

CHAPTER 4

Genetic disorders

(★ *Ghazi O Tadmouri*)

Introduction

Until recently, infectious or environmental diseases and malnutrition-related disorders constituted the major cause of ill health and mortality in Arab populations. However, progress made in healthcare standards in many Arab countries has decreased the impact of these disorders. Improved understanding of the spectrum of heritable disease and better recognition of genetically transmitted conditions as major causes of morbidity and mortality are increasing awareness of the importance of these conditions in the region.¹

Arab populations and diasporas in the world

Arab populations encompass a vast geographical region that extends from Iraq in the east to Morocco in the west. They occupy the whole of Mesopotamia, the Levant, the Arabian Gulf, North Africa, as well as some parts of East and West Africa. Arab populations are distributed throughout 23 different countries, namely: Algeria, Bahrain, Comoros, Djibouti, Egypt, Eritrea, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates (UAE) and Yemen. The total population of these countries is approximately 315 million.

Throughout history, Arab emigrants formed many diasporas in other continents of the world. The main countries of emigration are, in order of percentage: Yemen, Jordan, Lebanon, Egypt, Syria, Morocco, Algeria, Tunisia, Mauritania and Sudan. The main countries of immigration within the Arab world are those

of the Gulf Cooperation Council and Libya, which host more than two million Arabs. Outside the Arab world, the largest Arab communities live in Europe and North America. Arabs in the United Kingdom, Europe and the United States total some 12 million people, many of whom are well established.²

Demographic characteristics of Arab populations

Arabs are a large and heterogeneous group that resulted from the admixture with many other populations throughout history. Certain cultural and geographic considerations markedly affect the prevalence and natural history of genetic diseases in the Arab world. Some of these characteristics include:

- the presence of *isolates* (e.g. Armenians, Bedouins, Druzes, Jews, Kurds, Nubians and others) who share common gene pools due to recurrent inbreeding
- marriage at a young age³
- high birth rates (16–43 births per 1000 people)
- high infant mortality rate (10–76 deaths per 1000 live births)⁴
- childbearing at older maternal ages, often until menopause
- the lack of public health measures directed toward control and prevention of congenital and genetically determined disorders³
- large family sizes (2–7 children born per woman)
- high rates of inbreeding or consanguineous marriage – often a traditional practice followed within the same tribe, village or social unit.

Consanguinity in Arab people

One of the most important factors contributing to the preponderance of genetic disorders in Arab populations is the deep-rooted norm of consanguineous marriages. The term “consanguineous marriage” is defined as marriage between relatives. Geneticists usually classify unions between biologically related persons who are second cousins or closer as consanguineous.

Overall, it is estimated that 40–50% of marriages in the Arab world are consanguineous (*see* Figure 4.1). The specific types of consanguineous marriage vary between and within countries. First cousin marriages are the most common consanguineous bonds in the Arab world. Estimates indicate that the prevalence of first cousin marriages is approximately 11.4% in Egypt, 21% in Bahrain, 29% in Iraq, 30% in Kuwait, 31% in Saudi Arabia, and 32% in Jordan.

Religious, cultural and historical factors are important in maintaining the practice of consanguineous marriage. Contrary to popular assumptions, Islam does not advocate or encourage consanguineous marriages. In fact, Arabs probably practiced consanguinity long before the introduction of Islam in the 7th century. The preference for consanguineous marriage is not restricted to Islamic Arab communities. In some Christian communities (e.g. Lebanon), consanguinity is also common.

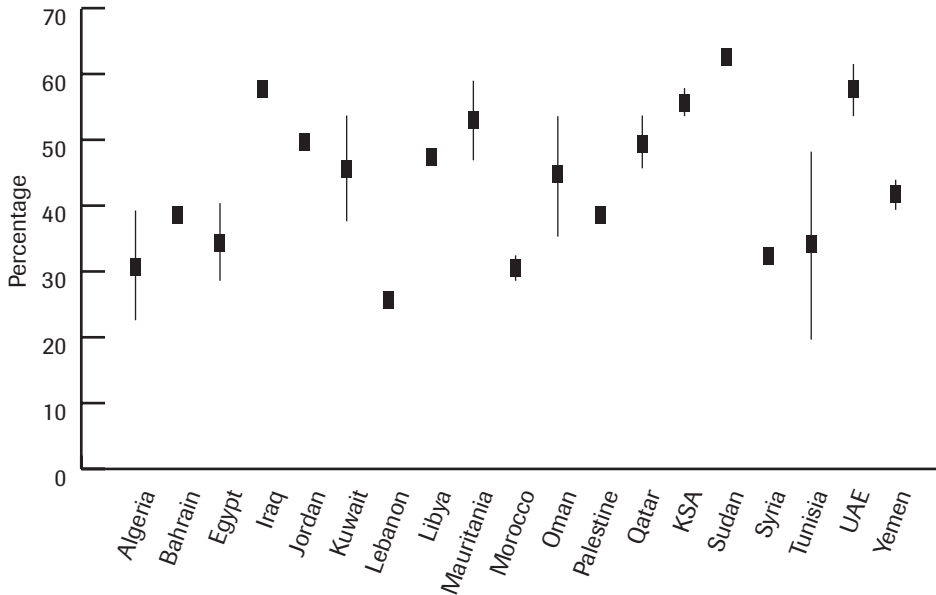


FIGURE 4.1 Percentage of consanguineous unions of total marriages in Arab countries Adapted from: Benallegue and Kedji, 1984 (Algeria);⁵ ENAF, 1992 (Algeria);⁶ Al-Arrayed, 1999 (Bahrain);⁷ Hafez *et al.*, 1983 (Egypt);⁸ ENPC, 1989 (Egypt);⁹ Al-Hamamy *et al.*, 1986 (Iraq);¹⁰ Khoury and Massad, 1992 (Jordan);¹¹ Al-Nasser *et al.*, 1989 (Kuwait);¹² Al-Awadi *et al.*, 1985 (Kuwait);¹³ Klat and Khudr, 1986 (Lebanon);¹⁴ Broadhead and Sehgal, 1981 (Libya);¹⁵ National Statistical Office, 1992 (Mauritania);¹⁶ Hammami *et al.*, 2005a (Mauritania);¹⁷ Azelmat *et al.*, 1987 (Morocco);¹⁸ Azelmat *et al.*, 1992 (Morocco);¹⁹ Oman Family Health Survey, 1995 (Oman);²⁰ Rajab and Patton, 2000 (Oman);²¹ Jaber *et al.*, 1992 (Palestine);²² Ministry of Health, 1999 (Qatar);²³ Bener and Alali, 2006 (Qatar);²⁴ Wong and Anokute, 1990 (Saudi Arabia);²⁵ El-Hazmi *et al.*, 1995 (Saudi Arabia);²⁶ Saha *et al.*, 1990 (Sudan);²⁷ Prothro and Diab, 1974 (Syria);²⁸ Aloui *et al.*, 1988 (Tunisia);²⁹ Kerkeni *et al.*, 2006 (Tunisia);³⁰ Fahmy *et al.*, 1993 (UAE);³¹ Al-Gazali *et al.*, 1995 (UAE);³² Jurdi and Saxena, 2003 (Yemen);³³ Gunaid *et al.*, 2004 (Yemen).³⁴

In addition to culture and history, the geographic concentration of population groups in small and isolated areas promoted the practice of consanguineous marriages. Many families also consider consanguineous marriage as a way to maintain the unity of family assets. Marriage to a relative is preferred, too, because of the comparative ease with which premarital negotiations can be conducted, and the greater stability of consanguineous unions due to familiarity between the female partner and her in-laws.³⁵

Studies indicate that several factors influence consanguinity rates in Arabs. These factors include urban–rural residence ratios of families, education levels and time trends. Studies in Jordan,¹¹ Egypt, Lebanon, Oman and Tunisia demonstrated a higher tendency of consanguineous unions among rural compared to urban inhabitants.³³

In some Arab countries, it is evident that the higher the level of education of

the female partner, the lower the consanguinity rate.¹¹ On the contrary, in some societies, highly educated men are more likely to be married to cousins.³³ A plausible explanation is that since a son with higher education becomes a more valuable asset, he is pressured to remain within the family.¹¹

While a declining trend of consanguineous marriages has been documented in Bahrain, Lebanon, Kuwait and Syria, a stable trend has been reported in Jordan and Oman.³³ However, these rates have increased over the last generation in Algeria,³⁶ the UAE³⁷ and Yemen.³³ The reason for the rising trend in consanguinity has been attributed to the increase in the availability of cousins due to high fertility.³³

Consanguinity and reproductive health

While the concept of inheritance is not clear in the minds of many lay people, consanguinity is linked to high incidences of congenital malformations, mental retardation and disability. Studies indicate that in populations where the practice of inbred marriages is high, the frequency of homozygosity for autosomal conditions and the incidence of congenital anomalies, abortions, stillbirths and early childhood deaths are likely to rise.^{3,38} The reason behind this observation is that the more closely two people are related, the more genes they share. A marriage between first cousins increases the risk of having a child with a severe congenital or genetic disorder by 2.5 times since parents share one-eighth of their genes. An average of 30% first cousin marriages in a population would increase the birth prevalence of many conditions by 5–15 times and their collective frequency by 5.5 times. Frequent consanguineous marriage increases the incidence of autosomal recessive disorders by 5–10 times at the population level. When first cousin marriage is considered, the risk of recessively inherited disorders is multiplied by 15–30 times; hence, there is a doubling of the total frequency of congenital and genetic disorders.³⁹

While the incidence of recessively inherited disorders increases with the increasing trend of consanguineous marriages, consanguinity has no effect on the frequency of autosomal dominant or X-linked conditions. Autosomal dominant conditions result from just one copy of a deleterious mutation. Thus, having two parents with the same autosomal dominant mutation does not make an individual more susceptible than someone with only one affected parent. Similarly, just one copy of a deleterious X-linked recessive mutation will result in disease in males. Hence, having related parents does not increase the risk of a male with X-linked recessive disease.

Recently, many studies from the region have drawn strong correlations between consanguinity and hearing loss,⁴⁰ death rates in children,⁴¹ respiratory allergies, eczema,⁴² congenital heart defects,⁴³ mental retardation, epilepsy, diabetes⁴⁴ and many other conditions.^{1,2}

Arab family structure and transmission genetics

The extended family structure, commonly present in Arab societies and mostly associated with consanguinity, tends to display unique distribution patterns for genetic diseases that are not present in many other societies. A major model that explains this concept is the vertical dissemination of a genetic mutation in an Arab or in a Western family. In the typical Western family, carriers of mutations usually become scattered through the general population through marriage. After a few generations, their genetic relationship to each other is unrecognized, therefore a family history suggesting a genetic basis for their predisposition to certain disease states is easily missed. On the other hand, in an Arab society mutation carriers mostly remain concentrated within the extended family, and the genetic nature of their disease predisposition is often much more obvious.

The economic impact of genetic disorders

Genetic disorders are chronic in nature and often require lifelong management with no definitive cure. In the Arab world, several disorders, including chromosomal (Down syndrome, Turner syndrome), single-gene (sickle cell disease, thalassemia, glucose-6-phosphate dehydrogenase deficiency, hemophilia, inborn errors of metabolism) and multifactorial disorders (coronary artery disease, arteriosclerosis, diabetes mellitus, hypertension, obesity) are common. Some of these disorders have assumed epidemic proportions, as in the cases of sickle cell disease, alpha-thalassemia, hypertension and diabetes mellitus. The impact of each of these disorders differs according to their severity, but many of them have medical, surgical or cosmetic consequences. Often, these conditions result in spontaneous abortion, neonatal death, and increased morbidity and mortality in both children and adults. They are a significant healthcare and psychosocial burden for the patient, the family, the healthcare system and the community as a whole.⁴⁵

In terms of economic burden, patients with genetic or partly genetic disorders have longer and more frequent hospital admissions with a higher number of surgeries than do other patients.^{46,47} Additionally, the total costs paid by patients with genetic conditions are slightly greater,⁴⁸ and these patients often must travel significant distances to get specialized treatment.⁴⁶

In recent years, health economists have made significant advances in calculating the costs of genetic disorders, as well as disabilities caused by various congenital abnormalities. There are now generally accepted “cost of illness” estimates for all common genetic conditions:

- ❖ *beta-thalassemia*: treatment of beta-thalassemia major is currently an expensive option and has great financial implications for any health authority where the disease is highly prevalent. The total lifetime (up to 60 years of age) treatment costs of a patient with beta-thalassemia are estimated to be \$416 000; thus, an average of about \$7000 annually.⁴⁹

- ❖ *sickle cell disease*: Davis and colleagues⁵⁰ estimated the direct cost of each hospitalization associated with sickle cell disease to be \$6300. Patients with sickle cell disease are frequent users of healthcare services. On average, a sickle cell disease patient is subject to one hospital admission per year and eight outpatient visits annually.⁵¹ Although much of the treatment cost is covered by governments or supported by non-governmental organizations in the region, this may be changing in some regions. Additionally, many of the patients must travel long distances, and this adds to the overall cost of treatment.
- ❖ *cystic fibrosis*: studies have shown that hospitalization costs for patients with cystic fibrosis vary according to the severity of their disease. However, economists have estimated that the total cost per person with cystic fibrosis to be about \$285 000 over their lifetime,⁵² with an annual average of about \$9400 per patient, of which 28% of total cost is attributable to drug costs.⁵³
- ❖ *hemophilia*: like other genetic disorders, hemophilia is a lifelong condition which results in profound physical, emotional, economic and social problems for those afflicted. The severity of bleeding episodes is correlated with the degree of deficiency of the Factor VIII protein in the blood. Accordingly, hemophiliacs suffer from mild, moderate or severe disease. Medical expenses vary among patients according to the severity of the deficiency. In the moderate-to-severe group, one study from 1972 estimated medical expenses to exceed \$1000 per year.⁵⁴ Hemophiliacs may be denied health insurance, thus shifting the costs to the family.
- ❖ *congenital bilateral permanent childhood hearing impairment*: a recent study estimating the economic costs of bilateral permanent childhood hearing impairment (PCHI) in the preceding year of life for children seven to nine years of age found that the mean societal cost was about \$26 700 per child, compared to \$8000 in children with normal hearing.⁵⁵

In 1995, Waitzman and colleagues estimated that the total economic cost of cerebral palsy, spina bifida, truncus arteriosus, single ventricle, transposition/double outlet right ventricle, tetralogy of fallot, tracheo-esophageal fistula, colorectal atresia, cleft lip or palate, atresia/stenosis of the small intestine, renal agenesis, urinary obstruction, lower limb reduction, upper limb reduction, omphalocele, gastroschisis, Down syndrome, and diaphragmatic hernia in the United States was \$10.8 billion (2004 normalized data) for a single year's cohort. This total cost comprises \$2.8 billion in direct healthcare costs and \$8 billion in indirect costs such as developmental services, special education and lost productivity. If we extrapolate these numbers adjusting for the differences in population between the United States and all Arab countries, and ignore the fact that many of these 18 birth defects occur more frequently in Arab countries than elsewhere, then the cost of these problems in Arab countries is about \$13 billion per year.

Preventive aspects of genetic disorders

The successful management of genetic disorders also incurs a high financial cost, which could be eased by the application of effective prevention programs in populations at risk of genetic disease.⁵⁶ Prevention programs are effective in decreasing the impact of genetic disorders on families and societies and also lead to early treatment and improvements in outcome and prognosis.⁵⁷ A majority of Arab countries have the expertise and resources to apply most of these preventive measures, especially in the areas of newborn screening and carrier screening for prevalent genetic disorders. However, having the technology and resources alone is not enough to start effective programs. For example, population screening should be performed only if the abnormal finding in question can change the clinical management, and if this management will improve the prognosis. Economic considerations are also a factor; the cost of screening should justify the financial savings and emotional impact involved in detecting affected individuals. In addition, no genetic screening program will be successful if it is not accompanied by extensive educational activities aimed at both the general public and healthcare providers to aid effective participation.⁵⁸ Furthermore, these programs are most successful when they are sensitive to the cultural backgrounds of populations in which they are applied.⁵⁹

Genetic disorders in Arab populations

The *Catalogue for Transmission Genetics in Arabs* (CTGA) database is a continuously updated catalogue of bibliographic material and observations on human gene variants and inherited, or heritable, genetic diseases in Arab individuals. The database is maintained by the Centre for Arab Genomic Studies (www.cags.org.ae). Since the public release of the CTGA database in 2004, our knowledge about genetic disorders in Arab populations continues to expand. This process is largely driven by various methods used at the Centre for Arab Genomic Studies (CAGS) to collect data and information on genetic conditions in Arab patients.¹

As of May 2007, the CTGA database has recorded the presence of 816 phenotype/disease entries in Arab individuals. However, data on only about 300 related genes are available in the CTGA database. This is a reflection of the fact that clinical observation is emphasized over molecular analysis in most of the research conducted in the region. The majority of disease records in the database come from the UAE [241], Saudi Arabia [148], Palestine [127], Lebanon [125], Bahrain [120], Tunisia [94], Egypt [92], Kuwait [83], Morocco [77], and Oman [67]. This distribution is highly preliminary since CAGS has carried out extensive surveys to define the extent of genetic disorders in the UAE (2004–05) and Bahrain (2006–07). Very recently, a new survey was launched in Oman and is due for completion in early 2008. On the other hand, data from other Arab countries have been collected through limited reviews of international bibliographic indices as well as paper submissions from their

corresponding authors. It is anticipated that in the coming five to ten years major surveys will be conducted in other Arab countries to obtain a more accurate picture of the extent of genetic disorders in the Arab world.

Classification and molecular complexity of genetic disorders in Arab populations

By employing the World Health Organization *International Classification of Disease*, version 10 (ICD-10), it is possible to categorize the distribution of genetic disorders in the Arab world according to disease taxonomies. Just over one-third of genetic disorders in Arab individuals result from congenital malformations and chromosomal abnormalities (34.6%). These are then followed by endocrine and metabolic disorders (17.8%) and diseases of the nervous system (9.9%). Other types of disorders seem to occur at lower frequencies in Arab populations (*see* Figure 4.2); these findings may be due to a relative lack of specific regional research or expertise in these areas.

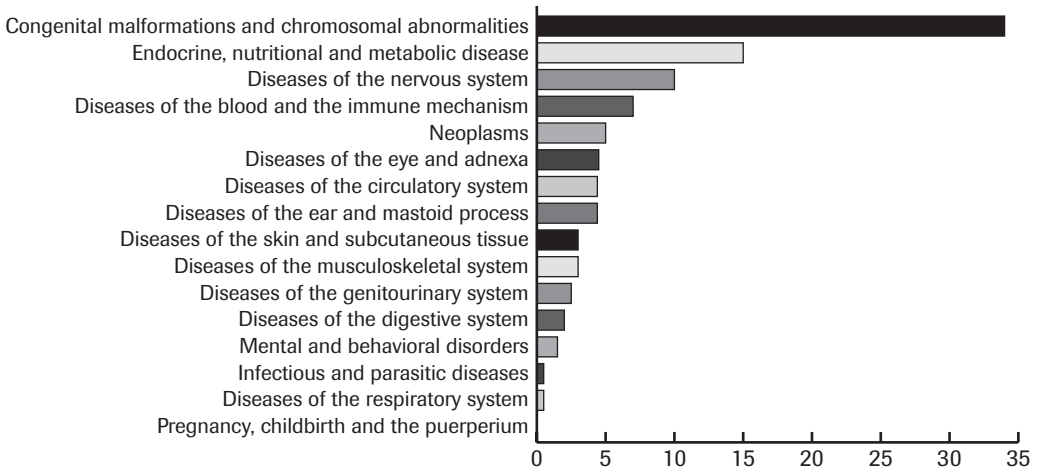


FIGURE 4.2 Classification of genetic disorders in Arabs according to the ICD-10

A detailed analysis of the molecular basis of defined genetic diseases indicates that just over half of the genetic disorders described in Arabs (54%) result from single-gene or gene loci alterations. Hence, in the presence of the necessary technical infrastructure, diagnostic services for people at risk and preventive programs may be applicable in many Arab communities.

The overwhelming proportion of genetically transmitted diseases in Arab patients are inherited through autosomal recessive modes (approximately 64%). These are followed by autosomal dominant (26%) and X-linked traits (6%). High consanguinity rates and extended family structure, which are common in Arab societies, are likely explanations for these phenomena.¹ Observations in support of this view include data from the UAE indicating that autosomal recessive and

dominant disorders comprise 56% and 33%, respectively, of all genetic disorders, with 50.5% of marriages being consanguineous.³⁷ On the other hand, the rate of autosomal recessive disorders decreases to 37% – compared to 45% for autosomally dominant disorders – in Bahrain, where the rate of consanguineous marriage is considerably lower, at 39%.⁷

The spectrum of genetic disorders in Arab populations

A recent introduction to the CTGA database is the ability to classify genetic disorders according to their incidence rates in the Arab world. Noteworthy are two groups of disorders:

- genetic disorders that are highly prevalent and occur at annual incidences (> 100 cases per 100 000 live births). This group encompasses all hemoglobin disorders (thalassemias, sickle cell disease and hemoglobin variants), glucose-6-phosphate dehydrogenase deficiency, Down syndrome, breast cancer, diabetes, anencephaly, Graves disease, Caffey disease, Takayasu arteritis, polycystic kidneys, and other ailments.
- many other disorders do occur in the Arab world at higher incidence rates when compared to data from the rest of the world. For example: tetralogy of fallot, familial Mediterranean fever, deafness, Noonan syndrome and ankylosing spondylitis.

Many of these disorders have been extensively researched and reported in the literature, reflecting their widespread presence in Arab populations. The overwhelming distribution of these diseases in Arabs is best explained by the exposure of Arab countries to common environmental factors that encouraged natural selection for these disorders such as malaria in the case of hemoglobinopathies, and dietary traditions in the case of glucose-6-phosphate dehydrogenase deficiency.

Other genetic disorders exhibit wide geographic distributions encompassing one or more neighboring regions, such as in the cases of the hemolytic-uremic syndrome and ankylosing spondylitis. Many genetic disorders indexed in the CTGA database exhibit sporadic distribution patterns over geographically distinct regions in the Arab world. These observations strongly advocate for more regional research on these disorders to complete the picture. Candidate disorders for further research might include: alpha-thalassemia, cystic fibrosis, familial Mediterranean fever, autosomal recessive polycystic kidney disease, anencephaly, Hirschsprung disease, and others.

On the other hand, some genetic diseases exhibit specific geographic distributions. Examples include:

- *the Maghreb region*: type II bare lymphocyte syndrome and the alpha erythrocytic 1 spectrin defect
- *North Africa*: type 2C of limb-girdle muscular dystrophy
- *the Middle East*: dyssegmental dwarfism

- ◆ *the Arabian Gulf*: Laurence-Moon syndrome, suppressor of tumorigenicity type 8 defect, and type I primary hyperoxaluria.

It is important to note that many new syndromes and variants have recently been described in Arab people. In many cases, Arab scholars and researchers were the first to describe some of these disorders, for example: the Teebi type of hypertelorism,⁶⁰ the Teebi-Shaltout syndrome,⁶¹ Al-Gazali syndrome⁶² and Megarbane syndrome.⁶³ Also, some genetic disorders seem to be specific to Arab populations, such as: the Lebanese type of mannose 6-phosphate receptor recognition defect,⁶⁴ the Algerian type of spondylometaphyseal dysplasia,⁶⁵ the Kuwaiti type of cardioskeletal syndrome,⁶⁶ the Yemenite deaf-blind hypopigmentation syndrome,⁶⁷ the Nablus mask-like facial syndrome,⁶⁸ the Jerash type of the distal hereditary motor neuropathy,⁶⁹ Karak syndrome⁷⁰ and the Omani type of spondyloepiphyseal dysplasia.⁷¹

Final notes

At present, congenital malformations are the second leading cause of infant mortality in countries of the Gulf Cooperation Council, including Bahrain, Kuwait, Oman and Qatar. Reports from Saudi Arabia indicate that congenital malformations account for about 30% of perinatal deaths.⁷² Additionally, in most Arab populations the birth prevalence of severe recessively inherited disorders may approach that of congenital malformations.³⁹

Approximately 36% of reported genetic disorders in Arabs remain confined to clinical observations with no significant attempts to depict their molecular pathologies. A large number of these disorders are confined to local families and communities and have not been described elsewhere. Mummifying these disorders at the clinical level represents a very serious loss for the global scientific community, since permanently burying information regarding hundreds or thousands of human gene variants might result in the loss of important information that could be used in future research, potentially leading to cures for genetically transmitted conditions. Unfortunately, no established system is yet available in many Arab medical research institutions to translate clinical observations into genetic data. The limited examples available in the Arab world are usually local efforts by medical practitioners and clinical geneticists who have developed a particular interest or have specialized in molecular studies. Increasing the emphasis on subjects such as molecular genetics in medical schools in the region will help to create future generations of physicians and other medical personnel capable of establishing the phenotype–genotype correlations that are key elements in modern medical applications of genetics.

Databasing prevalence data, in addition to the molecular pathologies leading to genetic disorders in Arabs, offers a solid groundwork to promote enhanced education in the field and employ knowledge-driven development to address urgent regional health needs. The organization of such information also

promotes Arab scientists to a position of strength and allows them to contribute to global research efforts in the field and build sustainable research activities based upon education and the improvement of human health.⁷³

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