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Inbreeding and Genetic Disorder

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1. Introduction

Inbreeding is usually defined as the mating between relatives and the progeny that result of a consanguineous mating between two related individuals is said to be inbred (Cavalli-Sforza & Bodmer, 1971; Hedrick, 2005; Vogel & Motulsky, 1997). As a result of inheriting the same chromosomal segment through both parents, who inherited it from a common ancestor, the individuals born of consanguineous unions have a number of segments of their chromosomes that are homozygous. Therefore, inbreeding increases the amount of homozygosity and, consequently, recessive alleles hidden by heterozygosity with dominant alleles will be expressed through inbreeding. On this basis, it is expected that recessive traits such as many human genetic disorders will occur with increased frequency in the progeny of consanguineous couples. In addition, since many recessive alleles present in natural populations have harmful effects on the organism, inbreeding usually leads to a decrease in size, vigor and reproductive fitness. In a broad sense, it is necessary to consider that inbreeding can occur under two quite different biological situations. There may be inbreeding because of restriction of population number. The degree of relationship between the individuals in a population depends on the size of that population since the individuals are more closely related to each other in a small population than in a large one. Thus, inbreeding is a phenomenon frequently associated with small populations. On the other hand, inbreeding can occur in a large population as a form of nonrandom mating when the frequency of consanguineous matings is higher than that expected by chance. In this case, the population will show a homozygote excess with respect to a random mating population in which genotypic frequencies are expected to be in Hardy-Weinberg equilibrium. The greatest extent of inbreeding is found in plants. A number of plant species are predominantly self-fertilizing which means that most individuals reproduce by self-fertilization, the most extreme form of inbreeding. In animals, inbreeding is less prevalent than in plants, even though some invertebrates have brother-sister matings as some Hymenoptera. Inbreeding also plays a very important role in animal and plant breeding because the number of breeding individuals in breeding programs is often not large. In this way, the inbreeding effects associated with small population size must be considered in the context of animal and plant breeding.

In humans, consanguineous marriage is frequent in many populations. In fact, it has been recently estimated that consanguineous couples and their progeny suppose about 10.4 % of

the 6.7 billion global population of the world (Bittles & Black, 2010). First-cousin marriage and other types of consanguineous unions are frequent in a number of current populations from different parts of the world. The extent of inbreeding of an individual is usually measured in terms of his or her inbreeding coefficient. The coefficient of inbreeding (F) is the probability that an individual receives at a given autosomal locus two alleles that are identical by descent or, equivalently, the proportion of the individual's autosomal genome expected to be homozygous by descent (autozygous) (Cavalli-Sforza & Bodmer, 1971; Hedrick, 2005). If genealogical information is available for a given individual, his or her inbreeding coefficient can be computed from pedigree analysis. The computation of the genealogical inbreeding coefficient assumes neutrality with respect to natural selection so that the transmission probabilities of alleles can be calculated from Mendelian ratios. In humans, the most extreme cases of inbreeding corresponds to incestuous unions defined as mating between biological first-degree relatives; i. e., father-daughter, mother-son and brother-sister. The progeny from an incestuous union will have an inbreeding coefficient of $\frac{1}{4}$ (0.25) in the three cases. Offspring of uncle-niece, first-cousin, and second-cousin marriages will have $F = 1/8$ (0.125), $1/16$ (0.0625) and $1/64$ (0.0156), respectively. In complex genealogies, the depth of the pedigree is very important for the computation of the inbreeding coefficient. In some cases, genealogical data from the most recent four or five generations seem to be sufficient to capture most of the information relevant to the calculation of the inbreeding coefficient (Balloux et al., 2004). This is due to the fact that recent inbreeding events have a disproportionately large influence on an individual's inbreeding coefficient relative to events deeper in the pedigree. However, in some large and complex pedigrees, ancestral or remote consanguinity can make a substantial contribution to the inbreeding of a given individual and the exploration of pedigrees limited to a shallow depth carries the risk of underestimating the degree to which individuals are inbred (Alvarez et al., 2009; Boyce, 1983; MacCluer et al., 1983). Computation of inbreeding coefficients from extended pedigrees will be necessary in order to obtain an accurate measure of the inbreeding level in those situations in which remote consanguinity is important.

Studies on genome-wide homozygosity through the genome scan technology have opened new avenues for inbreeding research. Thus, genome-wide homozygosity may be used to estimate the inbreeding coefficient for a given individual when genealogical information is not available. Furthermore, the study of genome-wide homozygosity is very important for the identification of recessive disease genes through homozygosity mapping as well as for the investigation of homozygosity effects on traits of biomedical importance. Long homozygous chromosomal segments have been detected in human chromosomes from the analysis of polymorphic markers in whole-genome scans (Broman & Weber, 1999; McQuillan et al., 2008). These long tracts where homozygous markers occur in an uninterrupted sequence are often termed runs of homozygosity (ROH) and can arise in the genome through a number of mechanisms (Broman & Weber, 1999; Gibson et al., 2006). The most obvious explanation for such tracts is autozygosity, where the same chromosomal segment has been passed to a child from parents who inherited it from a common ancestor. The length of an autozygous segment reflects its age since haplotypes are broken up by recombination at meiosis in such a way that long tracts are expected to occur by close inbreeding whereas a short autozygous segment is likely to be the result of the mating of very distantly related individuals. Homozygous tracts are significantly more common in

chromosome regions with high linkage disequilibrium and low recombination but since linkage disequilibrium is a local phenomenon would cause only short homozygous segments (Broman and Weber, 1999; Gibson et al., 2006). A genomic measure of individual autozygosity termed F_{roh} has been defined as the proportion of the autosomal genome in runs of homozygosity above a specified length threshold:

$$F_{roh} = \Sigma L_{roh} / L_{auto}$$

where ΣL_{roh} is the total length of all ROHs in the individual above a specified minimum length and L_{auto} is the length of the autosomal genome covered by the genomic markers (McQuillan et al., 2008). In a genome-wide study based on a 300,000 SNP panel, it has been found a strong correlation ($r = 0.86$) between F_{roh} and the genealogical inbreeding coefficient (F) among 249 individuals from the isolate population of the Orkney Isles in northern Scotland, for which complete and reliable pedigree data were available (McQuillan et al., 2008). F_{roh} values were computed for a range of minimum-length thresholds (0.5, 1.5 and 5 Mb) and the mean value of F_{roh} for 5 Mb was the closest F_{roh} to that of F computed from pedigree data. ROHs measuring less than 3 or 4 Mb were not uncommon in unrelated individuals. The size of the autozygous segments and their distribution throughout the human genome has been investigated in inbred individuals with recessive Mendelian disorders (Woods et al., 2006). Through a whole-genome scan of 10,000 SNPs, individuals affected with a recessive disease whose parents were first cousins drawn from two populations with a long history of consanguinity (Pakistani and Arab) presented, on average, 20 homozygous segments (range 7-32 homozygous segments) exceeding 3 cM and a size of the homozygous segment associated with recessive disease of 26 cM (range 5-70 cM). The proportion of their genomes that was homozygous varied from 5 to 20% with a mean value of 11%. This figure is increased about 5 % over the expected value for the offspring of a first-cousin union ($F = 0.0625$) but it is necessary to take into account that the proportion of the genome identical by descent has a large stochastic variation (Carothers et al., 2006). Moreover, the individuals analyzed were those children of first cousins presenting a genetic disorder so that they were a biased sample of a first-cousin progeny. Through the genome scan technology, several studies have shown that extended tracts of genomic homozygosity are globally widespread in many human populations and they provide valuable information of a population's demographic history such as past consanguinity and population isolation (Kirin et al., 2010; Nalls et al., 2009).

Autozygosity has practical implications for the identification of human disease genes. Homozygosity mapping is the method of choice for mapping human genes that cause rare recessive Mendelian diseases (Botstein & Risch, 2003; Lander and Botstein, 1987). The method consists of searching for a region of the genome that is autozygous in individuals affected by a given disease from consanguineous families. Thus, the disease locus is detected on the basis that the adjacent region will be homozygous by descent in such inbred individuals. The method is also known as autozygosity or consanguinity mapping and has the advantage that relatively few individuals are required. Homozygosity mapping became practical with the discovery of multiple highly polymorphic markers. The first polymorphic markers used were restriction length polymorphisms, subsequently, short sequence repeats and more recently single nucleotide polymorphisms (SNPs) (Woods et al., 2004). Since 1995 until 2003, nearly 200 studies were published in which homozygosity mapping was used to map human genes causing rare recessive disease phenotypes (Botstein and Risch, 2003).

Recently, the strategy of homozygosity mapping has been extended to analyze single individuals by means of high-density genome scans in order to circumvent the limitation of the number of consanguineous families required for the analysis (Hildebrandt et al., 2009). Homozygosity mapping in single individuals that bear homozygous disease gene mutations by descent from an unknown distant ancestor may provide a single genomic candidate region small enough to allow successful gene identification. Remote consanguinity will lead in the affected individual to fewer and shorter homozygous intervals that contain the disease gene. The analysis through homozygosity mapping of 72 individuals with known homozygous mutations in 13 different recessive genes detected, by using a whole-genome scan of 250,000 SNPs, the disease gene in homozygous segments as short as 2 Mb containing an average of only 16 candidate genes (Hildebrandt et al., 2009).

2. Consanguineous marriage around the world

Studies on the prevalence and pattern of consanguineous marriages in human populations show that consanguinity is widely extended in many current populations around the world (Bittles, 2001, 2006). In demographic literature a consanguineous marriage is usually defined as a union between individuals who are related as second cousin or closer ($F \geq 0.0156$ for their progeny). This arbitrary limit is based in the perception that an inbreeding coefficient below 0.0156 has biological effects not very different from those found in the general population. At the present time, it has been estimated that the consanguineous couples and their progeny suppose 10.4% of the global population (Bittles and Black, 2010). Marriage between first cousins ($F = 0.0625$ for their progeny) is considered the most prevalent consanguineous union in human populations. Also, matrimony among two second cousins is very frequent. Globally, unions between uncle and niece or double first cousins ($F = 0.125$ for their progeny, in both cases) are less common; however it is possible to find certain populations with high incidence of uncle-niece unions. Regarding incestuous unions between biological first degree relatives (father-daughter, mother-son, brother-sister; $F = 0.25$ for their progeny, in the three cases), a universal taboo for nuclear family mating exists in all societies. Incest is illegal in many countries and specifically forbidden by the big five religions, even though incestuous practices can be found sporadically in any society. The prevalence of incest around the world is difficult to establish due to its illegality and association with social stigma (Bennett et al, 2002).

Consanguinity is not homogeneously distributed around the globe, so that it is possible to associate certain geographic areas with high consanguinity incidence. The distribution of consanguineous marriages in four continents (Europe, America, Asia and Africa) obtained from data available at the web portal Consanguinity/Endogamy Resource (consang.net) is shown in Figure 1. This web portal compiles data of global prevalence of consanguinity from more than two hundred studies performed since middle of the 20th century. These studies gathered marital information through household and school, pedigree analysis, civil registrations and census, obstetric and hospital inpatients, as well as religious dispensations for more than 450 populations from 90 countries. In this data set, 63.0% of the populations are from Asia, 19.1% from South America, 8.9% from Europe, 6.4% from Africa and just 2.6% from Central and North America. In general, a more favorable attitude towards consanguinity is found in populations from Asia and Africa. In Sub-Saharan Africa, for example, 35 to 50% of the marriages are between relatives. In Egypt, on average, 42.1% of

total marriages are consanguineous; with a preference for double first cousin and second cousin, even though there is a great heterogeneity among populations due to different beliefs and cultural backgrounds. The most consanguineous populations studied so far are found in Asia. In Afghanistan, for instance, 55.4% of the matrimonyes in the country are between relatives. In the traditional nomadic *Qashqai* from Iran up to 73.5% of the marriages are consanguineous. Table 1 shows the results of a 10-year study performed in the cities of Bangalore and Mysore in the State of Karnataka, South India that involved a total number of 107,518 marriages (Bittles et al., 1991). For the entire sample, 31.4% of all unions were consanguineous and the mean consanguinity measured as the average inbreeding coefficient ($\alpha = \sum p_i F_i$) was 0.0299. Consanguinity was more prevalent among Hindus with 33.5% of consanguineous marriages and they had the highest average consanguinity ($\alpha = 0.0333$) because the high rate of uncle-niece marriages. In the Muslim community, 23.7% of marriages were consanguineous with an average consanguinity of 0.0160. Muslims avoid uncle-niece marriage because this type of consanguineous union is proscribed by the Quran. First-cousin marriage was the most prevalent consanguineous union in the Muslim community. Christians in Karnataka presented an 18.6% of consanguineous marriages including both uncle-niece and first cousin marriages with an average consanguinity of 0.0173. Unlike Asia and Africa, Europe and America seems to have a refusal attitude over consanguinity since most populations present less than 10% of their matrimonyes being consanguineous (Figure 1). In Europe, consanguinity appears to be more prevalent in Southern countries such as Spain or Italy where consanguineous unions represent 3.5% and 1.6% of total marriages respectively. North European countries appeared to have lower incidence of consanguineous marriages, for instance, 0.3% in Great Britain, 0.4 in Norway or 0.4 in Hungary. The American continent seems to be very similar to Europe. In South America, the average of consanguineous marriages in 39 Brazilian populations is 4.2%, with different preferences for union type depending on the community. In Colombia and Ecuador, data from six populations indicate that consanguineous marriages represent the 2.8% and 2.9% respectively, of total marriages. In USA, it has been estimated that only 0.2% of total marriages are consanguineous from a couple of populations from Wisconsin, a sample of all-USA of more than 130,000 people and a couple of minorities populations.

Type of marriage	Religion		
	Hindu	Muslim	Christian
Non-Consanguineous (F=0)	62.0	72.9	78.1
Beyond second cousin (F<0.0156)	4.5	3.5	3.4
Second Cousin (F=0.0156)	1.7	2.5	1.6
First cousin (F=0.0625)	10.8	17.5	6.8
Uncle-niece (F=0.125)	21.0	3.7	10.2

Table 1. Consanguineous marriages (%) and religion in Karnataka, India. The inbreeding coefficient (F) of the offspring for each type of marriage is given. (Form Bittles et al. 1991)

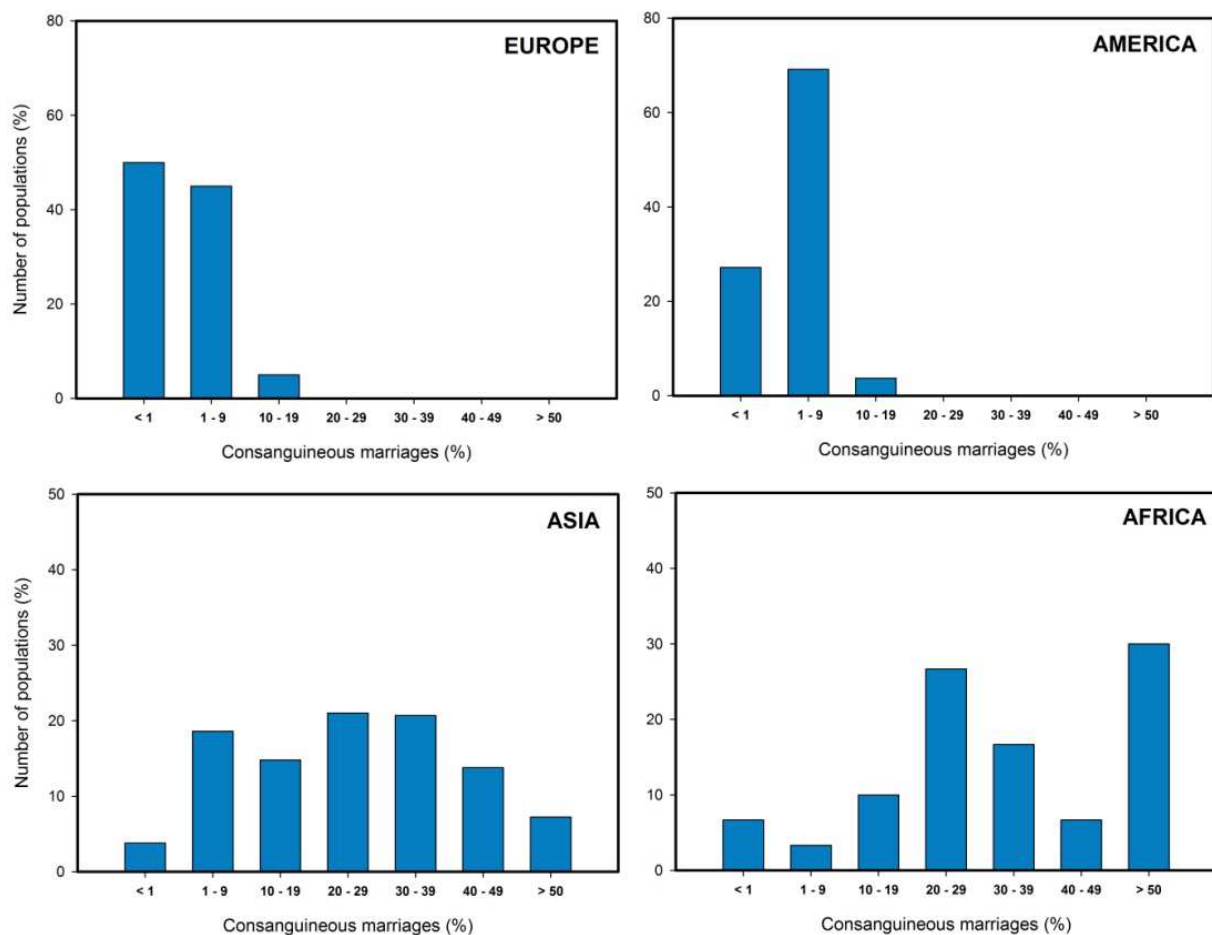


Fig. 1. Percentage of consanguineous marriages in human populations from four continents. (Data from consag.net)

Consanguinity studies in population minorities, isolates and migrants reveal that there is a great heterogeneity between close communities around the world. Figure 2 shows the incidence of consanguineous marriages in population minorities, isolates and migrants for more than 100 populations from 22 countries (data from consang.net). In the nomadic Bedouin Baggara Arabs community that inhabits Nyertiti state in Sudan, for example, 71.7% of their matrimonies are consanguineous marriages, with a clear preference for first-cousin unions. In Japan, where only 8.98% of all marriages are consanguineous, an isolate population as the Arihara community in the Kansai region presented 47.8% of consanguineous marriages. Samaritan isolate community from Israel has a clear preference for first cousin unions. While in Israel other Hebrew communities have on average 7.6% of consanguineous unions, Samaritans have 46.4%. In Europe, some migrant populations maintain their traditions while living abroad. For instance, Pakistani community of Great Britain living in Bradford has 67% of consanguineous marriages with average consanguinity being 0.0377. Pakistani community in Norway also has high incidence of consanguineous unions since 31% of their marriages are consanguineous. In the Unites States, where first cousin marriages are criminal offence in eight states and illegal in a further 31 states, exceptions have been incorporated to permit uncle-niece marriage within the Jewish community of Rhode Island. High incidence of consanguineous marriages has been reported in isolates minorities from USA such as a Gypsy community from Boston with

61.9% of consanguineous unions, and Christian Anabaptists Mennonites from Kansas with 33.0% of their matrimonies being between relatives.

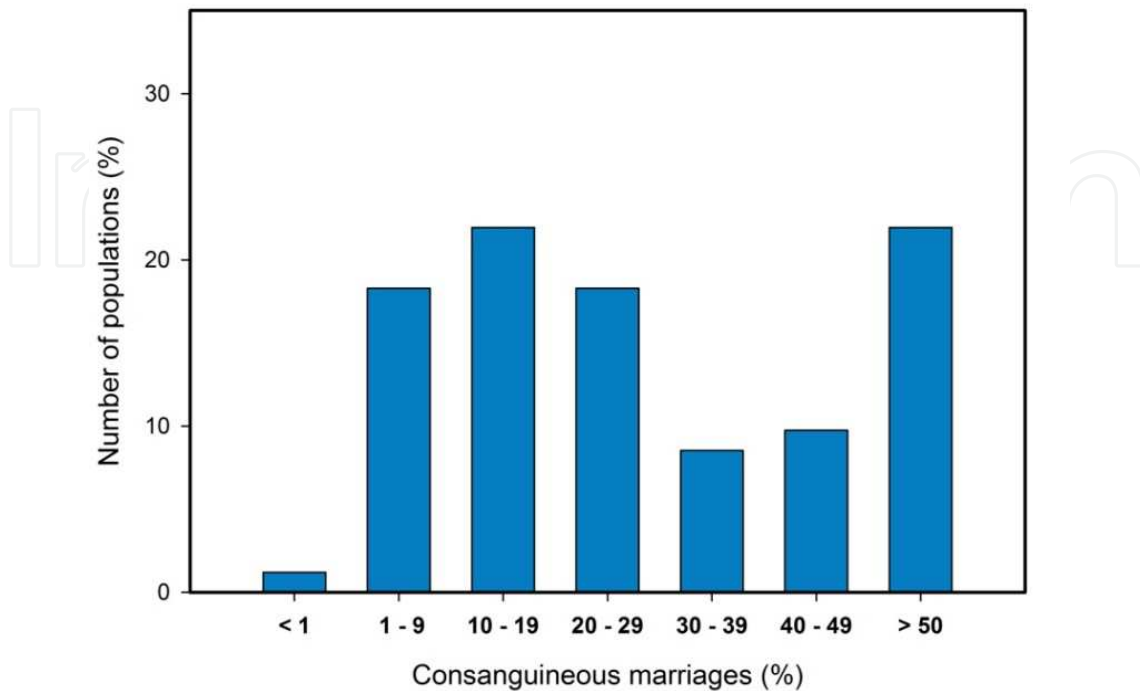


Fig. 2. Percentage of consanguineous marriages in minorities, isolates and migrant populations around the world. (Data from consag.net)

Consanguineous marriage is favored in many societies, especially from Asia and Africa, as a mean of preserving family goods and lands (Bittles, 2006). Social and cultural advantages such as strengthened family ties, enhanced female autonomy, more stable marital relationships, greater compatibility with in-laws, lower domestic violence, lower divorced rates or simplified premarital arrangements along with economic considerations may be the actual motives for the preference of consanguineous unions particularly in rural societies. Furthermore, consanguinity was also common among European royalty and aristocracy up until the middle of 1900s, and nowadays is still present punctually in rich families and aristocracy. Consanguineous marriage cannot be restricted to any specific society or religion, although the attitude of the different societies toward consanguinity is highly influenced by religious beliefs or creeds (Bittles et al., 1991). Marriage regulations in Islam permit first-cousin and double first-cousin unions and the Quran expressly prohibits uncle-niece matrimonies. Unlike Islam, Hinduism attitude over consanguinity is non-uniform. The Aryan Hindus of northern India prohibit marriages between relatives for approximately seven generations. By comparison, Dravidian Hindus of south India strongly favor marriage between first cousin of the type mother's brother's daughter, and particularly in the states of Andhra Pradesh, Karnataka and Tamil Nadu uncle-niece marriages are also widely contracted (Table 1). Buddhism and its two major branches Theravada and Mahayana which are spread through all Asia prohibit any type of consanguineous relationship in marriage. Christianity and Judaism attitude over consanguinity is based in the book of Leviticus, third book of the Hebrew Bible and Torah. Many examples of consanguineous unions are cited in the biblical texts, for example Abraham and Sarah, identified as half siblings (*Genesis 20:12*)

or Moses' parents, related as nephew and aunt (*Exodus* 6:20). However, in the book of Leviticus is expressed that "None of you shall approach any one of his close relatives to uncover nakedness. I am the Lord" (*Leviticus* 18:5). Despite these sentences, the Leviticus has been interpreted in different ways. Judaic law interpretation of the Leviticus led its followers to permit first-cousin and even uncle-niece unions. Christianity attitude over consanguineous marriage is characterized by its lack of uniformity. Orthodox churches have a strict interpretation of the Leviticus since they prohibit consanguineous marriage of any form. For members of the Latin Church the effect of the rules addressed in the Leviticus was to prohibit marriage with a biological relative usually up to and including third cousin. Dispensation could, however, be granted at Diocesan level for related couples who wished to marry within the prohibited degrees of consanguinity, albeit with payment of an appropriate benefaction to the church. Among the constellation of different churches arose from Reformed Protestant the existing biblical guidelines were generally adopted, although the closest form of approved union usually has been between first cousins. Paradoxically, the highest rates of consanguineous unions historically recorded in Europe, and even nowadays, appear to be in the southern Roman Catholic countries rather than in the northern Protestant European countries. This pattern is followed also by the Catholic countries of South and Central America in comparison with Protestants, Anabaptist, Anglicans and Restorationists from North America.

3. Inbreeding and genetic disease

In his classic study of inborn errors of metabolism, Archibald Garrod noted that an unusual high proportion of patients with alkaptonuria were progeny of consanguineous marriages. After this observation carried out at the early years of the 20th century, a very large number of studies have consistently shown that recessive traits occur with increased frequency in the progeny of consanguineous mates, and this outcome is one of the most important clinical consequences of inbreeding. In Europe and Japan, for example, the frequency of first-cousin marriages among the parents of affected individuals with recessive traits such as albinism, phenylketonuria, ichthyosis congenital and microcephaly is remarkably higher than frequency of first-cousin marriages in the corresponding general population (Bodmer & Cavalli-Sforza, 1976; pp. 372-377). In general, the rarer the disease, the higher the proportion of consanguineous marriage among the parents of affected individuals. Similarly, the closer the inbreeding, the higher the effect. The genetic explanation for these observations is simple and derives from basic principles of population genetics. In a random mating population, the frequency of recessive homozygotes aa will be q^2 for an allele a that has frequency q , according to the Hardy-Weinberg law. In an inbred population with inbreeding level F , the frequency of recessive homozygotes will be $q^2 + (1 - q)qF$ and therefore the ratio of the frequency of the homozygote aa in an inbred population relative to a random mating one will be $1 + F(1 - q)/q$. The ratio is very large for low allele frequencies and increases with the level of inbreeding. For example, when $F = 1/16$ corresponding to the progeny of a first cousin marriage and $q = 0.01$, there are more than seven times as many affected individuals in the inbred group as in the non-inbred population. For illustrative purposes, Table 2 shows the risk of recessive disease among progeny of first-cousin marriages and among progeny of unrelated parents for three values of allelic frequency. On this rationale, parental consanguinity can be a useful criterion in clinical diagnosis. Thus,

when the parents of a patient suffering from a previously unknown disease are consanguineous the diagnosis of a recessive genetic disease is of serious consideration.

Allele frequency (q)	Offspring of unrelated parents	Offspring of first cousins
0.01	1:10,000	1:1,400
0.005	1:40,000	1:3,000
0.001	1:1,000,000	1:16,000

Table 2. Risk of affected individual for rare recessive disease in offspring of unrelated and first-cousin parents

Several studies have reported the occurrence of a number of detrimental health effects in the progeny of consanguineous marriages. In general, the offspring of consanguineous couples presented increased levels of morbidity and significant medical problems such as major malformations, congenital anomaly and structural birth defects in first few days of life (Bennett et al., 2002; Bittles, 2001, 2006). The estimation of the absolute risk for the offspring of consanguineous unions is often very difficult because an important number of factors such as sociodemographic variables, methods of subject ascertainment and others that are influencing the risk of a given population. Many of these non-genetic variables are hardly controlled in the data analysis. A way to circumvent such problems is to compare the risk in the offspring of consanguineous marriages with that corresponding to non-consanguineous unions. In a compilation based on data from a number of studies, the increased risk for a significant birth defect in progeny of a first cousin marriage varied between 1.7 and 2.8% above that of the non-consanguineous population (Bennett et al., 2002). An important number of abnormalities have also been reported in the offspring of first degree incestuous unions. A compilation from data of several studies shows that 11.7% (25/213) of the incestuous progeny presented known autosomal recessive disorders, 16.0% (34/213) congenital malformations, 11.7% (25/213) nonspecific severe intellectual impairment and 14.6% (31/213) mild intellectual impairment (Bennett et al., 2002).

In contrast with the extensive evidence on the effect of inbreeding for Mendelian diseases the contribution of consanguinity to complex or multifactorial diseases is less known. There is, however, growing evidence for adverse effects of inbreeding on complex human diseases of public health importance. The relationship between inbreeding and blood pressure (BP), and the related late-onset disease, essential hypertension, has been investigated in isolate populations from Dalmatian islands, Croatia (Rudan et al., 2003b). A strong linear relationship between the inbreeding coefficient (F) and both systolic and diastolic BP among 2760 adult individuals from 25 villages within Croatian island isolates was found. The individual inbreeding coefficient was computed for each study participant based on pedigree information from four to five ancestral generations. An increase in F of 0.01 corresponded to an increase of approximately 3 mm Hg in systolic and 2 mm Hg in diastolic BP, and 10-15 % of the total variation in BP in those populations could be explained by recessive or partially recessive quantitative trait locus (QTL) alleles. It was estimated that several hundred (300-600) recessive QTLs could contribute to BP variation. Moreover, it was inferred that inbreeding accounts for 36 % of all hypertension in those populations. Dalmatian island populations have been also used to investigate the relationship between inbreeding and the prevalence of 10 late onset complex diseases: coronary heart disease,

stroke, cancer, schizophrenia, epilepsy, uni/bipolar depression, asthma, adult type diabetes, gout and peptic ulcer, which are commonly occurring disorders in those islands (Rudan et al., 2003a). The study was carried out in 14 isolate villages on three neighboring islands in middle Dalmatia which present a wide range of levels of inbreeding and endogamy, and relative uniformity of environment so that the potential effects of inbreeding on those complex diseases may be detected. Disease prevalence was investigated by comparisons between villages grouped by the level of inbreeding as high (average $F = 0.036$), moderate (average $F = 0.013$) and low (average $F = 0.006$). An increase in disease prevalence across villages associated with an increase in average inbreeding coefficient was observed for gout, depression, peptic ulcer, schizophrenia, cancer, epilepsy, coronary heart disease, stroke and asthma (the last three not statistically significant) but not for type 2 diabetes (Table 3). The results indicated that between 23 % and 48 % of the incidence of these disorders in the population sample (other than type 2 diabetes) could be attributed to inbreeding. These findings provide indirect evidence in support of a major polygenic component to disease susceptibility due to many deleterious recessive alleles located throughout the genome. Rudan et al. (2003a) have suggested that the genetic component of late onset diseases may be caused by large number of rare variants in numerous genes maintained at low frequency in populations by mutation-selection balance, according to the common disease/rare variant (CD/RV) hypothesis (Wright et al., 2003). From this point of view, the study of inbred populations could be very useful in the detection of genetic effects on complex disease since inbred individuals will show stronger phenotypic effects compared with outbred individuals, where most alleles are present in heterozygotes (Rudan et al., 2003b).

A number of evidences suggest that inbreeding is also an important risk factor in susceptibility to infectious diseases in humans. Association between inbreeding and susceptibility to infectious disease has been investigated through microsatellite genome scan data for tuberculosis (TB) in The Gambia, leprosy in India and persistent hepatitis B virus infection both in The Gambia and Italy (Lyons et al., 2009b). In this study, inbreeding coefficients were estimated from correlations in heterozygosity among markers because genealogical information was not available for the studied individuals; r^2 values between heterozygosities were calculated from two sets of randomly selected unlinked markers. In The Gambia, where the frequency of first-cousin marriage is approximately 30%, the correlations in heterozygosity among markers were larger in affected individuals than in unaffected ones for both hepatitis and TB. This result suggests that inbred individuals are more common among the infected cases for both hepatitis and TB and, therefore, consanguinity appears significantly to increase the risk of these two major infectious causes of death in humans. Significant differences in r^2 values between affected and unaffected individuals were not found for persistent hepatitis in the Italian genome scan, probably due to the low levels of inbreeding in that population. Correlations in heterozygosity among markers were not different between affected and unaffected individuals for leprosy in India, where the frequency of consanguineous marriages is high, suggesting no effect of inbreeding on this infectious disease. Furthermore, evidence for an association between infectious disease and homozygosity has been also reported. In a case-control study of fatal invasive bacterial diseases in Kenyan children that was performed by using a genome-wide scan with microsatellite markers, homozygosity was significantly increased in 148 children aged <13 years who died of invasive bacterial diseases such as bacteraemia, meningitis and

neonatal sepsis compared to the control sample constituted by 137 age-matched, healthy children (Lyons et al., 2009a). Of a total number of 134 microsatellite markers analyzed, homozygosity was strongly associated with mortality at five markers. These results indicate that homozygosity significantly contribute to the risk of childhood death due to invasive bacterial disease.

Disease	High Inbreeding (Mean F=0.036)	Moderate Inbreeding (Mean F=0.013)	Low Inbreeding (Mean F=0.006)
Coronary heart disease	13.28	11.95	11.23
Stroke	2.43	2.79	1.73
Cancer	4.54***	3.44*	1.93
Schizophrenia	1.23***	0.96*	0.14
Uni/bipolar depression	10.26***	7.63**	4.51
Asthma	3.63	2.64	2.60
Type II diabetes	6.02	7.35	6.77
Gout	9.25***	7.19***	3.96
Peptic ulcer	6.92***	4.29**	2.18
Epilepsy	1.47***	0.78	0.31

Statistically significance (P values) in highly and moderately inbred groups is calculated against the low inbreeding group: * P<0.05; ** P<0.01; *** P<0.001

Table 3. Prevalence (%) of 10 complex diseases in groups of villages with relatively “high”, “moderate” and “low” inbreeding coefficient (F) in Dalmatia islands, Croatia. (From Rudan et al., 2003a)

4. Inbreeding depression

One of the adverse effects of consanguineous mating is the phenomenon of inbreeding depression. In population genetics, inbreeding depression is usually defined as the decreased fitness of offspring from related parents (Charlesworth & Willis, 2009). Inbreeding depression occurs in many species of animal and plants as well as in humans and is caused by increased homozygosity of individuals. There are two major hypotheses to explain how increased homozygosity can lower fitness. The “overdominance hypothesis” suggests that heterozygotes at loci determining fitness are superior to homozygotes for either allele so that heterozygote advantage (overdominance) is responsible for inbreeding depression. The “partial dominance hypothesis” assumes that inbreeding depression is caused by recessive or partially recessive deleterious alleles maintained in the population at low frequencies by mutation-selection balance. A number of studies on the genetics of quantitative fitness traits in *Drosophila* and other species suggest that inbreeding depression is predominantly caused by deleterious alleles generated by mutation and kept at low frequency in the population by natural selection, even though some alleles at higher frequencies maintained by some form of balancing selection such as heterozygote advantage or temporal, spatial or frequency-dependent selection could be also involved (Charlesworth & Charlesworth, 1999; Charlesworth & Willis, 2009).

The first experimental research on the harmful effects of consanguinity including inbreeding depression was performed by Charles Darwin and was published in his book “*The effects of*

cross and self-fertilization in the vegetable kingdom" (Darwin, 1876). Darwin carried out carefully controlled experiments in the Down House greenhouse that involved self-fertilization and outcrossing between unrelated individuals in 57 plant species. In these experiments the offspring of self-fertilized plants were on average shorter, flowered later, weighted less and produced fewer seeds than the progeny of cross-fertilized plants. By these experiments Darwin documented the phenomenon of inbreeding depression for numerous plant species. Darwin's laborious study on inbreeding had its origin in his interest on plant reproductive systems. In fact, his experiments were performed to explain why numerous plant species have systems that prevent self-fertilization and why reproduction by outcrossing is prevalent in nature. However, it is very likely that Darwin also had a personal interest on this matter. Charles Darwin was married to his first cousin Emma Wedgwood and they had 10 children along their lifetime. Darwin was worried about the health of his children, who were very often ill and three of them died before adulthood. Darwin's own ill health led him to fear that his children could have inherited his medical problems but he also suspected that his marriage to his first cousin might have caused some of his children's health problems (Jones, 2008; Moore, 2005). For a long time, it has been commonly accepted that Charles Darwin's concerns on the harmful effects of first-cousin marriage were unjustified because they were based on the extrapolation from ill-effects of self-fertilization in plants to the outcomes of first-cousin marriage in humans. Nevertheless, recent researches on both survival and fertility in the Darwin/Wedgwood dynasty support the view that inbreeding was effectively involved in a number of health problems of Darwin's children (Berra et al., 2010; Golubosvky, 2008). First-cousin marriage had a widespread acceptance among the upper middle class of Victorian England in such a way that the first-cousin marriage of Charles and Emma was not unusual in that time. In fact, three of Emma's brothers were married to relatives: Josiah Wedgwood III married his first cousin Caroline Darwin, who was Charles's sister, Hensleigh Wedgwood was married to his first cousin Frances MacKintosh and Henry Wedgwood was married to his double first cousin Jessie Wedgwood. All these consanguineous marriages are represented in the pedigree of the Darwin/Wedgwood dynasty shown in Figure 3, which was specifically constructed to compute inbreeding coefficients for Charles Darwin, his progeny and related families combining genealogical information obtained from numerous sources. The inbreeding coefficients computed from the Darwin/Wedgwood pedigree shows that some individuals of the dynasty presented rather high levels of inbreeding. Thus, the children of Henry Wedgwood had a high inbreeding coefficient ($F = 0.1255$) because their parents were double first cousins. The progeny of both Charles Darwin and Josiah Wedgwood III had a moderate inbreeding coefficient ($F = 0.0630$), and the progeny of Hensleigh Wedgwood had an inbreeding of 0.0625. Charles Darwin's mother, Susannah Wedgwood, and her brother, Josiah Wedgwood II, had very low inbreeding values ($F = 0.0039$). All the remaining individuals in the pedigree depicted in Figure 1 had $F = 0$, as did Charles Darwin and his father, Robert Darwin. From these data, a statistically significant positive association between child mortality (deaths from birth to 10 years) and inbreeding coefficient was detected in the progeny of 25 marriages belonging to four consecutive generations of the Darwin/Wedgwood dynasty (Berra et al., 2010). Child mortality was clearly higher for those families whose progeny had high inbreeding coefficient (Figure 4). Mean child mortality in progeny of 21 non consanguineous Darwin/Wedgwood marriages was 10.67%, whereas progeny mortality was nearly twice in the consanguineous marriages: 20.00% in those

families with $F = 0.0625 - 0.0630$ and 16.67% in one family with $F = 0.1255$. Regarding the own Darwin family, the offspring of Charles and Emma had an inbreeding coefficient of 0.0630 and presented one of the highest mortalities (30.0%) among the 25 Darwin/Wedgwood families investigated. Of the three Darwin's children that died before adulthood (Anne Elizabeth, Mary Eleanor and Charles Waring), the cause of death is known for two of them. Anne Elizabeth (1841-1851), Darwin's second child and first daughter, probably died of child tuberculosis and Charles Waring (1856-1859), the last Darwin's child, died of scarlet fever. The recent evidence of inbreeding as an important risk factor in susceptibility to infectious diseases such as hepatitis and tuberculosis as well as the association between homozygosity and childhood mortality resulting from invasive bacterial disease (Lyons et al., 2009a,b) gives a strong support to the hypothesis that inbreeding was directly involved in a number of health problems in Darwin's children. Furthermore, it has been also suggested that inbreeding might have influenced the fertility of Darwin's children (Golubovsky, 2008). It is known that three of Charles Darwin's six children with long-term marriage history suffered from infertility (William Erasmus, Henrietta and Leonard) and a likely cause of that unexplained infertility might be the segregation of some recessive autosomal meiotic mutation manifested in Darwin progeny as a result of inbreeding.

At the present time, there is extensive evidence on the harmful effects of inbreeding on survival before adulthood in humans. Most of this empirical evidence comes from mortality data of the progeny of first cousins as this type of marriage is the most prevalent consanguineous union in human populations. A compilation based on data from 31 studies for various stages of prereproductive mortality showed that the offspring of consanguineous marriages have a higher risk of mortality compared with the offspring of unrelated parents (Khalt & Khoury, 1991; Khoury et al., 1987). The median relative risk for the progeny of first cousin marriages compared with the non consanguineous progeny was 1.41 for prereproductive mortality including all deaths from stillbirths to deaths below 20 years. In other meta-analysis based on data from 38 populations located in eastern and southern Asia, the Middle East, Africa, Europe and South America the progeny of first cousins presented an absolute increase in mortality from birth to a median age of 10 years of $4.4\% \pm 4.6$ (Bittles & Neel, 1994; Figure 5). The most recent compilation on inbreeding depression for survival in humans revealed an absolute increase in mortality from approximately 6 months gestation to an average of 10 years of age of 3.5 % among first-cousin progeny and comprised 69 populations resident in 15 countries located across four continents (Bittles & Black, 2010). It should be emphasized, however, that the above figures represent population averages and they do not reflect the fact that the magnitude of inbreeding depression is highly variable among human populations. Thus, the absolute increase in mortality at first-cousin level varied from nearly zero to approximately 19 % across populations in one of the above mentioned compilations (Bittles & Neel, 1994). Regarding inbreeding depression for high inbreeding levels, the available evidence is at present less abundant than that corresponding to moderate inbreeding from first-cousin marriage. In humans, the most extreme cases of close inbreeding correspond to incestuous unions such as father-daughter, mother-son and brother-sister. Several studies have investigated the adverse effects of inbreeding from children of such incestuous unions, but the results obtained are difficult to interpret because difficulties associated with sample size, unbiased data and suitable controls (Adams & Neel, 1967; Carter, 1967, Seemanová, 1971).

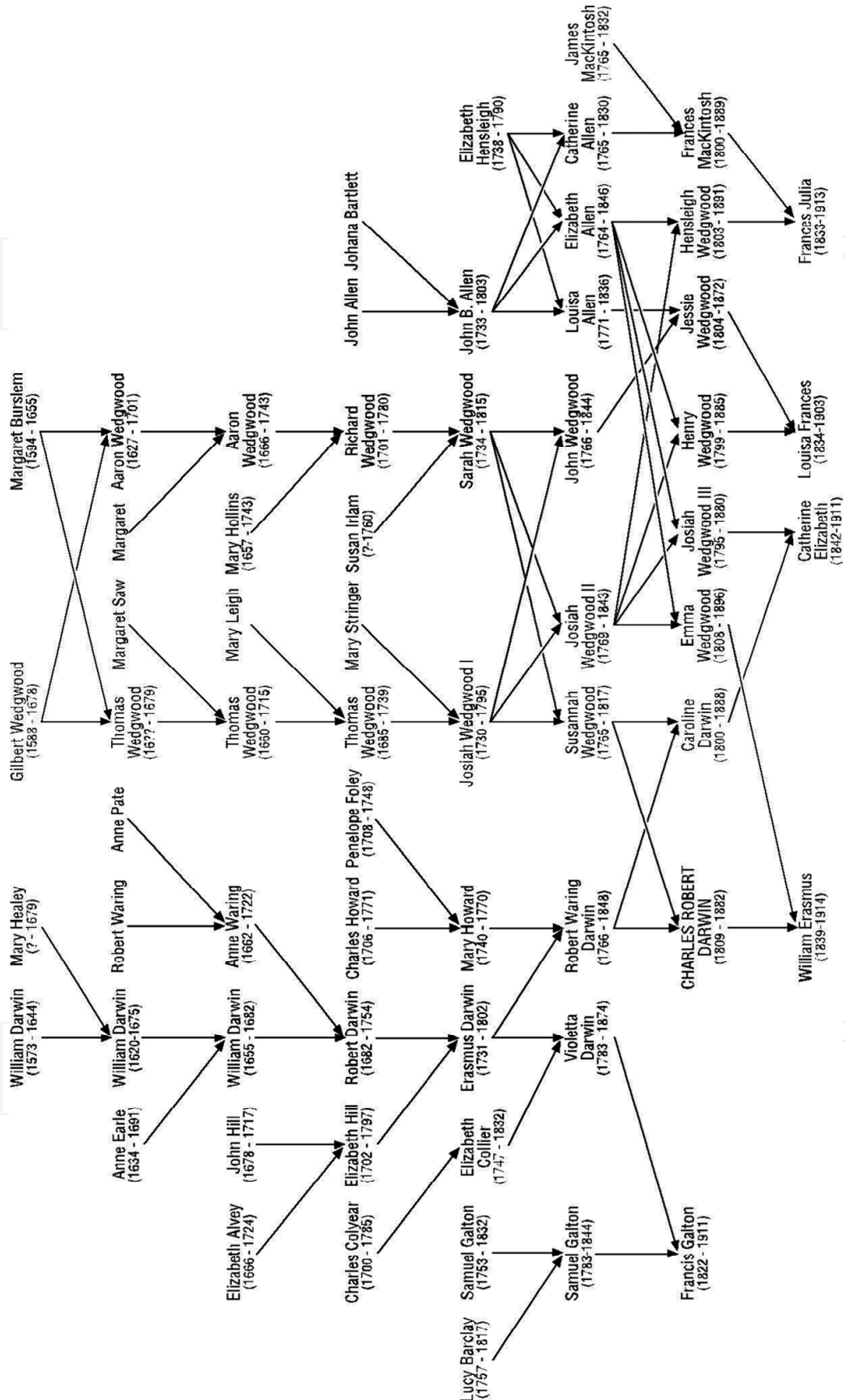


Fig. 3. Pedigree of the Darwin/Wedgwood dynasty. (From Berra et al., 2010)

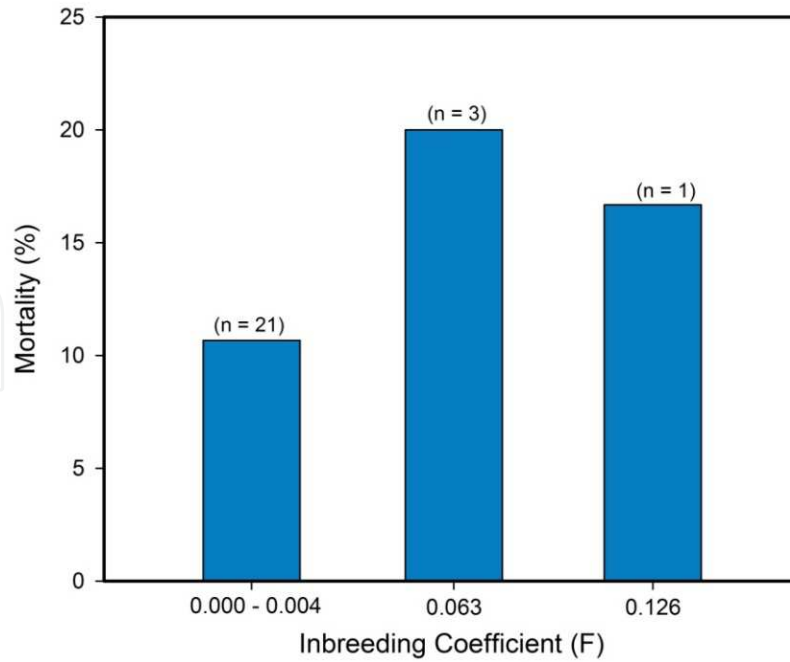


Fig. 4. Mortality from birth to 10 years and inbreeding coefficient (F) in offspring of 25 marriages of the Darwin/Wedgwood dynasty (n = number of marriages) (Data from Berra et al., 2010)

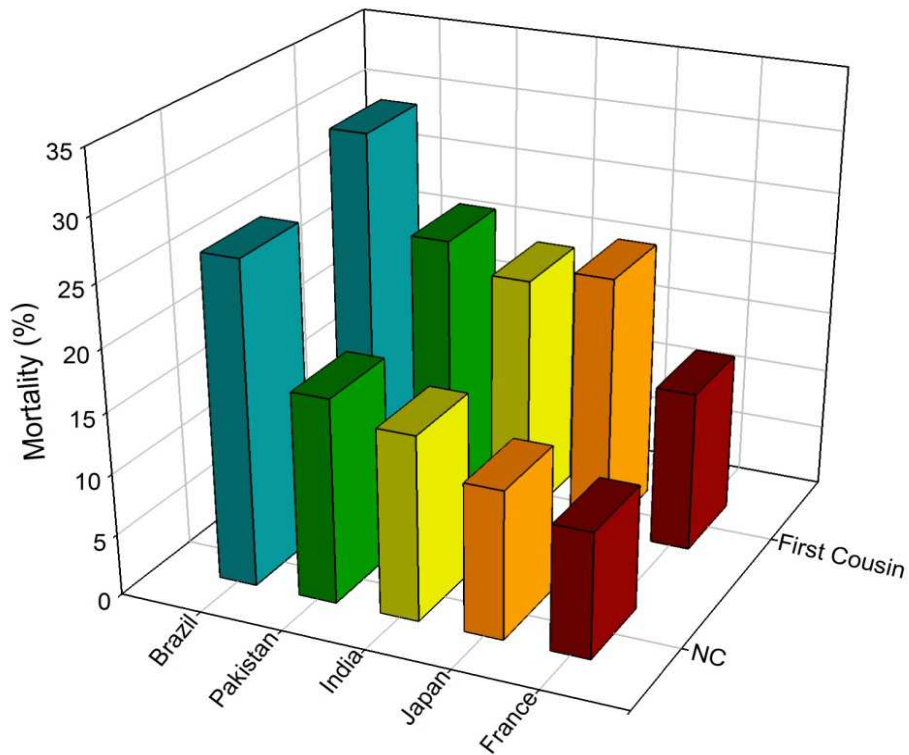


Fig. 5. Mortality in offspring of first cousin and non-consanguineous marriages in Brazil (average of 8 populations), Pakistan (average of 9 populations), India (average of 10 populations), Japan (average of 7 populations) and France (average of 2 populations). (Data from Bittles & Neel, 1994)

King	F	King's wife	F	Type of consanguineous marriage
Philip I (1478-1506)	0.025	Joanna I of Castile	0.039	Third cousins
Charles I (1500 - 1558)	0.037	Isabella of Portugal	0.101	First cousins
Philip II (1527 - 1598)	0.123	Mary of Portugal	0.123	Double first cousins
		Mary I of England	0.008	First cousins one removed
		Elizabeth of Valois	0.001	Remote kinship
		Anna of Habsburg	0.106	Uncle - niece
Philip III ¹ (1578 - 1621)	0.218	Margaret of Habsburg	0.139	First cousins once removed
Philip IV (1605 - 1665)	0.115	Elizabeth of Bourbon	0.007	Third cousins
		Mariana of Habsburg	0.155	Uncle - niece
Charles II ² (1661 - 1700)	0.254	Maria Luise d'Orleans	0.078	Second cousins
		Maria Anna of Neoburg	0.008	Remote kinship

1. Child of Philip II and Anna of Habsburg

2. Child of Philip IV and Mariana of Habsburg

Table 4. Inbreeding coefficient (F) of the Spanish Habsburg kings and their wives (From Alvarez et al., 2009)

The European royal dynasties of the Modern Age provide very rich materials for the study of the effects of high inbreeding levels in humans (Alvarez et al., 2009). Consanguineous marriages such as uncle-niece, first cousins and other non-incestuous unions were very frequent in those dynasties along prolonged periods of time and the genealogical records available in the historical sources are very extensive and accessible in such a way that inbreeding coefficients can be computed with extreme precision from extended pedigrees. One of the most important European royal dynasties of the Modern Age was the Habsburg dynasty (also known as the House of Austria) and the Spanish branch of this dynasty ruled over the world-wide Spanish Empire since 1517 until 1700. Along this time, the six kings of the Spanish Habsburg branch contracted 11 marriages and 9 (81.8%) of them were consanguineous unions in a degree of third cousins or closer: two uncle-niece marriages, one double first cousin marriage, one first cousin marriage and other consanguineous unions. The inbreeding coefficient of the Spanish Habsburg kings computed from an extended pedigree up to 16 generations in depth that involves more than 3,000 individuals experienced a strong increase along generations from 0.025 for king Philip I, the founder of the dynasty, to 0.254 for Charles II, the last Spanish Habsburg king (Table 4). The progeny of the Spanish Habsburg kings suffered an important inbreeding depression for survival in such a way that inbreeding at the level of first cousins ($F = 0.0625$) exerted an adverse effect on survival to 10 years (miscarriages, stillbirth and neonatal deaths not included) of $17.8\% \pm 12.3$. The relationship between survival and inbreeding coefficient in the progeny of 71 Habsburg marriages belonging to both branches of the dynasty (Spanish and Austrian Habsburgs) is shown in Figure 6 (unpublished results). The evidence of a strong inbreeding depression for survival in the Habsburg dynasty is confirmed from this large data set. The absolute decrease in survival to 10 years for the progeny of a first cousin marriage was

13.54% \pm 5.40 and the cost of inbreeding for an F value of 0.254, which is the inbreeding coefficient of Charles II, was 54.99%. Statistically significant deviations of a linear relationship between survival and inbreeding coefficient were not detected by the nonlinearity t test which compares the change in mean survival between two low levels of F and that between two high levels of F (Lynch & Walsh, 1998, p 267-268). Yet, departures from linearity were not detected for log-transformed data. These results must be taken, however, with caution because the statistical power of the test was probably not high enough to conclude that factors potentially promoting deviations of linearity such as epistatic interactions among loci or purging selection can be discarded. In any case, these findings suggest that linearity deviations for inbreeding depression on survival could be not very strong in humans so that, at least as a first approximation, estimates of inbreeding depression obtained from low inbreeding levels could be linearly extrapolated to predict the extent of depression for high inbreeding in a given population.

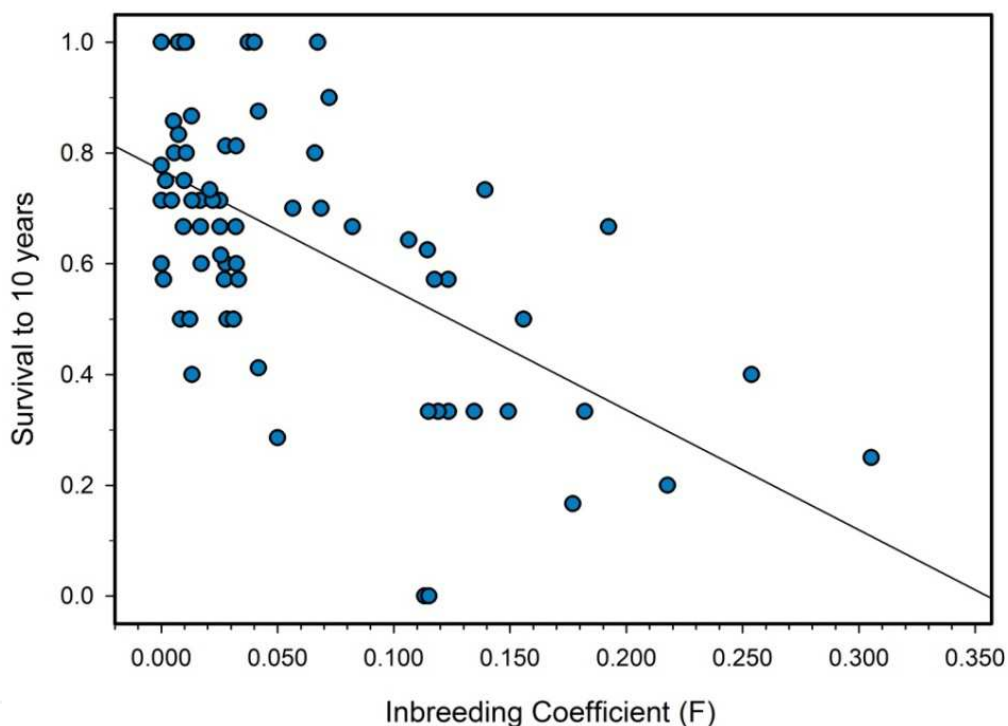


Fig. 6. Survival and inbreeding coefficient (F) of offspring of 71 marriages from the Habsburg royal dynasty

The Spanish Habsburg dynasty died out when Charles II, the last king of the dynasty, died in 1700 since no children were born from his two marriages. Indeed, the inbreeding depression on survival suffered by the dynasty was a relevant factor contributing to its extinction but, in the last instance, an effect of inbreeding on morbidity probably was also involved in the extinction of the Spanish Habsburg lineage. Charles II presented important physical and mental disabilities suffering from a number of different diseases during his life, hence being known in Spanish history as *El Hechizado* ("The Hexed") (Gargantilla, 2005). In the light of the knowledge of the current clinical genetics and taking into account that Charles II had an extremely high inbreeding coefficient ($F = 0.254$) which means that approximately 25.4% of his autosomal genome was autozygous, a tentative hypothesis

based on the simultaneous occurrence in this king of two recessive genetic disorders has been advanced to explain most of his complex clinical profile, including his impotence/infertility which in last instance led to the extinction of the Spanish Habsburg lineage (Alvarez et al., 2009). According to contemporary writings, Charles II was often described as “big headed” and “weak breast-fed baby”. He was unable to speak until the age of 4, and could not walk until the age of 8. He was short, weak and quite lean and thin. He was described as a person showing very little interest on his surroundings (abulic personality). He first marries at 18 and later at 29, leaving no descendants. His first wife talks of his premature ejaculation, while his second spouse complains about his impotency. He suffers from sporadic hematuria and intestinal problems (frequent diarrhoea and vomits). He looked like an old person when he was only 30 years old, suffering from edemas on his feet, legs, abdomen and face. During the last years of his life he barely can stand up, and suffers from hallucinations and convulsive episodes. His health worsens until his premature death when he was 39, after an episode of fever, abdominal pain, hard breathing and comma. From these evidences, two recessive genetic disorders, combined pituitary hormone deficiency (CPHD, OMIM 26260) and distal renal tubular acidosis (dRTA, OMIM 602722), could explain an important part of the complex clinical profile of Charles II. Combined pituitary hormone deficiency leads to a multiple endocrine deficit of pituitary hormones: thyroid stimulating hormone (TSH), growth hormone (GH), prolactin (PRL), gonadotropin and adrenocorticotrophic hormone (ACTH) (University of Washington, Genetest.gov). This disease shows a slow progression and is frequently caused by a genetic disorder produced by mutations of some of the transcription factors expressed in the pituitary gland, such as *PROP1* (5q), *POU1F1* (3p), *LHX3* (9q), *LHX4* (1q), *HESX1* (3p), *TBX19* (1q), *SOX2* (3q) and *SOX3* (Xq). Mutations occurring in *PROP1* are the most frequent genetic cause of hereditary CPHD, and they are inherited as autosomal recessives. Mutations in *PROP1* are associated with progressive endocrine deficiencies highly variable in both, intensity and in the first clinic sign manifestation (Kelberman & Dattani, 2007; Reynaud et al., 2005). Charles II showed clinical characteristics of hypothyroidism such as muscular weakness, hypotonia, delayed onset of speech and abulic behaviour, and the lack of GH could account for his short stature. His hypogonadotropic hypogonadism could explain his infertility/impotency, and a PRL deficit has been associated with decreased fertility in males. ACTH deficit usually presents in adults with common gastrointestinal symptoms such as nausea, vomit and diarrhoea. At the same time, the patients are fatigued, with general weakness, asthenia and hypotension. Any additional physical stress will exacerbate these clinical manifestations, often resulting in intense abdominal pain, fever, lethargy followed by hypovolemic vascular collapse (Agarwal et al., 2000; McGraw Hill, Access Medicine). The variety and scope of clinical symptoms afflicting Charles II could have been caused by an additional disease responsible for his muscular weakness at a young age, rickets, hematuria and his big head relative to his body size. These symptoms might have been manifestations of a secondary metabolic alteration originated in a renal disease such as severe hyperchloremic hypokalemic distal renal tubular acidosis (dRTA). This disease presents with alterations of the urine acidification mechanisms leading to severe metabolic hyperchloremic hypokalemic acidosis, prominent renal tract calcification with persistent hematuria and rickets. It may be caused by autosomal recessive mutations in *ATP6V0A4* (7q) or *ATP6V1B1* (2q) genes (Stover et al., 2002; Vargas-Possou et al., 2006). In this way, most of the symptoms showed by Charles II might be caused by these two

different recessive genetic disorders. From this perspective, inbreeding effects on both survival and fertility due to prolonged consanguineous marriage led to the fall of the Spanish Habsburg lineage which constitutes one of the most dramatic examples of detrimental effects of inbreeding in humans.

Because most studies of inbreeding depression in humans have focused on prereproductive stages of the life cycle, research on effects of inbreeding on fitness traits such as fertility has received less attention. The analysis of the effects of inbreeding on reproductive success are subject to a number of potential limitations associated with lack of control for important sociodemographic variables such as age at marriage, literacy, use of contraceptives and duration of marriage. A number of studies have compared the fertility in consanguineous unions with that of unrelated couples. In this way, the effect of the degree of relatedness between spouses on fertility is investigated. The relatedness between individuals is usually expressed as their kinship coefficient (θ), which is equal to the inbreeding coefficient (F) of their offspring (Hedrick, 2005, pp. 269; Lynch & Walsh, 1998, pp. 135-140). In several studies, the total number of offspring (completed fertility) produced by related couples has been found to be higher than that corresponding to unrelated ones (Bittles et al., 2002; Helgason, et al., 2008). In a meta-analysis based on data from a wide range of different human populations (30 populations) located in India, Pakistan, Japan, Kuwait and Turkey, the number of live born children produced by non-consanguineous unions were compared with the number of live born children in four categories of consanguineous unions: double first cousin or uncle-niece ($\theta = 0.125$ in the two cases), first cousin ($\theta = 0.0625$), first cousin once removed/double second cousin ($\theta = 0.0313$), and second cousin ($\theta = 0.0156$) (Bittles et al., 2002). A positive association between kinship and fertility was found at all levels of kinship tested, although the differences between consanguineous and non-consanguineous couples were statistically significant only for first cousin couples. Since these positive associations between consanguinity and fertility could largely be due to uncontrolled socio-demographic variables, Bittles et al. (2002) performed an analysis based on data of first cousin marriages from the National Family and Health Survey conducted in India during 1992-1993. Multivariate analysis showed that fertility is importantly influenced by a number of factors such as illiteracy, earlier age at marriage, lower contraceptive use, duration of marriage and reproductive compensation which were, in turn, positively associated with consanguineous marriage. When the effects of these various factors were adjusted at the multivariate analysis, differences in fertility between first cousin and non-consanguineous couples were not detected. In contrast with these results based on a large data set, some studies provide convincing evidence for a positive association between kinship and fertility in some particular human population. Thus, a significant positive association between kinship and fertility was detected in a study performed from all known couples of the Icelandic population born between 1800 and 1965 (Helgason et al., 2008). Iceland is one of the most socioeconomically and culturally homogeneous societies in the world and is characterized by relatively low levels of inbreeding. The kinship of couples was computed on a depth of up to 10 generations from each couple so that differences in fertility across a fine scale of kinship values was assessed. Research on the inbreeding effect on fertility at an individual level has been also performed through the measurement of fertility in inbred males and females. A significant effect of inbreeding on female fecundity has been found in a 15-year study performed in Hutterite colonies in South Dakota (Ober et al. 1999). The socio-economic conditions are relatively uniform within the Hutterite community so that

inbreeding effects can be studied without the confounding effects of uncontrolled socio-economic variables. Hutterite women with $F \geq 0.04$ showed significantly reduced fecundity as evidenced by longer interbirth intervals. There were no significant effects of father's F or of the kinship of couples on the interbirth interval. In contrast, completed family sizes did not differ among the more and the less-inbred Hutterite women who were born after 1920, even though the adverse effect of inbreeding on fecundity was evident in those cohorts. These results suggest that reproductive compensation may be occurring in the more inbred, less-fecund women probably to achieve a culturally defined optimal family size. An adverse effect of inbreeding on female fecundity has been also found in a study performed in a small and isolated village in the Swiss Alps where socio-economic factors are rather homogeneous (Postma et al., 2010). A significant negative effect of the inbreeding level of the mother on completed family size was detected so that inbred women had fewer children. On the contrary, an effect of either the inbreeding coefficient of the fathers or the kinship coefficient of the couples was not detected. Moreover, some empirical evidences suggest that sensitivity of fertility to inbreeding might vary with parental age. The effect of consanguineous marriages on reproduction studied in a cohort of women born in the late 19th century in north-eastern Quebec, Canada, showed that the inbreeding coefficient of the father strongly affects reproduction rates along reproductive period as inbred fathers showed a strong asymmetry in the number of children produced during the first half in comparison with the second half (Robert et al., 2009). These results suggest that temporal aspects of reproduction may be relevant in the study of inbreeding depression for fertility in humans.

5. Conclusion

Inbreeding defined as the mating between relatives is a phenomenon that occurs in many animal and plant species as well as in humans. Genetic effects of inbreeding are basically due to the fact that the inbred individual will frequently inherit the same gene from each parent, who inherited it from a common ancestor. In this way, inbreeding increases the amount of homozygosity so that recessive traits such as many human genetic disorders will occur with increased frequency in the progeny of consanguineous couples. Studies on genome-wide homozygosity through the genome scan technology have opened new possibilities for understanding inbreeding from a genomic perspective. Long homozygous chromosomal segments have been detected through whole-genome scans in human chromosomes. These long homozygous tracts are the result of autozygosity (homozygous by descent) because inbred individuals have segments of their chromosomes that are homozygous as a result of inheriting identical genomic segments through both parents. The distribution of such homozygous tracts throughout the genome has been studied in inbred individuals affected by recessive Mendelian disorders providing valuable information on the genomic architecture underlying human genetic diseases associated with inbreeding. Recent researches have shown that extended tracts of genomic homozygosity are globally widespread in many human populations providing new perspectives in the study of past consanguinity and population isolation. Autozygosity has also practical implications for the identification of human disease genes. Thus, at present, homozygosity mapping is the method of choice for mapping human genes that cause recessive traits from the DNA of affected children from consanguineous marriage. This approach involves the detection of

the disease locus on the basis that the adjacent region will be homozygous by descent in such inbred children.

Consanguineous marriage is frequently found in many human populations all over the world. The highest rates of consanguineous marriages occur in north and sub-Saharan Africa, the Middle East, and west, central, and south Asia, where, in some populations, 20 to 60% of all marriages are between relatives. First-cousin marriage is the most common form of consanguineous union in most human populations. There are clear social and economic advantages to consanguinity mainly associated with the maintenance of family structure and property, particularly in rural societies. Consanguineous marriages cannot be linked to any specific religion or religious rules. It is practiced among people of various religions, and the attitudes towards consanguineous marriages vary among followers of the same religion. Offspring of consanguineous parents are at risk both for monogenic autosomal recessive disorders and for conditions with multifactorial inheritance. Consanguineous marriage increases the chance that both members of a couple will carry any recessive variant that is being transmitted in their family, and that this will manifest in the homozygous state in their children. Thus, a large number of studies have reported this outcome as one of the most important clinical consequences of consanguineous marriage. In general, the offspring of consanguineous couples present increased levels of morbidity and significant medical problems such as major malformations, congenital anomaly and structural birth defects. Furthermore, consanguinity has been implicated in susceptibility to a number of complex diseases such as heart disease, cancer, depression, gout, peptic ulcer, schizophrenia, epilepsy and asthma. Consanguinity has been also proven to be a risk factor for infection by a diverse range of pathogens responsible for a number of human infectious diseases.

The phenomenon of inbreeding depression, that is, the reduced survival and fertility of offspring of related individuals, has been documented in many human populations reflecting the consequences of increased homozygosity for alleles affecting reproductive fitness. Estimates of inbreeding depression in survival have been obtained for a number of human populations comparing the prereproductive mortality in the progeny of first-cousin and non consanguineous marriages. The mean increase in mortality among the offspring of first-cousin marriages ($F = 0.0625$) was $4.4\% \pm 4.6$ from data of 38 worldwide human populations and a more recent estimate obtained from 69 populations was 3.5%, but it is necessary to emphasize that the extent of inbreeding depression on survival presents a large variation among populations. By contrast, there is little information on inbreeding depression in survival for inbreeding levels higher than those corresponding to first-cousin progenies. Recent studies conducted on European royal dynasties of the Modern Age where inbreeding coefficients were much higher than that corresponding to first-cousins are filling this gap of information. It is expected that these studies could provide a deeper understanding of the genetic basis of inbreeding depression in human populations.

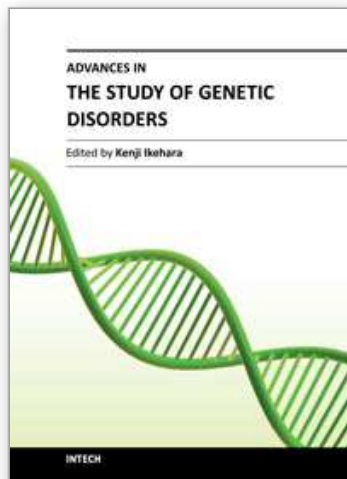
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The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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