cases no specific cause of death is determined because of inadequate diagnostic facilities and parental reluctance to sanction prenatal diagnosis or autopsy examinations [16, 68]. Where a diagnosis has been possible, 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 [13, 90].

17.4.2 Consanguinity and Childhood Morbidity

By definition, studies into the prevalence of birth defects are dependent on the diagnostic criteria employed and, in less developed countries, recognition of the symptoms of congenital disorders can often overlap with and reflect late fetal and neonatal survival rates. In developed countries, on average 4–5% of newborns have some form of birth defect [28]. A significant excess of major congenital defects has been diagnosed in consanguineous offspring, especially disorders with a complex etiology and a higher rate of recurrence, but the reported rates of birth defects associated with consanguinity have varied quite widely. Thus, in an Arab community in Israel first-cousin progeny had 3.8% excess major malformations [47], whereas 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 [89]. According to the Latin America Collaborative Study of Congenital

Malformations (ECLAMC) which examined 34,102 newborn infants for congenital anomalies, a significant association with consanguinity was found only for hydrocephalus, postaxial polydactyly, and bilateral cleft lip with or without cleft palate [74].

From these data it is difficult to identify major categories of disease that are specifically overrepresented in consanguineous progeny. Cognitive impairment is more common in consanguineous offspring, and a study of Arab schoolchildren in Israel indicated a 0.8- to 1.3-point decrease in mean IQ scores among first-cousin progeny by comparison with the children of unrelated parents, with a 2.6- to 5.9-point decline in the mean IQ scores of double-first-cousin progeny [8]. There also was a significantly higher level of variance in the IQ scores of the double-first-cousin progeny, suggesting the expression of detrimental recessive genes in some of these children. In Pakistan mild and severe intellectual and developmental disability also have been associated with consanguinity [32], although as with cognitive impairment poor social conditions may play significant causative roles in such cases.

As large, inbred pedigrees offer a cost- and time-effective strategy to locate disease mutations, the technique of homozygosity mapping in consanguineous families [52] has been widely adopted to identify the causative loci for disorders such as autosomal recessive nonsyndromal hearing loss, and blindness caused by early onset retinal dystrophies and childhood glaucoma, each of which has been reported at increased prevalence in specific consanguineous communities.

17.4.3 Consanguinity and Adult Mortality and Morbidity

Although potentially the most intriguing and challenging age range during which the adverse effects of consanguinity on health could be expressed, morbidity in adulthood has been underinvestigated. There is some preliminary evidence that certain cancers, especially breast cancer [54, 85], and specific forms of early-onset cardiovascular disease [46] are more prevalent in consanguineous individuals. The adult progeny of consanguineous unions also are overrepresented in institutions caring for persons with intellectual disability [13].

A major difficulty in assessing many of the findings obtained with adult-onset diseases is that they were derived from composite studies based on investigations conducted across discrete breeding populations, with little control for sociodemographic variables. Because of a lack of precise information on the composition and structure of the consanguineous and nonconsanguineous study groups, and appropriate matching for nongenetic variables, the comparisons drawn often prove to be irreproducible. An exception is the high prevalence of Alzheimer disease diagnosed in an Israeli Arab community, with more than one-third of the cases diagnosed members of a single clan (*hamula*) [35]. This supports an earlier study from the demographically well-characterized Saguenay area of Québec, Canada, which found that cases of late-onset cases of Alzheimer disease associated with the apolipoprotein (APOE) ε4 allele were significantly more inbred than controls [93].

Long-term studies conducted on the Dalmatian Islands, Croatia have suggested that inbreeding is a strong predictor for a wide range of late-onset disorders, including hypertension, coronary heart disease, stroke, cancer, uni-/bipolar depression, asthma, gout and peptic ulcer [76, 77]. At least in the short term, studies which concentrate on subcommunities of this type are more likely to provide information on disease-predisposing alleles than ethnically mixed populations. Although, even in population isolates with extensive pedigree data, failure to allow for the influence of distant genealogical loops can result in false positives in homozygosity mapping [55].

17.5 Incest

Incest is the most extreme example of human inbreeding, with the partners having a coefficient of relationship, *r,* of 0.5, so that any progeny born of an incestuous union would be expected to have a coefficient of inbreeding (*F*) of 0.25. Incest also differs from all other forms of inbred union since, in contemporary societies, it is universally regarded as both a criminal and a moral offense. Brother–sister marriages were recorded in Pharaonic and Ptolemaic Egypt, Zoroastrian Persia, the Inca Empire, and other historical dynasties, and they also were noted among nonroyal families in Roman Egypt from the first to the fourth centuries AD [81, 82]. Perhaps because of the high level of disapproval that incest attracts in modern societies, there are

very few credible data sets on the outcomes of incestuous pregnancies. Yet the numbers of reported prosecutions on grounds of incest, usually involving father–daughter relationships, suggest that incest may be more common than is generally supposed, with brother–sister incest especially underreported.

In many instances where a child is born to a very young mother, the father of the child is not identified, even though incest may be suspected. If the child is healthy it is probable that no further action will be taken even if the child is offered for adoption. But when a sick child is born there is a greater imperative to investigate the cause of the illness, which in turn may lead to incest being identified. Under these circumstances significant overestimation of the adverse outcomes of incest could result, suggesting that considerable caution needs to be applied in the interpretation of incest data.

17.5.1 Mortality and Morbidity Estimates for Incestuous Matings

As shown in Table 17.6, according to data on 213 children collated from the four best-known studies of incest, conducted in the USA, UK, Czechoslovakia, and Canada over some 50 years [1, 6, 25, 84], only 46.0% of incestuous pregnancies resulted in the birth of a healthy infant. Follow-up ranged from 0.5 to 37 years, and among the incestuous offspring 39.4% had a recognized autosomal recessive disorder or a congenital malformation, had succumbed to sudden infant death, or had severe nonsyndromic intellectual disability, with deaths in 14.1% of cases. A further 14.6% of subjects had a mild disorder, including intellectual and developmental disability. By comparison, just 8.0% of the 113 nonincestuous controls died or were diagnosed with a serious defect, suggesting a mean level of excess mortality or serious defect in the incestuous progeny of 31.4%.

It should be stressed that in many cases the incestuous mothers were very young, with gynecological immaturity a possible adverse factor in the pregnancy, and in a substantial percentage of these cases either the mothers or the fathers, and sometimes both, had serious pre-existing physical or mental disorders [17]. Therefore, it is probable that the adverse pregnancy outcomes may, in part, have been due to causes other than detrimental recessive gene expression. Clarification of this issue will be dependent on additional data becoming available, but as already observed, the collection of unbiased information on the health sequelae of incest is extremely difficult.

17.6 Genetic Load Theory and Its Application in Consanguinity Studies

All humans are heterozygous for a number of detrimental recessive genes, and the term ‘genetic load’ refers to the decrease in the average fitness of a population caused by the expression of genes which reduce survival. Lethal gene equivalents are defined as the number of detrimental recessive genes carried by an individual in the heterozygous state which, if homozygous, would result in death. Therefore, by comparing death rates in the progeny of consanguineous and unrelated couples, it is possible to estimate the numbers of lethal gene equivalents in a community or population.

The number of lethal gene equivalents in a 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 [58]. By plotting a

Table 17.6 Mortality and morbidity estimates for incestuous progeny. (From [55, 77, 81, 82])

Number studied	Follow-up (yr)	Autosomal recessive disorders	Congenital malformations/ sudden infant deaths	Nonspecific severe intellectual disability	Others, including mild intellectual disability	Normal
213	0.5–37	11.7%	16.0%	11.7%	14.6%	46.0%

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.

Since consanguineous individuals have a greater probability of inheriting the same mutant allele(s) from a common ancestor, their progeny will be at a higher risk of expressing one or more recessive disorders. By calculating the number of lethal gene equivalents, the results of inbreeding surveys could be transformed into a meaningful and reproducible format, which then could be comparatively applied to the results of surveys in different populations. A multinational meta-analysis conducted on over 600,000 pregnancies and live births collated from 38 study populations indicated 4.4% excess prereproductive mortality in first-cousin progeny (measured from approximately 6 months gestation to a median age of 10 years) [20]. This level of excess mortality equates to 1.4 lethal equivalents per zygote, and a subsequent study of first cousin versus nonconsanguineous marriages in Italy from 1911-1964 produced equivalent results, with 3.5% excess deaths at $F=0.0625$, i.e., 1.2 lethal equivalents per zygote [27].

17.7 Genomic Approaches to Measuring Inbreeding at Individual and Community Levels

The direct estimation of an individual's inbreeding coefficient by reference to genomic data offers many advantages, since it can include the influence of historical levels and patterns of inbreeding that may not be identifiable within a pedigree. A maximum-likelihood method of analysis has been developed using simulated whole genome data which permits inference of the identity by descent (IBD) status of both alleles of an individual at each marker along the genome. The method also provides a variance measure for the estimates and, for example, it was shown that while the mean value for IBD status for first cousins was 0.0625, at individual loci the calculated values ranged from 0.03 to 0.12 [53].

Microsatellite analysis of DNA samples obtained from UK ethnic migrants showed that in the Pakistani Muslim community, in which consanguineous marriage is widely favored and practiced, the observed F values were much higher than in a co-resident Indian Sikh community which avoided consanguinity [66]. This study also indicated significant genetic substructuring, which could interfere with estimates of the frequency of recessive disease genes. Using both SNP and microsatellite analysis, a subsequent study of UK Pakistani consanguineous individuals with a range of autosomal recessive diseases showed that, on average, persons whose parents were first cousins ($F=0.0625$) were actually homozygous at 11% of the loci tested, with a range of 5-20% [98].

The findings of these studies indicate the influence of cumulative inbreeding on genome structure at both individual and community levels. In addition, they confirm the desirability of a prior understanding among researchers and clinicians of the social structure of communities, in particular their marriage patterns, since information of this nature could have a major role in determining the patterns and frequencies of specific genetic disorders.

17.8 The Influence of Endogamy and Consanguinity in Human Populations

Inter- and intrapopulation fluctuations in the frequencies of coding genes are well recognized and documented, and it seems probable that similar variations will be demonstrated in the control of gene expression. Three quite different, representative human populations, Finland, India, and Israeli Arabs, will be used to illustrate the impacts of founder effect, random drift and consanguinity on genetic structure and the prevalence and expression of recessive disease genes.

17.8.1 The Finnish Disease Heritage

Finland is a small and formerly quite isolated country with a unique genetic history. The original inhabitants are thought to have been arctic northern European Uralic speakers who settled the territory of Finland some 6,500 years ago after the decline of the last Ice Age.

Somewhat later arrivals included peoples from south-eastern and western Europe between 5,000–6,000 and 4,500 years ago, respectively, with later minor waves of German, Scandinavian, and Baltic peoples [60].

The initial population settlement was concentrated in the south and west of the country, and at the start of the twelfth century the total number of inhabitants was less than 50,000. Commencing in the sixteenth century there was internal migration northward, and by the mid-seventeenth century the total numbers had increased to 400,000–450,000. But in the Great Famine of 1696–1697 approximately 25–33% of the inhabitants died, and additional major population losses occurred owing to plague at the beginning of the 1700s, and famine following crop failures in 1866–1868 [60].

The concept of the Finnish Disease Heritage (Table 17.7) was introduced in 1973 to describe some 36 mostly autosomal recessive diseases that are typical of the Finnish population while rare in other populations [59, 61]. Conversely, disorders which are common in most other northern European populations, such as cystic fibrosis and phenylketonuria, are very rare in Finland. The causative genes have been identified for 29 of the Finnish diseases [61], and four main groups of disorders can be categorized according to their patterns of geographic distribution in the current population of 5.3 million (www.findis.org).

For the most common diseases, such as congenital nephrosis, cartilage hair hypoplasia, and aspartylglucosaminuria, a lysosomal storage disease which causes intellectual and developmental disability, the birthplaces of the grandparents of affected individuals in the present generation are widely distributed throughout the country. With a second larger group of disorders, e.g., Mulibrey nanism, Usher syndrome type 3, and nonketotic hyperglycinemia, there is clustering in geographic subregions, usually areas initially populated from the sixteenth century onward. A third group, typified by Meckel syndrome and diastrophic dysplasia, is found predominantly in the western early settlement area. While the fourth group of disorders, comprising Northern epilepsy and the Finnish variant of late infantile neuronal ceroid lipofuscinosis, originated locally in the Kainuu region close to the eastern border and in Southern Ostrobothnia, respectively. Seven other autosomal recessive, autosomal dominant, and X-linked disorders have been included in the Finnish Disease Heritage, and a further five diseases are under investigation and may be incorporated in future years [61].

Table 17.7 The Finnish disease heritage. (From [61])

Disease	Incidence in Finland
Autosomal recessive	
Congenital nephrosis	1:8,000
Infantile neuronal ceroid lipofuscinosis	1:14,000
Meckel syndrome	1:15,000
Unverricht-Lundborg disease	1:17,000
Aspartylglucosaminuria	1:18,000
Cartilage-hair dysplasia	1:18,000
Spielmeyer–Sjögren disease	1:19,000
Hydrolethalus syndrome	1:22,000
Diastrophic dysplasia	1:22,000
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy	1:27,000
Lethal congenital contracture syndrome (Herva)	1:29,000
Congenital chloride diarrhea	1:33,000
Mulibrey nanism	1:37,000
Usher syndrome type 3	1:42,000
Salla disease	1:42,000
Cornea plana congenita	1:46,000
Congenital lactase deficiency	1:48,000
Muscle-eye-brain disease	1:52,000
Nonketotic hyperglycinemia	1:52,000
Lethal arthrogryposis with anterior horn cell disease (Vuopala)	1:53,000
Jansky–Bielschowsky disease variant	1:59,000
Hyperornithinemia with gyrate atrophy of choroid and retina	1:63,000
GRACILE syndrome (Fellman)	1:64,000
Selective malabsorption of vitamin B_{12}	1:68,000
Nasu–Hakola disease	1:71,000
Lysinuric protein intolerance	1:76,000
PEHO syndrome	1:78,000
IOSCA syndrome	1:90,000
Cohen syndrome	1:105,000
Rapadilino syndrome	1:105,000
Follicle stimulating hormone-resistant ovaries (Aittomäki)	1:127,000
Northern epilepsy	1:176,000
Autosomal dominant	
Meretoja disease	~1:6,000
Tibial muscular dystrophy	~3/year
X-chromosome	
Choroideremia	~2/year
Retinoschisis	~1:17,000

Given the dispersed nature of much of the population, and the small numbers of individuals, it might

have been expected that consanguinity contributed substantially to the prevalence of the various recessive disorders. In fact, except for some parishes in northern Finland with a substantial Sami minority, first-cousin marriage was historically rare in the country, in part because of the dispensation requirement for such marriages that remained in place until 1872, with fees payable to the King. Thus, even among the Swedish-speaking Lutheran minority of Finland the attitudes towards consanguinity differed from those in neighboring Sweden, where first-cousin marriage was freed from civil law restrictions in 1844, leading to an increase in first-cousin unions during the remainder of the nineteenth century [19]. Instead, the historical population profile of Finland was characterized by conditions under which founder effects, genetic drift, and demographic bottlenecks occurred, and it is these factors that have shaped and determined the present-day national and regional profiles of genetic disease [60].

17.8.2 Inter- and Intra-population Differentiation in India

The present-day population of India is estimated at some 1,200 million, having increased from 271 million in the year 1900 and 361 million in 1950, resulting in a greatly enlarged overall effective population size. From a genetic perspective a further significant aspect of the Indian population is that, in common with Middle Eastern and North African populations, and neighboring Pakistan and Afghanistan, where tribal and clan marriage boundaries are in place, marriage in India is contracted within highly endogamous castes [18].

Caste membership is hereditary and defines an individual's position within Indian society. The caste system is believed to have been in existence for at least 2,000 years, and in the past it appears to have been somewhat more flexible, with the emergence of new castes and subcastes recorded during the eighteenth and nineteenth centuries. As an example of the current level of demographic and genetic complexity within India, there are seven major religions, and 299 different languages spoken by 4,635 officially recognized ethnic communities, which in turn are composed of an estimated 50,000–60,000 highly endogamous subpopulations [37].

The majority Hindu population, which accounts for approximately 80% of the national population and so currently numbers over 1,000 million, is structured into four major hierarchical groups (*varna*), Brahmins, Kshatriyas, Vaishas, and Sudras, The four *varna* in turn are subdivided into numerous castes (*jati*) and subcastes, and virtually all Hindu marriages continue to be contracted within hereditary caste boundaries. As these institutions are reputed to have been in existence for some 2,000 years, there has been ample opportunity for intercaste genetic differentiation to have occurred via founder effect and genetic drift, especially given the much smaller, and multiply subdivided, population of India in historical times. Therefore, it would be expected that, through time, caste-specific genetic disease profiles would have developed.

There also is a major dichotomy between the majority Indo-Europeans of north India, who avoid consanguineous marriage, and the Dravidian Hindus of south India, where first-cousin and uncle-niece marriage is widely popular and in many communities preferential (Fig. 17.2). This subdivision is believed to date back to the Codes of Manu compiled around 200 BC [50], and it continues to the present day. Given the long-term preference for close consanguineous marriage it was proposed that the endogamous and largely consanguineous populations of south India would have purged lethal recessive genes from their gene pools [80]. Empirical evidence of the range and prevalence of genetic disorders in the current South Indian population has indicated that this outcome is improbable [71], probably due to reproductive compensation, which would effectively delay if not nullify the elimination of deleterious recessives from the gene pool(s).

17.8.3 Consanguinity and the Distribution of Disease Alleles in Israeli Arab Communities

Arab populations in Israel typify a third major form of human genetic organization. For some 500 years prior to the early twentieth century, Arab communities in the Holy Land were part of the Ottoman Empire. As such, members of these communities were able to mix freely with other neighboring Arab populations, although in most cases marriages were contracted within tribes and frequently at the level of the clan

(*hamula*). In addition, consanguineous unions were widely favored, in particular father's brother's daughter-first-cousin marriage (termed *ibn amm*), with double-first-cousin and second-cousin unions also quite common. Conditions favoring village endogamy increased markedly in the years following establishment of the state of Israel in 1948, with the initial movement of an estimated 700,000 people to other neighboring countries and the effective closure of the borders between Israel and the surrounding Arab states. Since 1948, the Arab population of Israel has undergone very rapid natural expansion and now totals over 1.2 million.

Autosomal recessive disorders were found to be more common in the progeny of consanguineous parents [101], and the prevalence rates of congenital malformations were higher in Palestinian Arab and Druze communities, where clan endogamy and consanguinity were strongly favored, than in the more exogamous Jewish and Christian communities [102]. As in Finland, some diseases, such as β-thalassemia, familial Mediterranean fever, and deafness are frequent in the whole Arab population, whereas others are restricted to specific regions or villages. For a specific, rare inherited disease, a single founder mutation would ordinarily be expected within a small geographic area. However, in the case of the lysosomal storage disorder metachromatic leukodystrophy caused by a deficiency of arylsulfatase A, multiple causative mutations were identified within a restricted region, suggesting the occurrence of a number of founder mutations at this disease locus [42]. Subsequent studies have further demonstrated some 19 mostly chronic autosomal recessive disorders in a village with 8,600 inhabitants, i.e., a prevalence for these disorders of approximately 1/70 [103].

A detailed investigation of 12 recessive mutations affecting the inhabitants of a single village has indicated both founder effects and de novo mutations, and the transfer of mutations between families via marriage. Under such circumstances, a single family with one or more family members diagnosed with a specific recessive disorder would usually indicate a recent event, whereas a rare disease affecting members of several families would be more convincingly interpreted as an older mutation [104]. But in all such cases, a thorough understanding of past and present marriage patterns is an essential prerequisite, and given the demographic history of founder effects, migration, population bottlenecking, and rapid expansion, in combination with clan endogamy and preferential consanguinity, the resultant overall picture becomes kaleidoscopic.

17.9 Evaluating Risk in Consanguineous Relationships

The three preceding examples illustrate some of the unexpected complexities that can be encountered when dealing with actual human populations, and the importance of at least a basic knowledge of the demographic structure of a population. They also highlight the difficulties that may be encountered in some populations in differentiating between random inbreeding, brought about by founder effect, endogamy and genetic drift, and preferential consanguinity. Yet this differentiation is critical in accurately assessing the outcomes of consanguineous unions, and in providing risk estimates in settings such as a genetic counseling clinic.

The importance of recognizing and controlling for remote levels of consanguinity in gene association studies has already been noted [55], as have the combined roles of consanguinity and population subdivision in many clinical situations [18]. Although it has been claimed that statistical methods such as principal components analysis can be employed to correct for population stratification in genome-wide studies [69], their successful application in societies as multiply subdivided as India would be a very major challenge. Greater care is therefore warranted in the selection of cases and controls for gene association studies and, if properly conducted, greater reproducibility in their outcomes should follow.

From a practical perspective, the ability to purvey risk in an unambiguous and readily understood manner is an all-important issue in human and medical genetics. Risk estimates expressed as relative risks, odds ratios, or attributable risks, i.e., the fraction of cases in a population that can be attributed to a particular risk factor, are very useful in epidemiological studies. However, in a genetic counseling setting the probability of an adverse outcome needs to be presented in as uncomplicated a manner as possible, taking into account factors such as the background population risk, degree of consanguinity, and relevant family history [11].

When dealing with a topic as potentially sensitive as consanguineous marriage, the avoidance of any potential misunderstanding or misinterpretation by clients and their families is critical.

17.10 Concluding Comments

The development of society-compatible education programs on consanguineous marriage, in combination with evidence-based screening and genetic counseling guidelines, is of paramount importance. It has been proposed that communities in which consanguineous marriage is preferential can be at an advantage when screening for deleterious mutations, for example, in the case of β-thalassemia in Pakistan [3], as there is a high probability that all family members will be homozygous for the same mutation. Under these circumstances, identification of the specific mutation in an affected individual can serve as a diagnostic marker for an extended family group at high genetic risk. Some caution is, however, needed in this approach, since past intermarriage with other unrelated families and communities could have led to significant gene admixture and hence increased the likelihood of compound heterozygosis. But in general the concept is valid and useful, as indicated by a successful screening program for autosomal recessive nonsyndromic intellectual disability in an Israeli Arab community [7].

The future status of consanguineous marriage is a matter of conjecture. Currently an estimated 1,000 million people live in countries where from 20% to over 50% of marriages are consanguineous [18], and it seems highly improbable that a form of marriage which remains so widely popular would rapidly decline in popularity. But strenuous semiofficial efforts are being made to lessen the appeal of consanguinity in many developing countries, often to the distress and embarrassment of consanguineous couples. The situation for migrant communities in western societies is different again, since there is both an attraction to continue with a form of marriage that has been undertaken for many generations in their countries of origin, and at the same time a desire among some younger members of migrant families to adopt the social mores of their new homeland, including exogamous marriage customs.

Within migrant communities there is a much greater awareness of genetic disease than would have been the case in their homeland, and of the increased risk of an affected child being born to a consanguineous couple [13]. 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. However, it also has to be acknowledged that the presence of several family members with a major disabling disorder may severely limit the marriage opportunities of other family members, thus increasing the probability of further intrafamilial unions [7, 18].

While medical genetics is a relatively new subject, consanguineous marriage has been, and remains, a core feature of many successful human societies. A recent World Health Organization Report on Medical Genetics Services in Developing Countries advised that: ‘Preference for consanguineous marriage is a feature of the socio-cultural context within which medical genetic services must work’ [97]. Adoption of this eminently sensible and nonjudgmental approach should ensure that the health needs of families and communities in both the developing and developed world can best be met.

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