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Consanguinity and Inbreeding in Health and Disease in North African Populations

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North Africa, consanguinity, endogamy, genetic disease, founder mutation

Abstract

North Africa is defined as the geographical region separated from the rest of the continent by the Sahara and from Europe by the Mediterranean Sea. The main demographic features of North African populations are their familial structure and high rates of familial and geographic endogamy, which have a proven impact on health, particularly the occurrence of genetic diseases, with a greater effect on the frequency and spectrum of the rarest forms of autosomal recessive genetic diseases. More than 500 different genetic diseases have been reported in this region, most of which are autosomal recessive. During the last few decades, there has been great interest in the molecular investigation of large consanguineous North African families. The development of local capacities has brought a substantial improvement in the molecular characterization of these diseases, but the genetic bases of half of them remain unknown. Diseases of known molecular etiology are characterized by their genetic and mutational heterogeneity, although some founder mutations are encountered relatively frequently. Some founder mutations are specific to a single country or a specific ethnic or geographic group, and

others are shared by all North African countries or worldwide. The impact of consanguinity on common multifactorial diseases is less evident.

INTRODUCTION

The term consanguinity derives from two Latin words: *con*, which means "shared," and *sanguis*, which means "blood." It refers to unions between two persons who are related and therefore share common ancestors (a shared blood relationship), and consanguineous marriages are thus those between two people who are genetically related by descent from a common ancestor (33). In clinical genetics, a consanguineous marriage is defined as a union between two individuals who are at least second cousins (33).

Approximately 20% of the world population (1.1 billion individuals) live in communities with a preference for unions between relatives (36, 53, 69, 112); consanguinity rates differ among communities with different cultural practices and religions, with higher frequencies recorded in many Arab countries (36). Intrafamilial unions account for 20% to more than 50% of all marriages in these countries, which span the region from North Africa to the Middle East and western Asia (36). In this review, we report on consanguinity in North Africa and its impact on the health and genomic structure of North African populations. We begin by providing an overview of North African population structure and history.

GEOGRAPHIC, DEMOGRAPHIC, AND ETHNIC CHARACTERISTICS OF NORTH AFRICA

North Africa is defined as the northernmost geographical region of the African continent, separated from the rest of the continent by the Sahara and from Europe by the Mediterranean Sea. It includes five countries: Egypt, Libya, Tunisia, Algeria, and Morocco, the latter four of which are also known as Maghreb countries. From a political point of view, Mauritania is also considered part of the Maghreb countries. The current population of North Africa is estimated to be approximately 75 million. The demographic features include high population growth rates, high birth rates, and high infant mortality rates. Until the middle of the twentieth century, the familial structure was large, with more than 7 children per woman in Algeria; today, North African families show much lower fertility rates, which reached their lowest value of 2.2 children per woman in Tunisia (127, 155).

The history of the settlement of North Africa includes several invasions, starting with the occupation of the city of Carthage in 814 BC, which displaced the local inhabitants, known as the Amazigh or Berbers; this was followed by a series of invasions by the Romans, Vandals, and Arabs and, more recently, occupation by the French, Italians, and British. Today, there are two major ethnic groups in the North African region: the Amazigh and the Arabs. The current Amazigh population in North Africa consists of approximately 20 million people, of which 20% live mainly in Algeria and 40% in Morocco. A minority (approximately 100,000) live in Tunisia and Libya (39). In addition to the major ethnic groups, Jews from Tunisia, Libya, Morocco, and Algeria, referred to as North African Jews, Sephardic Jews, and/or non-Ashkenazi Jews, constitute a minority, together with Christians.

The richness of the prehistoric and historic cultural inheritance of North African civilizations has contributed to the richness and complexity of the genetic pool of its populations. According to molecular studies (based on mitochondrial DNA, Y chromosome, autosomal short tandem repeats,

and so on), the North African population is a mosaic of North African, Eurasian, and sub-Saharan components (17, 59, 82).

CONSANGUINITY AND ENDOGAMY DISTRIBUTION IN NORTH AFRICA

The practice of consanguineous marriage in North Africa seems to be a deep-rooted norm; it has been recorded since ancient times in pharaohs' pedigrees in order to maintain the royal blood. It has continued to the present day due to complex interactions of social, cultural, and economical factors. Mate selection is performed inside families or clans, leading to endogamy and consanguinity (28). Cousin marriage is considered ideal and actively encouraged, and even treated as a familial obligation, since any deviation could provoke social and familial reprobation and sanction (28). Tradition and social and educational levels, especially of women, are the main factors that favor consanguineous marriages, especially in rural surroundings (84, 129, 158). Religion has also been suggested as an additional factor contributing to such unions. However, contrary to common opinion, Islam does not encourage consanguineous marriages, and this type of mating is not restricted to Muslim communities; unions between relatives also occur among Christians and Jews from North Africa and Middle East (36). Although the three monotheistic religions condemn incestuous mating, some Moroccan Jews still practice uncle–niece marriages (61).

The prevalence of consanguineous unions differs both within and among countries (**Table 1**). Studies have estimated that the frequency of consanguineous marriages in Tunisia ranges from 29.8% to 38.0% (23). These values vary across different regions and cities, ranging from 16–31.6% in the north (125) to 49.6% in the central region and 65.3% in the southern village of Douiret (22) (**Table 1**). In Morocco, consanguineous marriages represent 19.9–25.4% of all marriages (93, 143). In Algeria, a study of national civil registries estimated that 22.6% of all marriages in the sample population were between relatives (30), but a more recent national survey found a higher value of 39% (64). Similar proportions have been found in the Tlemcen region of western Algeria (158). Consanguineous marriage rates are also high in Egypt, with an initial estimate of 23.2–35.3% (66, 138), varying by region; the rate is higher in Nubia (63.6%), Sohag in Upper Egypt (42.%), and Cairo in Lower Egypt (36.1%) than it is in Assiut in Upper Egypt (21.7%) (10, 138). The frequency of consanguineous marriage also varies among ethnic and religious groups in Nubia and is highest among Arabs (10). Data on the prevalence of familial unions are scarce in both Libya and Mauritania, although the rates are thought to be high. In Libya, a survey of family clinic data showed that 37.6% of all marriages are intrafamilial in the city of Benghazi (2), and a study in Mauritania estimated a rate of 47.2% (71).

Despite all of these differences in prevalence, studies have consistently found that the most common type of consanguinity is between first cousins, particularly paternal first cousins (and including double-first-cousin marriages). Indeed, first-cousin marriages accounted for 16.2–26.5% of consanguineous marriages in Tunisia (23, 27, 143). In Egypt, they accounted for 8.6% (138) to 22.2% (88) of all consanguineous marriages, and the proportion was even higher in some cities, such as in Giza (57.2%) (138) and Cairo (61.1%) (73).

THE EFFECT OF CONSANGUINITY ON THE SPECTRUM AND MODE OF INHERITANCE OF GENETIC DISEASES IN NORTH AFRICA

Complete epidemiological studies and the establishment of patient registries are undoubtedly the best way to assess the burden of genetic disorders in a population. In developing countries, molecular, genetic, and epidemiological data are becoming more widely available following the

Table 1 Consanguinity profiles in North African populations

Country	Location	Consanguinity (%)	Coefficient of inbreeding (α)	Reference
Algeria	All Algeria	22.6	NA	30
		39.0	NA	64
	Urban areas	27.5	0.0136	30
	Rural areas	34.0	0.0169	30
	West Algeria (Tlemcen)	34.0	NA	158
Egypt	All Egypt	35.3	NA	138
		23.2	0.0145	66
	Urban areas	17.7	NA	138
		22.1	0.0092	67
	Semi-urban areas	23.5	NA	138
	Rural areas	59.9	NA	138
		39.1	0.0147	67
	Alexandria	32.8	NA	141
	Nubia	60.5	0.0245	79
		63.6	0.0334	10
	Nubia (Fadetchi)	61.4	0.0329	10
	Nubia (Kenuzi)	62.0	0.0335	10
	Nubia (Arabs)	69.8	0.0338	10
	Sohag	42.2	0.019	138
	Cairo	36.1	NA	138
	Assiut	21.7	NA	138
Libya	Benghazi	37.6	0.0209	2
Mauritania	All Mauritania	47.2	NA	71
Morocco	All Morocco	19.9	0.0089	93
	High Atlas valleys	25.4	NA	143
Tunisia	All Tunisia	38.0	NA	157
		29.8	NA	23
	Urban areas	16.3	NA	26
	Rural areas	25.4	NA	26
	Northern Tunisia	31.6	0.0213	125
	Bizerte	16.0	0.0093	125
	Kef	38.0	0.0157	125
	Siliana	41.4	0.0178	125
	Beja	36.0	0.0146	125
	Central Tunisia	49.6	0.0213	32
	Nabeul	33.6	0.0132	98
	Sfax	35.5	0.0139	58
	Greater Tunis area	32.7	0.0139	27
	Douiret	65.3	0.0216	22
	Monastir	20.1	0.0084	83
		24.8	NA	83

Abbreviation: NA, not available.

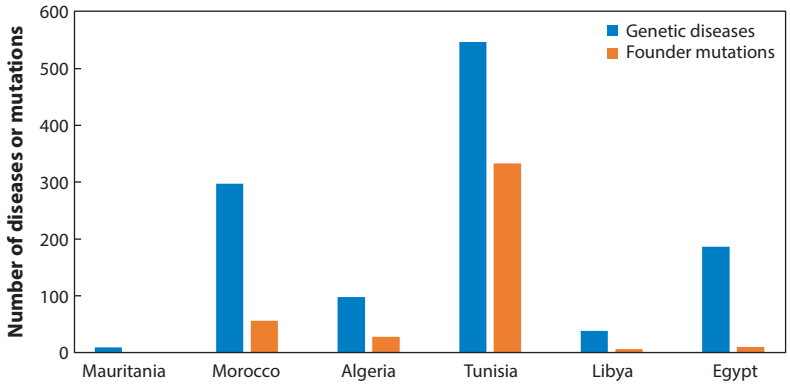

Figure 1

Distribution and number of reported monogenic diseases and founder mutations in North Africa.

introduction of diagnostic facilities and the development of biomedical health research activities and international collaborations that provide access to high-throughput next-generation sequencing. In the meantime, mining the literature, including gray literature, has provided an indirect way to determine the spectrum of such diseases as well as their phenotypic particularities (127, 128). One study identified a nonexhaustive list of 532 genetic diseases in the populations of the five North African countries (127). Classification of these diseases by their transmission mode highlighted the large proportion of autosomal recessive disorders (60%), followed by autosomal dominant disorders (27.2%) (127). A study in Tunisia identified 346 genetic diseases, of which 62.9% were autosomal recessive (128), and a recent update reevaluated this count at 547 genetic diseases (**Figure 1**). Among these diseases, 60.1% were due to recessive mutations in autosomal genes (L. Romdhane, N. Mezzi & S. Abdelhak, unpublished data). A similar study from Morocco identified 297 genetic diseases, and data are available from a recently updated database (120). The rate of autosomal recessive disease is higher (73.1%) (120). Recent data on the spectrum of diseases in other North African populations are not available except from the Centre for Arab Genomic Studies database, which shows that only 184 pathogenic entities have been identified in Egypt, 98 in Algeria, 38 in Libya, and 9 in Mauritania (41). Classification of the genetic diseases' spectrum based on the 10th version of the World Health Organization's *International Statistical Classification of Diseases and Related Health Problems* (156) revealed three major disease groups. The most commonly reported disease group is congenital malformations, deformations, and chromosomal abnormalities, which are obvious at birth and represent 29.4% of the genetic diseases (127). The next most important group is endocrine, nutritional, and metabolic diseases (22.4%), and the third is diseases of the nervous system (14.3%) (127).

In an attempt to evaluate the risk associated with inbreeding based on the mode of inheritance of a large class of monogenic and multifactorial diseases, Ben Halim et al. (23) conducted a study of 1,121 patients and 963 healthy individuals from Tunisia. Parental consanguinity was associated with an 8–9-fold-increased risk of recessive disease expression [odds ratio (OR) = 8.53, 95% confidence interval (CI) = 6.70–10.86, $p < 10^{-3}$]. The risk remained high even after correction for confounding demographic variables such as sex, age, and geographical origin. Moreover, the excess risk associated with familial endogamy increases significantly with the level of inbreeding. A more recent study again highlighted the differential impact of inbreeding on the expression of autosomal recessive diseases (24). Consanguinity was observed in 65.0% of the studied patients, and the consanguinity rates for each disease ranged from 51.3% to 75.6%. The study found that

inbreeding led to an approximately 6-fold increase in relative risk for Gaucher disease (OR = 5.53, CI = 1.77–17.26, $p = 0.03$). Inbreeding led to a 16-fold increase in the relative risk for dystrophic epidermolysis bullosa (OR = 15.17, CI = 3.67–62.91, $p < 10^{-3}$) and a 25-fold increase in the relative risk for xeroderma pigmentosum (OR = 24.41, CI = 9.99–59.61, $p < 10^{-3}$) (24).

It is generally believed that consanguinity has no significant effect on the occurrence of autosomal dominant or X-linked diseases, but we hypothesize that an influence on autosomal dominant diseases cannot be completely ruled out. Such an effect cannot be easily demonstrated due to the complex interplay among disease severity, inbreeding depression, natural selection, and other factors, such as the degree of development of the health-care system. Indeed, several autosomal dominant diseases, particularly mild skin disorders, are underdiagnosed in North African populations. This is the case for the simplex form of hereditary epidermolysis bullosa, which is the most common form of this type of disease in outbred populations and appears to be less frequently encountered among consanguineous populations, likely because there are a substantial number of undiagnosed cases. Indeed, according to referral centers in Tunisia, patients with this form of the disease do not seek treatment because of the patients' inattention to mild skin lesions and poor access to tertiary care centers (M. Mokni, unpublished data). In addition, consanguineous marriages increase the possibility of homozygosity for dominant mutations. In this case, when homozygous carriers are viable, a more severe phenotype, or in some cases a different phenotype, is observed. This was the case in a consanguineous family in which the parents were heterozygous for a mutation in the *CASR* gene: The parents presented with familial hypocalciuric hypercalcemia, whereas a proband who was homozygous for the same mutation had severe neonatal hyperparathyroidism (131, 137).

CONSANGUINITY AND THE MOLECULAR ETIOLOGY OF GENETIC DISEASES IN NORTH AFRICA

The familial structure and high rates of consanguinity in North Africa sparked interest from the international scientific community in the most prevalent genetic disease groups in these populations. Several disease loci and genes were subsequently identified, mainly using a homozygosity mapping approach. The most illustrative examples were Maghrebian myopathy, bare lymphocyte syndrome type II, Creutzfeldt–Jakob disease, and xeroderma pigmentosum.

Maghrebian myopathy, or Tunisian muscular dystrophy, was the first term used for a new type of recessively inherited muscular dystrophy described by Ben Hamida & Fardeau (25) in 1980. This form of myopathy is by far the most frequent in Tunisia and North Africa. It was later called limb-girdle muscular dystrophy type 2C (LGMD2C) after the identification of the morbid locus on chromosome 13q in Tunisian families (117).

Bare lymphocyte syndrome type II is an autosomal recessive defect of the expression of the major histocompatibility complex (MHC) class II genes caused by mutations in *RFXANK*. The majority of the patients described with the disease are of North African origin (153).

Creutzfeldt–Jakob disease, the most prevalent of the human spongiform encephalopathies, is a progressive neurodegenerative disease. The largest cluster of this disease occurs among Libyan Jews, where the incidence (1:10,000) is 100 times that of other populations (46).

Xeroderma pigmentosum is recessively inherited photodermatosis. It is characterized by hypersensitivity, DNA repair defects, and a high incidence of skin cancers. Its prevalence in the United States and Europe is estimated at 1:300,000, but it seems to be more frequent in the Maghreb countries, especially in Tunisia, where its prevalence is estimated at 1:10,000 (159).

Nonsyndromic hearing loss also accounts for a major proportion of sensorial handicaps in the region. Its prevalence could be especially high in isolates, in which it ranges from 2% to 8% (21).

The autosomal recessive forms are the most frequent of the prelingual genetic forms of deafness, representing 80% of the studied cases (21). Several genes involved in hearing loss were identified as a result of investigations in North African families (16, 47, 48, 54, 65, 101).

As facilities for genetic studies do not cover the region equally, mainly due to a lack of resources, international collaborations have helped not only to decipher the molecular basis of several genetic diseases but also to train and build local capacities. Among the 532 genetic diseases reported in North African populations, half have still not been genetically investigated (127). The molecular etiologies of genetic disorders in North Africa show a high degree of locus and allelic heterogeneity, but founder mutations have been identified for several diseases as a consequence of the high rates of consanguinity. Historical events and human diasporas in the region have shaped the distributions of these founder mutation (127). The mutation spectrum of North African populations has not been fully identified, and most of the published studies are fragmented and are often disease and country specific. In an attempt to establish the mutation spectrum of the Tunisian population, more than 800 mutations were identified as the cause of 320 genetic diseases, of which at least 73 are caused by at least one founder mutation (127; L. Romdhane, N. Mezzi & S. Abdelhak, unpublished data). Among these diseases, 43 are caused by founder mutations that were also reported in neighboring populations, mainly in North Africa but also in the Middle East and Europe (**Figure 2**). Consanguinity contributes to the occurrence of these diseases, as 63 of them (86%) are autosomal recessive in addition to displaying allelic heterogeneity (127).

The diseases fall into two broad molecular distribution categories. In the first, one major frequent mutation is the cause of the disease, due to founder effects and genetic drift; another, less frequent gene lesion could also be present. This is the case for the predominant founder deletion c.521delT in the *SGCG* gene, which leads to Maghrebian myopathy (or LGMD2C) in the Tunisian population. In addition to this mutation, another private gene lesion was reported in two families from Tunisia and Libya (76). In the second category, more than one frequent mutation is involved in the disease, suggesting that natural selection could have acted as a factor for the disease's recurrence in the region. The genes that have accumulated multiple founder mutations are those causing beta-thalassemia (68), glucose-6-phosphate dehydrogenase deficiency (68), cystic fibrosis (110), and familial Mediterranean fever (42). Overall, 190 founder mutations have been identified in North African populations and are available in the Mediterranean Founder Mutation Database (43) (**Figure 1**).

In consanguineous and isolated populations in North Africa, allelic homogeneity is not systematically found, thus challenging the concept of unique founder mutation segregation in such isolation. As an example, compound heterozygosity for the *GJB2* gene has been described in an isolate from northern Tunisia (20). Moreover, allelic heterogeneity within the same family has been reported for several diseases, including xeroderma pigmentosum group A (109). The combination of a founder mutation with a novel private gene lesion in the *XPA* gene led to an atypical clinical manifestation of the disease (108).

Knowledge of the mutation spectrum of a population, with an emphasis on founder mutations, provides an efficient and rapid diagnosis strategy for disorders such as metabolic diseases (13) and severe genodermatosis (108, 119). This strategy helps avoid the need for invasive biopsies to confirm a biochemical or histological diagnosis, especially in countries with limited resources (130).

CONSANGUINITY AND COMORBIDITY IN NORTH AFRICAN FAMILIES

The impact of consanguinity on the expression of autosomal recessive diseases in North African families is largely supported by their high rates in the region, but also in the association of more

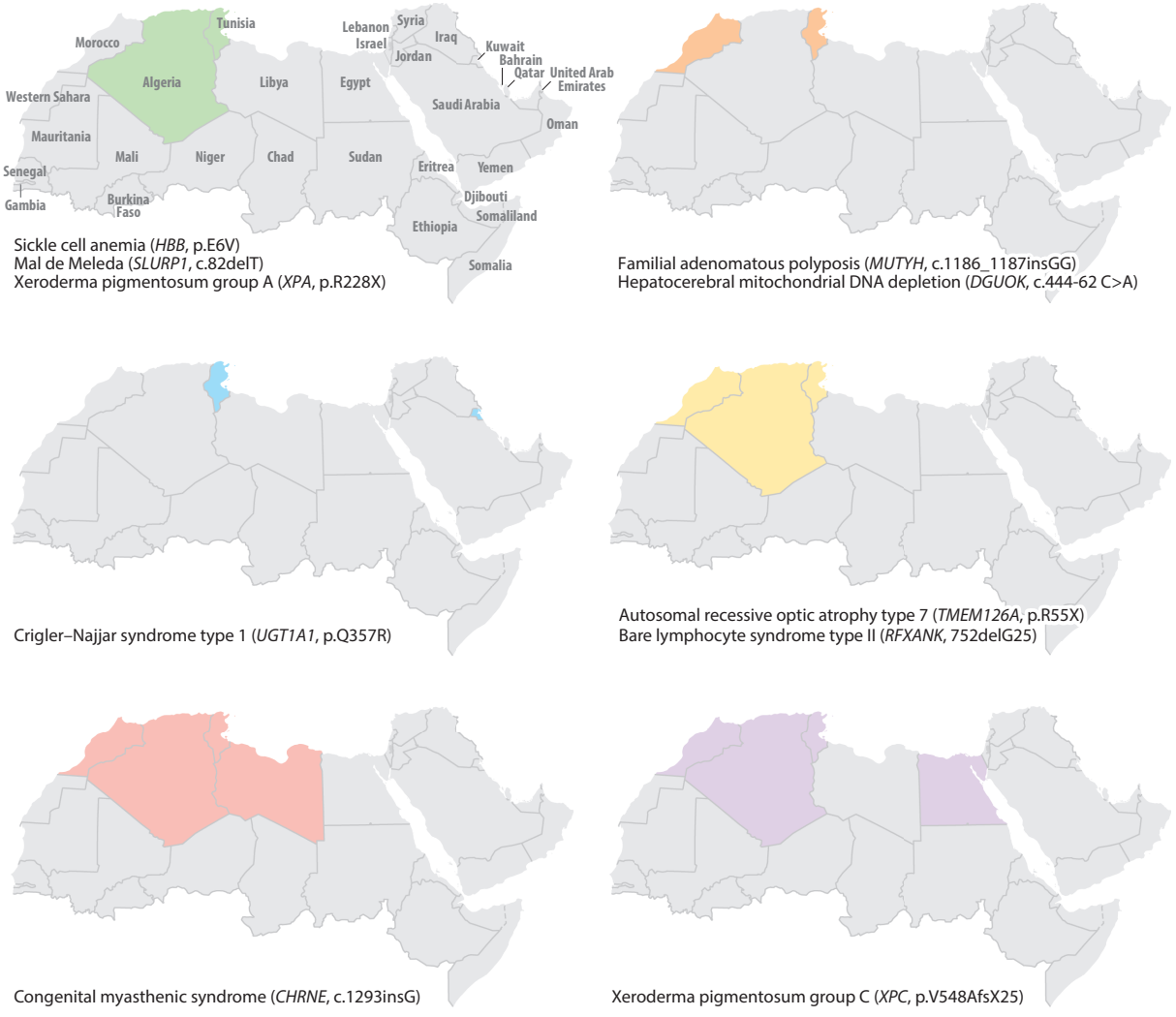

Figure 2

Geographic distribution of some North African founder mutations.

than two genetic conditions in the same individual or in different members of the same family. This phenomenon, termed comorbidity, seems to be relatively common in the region (127, 131). The co-occurrence of multiple monogenic disorders in siblings or an individual has been reported in multiple families from the region, often in association with parental consanguinity; rates of parental consanguinity among offspring with multiple genetic disorders could reach up to 77% in Egypt (127, 149). In the Tunisian population, 75 such disease associations have been identified (131). Among the comorbid associations reported in the Tunisian populations, 34 primary diseases and 12 associated conditions were the consequence of 32 distinct mutations: 21 are founder mutations, of which 16 are shared founder mutations and 5 are specific to Tunisian populations. The remaining mutations are private and therefore reported only once (131).

Different patterns of comorbid associations have been described. Individual comorbidity refers to a comorbid disease association in one individual, while familial comorbidity means the

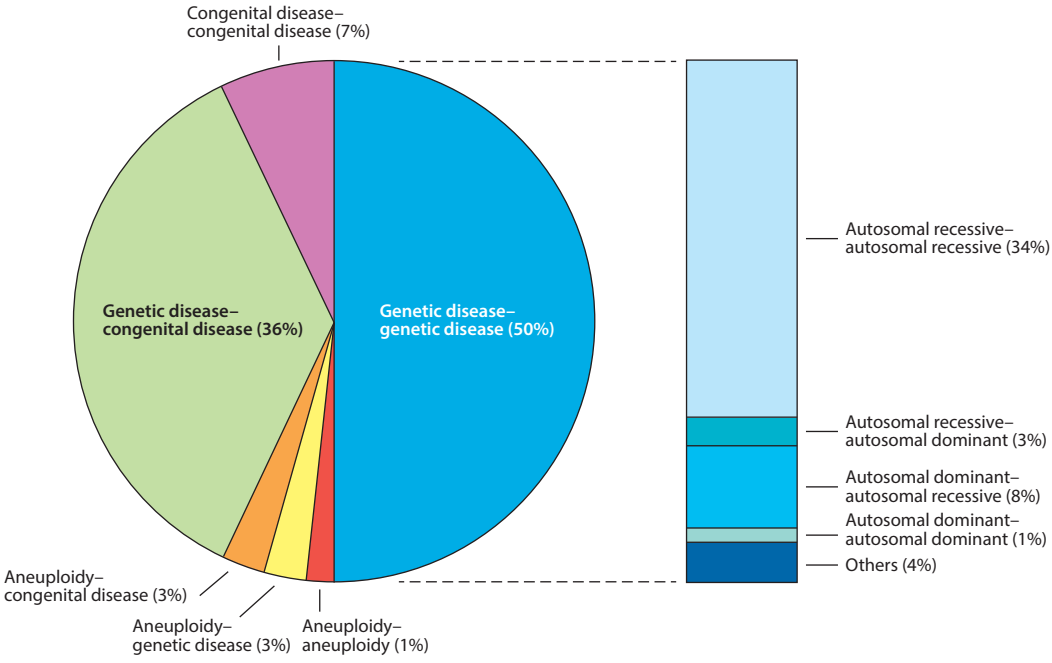

Figure 3

Comorbidity classes in the Tunisian population. Genetic disease is defined as a condition caused by mutations in known genes; when the transmission mode is uncertain, then the condition is defined as a congenital disease. Figure adapted from Reference 131.

occurrence of multiple genetic conditions in different members of the same extended family in a combinatorial manner (131). Consanguinity has been noted in approximately half of the total comorbid associations (131). Classification of these comorbid associations revealed that the genetic disease–genetic disease class is the most frequent (50%) (**Figure 3**). Moreover, stratification according to the transmission mode showed that the disease combination could include entities with or without the same mode of transmission. The prevalence of the comorbid class involving only autosomal recessive diseases (34%) clearly suggests the role of the deeply rooted consanguinity practices in the population (131) (**Figure 3**).

The consequences of comorbid association can be dramatic, as the association renders the diagnosis challenging even when the mutations are known, especially when the comorbid diseases belong to the same pathological group. Thus, combinations of different forms of neuromuscular diseases have been described [e.g., LGMD2C-LGMD2D, LGMD2A–congenital muscular dystrophy, and ataxia with vitamin E deficiency–Friedreich's ataxia–autosomal recessive spastic ataxia of Charlevoix-Saguenay (AVED-FRDA-ARSACS)], as well as genodermatoses involving xeroderma pigmentosum–ichthyosis and xeroderma pigmentosum–Bloom syndrome and sensorineural diseases such as Usher syndrome type 2–retinitis pigmentosa (131). Another pattern of comorbidity, known as allelic comorbidity, corresponds to phenotypic associations resulting from distinct allele variants located on the same gene. Allelic comorbidity was especially notable for diseases caused by mutations in the *HBB* gene that lead to a severe phenotype, mainly in northwestern Tunisia, a region thought to have been exposed to malaria in the past (131). This finding supports the selective advantage hypothesis, in which an evolutionary fitness advantage gives rise to multiple mutations in the same individual.

The co-occurrence of two or more conditions will be definitively diagnosed more frequently as a result of the availability of next-generation sequencing technologies. In a recent example, whole-exome sequencing allowed the identification of an *SLC26A4* mutation and a novel *CYP4F22* mutation in a consanguineous Tunisian patient with a co-occurrence of ichthyosis and hearing loss, a phenocopy of keratitis-ichthyosis-deafness syndrome (M. Sayeb, Z. Riahi, N. Laroussi, C. Bonnet, L. Romdhane, et al., manuscript in revision).

CONSANGUINITY AND COMPLEX DISORDERS

The contribution of inbreeding to complex disorders remains contentious and underinvestigated. Some authors have suggested that inbreeding could exert a greater influence on the etiology of multifactorial diseases when autosomal recessive alleles are causally implicated (36). However, other reports claim that it is unlikely that consanguinity contributes significantly to complex diseases once basic lifestyle factors have been controlled for, as highlighted by an editorial in *Nature Genetics* (62). In the following sections, we provide some examples that illustrate the investigation of the impact of consanguinity on various complex diseases or health conditions.

Consanguinity and Malformations

Consanguinity has been identified as a risk factor for congenital malformations and major medical conditions. Several studies of North African inbred communities have reported comparisons of rates of birth defects and/or genetic diseases among the offspring of interfamilial marriages and those of unrelated couples. In Tunisia, reports from the 1980s described correlations between consanguinity and some genetic conditions, such as polydactyly (19) and degenerative spinocerebellar diseases (57). In Egypt, parental consanguinity in groups of patients with various birth defects resulted in significant differences in the prevalence of genetic disorders compared with the general population (148). In addition, the same study confirmed a strong positive correlation between consanguinity rates and the number of referred cases for genetic disorders ($r = 0.801$, $r^2 = 0.642$). Nasri et al. (116) assessed the influence of consanguinity on neural tube defects in Tunisia. They recorded more than 700 stillborns with neural tube defects over a period of 20 years (1991–2011) and found that spina bifida was the most frequent disorder in these stillborns (38.9%), followed by anencephaly (22.8%) and encephalocele (17.8%). The estimated consanguinity rate was 36.7%, which is close to the rate in the general population.

Consanguinity and Reproductive Health

With the aim of delineating the role of consanguinity and advanced maternal age in reproductive losses in Egypt, Mokhtar & Abdel-Fattah (113) performed a case–control study of 730 couples with reproductive losses and 2,081 without such losses. Of the couples with reproductive losses, 68.8% were consanguineous, and 56.2% of those couples were first cousins. Consanguinity was clearly associated with prenatal loss and infant death ($p < 0.0001$) and increased the relative risk of repeated abortion (OR = 3.95, CI = 3.04–5.14), neonatal death (OR = 17.2, CI = 10.8–27.3), postneonatal death (OR = 14.5, CI = 10.6–19.9), and total reproductive losses (OR = 8.3, CI = 6.9–10.1). Kerkeni et al. (83) assessed the associations among social status, the prevalence of consanguineous marriages, and the effects of consanguinity on reproductive behavior and mortality in Tunisia. Marriages between relatives represented 24.8% of marriages, and 70.1% of the consanguineous marriages were between first cousins. Consanguineous couples had a lower age at marriage and a higher fertility index than nonconsanguineous couples (83). In addition,

consanguineous couples had higher rates of neonatal deaths ($p < 0.008$), postneonatal deaths ($p < 0.017$), and deaths of children younger than five years old ($p < 0.005$) (83). Consanguinity did not correlate with rates of spontaneous abortions or stillbirths (83). As this study was specific to the central coastal region of Tunisia, it is not fully representative of the whole country.

In general, the factors that are positively associated with consanguinity are high fertility and large family size, which may be thought of as compensation for increased mortality of children in consanguineous marriages (31, 37). Because consanguineous unions have prevailed over time for socioeconomic and cultural reasons, these factors may have been considered important reasons (especially for women) to marry and have children at younger ages. However, because many direct and indirect fertility determinants are associated with consanguinity—including lower socioeconomic status, religious convictions, younger maternal age at marriage, lower contraceptive use, longer duration of marriage, and rural residence—the results must be interpreted with caution if these parameters are not adequately controlled for (34, 78, 89, 91). Conflicting results regarding associations between consanguinity and spontaneous abortion or increased risk of repeated abortion may be due to the study design (113). The number of spontaneous abortions may be greater, suggesting possible underreporting, since abortions could have taken place in the first three weeks of pregnancy and not been detected by women included in the study (83, 89). This suggests a possible natural selection of inbreeding operating before the prenatal period, or, more precisely, before the first trimester of pregnancy (89). In a review of studies of inbreeding effects on mortality, Khoury et al. (90, p. 254) noted that "the excess mortality for offspring of first cousin marriages can be seen for all periods of prereproductive life, but to a lesser extent for miscarriages and stillbirths."

Consanguinity and Disorders of Sex Development

Disorders of sex development (DSDs) are defined as "congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical" (94, p. e488) and form a heterogeneous group of complex conditions. In addition to impacts on internal and external genitalia, these conditions can affect fertility potential to various degrees (151). Data on the actual prevalence of DSDs in endogamous populations are largely unavailable and limited to published studies for small series of patients. The DSD prevalence in European countries has been estimated to range from 1:4,500 to 1:5,500 live births, far lower than the prevalence in Egypt, which was assessed at 1:2,500 (15, 103). Moreover, a study in Germany revealed that the incidence of DSDs in offspring of non-German origin was four times higher than that of the general population, mainly due to higher rates of consanguinity in migrant communities (150). These findings suggest that consanguinity may contribute to increased incidence of DSDs, as several DSD conditions are autosomal recessive. Mazen et al. (103) reported on the consanguinity and parental origins of 208 Egyptian DSD patients and found that consanguinity was present in 62.8% of all DSD cases, 72% of 46,XX DSD cases, and 59.5% of 46,XY DSD cases (103).

The DSD distribution pattern in Egypt differs from that in Saudi Arabia, representing two highly endogamous populations. In Egypt, 46,XY DSDs are more common (representing 65.9% of all DSD cases) than they are in Saudi Arabia (60%) (6, 103). The relatively low rate of 46,XX DSDs in Egypt may be a result of patient selection bias: Patients with severe 46,XX DSDs due to congenital adrenal hyperplasia could have died from a crisis that was misdiagnosed as infectious gastroenteritis before coming to medical attention (103). Alternatively, the different rates could represent regional differences in the general incidence and nature of pathogenic mutations leading to DSDs (15). Familial cases of 46,XX DSD have been described for whom mutations in the *SRY* gene were absent, suggesting a monogenic recessive mode of inheritance. Many of these pedigrees

originated from North Africa and the Middle East, suggesting recessive loss-of-function mutations in these populations (15, 81, 104, 147).

Molecular findings have highlighted numerous genes in the networks that control testis determination and lead to 46,XY complete gonadal dysgenesis and 46,XY partial gonadal dysgenesis when mutated, including *NR5A1* (15). Although the majority of mutations in *NR5A1* are heterozygous, recessive mutations have been described but are rare. Homozygosity for *NR5AI* mutations leads to a mean functional activity of the corresponding protein of approximately 50% of the wild-type protein activity, which is similar to the effect in heterozygous mutants with a complete loss of function (96). Rare mutations in *NR5A1* in patients from North Africa were identified in the heterozygous state, suggesting that endogamy has no apparent influence on the phenotype (14). Nevertheless, numerous 46,XY gonadal dysgenesis cases remain unexplained.

DSDs are frequently reported as a result of anomalies in androgen synthesis or action. The most illustrative example is congenital adrenal hyperplasia, which is the most common inherited metabolic disorder. Mutations in two genes, *CYP21A2* and *CYP11B1*, cause 21-hydroxylase deficiency and 11β-hydroxylase deficiency, respectively. The published data on the incidence of congenital adrenal hyperplasia in some Arab countries demonstrate relatively high rates, such as 1:1,209 in Alexandria, Egypt (144), 1:5,000 in Saudi Arabia (140), and 1:9,030 in the United Arab Emirates (5), all of which are higher than the rates in nonendogamous populations, such as the United States (1:20,800) and the United Kingdom (1:18,000) (77). The most common cause of the 46,XX DSD is 21-hydroxylase deficiency. In a study by Kharrat et al. (86), consanguinity was present in 31 of 51 Tunisian families (60.8%) with congenital adrenal hyperplasia; the consanguineous families were unrelated and originated from different regions of Tunisia. A single p.Q318X mutation in *CYP21A2* had a high prevalence of 35.3%, in contrast to the prevalence of 0.5–13.8% described in other populations (86). This is likely to be a founder mutation, since the study found linkage disequilibrium between this mutation and a *CYP21* gene polymorphism in 83.3% of alleles. In a more recent study, Kharrat et al. (85) estimated the carrier rate for this founder mutation in the healthy population. Surprisingly, they found a rate of 12.5% (CI = 7.86–19.2%) with a duplicated *CYP21A2* gene haplotype. This result complicated the molecular diagnosis of 21-hydroxylase deficiency, suggesting that a study of the structure of the *CYP21A2* region will be necessary to discriminate between the severe p.Q318X mutation and the normal p.Q318X variant (85).

Similarly, 11β-hydroxylase deficiency is present at higher frequencies in North African populations, especially in families of Israeli Moroccan and Tunisian origins (133). The incidence was assessed to be 1:5,000–1:7,000 births in Moroccan Jews (132). The founder mutation p.R448H was identified in six independent Israeli Moroccan families, with a carrier rate of 1:40 (152). Nevertheless, two prevalent founder mutations, p.Q356X (26.6%) and p.G379V (73.3%), were reported in the *CYP11B1* gene in Tunisian families, 80% of which were consanguineous (87).

Consanguinity and Neurocognitive and Neurodegenerative Disorders

Few studies have examined the associations between inbreeding and psychotic disorders, but the available data suggest an increased rate of schizophrenia and bipolar disorders in the offspring of consanguineous patients. A family-based study of 130 Tunisian individuals with bipolar I disorder investigated whether consanguinity increases the risk for this disorder (105). The authors estimated that the rate of consanguinity in this group was 28.5% and found that bipolar I patients with consanguinity were characterized by a high frequency of affective episodes and a greater severity of their last affective episode, but these differences were not statistically significant. However, the frequency of affective disorders was significantly increased in first-degree relatives of

probands with consanguinity (10.5% versus 6.1%; $p = 0.01$) and in first- and second-degree relatives of probands with consanguinity (4.5% versus 29%; $p = 0.02$). On the basis of their results, the authors hypothesized that the influence of consanguinity on the clinical characteristics and frequency of affective disorders in first- and second-degree relatives of bipolar patients is consistent with recessive polygenic transmission of bipolar disorder.

Mansour et al. (100) performed a case–control study and an epidemiological survey in Egypt, and the self-reported consanguinity rates were higher among bipolar I patients in both analyses. In addition, the risk of bipolar I disorder associated with inbreeding was high in both studies [OR = 2.66, CI = 1.34–5.29 (for the case–control study), and OR = 4.64, CI = 2.01–10.34 (for the epidemiological survey)] (100). The same team performed a similar analysis of schizophrenia in Egypt (99). They again found elevated rates of parental consanguinity in schizophrenic patients (46.6%; chi-square $p = 5.8 \times 10^{-6}$) versus controls, and showed that the risk of schizophrenia in children of consanguineous parents was three times higher than that of controls (OR = 3.53, CI = 1.88–6.64), suggesting that inbreeding is an important risk factor for mood disorders in Egypt (99, 100). They also assessed the impact of consanguinity on the genome by genotyping 64 short tandem repeats from samples from offspring, and the DNA-based consanguinity rates showed significant case–control differences (99).

A few studies have assessed the impact of consanguinity on neurodegenerative disorders in North Africa, mainly in the Tunisian population. Sellami et al. (136) performed a 12-year retrospective cross-sectional study involving 429 Alzheimer disease patients with a familial history of this disease, which is the case for approximately one-third of all Alzheimer patients. Consanguinity was found in 34.5% of the patients. Autosomal dominant inheritance was found in 16.7% of the patients, genetically complex inheritance was found in 73.3%, and, surprisingly, autosomal recessive inheritance was found in 10%. This study highlights that familial Alzheimer disease is frequent in the Tunisian population and that additional genetic investigations may lead to the identification of a new genetic subtype in this population.

CONSANGUINITY AND GENETIC SUSCEPTIBILITY TO INFECTIOUS DISEASES

Research on the association between consanguinity and susceptibility to human diseases has been facilitated largely by the availability of pedigree information. Infectious diseases have received less attention than genetic diseases for many reasons, including the difficulty of obtaining well-resolved pedigrees in the developing world, where the major infectious diseases are common. Molecular tools have helped to overcome this difficulty (97). As studies of natural populations suggest that low genetic heterozygosity is an important risk factor for infection by a diverse range of pathogens, several studies have found an association between homozygosity and mortality caused by bacterial and viral infections (e.g., 97). Similar studies have not been conducted in North Africa. However, studies have examined whether consanguinity can affect microbial infections (parasite, virus, and bacteria) in the specific genetic context of Mendelian diseases.

Parental consanguinity is a known risk factor for primary immunodeficiencies (PIDs)—a heterogeneous group of genetic disorders of the immune system that predispose patients to infections, autoimmune diseases, lymphoproliferation, and malignancy—in North Africa (11). In Tunisia, Barbouche et al. (12) studied a large cohort of PID patients (168 patients belonging to 122 families) and found that they had a high level of parental consanguinity (61.9%). There was also a high frequency (55.4%) with a family history that included early deaths, similar clinical features, and/or previously identified PIDs among relatives. The consanguinity rate was particularly high in patients with Omenn syndrome (88.8%), phosphoglucomutase 3 (PGM3) deficiency (85.7%),

leukocyte adhesion deficiency type 1 (76.4%), and MHC class II deficiency (70.3%) (12). These values are consistent with previous results obtained for one of the largest series of North African MHC class II patients, which reported a consanguinity rate of 81.8% (118), as well as for PIDs from a patient series originating from Egypt (118). Molecular investigation of PIDs in North Africa confirmed that the autosomal recessive mode of inheritance is the most common in Tunisian patients, accounting for 73% of all investigated PIDs (12), and that rare autosomal recessive PIDs appear at higher frequencies in North Africa in the specific context of inbreeding (29, 72, 106, 118). Furthermore, the study by Barbouche et al. (12) also showed that, for PIDs with more than one known mode of transmission, the autosomal recessive trait was the most frequent or proportionately more represented than in other series and registries from nonconsanguineous populations (12).

The number of novel forms of known syndromes and/or diseases reported in the Tunisian population (128) has been continuously increasing, notably with the identification of novel forms of PIDs, such as autoimmune lymphoproliferative syndrome (4). Immunodeficiency, which is characterized by low serum immunoglobins and different infections, is a consistent feature of Bloom syndrome, a rare autosomal recessive DNA repair disease (135). Its worldwide prevalence is unknown, but only 272 patients have been reported in the Bloom syndrome registry (134). A recent investigation revealed that Bloom syndrome is more common in Tunisia than it is elsewhere; at least 21 affected individuals have been identified, which represents approximately 8% of the worldwide cohort and the largest unreported patient series (M. Ben Rekaya, S. Elouej, D. Ezzine, A. Lagarde, N. Ghedira, et al., unpublished data).

In contrast to the discussion above regarding the deleterious effect of consanguinity on various health conditions, resistance to parasite infection provides a good example of a potential benefit of inbreeding. Inherited red blood cell diseases, which are well established as the most common monogenic disorders in humans, provide a good example. Beta-thalassemia and alpha-thalassemia occur at polymorphic frequencies in almost all North African countries, with carrier rates ranging from 1.1% to 11.1% and from 1% to 9.25%, respectively, as detailed in **Table 2**. The overlap between the geographic distributions of malaria, the thalassemias, and other red blood cell conditions that protect against malaria and the distribution of consanguineous marriages led to the seemingly counterintuitive hypothesis that inbreeding could be beneficial in this respect (51). This hypothesis was further supported by two additional observations: that the distribution of different intensities of malaria infestation corresponds with the frequency of intrafamilial unions, and that the presence of two mutations in homozygotes imparts better protection against malaria than the presence of one or no mutations (heterozygous or normal genotypes, respectively) (8). Consanguinity therefore increases the number of homozygotes, especially at a low allele frequency, thus contributing to human fitness (51). Inbreeding increases the speed of fixation of recessive and codominant alleles, which was illustrated by a computer simulation that used alpha+-thalassemia as example (40, 50). The positive genetic effect of inbreeding, which is shaped by the positive selection of protective alleles against malaria, depends on the prevalence of the allele and is largest when the prevalence is approximately 0.5 (50). Thus, it was proposed that the culture of consanguineous marriages and the genetics of protection against malaria have coevolved by fostering survival against malaria through better retention of protective alleles in extended families (51).

CONSANGUINITY AND SUSCEPTIBILITY TO CANCER

Approximately half of familial risk of breast cancer is explained by known susceptibility alleles that are divided into two main groups, with variable levels of relative risk, penetrance, and frequency (95). The first group comprises rare hereditary mutations in single dominantly acting genes of

Table 2 Beta- and alpha-thalassemia carrier prevalence and malaria endemicity in North Africa

Country	Beta-thalassemia carrier prevalence	Available sample number	Reference(s)	Alpha-thalassemia carrier prevalence	Available sample number	Reference(s)	Malaria endemicity[a]
Algeria	1.5–3%	NA	38, 92	4.6%	153	107	3.0
Egypt	1.2%	1,000	115	9.25%	410	126	2.0
	9–10%	NA	145				
	9%	1,000	55				
	5–9%	NA	56				
Libya	7.8%	1,350	80	<1–5%	NA	146	1.0
Mauritania	1.12–11.1%, 2.57% overall	700	52	NA	NA	NA	4.5
Morocco	1.5–3%	NA	3	<1–5%	NA	146	NA
				2.2%	NA	68	
Tunisia	2.2%	44,299	60	2% in all of Tunis, 4% in the northern region	304	160	3.0
	3.1% in Kebili	1,400	114	7.38%	529	139	

Table adapted from Reference 70. Abbreviation: NA, not available.

[a]Malaria endemicity for the period before 1900 is estimated from the Lysenko map in Reference 74: 5, holoendemic; 4, hyperendemic; 3, mesoendemic; 2, hypoendemic; 1, epidemic; 0, malaria free.

high to moderate penetrance that confer high risk of breast cancer (relative risk >2) and explain almost 25–35% of familial breast cancer genetic susceptibility. This group includes the two most important breast cancer susceptibility genes, *BRCA1* and *BRCA2* (63). The second group comprises more than 100 common low-risk variants (relative risk <1.5) that act in a polygenic model and explain 15–25% of familial breast cancer genetic susceptibility (102). In North Africa, breast cancer is the most common cancer among women, representing 25–35% of all female cancers (45).

The majority of genetic studies of breast cancer in North Africa have been restricted to the *BRCA* genes. A set of pathogenic mutations have been identified in these two genes; some of these are specific to a single North African country, whereas others showed a founder effect in the region, such as c.798_799delTT on *BRCA1* and c.1310_1313del on *BRCA2*, which are considered to be the first non-Jewish founder mutations described in North Africa (1). Remarkably, very few *BRCA* mutations have been identified in North Africa compared with western countries. This discrepancy could be explained in part by the small cohorts that have been investigated, the lack of comprehensive data, and the methodology used in these genetic studies, since the great majority conducted targeted mutation research instead of carrying out a complete screening of the two genes. More recently, the low frequency of *BRCA* mutations in North Africa has been explained by the high rate of consanguinity in this region (44, 49). Indeed, in families with deleterious mutations, consanguinity increases the chances of *BRCA* homozygosity among offspring, which is most likely embryonically lethal. Therefore, consanguinity will lead to an apparent loss of *BRCA* mutation carriers and thus a decrease in the frequency of *BRCA1* and *BRCA2* mutations in consanguineous subgroups, suggesting a protective effect on breast cancer risk among offspring of consanguineous parents (18).

Biallelic or homozygous mutations in *BRCA1*, *BRCA2* (*FANCD2*), *PALB2* (*FANCN*), and *BRIP1* (*FANCJ*) may also result in childhood Fanconi anemia, a rare autosomal recessive disease characterized by skeletal defects, skin pigmentation, short stature, and microphthalmia (9). Moreover, homozygous mutations in *ATM*, a breast cancer susceptibility gene, are associated with ataxia–telangiectasia, another recessive multisystem disorder (122). Therefore, consanguinity would be expected to increase the prevalence of these monogenic diseases. On the other hand, by increasing homozygosity, consanguinity will increase the breast cancer risk caused by low-penetrance polymorphisms that, when homozygous, confer a relatively higher risk of breast cancer.

Based on this evidence, consanguinity is clearly associated with an increased incidence of recessive monogenetic diseases that predispose to cancer, such as Fanconi anemia and ataxia–telangiectasia. However, the impact of consanguinity on breast cancer incidence remains unclear, since it seems to decrease the frequency of high- to moderate-penetrance variants associated with breast cancer susceptibility while increasing the frequency of low-penetrance variants. Therefore, an overall assessment of the impact of consanguinity on breast cancer incidence needs an accurate and precise assessment of the frequency of all breast cancer genetic susceptibility loci, including low-penetrance variations, in consanguineous versus nonconsanguineous families.

CONSANGUINITY AND HUMAN GENOME STRUCTURE

Individuals born to intrafamilial unions have segments of their genomes that are homozygous because they inherited identical ancestral genomic regions from both parents (154). The coefficient of inbreeding is defined as the probability that a locus will be identical by descent in an individual and therefore reflects the proportion of the autosomal genome that will be homozygous, or, more properly, autozygous (35). Theoretical work has predicted that 1/16th (6.25%) of the genome of a child of first cousins will be homozygous and that the average homozygous segment will be 20 cM in size (35). A study of recessive disease in the offspring of first-cousin marriages found that, on

average, 11% of their genomes were homozygous, with each individual bearing 20 homozygous segments exceeding 3 cM, and that the size of the homozygous segment linked to the recessive disease was 26 cM (154). The authors concluded that prolonged parental inbreeding has led to an approximately 5% increase in the background level of homozygosity above that predicted by simple models of consanguinity (154).

How consanguinity could shape genomes of individuals in inbred populations from North Africa in terms of genomic organization and deleterious variant enrichment is unknown. Access to genome-wide scan technologies such as single-nucleotide polymorphism (SNP) microarrays has enabled studies of the impact of consanguinity on genome structure through the analysis of long homozygous genomic regions, termed runs of homozygosity (ROHs), in healthy North African individuals. Henn et al. (75) analyzed genome-wide SNP genotyping array data from seven North African populations, spanning from Egypt to Morocco, and one Spanish population, in an attempt to establish their genomic ancestry. They found that most of the North African populations shared few identical-by-descent sequences, suggesting that the great majority of individuals in these populations were only distantly related. Nevertheless, the Tunisian Berber population displayed an excess of pairs of individuals sharing 200–1,200 cM of identical-by-descent sequence. This particular distribution suggests that many first- and second-cousin genetic-equivalent pairs were present in this sample even though the donors declared themselves to be unrelated. Moreover, analysis of long ROHs revealed that, on average, the Tunisian Berber population had almost twice as much of their genomes in ROHs than other North African populations did (230 kb and 120 kb, respectively). The authors concluded that the pattern of ROH and pairwise identical-by-descent segments in the Tunisian Berbers is likely the result of endogamy due to geographic isolation or cultural marriage preferences (75).

Ben Halim et al. (24) performed a more recent study of 15 individuals from a small, isolated, southern Tunisian community of Berber origin, revealing a large average number of ROHs per individual (48.2), considering a ROH at a minimum length of 500 kb. The smallest ROH category (0.5–1.49 Mb) represented 0.93% of the whole genome, while medium-size (1.5–4.99 Mb) and long (≥5 Mb) ROHs covered 1.18% and 0.95%, respectively. Moreover, the authors showed that genealogical individual inbreeding coefficients based on three- to four-generation pedigrees are not reliable indicators of the current proportion of genome-wide homozygosity inferred from ROHs (24). This study emphasizes how reproductive isolation and the prolonged practice of consanguinity could limit genetic heterogeneity and provides evidence of the contributions of both recent and ancient parental relatedness to the current level of genome-wide homozygosity. Together, the studies by Henn et al. (75) and Ben Halim et al. (24) constitute the first attempt to decipher genomic organization in terms of the distribution of ROH and identical-by-descent segments in North Africa populations, and further efforts will be needed to unravel how demography could affect the proportion of nonsynonymous SNPs in consanguineous populations.

Szpiech et al. (142) demonstrated that mapping ROHs derived from recent inbreeding within consanguineous populations could be a powerful approach to localize deleterious mutations. They showed that long ROHs, resulting from recent inbreeding, harbor more deleterious variants than expected, which was recently confirmed by a study on a Qatari sample (111, 142). We hypothesize that, because no genomic data are currently available on the general (healthy) consanguineous population, enrichment of ROHs with health-beneficial alleles cannot be excluded. Indeed, genotyping of healthy family members (i.e., grandparents of patients with ichthyosis and hearing loss) showed that they had larger ROH segments, with no genetic or common chronic diseases recorded during their life spans (M. Sayeb, unpublished data).

The autozygome-guided exome strategy, which relies on the particular arrangement of genomic autozygome segments, was an efficient strategy for unraveling the genetic basis of

heterogeneous diseases in Tunisian, North African, and Middle Eastern families (7). Because the responsible mutations in autosomal recessive diseases in consanguineous populations are usually homozygous, a scan filter can be applied to filter out heterozygous single-nucleotide variants from next-generation sequencing data. This strategy led to the identification of the causal variants for numerous diseases in the region, including nonsyndromic hearing loss in Tunisian and Moroccan families in whom no *GJB2* mutation was identified (124) and Usher syndrome in four unrelated Tunisian patients affected by apparently isolated congenital profound deafness with normal ocular fundus examination (123). Exome sequencing combined with ROH analysis of two patients who belonged to two multiplex consanguineous families suspected of having xeroderma pigmentosum group V with mild dermatological manifestations, an absence of neurological abnormalities, and late onset of skin tumors revealed the presence of two mutations on distinct genes (121): an *ERCC2* mutation in a medium-size ROH region, suggesting ancient relatedness, and a *DDB2* deletion in a large ROH region, suggesting recent inbreeding. These results allowed the identification of xeroderma pigmentosum groups D and E for the first time in Tunisia and North Africa, as these groups are rare and underdiagnosed (121).

CONCLUSION

This article has reviewed the impact of inbreeding on health, drawing examples from monogenic and multifactorial disorders. It has also argued that inbreeding provides not only socioeconomic advantages but also may contribute certain health benefits. Monogenic diseases in consanguineous populations from North Africa have inspired geneticists to investigate the pathogenicity of rare variants and further annotate the human genome. With the availability of new technologies, large consanguineous families should now be investigated from a different perspective, by focusing on healthy individuals and epigenetic factors. In addition, investigation of autosomal dominant diseases in these families will help in understanding penetrance, an issue fundamental to all genetic traits. From a public health perspective, the health risks (at least for autosomal recessive diseases) that constitute a major burden on health-care systems in North African countries should be seriously taken into consideration. There is an urgent need to increase public awareness of the potential deleterious effects of consanguinity by establishing an education program for all stakeholders. Patients and their families, with the help of patient support groups and other civil society organizations, should also be engaged more actively in research on consanguinity and health through a multidisciplinary approach.

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