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Consanguinity and genetic diseases in North Africa and immigrants to Europe

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Endemic diseases are caused by environmental and genetic factors. While in this special issue several chapters deal with environmental factors, including infections, the present focus is on genetic causes of disease clustering due to inbreeding and recessive disease mechanisms. Consanguinity is implying sharing of genetic heritage because of marriage between close relatives originating from a common ancestor. With limited natural selection, recessive genes may become more frequent in an inbred compared with an outbred population. Consanguinity is common in North Africa (NA), and the estimates range from 40 to 49% of all marriages in Tunisia and 29–33% in Morocco. As a consequence, recessive disorders are common in the NA region, and we give some examples. Thalassaemia and sickle cell disease/anaemia constitute the most common inherited recessive disorders globally and they are common in NA, but with immigration they have spread to Europe and to other parts of the world. Another example is familial Mediterranean fever, which is common in the Eastern Mediterranean area. With immigrantion from that area to Sweden, it has become the most common hereditary autoinflammatory disease in that country, and there is no evidence that any native Swede would have been diagnosed with this disease. The examples discussed in this chapter show that the historic movement of populations and current immigration are influencing the concept of 'endemic' disease.

Introduction

Endemic disease clusters are caused by environmental and genetic factors shared by people in the cluster. Infectious diseases are the most obvious environmental factors for disease clustering; these are discussed in a specific chapter in this volume. Infectious agents also cause some cancers, which are referred to in a separate chapter in this volume. Other environmental factors that may cause endemic diseases are dietary, residential and lifestyle-related factors shared by a defined population, including dietary deficiencies or ingested toxic substances, environmental pollution, and unhealthy customs and habits. Many of these predisposing factors are likely to change when residential circumstances change, for example, upon moving or emigration.

A small defined population often shares genes because of inbreeding and eventually consanguinity (derived from a Latin word 'blood relation'), implying sharing of genetic heritage because of marriage between close relatives originating from a common ancestor (i.e., mating of relatives). With limited natural selection, recessive genes may become more frequent in an inbred compared with an outbred population. In European history, already the Roman civil law prohibited a marriage if the couple was within four degrees of consanguinity. Such prohibitions were also adopted by the church. However, the rules did not reach all of Europe, and consanguinity has been common particularly in cultural and geographic isolates. European nobility kept itself above the common law, and interrelated marriages were convenient in consolidating class, land and power. In many other cultures, rules were enacted against marriage between relatives, while in some others inbreeding has been and still is commonplace. In some large populations of Asia and Africa 20 to 50% of all marriages, and in certain areas of Pakistan most marriages have been consanguineous.[1] The reasons to practice inbreeding at a large scale include religion and culture, socio-economic class and royalty, and geographic isolation and small populations.

Inbreeding is considered a problem because it increases the chances of receiving deleterious recessive genes (i.e., two mutated copies, alleles, required to cause disease) inherited from a common ancestor. Inbreeding coefficient is defined as the probability of receiving two copies (one from mother and the other from father) of the same ancestral gene, which are identical by decent. The coefficient is 1/16 for first cousins and 1/64 for second cousins. Persons with genetic diseases may be seriously handicapped and unable to breed. Dominant alleles (only one disease allele required to cause disease) often cause disease at early age, and the disease alleles tend to disappear from the population because of selection during consecutive generations. Recessive diseases are insidious because carriers of single disease alleles are healthy and they may reproduce normally even though disease alleles are usually a selective disadvantage. Affected are only some children (by average 25%) of the parents, both of whom are carriers of the disease allele. In outbred populations, recessive disease alleles are usually rare because they are selected against over generations; thus, the likelihood of inheriting two recessive disease alleles is low. In inbred populations, the selection against deleterious alleles is less efficient because they are reintroduced into decedents a few generations later. The literature on human genetics is full of examples on rare genetic diseases in inbred populations, which were geographically isolated (e.g., Finns and French Canadians) or cultural distinct (Ashkenazi Jews).[1–4] Curiously, despite the ancient rules against consanguinity, the scientific evidence on the deleterious effects has been relatively recent. The first reports were published at the time of Charles Darwin in the mid-1800s. He had a personal reason to be upset and to demand scientific evidence because he married his first cousin. Darwin remained sceptical, and all his 10 children were healthy.

In the present chapter, we discuss consanguinity in North Africa (NA) and other parts of the world, and some of its deleterious consequences in indigenous and immigrant populations. It should be noted that many immigrant communities, at least in Europe, are

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quite inbred partly because of their cultural isolation and partly because the immigrants constituted close relatives who then settled in their own communities. For example, in the UK, it is estimated that more than half of marriages of some Pakistani Muslim immigrants are between first cousins. NA is also an endemic area for deleterious recessive diseases, which are very common in the population, including sickle cell anaemia and thalassaemia. The mechanism for such recessive diseases was a puzzle to population geneticists, who were used to the paradigm that pathological conditions have a selective disadvantage. The measure relating to selection was 'fitness', and individuals with deleterious mutations would have less than optimal fitness. Infections, particularly before reproduction, were considered the main selective force. Sickle cell anaemia taught another paradigm of fitness and recessive diseases because the disease provided a survival advantage in regions where malaria was endemic.

Consanguinity in NA

Consanguineous marriages have been practiced since the early existence of modern humans. At present, ~20% of world populations live in communities with a preference for consanguineous marriage.[5] Consanguinity rates vary from one population to another depending on religion, culture and geography. Noticeably, many Arab countries display some of the highest rates of consanguineous marriages.[6] As can be seen from figure 1, an important cluster of countries with high levels of consanguinity is observed in most communities of NA, the Middle East and West Asia, a transverse belt that runs from Pakistan and Afghanistan in the east to Morocco in the west, and in South India, with intra-familial unions collectively accounting for 20–50+% of all marriages.[6] The highest consanguinity rates were reported among Pakistan army personnel and isolated Egyptian Nubians (76 and 80.4%, respectively). First cousin unions are especially popular, comprising 20–30% of all marriages in some populations, in particular, the paternal parallel subtype in Arab societies.[6] Contrary to common opinion, consanguinity is not confined to Muslim communities. In NA and the Middle East, for example, marriages between relatives are also observed among Christians and Jews. It has been argued that consanguinity must be seen as a cultural rather than an Islamic or religious trait.

Marriage choice and decision-making is a complex interaction of various social and cultural patterns of behaviour and norms. The main reasons for a preference for consanguineous unions are historical, cultural, socio-economic and geographical. Consanguineous unions are estimated to represent 40 to 49% and 29 to 33% of all marriages in Tunisia and Morocco, respectively. In Algeria, data from the 2007 survey showed that 39% of marriages in the sample population were between cousins. Similar estimates have been reported from the Tlemcen region of West Algeria. In Egypt, prevalence figures for consanguineous unions ranged from 20 to 33% across different studies and 39% as determined by the National Population Council. The prevalence of consanguineous unions also varies by place of residence in Egypt. It ranges from 25.4% in Lower Egypt to 55.2% in Upper Egypt.

Estimates indicate that first-cousin marriages are approximately two-thirds of all consanguineous marriages in Morocco and 40% in Algeria. Close consanguinity accounts for 22% of the total marriages in Egypt and is higher in rural areas. A consanguinity rate of 32% with first cousin unions was observed in Tunisia. In Morocco, it (parallel and cross cousins) accounts for 42% of all consanguineous union. Similarly, in Egypt, the husband was more likely to be a relative from the father's side than the mother's side (14 and 8%, respectively). Surprisingly, it has been recently reported that unlike

Figure 1 Global prevalence of consanguinity as cited by Bittles AH, Black ML (ref. 6: reproduced with permission from http://www.consang.net/index.php/Global_prevalence)

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the previous generations, paternal first-cousin marriages in Algeria were lower than the paternal first cousin subtype in the new generation.

Generally, the highest rates of marriages to close relatives are consistently reported in lower educational and socio-economic groups, the traditionally religious and the early married; the rates tend to decline with modernization; however, not in all populations.[6] Reports from North African countries have shown that consanguinity rates are lower in urban compared with those in rural settings. Urban to rural first cousin rates in Egypt were 8.3 and 17.2%, respectively. The highest level of consanguineous marriage was found in rural Upper Egypt. Likewise, the frequency of unions between relatives was lower in the urban than in the rural areas in Morocco (25.9 and 33.3%) and Algeria (30.6 and 40.5%). For Morocco immigrants, ethnicity (distinction Berber vs. Arab) is a better predictor of consanguineous marriage than the region of origin, as Berbers in Belgium are more often married to a relative than Arabs. The higher the level of education of the female partner, the lower is the consanguinity rate. In Egypt, for example, a woman's chance of marrying a relative decreased from 35% among women who had never attended school to 23% among women with a higher education level. The comparable figure for Algeria was 58% in non-educated women and 7% in highly educated women. According to two different studies, only 6.3 to 7% of highly educated females would marry their first cousins, whereas 12 to 15% of highly educated males tend to marry first cousins. Similar trends of lower consanguinity rates among educated women, but not educated men, were noticed in Tunisia and Morocco.[7] In a Moroccan multinomial logistic analysis, considering variables education and residence, it was shown that women's education was found to be the most significant variable in distinguishing kin groups from the outbred. The more urbanized the place was, the lower the consanguinity rate.

Variable secular trends in the consanguinity rates have been noticed in most North African populations. In Algeria, for example, consanguinity rates are increasing in the current generation (from 32 in the old generation to 40% in the new generation),[8] while in others such as Egypt and Tunisia the frequency of consanguineous marriage may be decreasing. According to two Moroccan surveys from 1987 and 1992, the prevalence of consanguineous marriages declined by 4 percentage points. Amongst the contributing factors are the increasing higher female education levels, the declining fertility resulting in lower numbers of suitable relatives to marry, mobility from rural to urban settings and the improving economic status. On the other side, social, religious, cultural, political and economic factors still play important roles in favouring consanguineous marriages among the new generations, just as strongly as they did among the older generations particularly in rural areas.[9] As previously suggested by different authors, consanguinity rates are not declining in some North African countries because it is generally accepted that the social advantages of consanguinity outweigh the disadvantages, and consanguinity is regarded as a deeply rooted cultural trend. It is believed that the practice of consanguinity has significant social and economic advantages.[9]

In Europe, although the practice of consanguineous marriages has almost completely disappeared in the main population, the trend of intermarriages among ethnic minorities exists. With a tradition of consanguineous marriage is maintained, for instance, people of North African origin in France and Belgium, or people of Turkish origin in Germany and the Scandinavian countries. This tendency is facilitated by constraints imposed by migration, disintegration and cultural diversity. Indeed, ethnic minorities face two problems: the limited availability of suitable persons in the restricted local community and the fact that their circle of acquaintance in the country of origin tends to shrink within the limits of the extended family. Immigration into a new country often progresses stepwise, and after the first successful settlement, other family members follow and soon a clan has been established in the new country. This is also promoted by immigration legislation, which gives family members a favoured status of entrance. Among many immigrant groups, it is common that young men fetch a wife from the home country, and for natural reasons the designated bride is a family member.

Among first cousins, the spouses share one-eight of their genes inherited from a common ancestor, and so their progeny are homozygous (or more correctly autozygous) at 1/16 of all loci. The progeny are predicted to have inherited identical gene copies from each parent at 6.25% of all gene loci, and this figure is far above the baseline level of homozygosity in the general population. An increase in the rate of homozygotes for autosomal recessive disease genes, manifesting often in childhood, is therefore the result of consanguinity.

Sickle cell anaemia and thalassaemia

According to data of the Catalogue of Transmission Genetics in Arabs database on genetic disorders in Arab populations, there is a relative abundance of recessive disorders in the Middle Eastern and North African regions relating to the practice of consanguinity. Thalassaemias and sickle cell diseases/anaemia (SCD) constitute the most common inherited recessive haemoglobin disorders in the world: ~3–7% of the global population carries an abnormal haemoglobin gene, and 400 000 affected children are born each year. Initially described in the tropical and subtropical regions, these diseases are now common all around the world because of migration. According to 2010 estimates, high SCD allele frequencies are found across most of sub-Saharan Africa, Middle East and India, and following migrations to Western Europe and the eastern coast of the Americas. The global number of neonates affected by haemoglobin S (HbS) included 5.5 million heterozygotes and >300 000 homozygotes.[10] Beta-thalassaemia is frequently identified in subjects from the Mediterranean area (Italy, Sardinia, Sicily, Greece and NA), but it is also found in patients coming from Africa and parts of Asia (Iran, India, Vietnam and Thailand). It is estimated that ~60 000 children are born with beta-thalassaemia.[11]

SCD is caused by a point mutation at the sixth position of the beta-globin chain, causing glutamic acid to be replaced with valine. In SCD, haemoglobin two wild-type alpha-globin subunits are associated with two mutant beta-globin subunits to forms HbS. Under low-oxygen conditions, HbS has a tendency to aggregate, which distorts red cells into a sickle shape. SCD is characterized primarily by chronic anaemia and periodic episodes of pain. This leads to further slowing of circulation, reduction in oxygen tension and more red cells sickling and an eventual blockage of a vessel. The blockage is the cause of the painful crisis characterizing SCD. Thalassaemia is caused by a variant or missing globin gene. In beta-thalassaemia, there is a reduced or absent production of beta-globin, encoded by a single gene on chromosome 11. In alpha-thalassaemia, the defect is in alpha-globin genes but because there are two copies of them in different chromosomes, usually only one is defective. A child born with thalassaemia major has two defective alleles for beta-chain gene and he is homozygous for beta thalassaemia. The individual with thalassaemia minor has only one copy of the defective beta-globin gene and he is heterozygous for beta thalassaemia. Thalassaemia major causes a marked deficiency in beta-chain production, leading to severe anaemia with sequelae such as retarded growth, bone deformities, reduced energy generation—and ultimately death at a young age. Persons with thalassaemia minor have mild anaemia or none at all, and no treatment is necessary.

In Tunisia, the average frequency of SCD is 1.9%; it is between 0.8 and 3.5% in Algeria and 1.2% in Morocco.[11,12] In Egypt, along the Nile Valley, the HbS gene is almost non-existent, but in the western desert near the Libyan border, variable rates of 0.4% in the coastal areas to 9.0% in the New Valley oases have been reported. In North

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African countries, most SCD patients have a severe disease, though cases with the mild form have also been reported.[12] For thalassaemia, epidemiological data show that in the East Mediterranean region, the carrier rate ranges between 1.5 and 6% of the total population. The carrier rates are 1.5 to 3.0% in the Maghreb countries and higher at 5–9% in Egypt.[11,13] Alpha-thalassaemia is found mainly in populations of Southeast Asia, the Mediterranean Basin and Central African countries. The incidence has been reported at 5% in Tunisia, 9.0% in Algeria and 2% in Morocco.[11,13]

Genetic studies have found that thalassaemia mutations show heterogeneity in NA, especially between Algeria, Tunisia and Morocco, which could be explained by new mutational events and gene flow due to human migrations and colonization.[13] Among the >45 mutations identified in the beta-globin gene in North African countries, the most common in Tunisia and in Algeria is codon 39 (C > T) and IVS-I-110 (G > A), accounting for >50% of all mutations. In Morocco, the predominant mutations are at codon 39 and frameshift codon 8 (–AA) (11). The codon 39 mutation is most common in the western part of NA compared with the eastern part of the Mediterranean Basin, while the IVS-I-110 mutation is more common in the Eastern Mediterranean region. Studies of globin gene haplotypes have been used to trace the origins and timing of the mutations and their subsequent flow. For the codon 39 mutation, an occidental and ancient origin is predicted with introduction into the Maghreb during the Roman period through Italy and Spain. For IVS-I-110, an Eastern Mediterranean origin is likely.[13] It could have been introduced in Tunisia and Algeria during the Ottoman rule in the 17th century.[14] Evidence suggests that the North African HbS mutation originates from Central West Africa (Benin), where it arose ~3000 years ago. Carriers of this allele later travelled across the then fertile Sahara to the North. The arrival of the carriers to NA was probably more recent and could follow forced migrations from black Africa through slavery roads and/or to the continuous influx of sub-Saharan Africans through the caravan routes.

A UK study found 68 different beta-thalassaemia mutations in antenatal diagnostics, and of these mutations, 59 were found in immigrants. A total of 40 different alpha-thalassaemia mutations were found, including all the Southeast Asian and Mediterranean alpha-thalassaemia mutations.[14]

Periodic fever syndromes

The periodic fever syndromes (also known as autoinflammatory syndromes) are diverse disorders, which are caused by dysfunction of the inflammasome complex of the innate immune system.[15,16] As the mechanisms controlling inflammation are disturbed, the result is an uncontrolled inflammation throughout the body manifesting as high recurring fever, joint and abdominal pains, and amyloidosis as a chronic complication. Hereditary periodic fever syndromes include pyrin-associated familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome, mevalonate kinase deficiency and tumour necrosis factor receptor-associated periodic syndrome.[15] However, because FMF is the most common hereditary syndrome, we will focus on this disease.[17] FMF is common in the Eastern Mediterranean area but rare elsewhere, as are the other periodic fever syndromes. Many of these diseases are diagnosed by paediatricians and, for example, 80% of FMF cases occur before the age of 20 years.[15] FMF is, according to a review, almost always restricted to Turks, Armenians, Arabs and non-Ashkenazi Jews or emigrants with these ethnicities and, according to this source, no cases have been described in individuals of Scandinavian origin.[18] Autoinflammatory conditions may give rise to reactive amyloidosis, which may manifest initially as renal problems; the amyloid precursor is serum amyloid A, the normal and not a mutated protein.[15,16,18–20] The kidneys and the gastrointestinal tract are the vulnerable organs when the patients have developed amyloidosis.[15,21,22] However, the development of amyloidosis in hereditary autoinflammatory disease patients depends on the severity of the condition and may be rare in patients responding to treatment, which for FMF includes colchicines.[18,23,24]

We recently carried out a nation-wide study on diseases in Sweden.[25] Patients were identified from the Swedish Hospital Discharge Register and from the Outpatient Register for 2001 through 2008. Familial autoinflammatory disease was diagnosed in 210 patients, with an incidence of 2.83 per million. At least 98% of the patients were immigrants, most of whom were from the Eastern Mediterranean area. Young Syrian descendants had the highest incidence rate, which was >500-fold higher than that in individuals with Swedish parents. Even the early onset of these conditions identified them as familial autoinflammatory diseases. We concluded that familial autoinflammatory disease was brought into the country as a result of immigration, mainly from the Eastern Mediterranean area. Although we could not specify the diagnosis, all indications suggested that it was FMF. This was a rather remarkable example on how population movements may bring forth new medical problems. There had been no previous literature on FMF being diagnosed in Sweden. A European registry on autoinflammatory diseases included 1049 patients with monogenic diseases, but it reported only one patient in Sweden and without diagnostic details.[17] However, concurrent to our publication, another study appeared from Sweden that reported 37 FMF patients originating from the Eastern Mediterranean area; none of them were of Swedish origin.[26] Our conclusion about the origins of the 210 patients, which probably included the 37 FMP patients, was that there was no evidence of any patient with a Swedish origin.[25]

Reports on FMF patients in other European countries have started to appear. Germany has a large Turkish immigrant population, and most FMF patients had a Turkish origin.[27–29] An incidence of 55 per million was estimated for children of the Turkish origin. This compared our estimate of 140 per million for Syrian descendants.[25] In endemic areas, rates have been estimated to be as high as 1000 per million.[18]

Diabetes mellitus

The two most common forms of diabetes are type 1 diabetes (T1D), previously known as insulin-dependent diabetes, and type 2 diabetes (T2D), previously known as non-insulin-dependent diabetes. Both types are caused by a combination of genetic and environmental risk factors. Diabetes mellitus is a chronic debilitating disease defined as a group of heterogeneous disorders with the common elements of chronic hyperglycaemia and glucose intolerance due to insulin deficiency, impaired effective of insulin action or both.[30] Diabetes is now one of the most common non-communicable diseases globally. It is the fourth or fifth leading cause of death in most high-income countries, and it is epidemic in many low- and middle-income countries.[31]

T1D is caused by the autoimmune destruction of the beta cells of the pancreas, and represents ~10% of all cases with diabetes. The incidence of T1D is increasing worldwide at a rate of ~3% per year. The recent increase in T1D incidence points to a changing global environment rather than variation in the gene pool, which require the passage of multiple generations.[32] Recent prospective studies are helping to elucidate the role of viruses to the aetiology of T1D. For example, enteroviral infections occurring as early as *in utero* appear to increase a child's subsequent risk of developing the disease.[33] Other viruses, including mumps,[34] cytomegalovirus, rotavirus[35] and rubella,[36] have also been associated with the disease. First-degree relatives have a higher risk of developing T1D than unrelated individuals from the general population (~6 vs. <1%, respectively). These data suggest that genetic factors are involved with the development of the disease. At present, there is evidence that >20 regions of the genome may be involved in genetic

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susceptibility to T1D. However, none of the candidates identified have a greater influence on T1D risk than that conferred by genes in the human leucocyte antigen (HLA) region of chromosome 6. This region contains several hundred genes known to be involved in immune response. Those most strongly associated with the disease are the HLA class II genes (i.e., HLA-DR, DQ and DP), contributing ~40–50% of the heritable risk for T1D, but even non-HLA genes have been implicated.[37–39]

T2D is the most common form of the disease, accounting for ~90% of all affected individuals. It is caused by relative impaired insulin secretion and peripheral insulin resistance. Typically, T2D is managed with diet, exercise, oral hypoglycaemic agents and sometimes exogenous insulin. In 2000, it is estimated that 171 million people (2.8% of the world's population) had diabetes and that by 2030 this number will be 366 million (4.4% of the world's population). It has long been known that T2D is, in part, inherited. Family studies have revealed that first-degree relatives of individuals with T2D are ~3 times more likely to develop the disease than individuals without a positive family history of the disease.[40] To date, >50 candidate genes for T2D have been studied in various populations worldwide.[41]

Three of the world's top 10 countries with the highest prevalence (%) of diabetes are in the Middle East and NA (MENA) region: Saudi Arabia, Kuwait and Qatar. The MENA region has the highest comparative prevalence of diabetes (10.9%). According to the latest estimates, 35 million people, or 9.2% of the adult population, have diabetes. This number is set to almost double to 68 million by 2035.[31,32] Diabetes in the MENA region is mainly T2D. The number of people with impaired fasting glucose is estimated to be 25.2 million people, or 6.7% of the population, who are therefore at high risk of developing diabetes.[42] The highest prevalence of impaired glucose tolerance (13.1%) was found in rural Egypt, and the lowest prevalence was found in rural Sudan with a prevalence of 2.2%. One study in Tunisia reported on impaired fasting glucose, and the prevalence was 5.3% in men and 5.1% in women. Through reviewing 12 community-based studies, the prevalence of undiagnosed diabetes ranged from 18% in urban Libya to 75% in Tunisia. The prevalence of diabetes varied across North African countries, and it was found that the prevalence in urban areas than in rural areas range from 2.6% in rural Sudan to 20% in urban Egypt.[43–45] Diabetes mortality estimated to be >10% of all adults in the MENA region, i.e. 368 000 deaths with 146 000 men and 222 000 women in 2013.[42]

Diabetes in immigrants from Africa is high as in African Americans (12–15%), closely followed by Caribbeans of African descent and low among indigenous African origin populations (1–6%). In the African diabetes, majority of cases are T1D (70–90%), followed by T1D (5–20%) and atypical presentation accounts for 5–15%.[46] There are limited data on T1D among African, but is becoming increasingly more prevalent and the available evidence suggests that in African the age of onset occurs later than in the developed world.[47]

According to a systematic review, the prevalence of retinopathy ranged from 8.1% in Tunisia to 41.5% in Egypt. Albuminuria prevalence ranged from 21% in Egypt to 22% in Sudan; nephropathy ranged from 6.7% in hospital outpatient clinics in Egypt to 46.3% in hospital inpatients in Egypt. The prevalence of diabetic neuropathy ranged from 21.9% in hospital outpatient clinics to 60% in hospital inpatient clinics in Egypt.[43] The impact of increasing prevalence of diabetes is translated into severe economic burden, high morbidity and mortality rates.[48] Effectively the economic capabilities of the health care system in most of Africa countries are not sufficient to withstand the burden of diabetes effective. Thus, sustainable strategies are needed to promote diabetes awareness and public health policies that empower individuals to diabetes self-management to improve the quality of life, reduce morbidity and premature mortality.[49,50]

Rare recessive diseases

North African and Middle Eastern populations share disease alleles, for example, the Tunisian population shares founder mutations with other North African and Middle Eastern populations for 43 inherited conditions. Founder chromosomal segments described in Tunisian patients with Meckel syndrome (characterized by renal cystic dysplasia), sickle cell anaemia and xeroderma pigmentosum (XP) group A (XPA) are identical to those described in Algerian patients.[51] The founder mutations leading to adenomatous polyposis of the colon and the hepatocerebral mitochondrial DNA depletion syndrome are reported on the same haplotypes between Tunisian and Moroccan patients.[52] Tunisian, Algerian and Moroccan patients share haplotypes for autosomal recessive non-syndromic optic atrophy, Bare lymphocyte syndrome and for the major founder mutation p.R228X in XPA—beta-thalassaemia and FMF were discussed earlier.[51]

Severe childhood autosomal recessive muscular dystrophy is the most frequent muscular dystrophy in Tunisia, and most patients are homozygous for founder mutation c.del521T mutation in SGCG gene.[53] The recurrent mutation p.V548AfsX25 in the XPC gene and leading to XPC, a rare severe genodermatosis associated with skin tumours, was first described in Algerian and Moroccan patients at homozygous state.[54] For Hurler syndrome, also known as mucopolysaccharidosis type I and often classified as a lysosomal storage disease, is caused by a defective IDUA gene, encoding iduronidase enzyme. Over 50 different mutations in the IDUA gene have been shown to cause Hurler syndrome. Point mutation P533R is a founder mutation in the Tunisian population and it is frequent in all the Maghrebian populations even in the Maghrebian immigrant population in France.[51] For congenital myasthenic syndrome, patients originating from four North African countries and living in France share the same haplotype bearing the c.1293insG mutation affecting the CHRNE gene.[55] The strong evidence for a single ancestral founder event in the North African population simplifies diagnostics of congenital myasthenic syndrome.[56] Cystic fibrosis (CF), also known as mucoviscidosis, is an autosomal recessive genetic disorder that not only most critically affects the lungs, but also the pancreas, liver and intestine.[57] CF is caused by a frameshift mutation in the gene for the protein CF transmembrane conductance regulator, regulating the movement of chloride and sodium ions across epithelial membranes and influencing the composition of sweat, digestive fluids and mucus.[58] CF is diagnosed in males and females equally, but for unknown reasons males tend to have a longer life expectancy than females.[59]

The geographic distribution of 272 CF mutations was studied by assessing the origin of 27 177 CF chromosomes in 29 European and 3 North African countries. The most common mutations are delta F308 (66.8%), G542X (2.6%), N1303K (1.6%), G551D (1.5%) and W1282X (1.0%). The delta F508 mutation has the highest frequency in Denmark (87.2%) and the lowest in Algeria (26.3%). Mutation G542X is common in Mediterranean countries, with a mean frequency of 6.1%. N1303K is found in most of the Western and Mediterranean countries and has the highest frequency in Tunisia (17.2%). G551D is common in north-west and central Europe, but is uncommon in other parts of Europe. W1282X has the highest frequency in Israel (36.2%), being also common in most Mediterranean countries and NA.[60] The wide distribution of these mutations suggests an ancient origin.

Triple A syndrome (Allgrove syndrome) is a highly heterogeneous autosomal recessive disorder with high lethality. It is associated with mutations in the AAAS gene, which encodes a protein known as aladin. Both the geographical distribution of carriers of the mutation (Algeria and Tunisia) and the size of the common ancestral haplotype, indicate that the triple A mutation in the North African population is very old and occurred in the ancient Arabian population a long time before it entered NA.[61]

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Conclusions

In the present chapter, we discuss consanguinity in NA, and some of its deleterious consequences in indigenous and immigrant populations. The distribution of founder mutations is the result of historical migratory movements, and many common disease alleles in the current NA have origins elsewhere, but the disease burden in NA is largely the result of inbreeding. NA has been a main source of European immigrants, and the disease alleles have been introduced to the national gene pools. However, for recessive diseases, the most frequent disease manifestations are in inbred immigrant populations. It remains unclear how well European health care providers are able to cope with the imported diseases. The example of periodic fever syndromes showed that a new disease may be introduced into immigrant-dense countries with little notice by the medical community. Diagnostics of recessive disease require demonstration of specific mutations in target gene. Thus, knowledge of the common founder mutations in ethnic immigrant populations is required and diagnostic tests used in NA could be applied.

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Conflicts of interest: None declared.

Key points

- Consanguinity is common in NA, as a consequence, recessive disorders are common in the region, SCD being most prevalent, followed by thalassaemia.
- Immigration is influencing the pattern of recessive diseases in Europe.
- These disorders are likely to be further propagated because the habit of inbreeding is continuing in many immigrant communities.

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EV0331

Does consanguinity increase the risk of mental illnesses? A population based study

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The aim of this study was to assess the impact of consanguinity on risk for mental disorders especially in primary health care-PHC settings. It was decided to ascertain prevalence of common mental disorders and consanguinity. We set out to study the burden of commonest psychiatric disorders among consanguineous marriages at PHC using the WHO Composite International Diagnostic Interview (WHO-CIDI) and examine their symptom patterns and co-morbidity in Qatar. A prospective cross sectional study was carried out over a year between November 2011 to October 2012. A total of 2.000 Qatari subjects aged 18 to 65 years were approached; 1.475 (73.3%) gave consent and participated in this study. Prevalence of psychiatric disorders using the WHO Composite International Diagnostic Interview (CIDI, version 3.0) showed that six most common disorders were major depression disorders (18.3%), any impulse control condition (18.3%), any anxiety disorders (17.2%), any mood disorders (16.9%), followed by separation anxiety disorders (15.2%), personality disorder (14.1%). The mean age ± SD of the 1.475 subjects interviewed was 39.3 ± 9.8 years. The rate of consanguinity in the present generation was 31.5% [95% CI = 29.1–33.7]. There were statistically significant differences between consanguineous and non-consanguineous with regards to age, educational status, occupation status, household income as well as BMI, cigarette smoking and sheesha smoking. One-fifth of all adults who attended the PHC center 20% had at least one psychiatric diagnosis. The prevalence of the generalized anxiety disorders; social phobia, specific phobia, major depression, and personality disorders were significantly higher in consanguineous marriages than in non-consanguineous.

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EV0332

Risk factors in emotional and personal development of senior preschool children from different social strata (middle-high and middle-low social layers)

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Introduction Methodological basis of Vygotsky's scientific school implemented in the study provides possibility to detect risk variants in emotional and personal development of children from different social strata and to explore the mechanisms responsible for pathological development.

Objectives and methods The study included two groups:(1) children from a middle-high social stratum ($n = 31$); (2) children from a middle-low social stratum ($n = 36$). All the children were between ages 5.5–7 years at the moment of research, lived in Moscow and attended extracurricular activities. Following methods were used: objective description of child's development in socio-cultural context; semi-structured interview; long-term overt and covert observations; diagnostics of intellectual, emotional and personal school readiness.

Results Children from the 1st group demonstrate higher level of intelligence; they are more successful in solving unusual tasks. Children from the 2nd group tend to follow instructions given by teacher. Children from the 1st group unlike those from the 2nd one are characterized by lower level of social competence; they encounter difficulties in establishing contacts and don't perceive hierarchy in adult–child relationship. Mass protection typical for children from the 1st group and hyper-satisfaction of their needs determine decrease of frustration and don't deepen their personal experience providing basis for pathological development. Children from the 2nd group are more inclined to demonstrate alarm reactions, but in general they possess higher level of emotional and personal maturity and social flexibility.

Conclusion Socio-cultural environment has a direct say in potential risk zones of child development.

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EV0333

Parental expectations in families from different social and cultural groups and their influence on emotional and personal development of a child

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Introduction The study explores subjective image attributed by parents to their child that was formed under the influence of different socio-cultural conditions and affects communication with a child. Methodological basis of Vygotsky's scientific school was used in the research.

Objectives and methods The study included two groups of families from different social strata: group 1 — middle-high stratum, group 2 — middle-low stratum ($n_1 = 31$, $n_2 = 36$), all the families live in Moscow; the children (5.5–7 years old) attend extracurricular activities. Following methods were used: analysis of social context of child's development; long-term overt and covert observations; analysis of complaints, ambitions and expectations — "a project of future development" of a child imagined by parents followed by reconstruction of their relations that appear to be the basis for the "project"; method of semi-structured interview.

Results First group demonstrates high level of irrelevance in subjective extra-positive image of a child. That poses risk for child's emotional and personal development. Families from different strata tend to demonstrate irrelevance between ambitions and real success of a child. First group tend to overstate, 2nd group — to understate. In some cases parents' mindsets cause emotional peculiarities of the child: individuality and as a result inflated ego, demonstrative behavior accompanied by interest to external attributes. In 2nd group children are mostly anxious and encounter difficulties in demonstration their abilities, but they possess higher level of emotional and personal maturity and social flexibility.

Conclusion Socio-cultural features of the stratum influence parental expectations that form potential risk zones in child development.

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EV0334

Death in the work of Jorge Amado: The function of art in education for death

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