Chapter 1

Genetic Disorders in Arab Populations: A 2008 Update

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Introduction

Genetic and inherited disorders accompanied the human race since its earliest existence. Several archeological remains were discovered in prehistoric sites with pathologies suggestive of inherited disorders. These include a 1.5 million year old fossil of a 2-year-old *Homo erectus* child with amelogenesis imperfecta (Zilberman *et al.*, 2004) and ancient DNA analysis which revealed a β-thalassemia mutation in the skeletal remains of an Ottoman child with severe porotic hyperostosis (Filon *et al.*, 1995). In the 1960s, Prof. J.L. Angel put forward the hypothesis of prehistoric thalassemia in the Eastern Mediterranean on the basis of the frequency of porotic bone lesions in Neolithic skeletal remains from this region (Angel, 1966). Since then, several observations on the occurrence of human disorders were noted in ancient populations in the region (Frohlich *et al.*, 1988). In Egypt, scientific investigation of mummies from the huge necropolis of Thebes-West in Upper Egypt revealed osseous manifestations suggestive of metabolic and chronic anemia in a high frequency in the populations of the "Middle Kingdom" (2050-1750 BCE; Nerlich *et al.*, 2002).

Genetic Disorders in World Populations

To date, records for more than 6000 inherited disorders have been indexed and maintained at the Online Mendelian Inheritance in Man (OMIM) database (McKusick, 2007). Many of these disorders are rare entities that have been described in limited geographical regions, towns, or families. More common disorders show a worldwide spread supported by natural selective forces or stimulated by socially-oriented reproductive choices.

OMIM is a comprehensive compendium of human genes and genetic phenotypes. Its robust search engine permits the user to mine information on genetic disorders according to population groups or ethnicities by using proper search syntaxes (Table 1.1). However, this strategy only gives a rough estimate on the number of genetic disorders in a population with possibly very large deviations from actual figures. For example, early attempts to catalogue genetic disorders in the Turkish population indicated the presence of more than 800 genetic disorders (unpublished observations, 2004), a number that is almost three times what could be extracted from a simple search in OMIM (Table 1.1). On the other hand, some populations appear to be over-represented in the database, possibly due to the reliance of OMIM editors on internationally indexed journals; a strategy that would favor data from developed countries and leaves those from less developed regions trailing far behind.

Arab Populations and Diasporas in the World

Defining the term Arab is a challenging task. Linguistically, Arab populations encompass a vast geographical region that extends from south of Iran in the east to Morocco in the west including parts in the south-east of Asia Minor, East, and West Africa. However, the political definition of Arab populations is more conservative as it only includes those populations residing in 23 Arab States, 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, and Yemen.

Throughout history, Arab emigrants formed many Diasporas in other continents of the world. The main countries of emigration are: Algeria, Egypt, Iraq, Jordan, Lebanon, Mauritania, Morocco, Palestine, Sudan, Syria, Tunisia, and Yemen. Within the Arab World, the main countries of immigration are countries of the Gulf Cooperation Council, which host more than 2 million Arabs. In the year 2007, the United Nations High Commissioner on Refugees estimated that over 2.2 million Iraqis had been displaced to neighboring countries, with up to 100,000 Iraqis fleeing to Syria and Jordan each month.

Outside the Arab World, the largest Arab communities live in Latin America with an estimated presence of more than 16 million people of Arab descent. Brazil has over 12 million Brazilians of Arab ancestry mainly from Lebanon, Syria, and Palestine. Of these, over 9 million are of Lebanese ancestry, which makes Brazil's Lebanese population two times greater than that of Lebanon itself. There are also large Arab communities in Argentina (400,000 of Lebanese descent), Mexico (400,000 of Lebanese descent), Chile (300,000 of Palestinian descent), Honduras (200,000 of Palestinian descent), El Salvador (150,000 of Palestinian descent), Colombia, Dominican Republic, Ecuador, Haiti, Jamaica, Trinidad and Tobago, and Venezuela (Salloum, 2000; Luxner, 2001).

On the other hand, Arabs in North America and Europe total some 14 million people, many of whom are

Table 1.1. Genetic disorders in world populations and ethnicities according to the OMIM database (August 2008).

Population	OMIM Search Term	Genetic Disorders	Population Size
Japanese	Japan*	592	127,288,419
German	German*	347	82,369,548
Turkish	Turkey OR Turkish	270	71,892,807
Chinese	China OR Chinese	248	1,330,044,605
Asian Indian	India* NOT "American Indian"	229	1,147,995,898
Arab	Arab OR Arabian	203	351,905,774
Jewish	Jewish	200	13,089,800
Pakistani	Pakistan*	179	167,762,040
Brazilian	Brazil*	167	191,908,598
Mexican	Mexic*	138	109,955,400
Iranian	Iran*	89	65,875,223
Bedouin	Bedouin	58	-
Egyptian	Egypt*	43	81,713,517

well established. In North America, Arabs arrived in several waves of immigrations from countries of south-western Asia and North Africa since the 1880s. In the United States, there are around 3.7 million people of Arab ancestry mostly from Lebanon, Syria, or Palestine. In Canada, Arabs mainly come from Lebanon (400,000), Morocco, Algeria, Egypt, Syria, and Palestine. In Europe, the history of Arab immigrations started as early as 1898 with the arrivals of the Somali and Yemeni communities in the United Kingdom. However, the European country with the largest number of Arab immigrants is France, with nearly 7 million Arabs, mostly from North Africa and Lebanon. An estimate of 1,000,000 Arabs live in the United Kingdom representing 1.7% of the country's population. The vast majority of these originate from Iraq (250,000) and Egypt (some 150,000). The number of Arab immigrants in Germany is between 280,000-350,000, Belgium hosts nearly 150,000, and in Sweden there are about 80,000 Iraqis forming the country's second largest immigrant group. Other European countries with significant communities of Arab descent include: Belarus, Bulgaria, Denmark, Italy, the Netherlands, Romania, Spain, and Turkey (reviewed in Tadmouri, 2004).

In Southeast Asia, most of the prominent Indonesians, Malaysians and Singaporeans of Arab descent have their origins in the southern part of the Arabian Peninsula, especially the coastal Hadhramaut region of Yemen and Oman. Estimates indicate that as many as 4 million Hadramis live in Indonesia and 10,000 are in Singapore (Talib, 1997).

In Australia, Arabic is the fourth most widely spoken second-language due to the presence of a considerable Arab community with roughly 400,000 people from Arab countries (mostly Lebanese; Price, 1999). Some estimates place the number of Australians of Arab origin at almost 1 million, more than 500,000 of which are of Lebanese descent.

In Africa most of the Arab immigrants reside in the Ivory Coast (home to over 300,000 Lebanese and Syrians), Senegal (roughly 20,000 Lebanese), Sierra Leone (roughly 6,000 Lebanese), Liberia, and Nigeria (Robert, 1988).

Demographic and Medico-Economic Characteristics of Arab Populations

Arabs are a large and heterogeneous group that resulted from the admixture with many other populations throughout history. Current estimates indicate that the total population size in Arab countries is approximately 350 million. Although Arabs may share a commonality of language, history and religion, their societies are at variance when it comes to demographic and medico-economic characteristics. Some of the aspects that markedly affect the prevalence and natural history of genetic diseases in the Arab World include:

1. High fertility rates (1.7-6.6 children born/woman) compared to the world average (2.6 children born/woman).
2. High birth rates (15.5-44.1 births/1,000 people) compared to the world average (20.0 births/1,000 people).

3. Annual population growth rates of 1.0-3.8% leading to growing stress on educational, health, and social systems.
4. Extremely high rates of birth defects occurring at prevalence rates of 63-82/1000 live births (Christianson *et al*., 2006; Figure 1.1), possibly accounting for some of the high infant mortality rates (2.1-19.2 deaths/1,000 people) compared to the world average (8.3 deaths/1,000 people).
5. High rates of inbreeding or consanguineous marriages.
6. Large family sizes (2-7 children born/woman) making patriarchal relations in the family as the basic economic and social unit in many Arab communities.
7. Child bearing at either very early or old maternal ages.
8. The presence of isolates (e.g., Armenians, Bedouins, Druzes, Jews, Kurds, Nubians, and others) who share characteristic gene pools due to recurrent inbreeding.
9. The great variability of wealth among Arab States; in Qatar, for example, GDP per capita is the highest in the world at US$ 80,900 and is strikingly contrasting with a GDP per capita of only US$ 600 in Somalia (Table 1.2).
10. The lack of public health measures directed toward control and prevention of congenital and genetically determined disorders.

Health Care in the Arab World

Despite the demographic characteristics, unprecedented achievements have been especially prominent in the health care sector during the last few decades in almost all Arab countries. Improvements have been reflected in the reducing rates of infant mortality (per 1000 live births), mostly below the global average of 42.6 (Table 1.2). Other positive indicators include the increasing rate of literacy far beyond the global level of 82% of total populations and the increase in life expectancies beyond the global level of 66.1 years. In many Arab countries life expectancies are calculated to be higher than 70 years, reaching up to 78.7 years as in Jordan (Table 1.2).

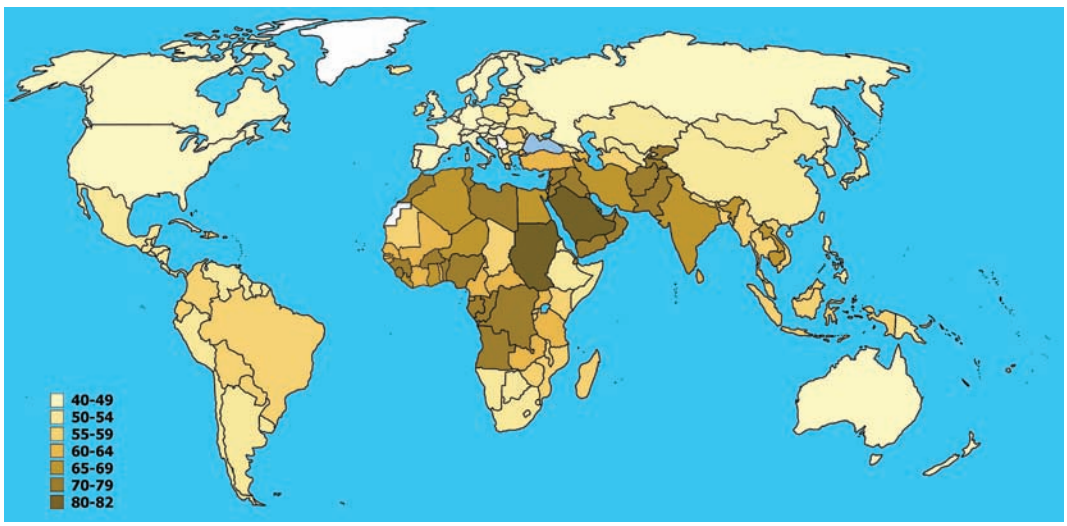


Figure 1.1. Global birth defects prevalence per 1,000 live births (adapted from Christianson *et al*., 2006).

Table 1.2. Selected demographic and health care indicators for Arab States in (a) Asia and (b) Africa. Data are for year 2008 unless otherwise indicated (WHO, 2008). Blue boxes indicate favorable values while red boxes indicate unfavorable values.

(a)

Indicators	Bahrain	Iraq	Jordan	Kuwait	Lebanon	Oman	Palestine	Qatar	Saudi Arabia	Syria	UAE	Yemen
Demography												
Area (square kilometers)	665	437,072	92,300	17,820	10,452	212,460	6,220	11,437	2,149,690	185,180	83,600	527,970
Population	718,306	28,221,181	6,198,677	2,596,799	3,971,941	3,311,640	4,149,173	928,635	28,161,417	19,747,586	4,621,399	23,013,376
Urban population (% of total)	97 (2006)	67 (2006)	83 (2006)	98 (2006)	87 (2006)	71 (2006)	58 (2004)	96 (2006)	81 (2006)	51 (2006)	77 (2006)	28 (2006)
Population median age (years)	29.9	20.2	23.9	26.1	28.8	18.9	17.8	32.1	21.5	21.4	30.1	16.7
Birth rate (per 1000 population)	17.3	30.8	20.1	21.9	17.6	35.3	33.3	**15.6**	28.8	26.6	16.1	**42.4**
Death rate (per 1000 population)	4.3	5.1	2.7	2.4	6.1	3.7	3.7	4.9	2.5	4.7	**2.1**	**7.8**
Population growth rate (%)	1.3	2.6	2.3	3.6	**1.2**	3.2	3.2	2.3	1.9	2.2	**3.8**	3.5
Fertility rate (total)	2.5	4.0	2.5	2.8	**1.9**	5.6	4.6	2.7	3.9	3.2	2.4	**6.4**
Socioeconomy and Health Expenditure												
Adult (15+ years) literacy rate, total (%)	86.5 (2005)	74.1 (2000)	91.1 (2005)	**93.3 (2005)**	87.4 (2003)	81.4 (2003)	92.4 (2004)	89.0 (2004)	82.9 (2004)	79.6 (2004)	88.7 (2004)	**54.1 (2004)**
Per capita GDP (US$)	32,100 (2007)	3,600 (2007)	4,900 (2007)	39,300 (2007)	11,300 (2007)	24,000 (2007)	**1,100 (2006)**	**80,900 (2007)**	23,200 (2007)	4,500 (2007)	37,300 (2007)	2,300 (2007)
Expenditure on health as % of GDP (total)	4.1 (2003)	2.7 (2003)	9.4 (2003)	3.5 (2003)	8.7 (2005)	3.2 (2003)	**13.5 (2003)**	2.7 (2003)	4.0 (2003)	5.1 (2003)	**2.6 (2005)**	5.5 (2003)
Ministry of health budget (% of government budget)	7.0 (2005)	4.7 (2005)	5.7 (2005)	6.3 (2004)	**3.6 (2005)**	4.7 (2005)	-	7.0 (2003)	6.0 (2004)	3.7 (2004)	**7.7 (2001)**	5.2 (2003)
Human and Physical Resources												
Physicians (per 10000 population)	**27.2 (2005)**	6.6 (2005)	23.6 (2005)	18.0 (2005)	23.6 (2005)	16.7 (2005)	9.7 (2004)	26.4 (2005)	19.0 (2004)	14.4 (2004)	16.9 (2002)	**2.2 (2004)**
Dentists (per 10000 population)	4.1 (2005)	1.2 (2005)	7.6 (2005)	3.0 (2005)	**8.8 (2004)**	1.8 (2005)	**0.9 (2004)**	8.5 (2005)	2.1 (2004)	8.5 (2004)	2.9 (2002)	1.0 (2004)
Pharmacists (per 10000 population)	5.7 (2004)	1.1 (2005)	12.9 (2005)	5.0 (2005)	8.1 (2004)	3.0 (2005)	1.4 (2004)	**13.5 (2005)**	3.4 (2004)	7.1 (2004)	4.1 (2002)	**1.0 (2004)**
Hospital beds (per 10000 population)	27 (2006)	13 (2005)	19 (2006)	19 (2005)	**36 (2005)**	21 (2006)	13.3 (2004)	25 (2006)	23 (2005)	14 (2006)	18 (2005)	**7 (2006)**
Coverage with Primary Health Care Services												
Population with access to local health services (%)	**100 (2005)**	97 (2005)	99 (2004)	**100 (2005)**	98 (2000)	97 (2002)	**100 (2004)**	**100 (2005)**		95 (2004)	**100 (2002)**	**50 (2003)**
Antenatal care coverage (%)	**100 (2005)**	**45 (2005)**	99 (2004)	**100 (2005)**	76 (2004)	99 (2005)	94 (2004)	**100 (2005)**	96 (2004)	71 (2004)	**100 (2003)**	50 (2003)
Births attended by skilled health personnel (%)	99 (2005)	89 (2006)	**100 (2002)**	**100 (2006)**	98 (2004)	98 (2006)	97 (2004)	**100 (2006)**	96 (2004)	93 (2006)	**100 (2005)**	**28 (2003)**
Health Status												
Life expectancy at birth (total years)	74.9	69.6	**78.7**	77.5	73.4	73.9	73.2	74.4	76.1	70.9	75.9	**62.9**
Infant mortality rate (per 1000 live births)	15.6	45.4	15.6	**9.2**	22.6	17.4	19.4	16.9	12.0	26.8	13.1	**56.3**
Maternal mortality ratio (per 10000 live births)	3.2 (2005)	30.0 (2005)	6.2 (2005)	**0.4 (2005)**	15.0 (2005)	6.4 (2005)	11.0 (2004)	1.2 (2005)	1.8 (2005)	13.0 (2005)	3.7 (2005)	**43.0 (2005)**

(b)

Indicators	Algeria	Comoros	Djibouti	Egypt	Eritrea	Libya	Mauritania	Morocco	Somalia	Sudan	Tunisia
Demography											
Area (square kilometers)	2,381,740	2,170	23,000	1,001,450	121,320	1,759,540	1,030,700	446,550	637,657	2,505,810	163,610
Population	33,769,669	731,775	506,221	81,713,517	5,502,026	6,173,579	3,364,940	34,343,219	9,558,666	40,218,455	10,383,577
Urban population (% of total)	64 (2006)	38 (2006)	87 (2006)	43 (2006)	20 (2006)	85 (2006)	41 (2006)	59 (2006)	36 (2006)	42 (2006)	66 (2006)
Population median age (years)	26	18.7	18.2	24.5	18.1	23.6	17.2	24.7	17.5	18.9	28.8
Birth rate (per 1000 population)	17.0	35.8	38.6	22.1	33.6	25.6	40.1	21.3	**44.1**	34.3	**15.5**
Death rate (per 1000 population)	4.6	7.8	**19.2**	5.1	9.2	**3.5**	11.6	5.5	15.9	13.6	5.2
Population growth rate (%)	1.2	2.8	1.9	1.7	2.4	2.2	**2.9**	1.5	2.8	2.12	**1.0**
Fertility rate (total)	1.8	4.9	5.1	2.7	4.8	3.2	5.7	2.6	**6.6**	4.6	**1.7**
Socioeconomy and Health Expenditure											
Adult (15+ years) literacy rate, total (%)	69.9 (2002)	56.5 (2003)	67.9 (2003)	71.4 (2005)	58.6 (2003)	**84.2 (2004)**	51.2 (2000)	52.3 (2004)	**37.8 (2001)**	61.1 (2003)	74.3 (2004)
Per capita GDP (US$)	6,500 (2007)	1,100 (2007)	2,300 (2007)	5,500 (2007)	800 (2007)	**12,300 (2007)**	2,000 (2007)	4,100 (2007)	**600 (2007)**	2,200 (2007)	7,500 (2007)
Expenditure on health as % of GDP (total)	-	-	5.7 (2003)	**5.8 (2003)**	-	4.1 (2003)	-	5.1 (2003)	**3.1 (2001)**	4.3 (2003)	5.4 (2003)
Ministry of health budget (% of government budget)	-	-	7.2 (2003)	3.4 (2004)	-	-	-	5.4 (2004)	-	**2.4 (2004)**	**7.6 (2005)**
Human and Physical Resources											
Physicians (per 10000 population)	11.0 (2002)	2.0 (2004)	1.8 (2005)	**24.3 (2005)**	**<1.0 (2004)**	12.5 (2004)	1.0 (2004)	5.6 (2004)	**<1.0 (1997)**	5.5 (2004)	13.0 (2004)
Dentists (per 10000 population)	3.0 (2002)	<1.0 (2004)	0.7 (2005)	**3.4 (2005)**	<1.0 (2004)	1.5 (2004)	<1.0 (2004)	1.1 (2004)	<1.0 (1997)	**0.8 (2006)**	1.9 (2004)
Pharmacists (per 10000 population)	2.0 (2002)	<1.0 (2004)	3.3 (2004)	**12.5 (2005)**	<1.0 (2004)	2.0 (2004)	<1.0 (2004)	2.3 (2004)	<1.0 (1997)	**0.2 (2004)**	2.1 (2004)
Hospital beds (per 10000 population)	17 (2004)	17 (2006)	16 (2000)	22 (2005)	12 (2006)	**37 (2006)**	**4 (2006)**	9 (2004)	-	7 (2006)	19 (2006)
Coverage with Primary Health Care Services											
Population with access to local health services (%)	-	-	80 (2002)	**100 (2005)**	-	**100 (2004)**	-	85 (2002)	72 (2003)	**66 (2000)**	95 (2005)
Antenatal care coverage (%)	41 (2002)	52 (1996)	67 (2003)	70 (2005)	41 (2002)	**96 (2003)**	**16 (2001)**	68 (2004)	47 (2002)	72 (2000)	92 (2004)
Births attended by skilled health personnel (%)	95 (2006)	62 (2000)	93 (2006)	74 (2005)	**28 (2002)**	**100 (2006)**	53 (2001)	63 (2004)	33 (2006)	49 (2006)	90 (2000)
Health Status											
Life expectancy at birth (total years)	73.8	63.1	**43.3**	71.8	60.0	**77.1**	53.9	71.5	49.2	50.3	75.6
Infant mortality rate (per 1000 live births)	28.8	68.6	99.1	28.4	44.2	**21.9**	66.6	38.2	**111.0**	87.0	23.4
Maternal mortality ratio (per 10000 live births)	18.0 (2005)	40.0 (2005)	65.0 (2005)	13.0 (2005)	45.0 (2005)	**9.7 (2005)**	82.0 (2005)	24.0 (2005)	**140.0 (2005)**	45.0 (2005)	10.0 (2005)

However, these improvements will solidify once attention is focused on basic health problems, as well as on underlying factors such as poverty and illiteracy. As matters currently stand, many factors combine to undermine commitment to such priorities including rapid population growth and urban expansion, spiraling health and medical costs, fascination with high-tech medicine and sophisticated high-profile hospitals, and inappropriate medical education and emigration of trained personnel (Stephen, 1992).

Medical education in the Arab World is not immune either. In the cases of many governmental institutes of higher education, students are fettered by examination-oriented courses that are pattern-bound and overcrowded. In such systems, students fail to acquire professional skills, self-learning ability, and correct ethical attitudes. They are also expected to lose competitiveness in a future world of physicians working in settings requiring coordination of clinical data, utilization of consultants and physician extenders, literature retrieval and health care delivery (Al-Hussaini, 1999; Al-Hussaini, 2001). At the bright side, however, stand many deep-rooted medical education institutes that, perhaps, are equivalent to those of the developed countries (Akl *et al*., 2007). Many of these institutes are active hubs for biomedical research (Tadmouri and Tadmouri, 2002; Bissar-Tadmouri and Tadmouri, 2008) and several have received recognitions such as the prestigious Sheikh Hamdan Award for Medical Sciences. More recently, a large number of modern medical schools, designed on the western style and supported by state-of-the-art hospitals, provide high quality training for thousands of Arab students each year (Khalid, 2008). Many of these emerging universities and medical schools are better placed than traditional ones because of the implementation of problem-based and informatics-oriented curricula since starting from scratch (Hamdy and Anderson, 2006).

Consanguinity in Arab People

Consanguineous marriage is a term used to describe unions contracted between biologically-related individuals as second cousins or closer. In population genetics, consanguinity may also refer to unions of individuals with at least one common ancestor such as those occurring within population isolates, small towns, and tribes. Consanguineous marriages have been practiced since the early existence of modern humans.

Consanguinity rates vary from one population to another depending on religion, culture, and geography. The practice of consanguineous marriage declined substantially in industrialized countries. In Sweden, for example, a study of 14,639 marriages that took place during 1720-1899 indicated a consanguinity rate of 20.8% with a significant preference for cousin marriages (Bittles and Egerbladh, 2005). In the 1950s, the rate of consanguineous marriages in Sweden decreased to almost 0.6% (Table 1.3). In Japan, a substantial decrease in consanguineous marriage occurred between 1947 and 1972 from 13% in urban and 21% in rural areas to 2.9% in urban and 4.3% in rural areas, respectively (Saito, 1988). Similar observations could also be seen in the United States and in many European

countries. However, consanguinity rates are increasing in the Indian sub-continent, Asia, and Africa (Table 1.3; Figure 1.2; Figure 1.3).

Sociocultural factors play a crucial role in the variation of consanguinity in Arab populations. Unlike what is widely thought, consanguinity in the Arab World is not only confined to Muslim communities. Several other communities, including the Lebanese and Palestinian Christian populations, do also practice consanguinity (Khlat, 1988; Vardi-Saliternik *et al*., 2002). In Islam, the Holy Quran contains no specific guidance that could be interpreted as encouraging consanguinity. On the opposite, the Quran includes indications that encourage human dispersal: "*O mankind! We created you from a single (pair) of a male and a female, and made you into nations and tribes, that ye may know each other*" (AlHujurat 049.013), and the appreciation of human variation: "*And among His Signs is the creation of the heavens*

Table 1.3. Consanguinity rates in some World populations.

Continent	Country	Consanguinity (%)	Reference
Africa	South Africa	0.4-6.1	Stevenson *et al*., 1966
America	Argentina	0.6	Castilla *et al*., 1991
	Bolivia	0.6	Freire-Maia, 1968
	Brazil	4.8	Freire-Maia, 1957
	Canada	1.5	Freire-Maia, 1968
	Chile	1.3	Freire-Maia, 1968
	Columbia	3	Freire-Maia, 1968
	Ecuador	6.3	Freire-Maia, 1968
	Mexico	1.3	Freire-Maia, 1968
	Panama	1.7	Stevenson *et al*., 1966
	Peru	4.1	Freire-Maia, 1968
	Uruguay	4.5	Freire-Maia, 1968
	USA	0.2	Freire-Maia, 1968
Asia	Afghanistan	55.4	Wahab *et al*., 2006
	China	1.8	Stevenson *et al*., 1966
	India	22	Hussain and Bittles, 2000
	Iran	38.6	Saadat *et al*., 2004
	Japan	3.9	Imaizumi, 1986
	Malaysia	7.6	Stevenson *et al*., 1966
	Pakistan	61.2	Ahmed *et al*., 1992
	Philippines	0.4	Stevenson *et al*., 1966
	Singapore	5	Stevenson *et al*., 1966
	Turkey	22	Koc, 2008
Europe	Belgium	1	Twiesselmann *et al*., 1962
	Croatia	0.1	Stevenson *et al*., 1966
	Czechoslovakia	0.2	Stevenson *et al*., 1966
	France	0.8	Sutter and Goux, 1964
	Hungary	0.1	Czeizel *et al*., 1976
	Ireland	0.5	Masterson, 1970
	Italy	0.5	Fraccaro, 1957
	Netherlands	0.2	Freire-Maia, 1982
	Norway	0.7	Magnus *et al*., 1985
	Portugal	1.5	Freire-Maia, 1982
	Slovenia	0.6	Stevenson *et al*., 1966
	Spain	1.1	Stevenson *et al*., 1966
	Sweden	0.6	Romanus, 1953

and the earth, and the variations in your languages and your colours: verily in that are Signs for those who know." (AlRum 030.022).

In Arab populations, consanguinity rates are changing in either way (Table 1.4; Figure 1.4). In Jordan, first-cousin marriage rate showed a significant decline among marriages contracted after 1980 compared to marriages contracted between 1950 and 1979 (Hamamy *et al.*, 2005). In Lebanon, consanguinity rates significantly decreased from 30% before 1950, to 25% in 1950-1969, to about 20% since 1970 (Khlat, 1988). In the Occupied Territories, the frequency of consanguineous marriage was highest in the period 1961-1965 (50.6%), decreased in couples married in 1980-1985 (33.1-40.6%), and further decreased to 25.9% in couples married in 2000-2004 (Jaber *et al.*, 2000; Sharkia *et al.*, 2008). Similar decreasing trends of consanguineous

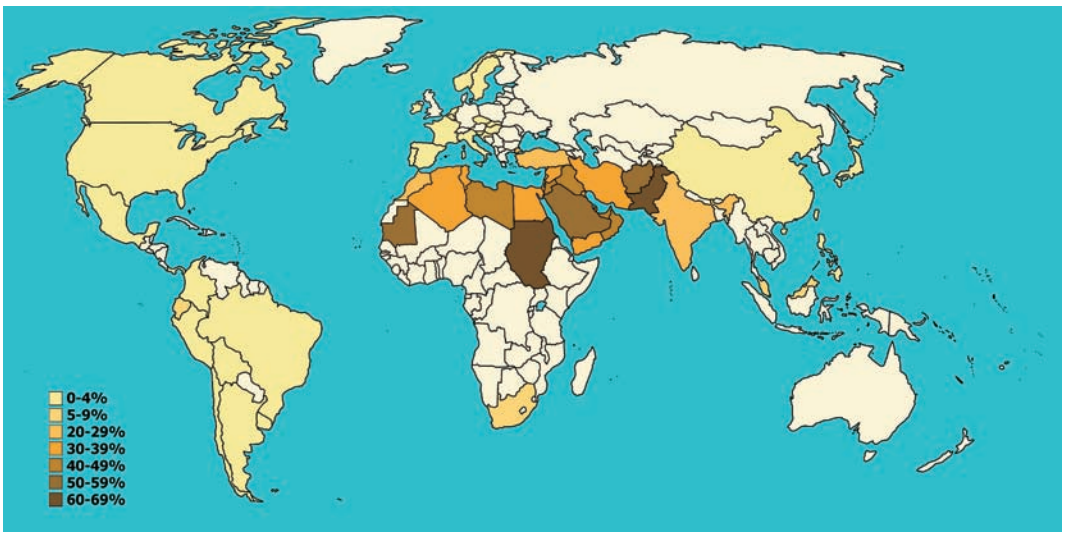


Figure 1.2. Schematic representation of consanguineous marriage rates worldwide (adapted from Tables 1.3 and 1.4).

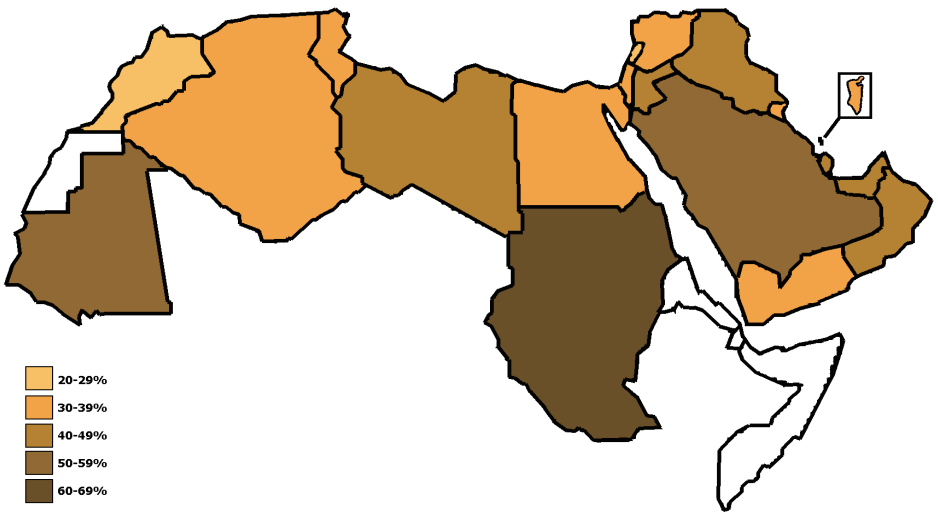


Figure 1.3. Schematic representation of consanguineous marriage rates in Arab populations (adapted from Table 1.4).

marriages have been also recorded in Egypt, Kuwait, Libya, and Tunisia (Figure 1.4). Additionally, detailed analysis of data from Bahrain indicates a relative decrease in consanguinity rate between past (45.5%) and present (39.4%) generations (Al Arrayed, 1995). Also, an extensive analysis in Iraq indicates a decrease of consanguinity rate from 46.4% in 1986 (Al-Hamamy *et al*., 1986) to 33% almost one generation later (COSIT, 2005).

On the contrary, an increasing consanguinity rate has been recorded in Morocco among the previous (21.5%) and present (25.4%) generations (Talbi *et al*., 2007). Consanguinity rate seems to be increasing at a higher pace in Qatar since it increased from 41.8% to 54.5% within the same generation (Bener *et al*., 2004; Bener and AlAli, 2006). Similarly, consanguinity rates also increased over the last generation in Algeria, Oman, Sudan, Syria, the United Arab Emirates, and Yemen (Table 1.4). Some of the plausible reasons behind the rising trend in consanguinity include urban-rural residence ratios of families, education levels, and the increase in the availability of cousins due to high fertility (Jurdi and Saxena, 2003).

In between these two extremes, the incidence of consanguinity in Saudi Arabia has not changed significantly, even among the younger generation, and fluctuates between 43.4% (Al-Abdulkareem and Ballal, 1998) and 57.7% (El-Hazmi *et al*., 1995). Consanguinity data seem not to be available in the Arab Eastern African countries of Djibouti, Eritrea, and Somalia.

Consanguinity, the Arab Family Structure, and Reproductive Health

Recently, many studies from the region have drawn strong correlations between consanguinity and the frequency of hemoglobinopathies (Rajab and Patton, 1997), hydrocephalus (Rajab *et al*., 1998), kidney diseases (Barbari *et al*., 2003), congenital heart defects (Nabulsi *et al*., 2003; Yunis *et al*., 2006), hearing loss (Al Khabori, 2004; Ben Arab *et al*., 2004; Bener *et al*., 2005), death rates in children (Hamami *et al*., 2005), respiratory allergies, eczema (Bener and Janahi, 2005), non-chromosomal multisystem malformations (Dawodu *et al*., 2005), mental retardation, epilepsy, diabetes (Bener and Hussain, 2006), and many others (Tadmouri, 2004; Tadmouri, 2006a). Consanguineous pregnancies are more likely to result in miscarriage and fetal wastage (Al-Awadi *et al*., 1986; Hamamy and Al-Hakkak, 1989; Khoury and Massad, 2000; Saad and Jauniaux, 2002).

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 difference in the vertical dissemination of a recessive genetic mutation between Arab and Western families. In the typical Western family, carriers of mutations usually become scattered through the general population due to marriages contracted outside the family. After a few generations, the genetic relationship of these family members become unrecognizable due to elevated gene flow mechanisms.

Table 1.4. Consanguinity rates in Arab populations.

Country	Location	Collection Period	Sample Size	Consanguinity (%)	Reference
Algeria		1979	120,491	22.6	Benallegue and Kedji, 1984
		1988	239	16.7-27	Grassivaro Gallo and Florio, 1993
		1992?		40	ENAF, 1992
		1994?		36.4	ANSO, 1994
	Tlemcen	2002?	3,983	34	Zaoui and Biémont, 2002
Bahrain		1983	141	10.6	El-Shafei *et al*., 1986
		1989	10,070	45.5	Al-Naser, 1994
		1989	500	31.8	Al Arrayed, 1994
		1995?		32	Ministry of Health [Bahrain], 1995
	Previous generation	1995	100	45.5	Al Arrayed, 1995
	Present generation	1995	500	39.4	Al Arrayed, 1995
		1999		39	Al-Arrayed, 1999
Egypt	Alexandria	1961-1964	9,475	32.8	Stevenson *et al*., 1966
	Nubia	1965-1967	281	60.5	Hussien, 1971
	Nubia	1967-1968	1,782	63.6	Badr, 1972
		1970s	505	23.2	Habib and Böök, 1983
		1983?	26,554	29	Hafez *et al*., 1983
		1989		41	ENPC, 1989
	Alexandria	1995?	500	22.8	Mohamed, 1995
		1996?		39	ENPC, 1996
Iraq	Kurds	1951	61	32.8	Barth, 1954
	Baghdad	1986?	4,491	46.4	Al-Hamamy *et al*., 1986
	Baghdad	1989?	382	53.4	Hamamy and Al-Hakkak, 1989
		2004	23,937	33	COSIT, 2005
Jordan	Irbid	1963-1964	1,097	52.1	Cook and Hanslip, 1966
		1969-1979	1,989	39.7	Khoury and Massad, 1992
	Balqa	1986	340	40.3	Nabulsi, 1995
	Irbid	1993?	900	63.7	Al-Salem and Rawashdeh, 1993
	South Ghor	2003?	608	58.1	Sueyoshi and Ohtsuka, 2003
	Amman	2004	2,594	25.6	Hamamy *et al*., 2005
Kuwait		1967-1968	2,220	53.9	El-Alfi *et al*., 1968
		1969?	2,133	38.4	El-Alfi *et al*., 1969
		1983	5,007	34.3	Al-Awadi *et al*., 1985
		1989?		54	Al-Nasser *et al*., 1989
		1996?		36	Ministry of Health [Kuwait], 1996
	Kuwait-Jahra	1999?	482	22.6-42.1	Radovanovic *et al*., 1999
Lebanon	Beirut	1981-1982	750	26	Klat and Khudr, 1986
	Beirut	1983-1984	2,854	25	Khlat, 1988a
	Beirut	1983-1984	3,033	25	Khlat, 1988b
		1998?		21	Ministry of Public Health [Lebanon], 1998
Libya	Benghazi	1981?	<500	48.4	Broadhead and Sehgal, 1981
		1996?		46.5	GPCHSI, 1996
Mauritania		1990-1991		60.1	National Statistical Office [Mauritania], 1992
		2005?	2,413	47.2	Hammami *et al*., 2005
Morocco	High-Atlas Valleys	1904-1985		23.1	Baali, 1994
		1940	582	21.5	Talbi *et al*., 2007
		1984	291	25.4	Talbi *et al*., 2007
		1982-1992	4,773	19.9	Lamdouar Bouazzaoui, 1994
		1987?		29?	Azelmat *et al*., 1987
		1992?		33?	Azelmat, 1992
	High-Atlas Valleys	2005?	438	28	Cherkaoui *et al*., 2005
Oman		1994-1997	60,895	35.9	Rajab and Patton, 2000
		1996		54	Ministry of Health [Oman], 1996

Country	Location	Collection Period	Sample Size	Consanguinity (%)	Reference
Palestine		1977	3,203	34.2	Bashi, 1977
	Western Galilee	1976-1983	1,546	32.2	Gev *et al*., 1986
	Western Galilee	1984	550	39	Freundlich and Hino, 1984
		1980-1985		33.1	Sharkia *et al*., 2008
		1981-1985	3,328	26.6	Jaber *et al*., 2000
		1990-1992	1,525	34.4	Vardi-Saliternik *et al*., 2002
		1992	8,521	44.3	Jaber *et al*., 1994
	Gaza	1995	10,409	27.2	Pedersen, 2002
	West Bank	1995	5,778	31.6	Pedersen, 2002
	Jordan	1996	4,950	26.1	Pedersen, 2002
	Lebanon	1998	3,972	19.8	Pedersen, 2002
	Jordan	1999	2,888	26	Pedersen, 2002
	Lower Galilee	1970-2000	483	17.5	Zlotogora *et al*., 2002
	Syria	2001	4,195	18.3	Pedersen, 2002
		2000-2004		25.9	Sharkia *et al*., 2008
		2004	4,071	45	Assaf and Khawaja, 2008
Qatar		1999?		46	Ministry of Health [Qatar], 1999
		2004?		41.8	Bener *et al*., 2004
	Doha	2004	1,515	54	Bener and Alali, 2006
		2004-2005	876	51	Bener *et al*., 2007
Saudi Arabia		1980s	143	18.9	Chaleby and Tuma, 1987
	Riyadh	1979-1980	1,149	55	Serenius *et al*., 1988
	Riyadh	1983-1986	4,497	54.3	Saedi-Wong and Al-Frayh, 1989
	Riyadh	1989-1990	6,421	45.1	Zakzouk *et al*., 1993
	Riyadh	1993	2,001	51.3	Al Husain and Al Bunyan, 1997
		1995?	3,212	57.7	El-Hazmi *et al*., 1995
	Dammam	1998?	1,307	43.4	Al-Abdulkareem and Ballal, 1998
		2004-2005	11,554	56	El Mouzan *et al*., 2008
Sudan	Gezira	1969-1974	2,999	44.2	Ahmed, 1979
	Khartoum	1988?	4,833	52	Saha and El Sheikh, 1988
	Khartoum	1990?	926	63.3	Saha and Hamad, 1990
		1995?		65	FMHNCHS, 1995
Syria		1974?		33	Prothro and Diab, 1974
		1995?		38	Central Bureau of Statistics [Syria], 1995
Tunisia		1988		49	Aloui *et al*., 1988
	Northern Tunisia	1989?	5,767	26.9	Riou *et al*., 1989
	Monastir	1989-1990	1,741	24.8	Kerkeni *et al*., 2007
		1996?		40	Ministry of Public Health [Tunisia], 1996
	Monastir	2003-2004	1,016	20.1	Kerkeni *et al*., 2006
UAE		1993?		51	Fahmy *et al*., 1993
	Al Ain	1992-1994	16,419	54	Al-Gazali *et al*., 1995
	Al Ain	1994-1995	1,502	54.2	Al-Gazali *et al*., 1997
	Dubai	1994-1995	531	40	Al-Gazali *et al*., 1997
Yemen		1997	9,762	33.9	Jurdi and Saxena, 2003
	Sanaa	2000	1,050	44.7	Gunaid *et al*., 2004

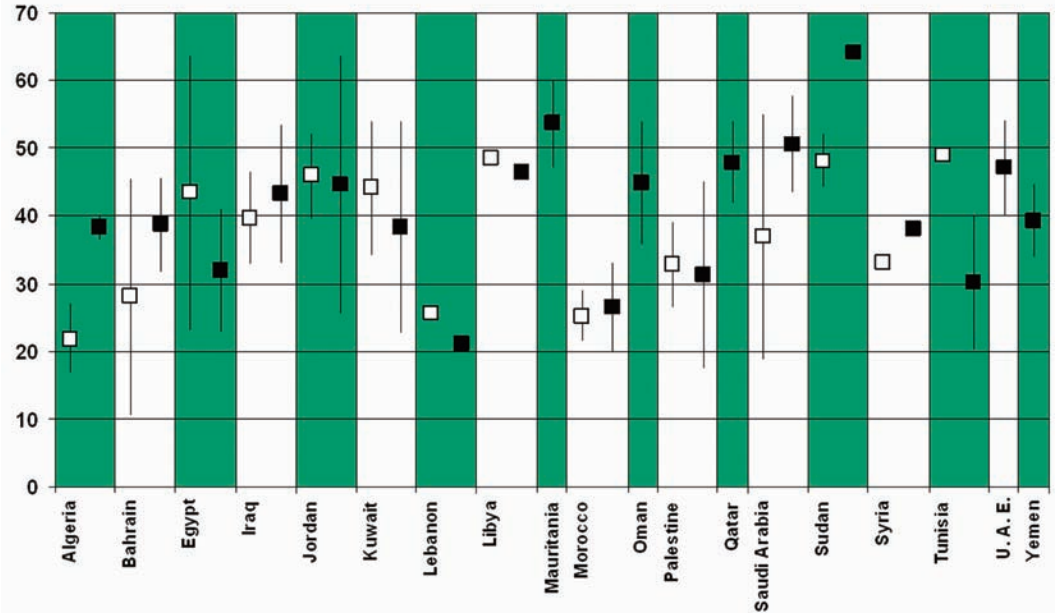


Figure 1.4. Past (white boxes) and present (black boxes) consanguineous marriage percent rates in Arab States (adapted from Table 1.4).

Therefore, a family history suggesting a genetic basis for their predisposition to recessive 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 due to decelerated human dispersal. This situation is further accentuated when consanguinity is practiced, which in population genetic concepts, leads to further slow down of gene flow and significant heterozygote deficiencies (Rajkumar and Kashyap, 2004; Cadenas *et al*., 2008).

Origin of the CTGA Database

Several attempts have been made to catalogue genetic disorders in certain Arab countries (Der Kaloustian *et al*., 1980; Hamamy and Alwan, 1994; Teebi and Farag, 1997). Yet, similar publications are rapidly outdated as new disorders are continuously described in Arabs. To overcome this problem, Tadmouri and Bissar-Tadmouri (1999) initiated an early attempt to maintain offline tabular lists of genetic disorders described in Arab individuals, with corresponding references, by monitoring international disease databases and scanning bibliographic indices. Using this strategy, 374 entries for genetic disorders in Arabs were recorded in 1999. This number increased to 752 entries early in 2004. In March 2004, the name 'Catalogue of Transmission Genetics in Arabs' (CTGA) Database was coined for any future online database that may materialize out of this survey (Tadmouri, 2004).

To this end, the Centre for Arab Genomic Studies (CAGS) adopted the proposal to launch a pilot project to

construct the CTGA Database with the aim of educating the medical community and raising public awareness in at-risk populations. Initially, major software components of the CTGA Database were constructed and tested separately. The database was then assembled and tested with limited amount of data prior to its public release on the 30th of November 2004 (Tadmouri *et al*., 2006a).

Methods of Data Collection for the CTGA Database

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 (Tadmouri *et al*., 2006a). Since the public release of the CTGA Database in 2004, our knowledge on the presence of genetic disorders in Arab populations is continuously expanding. This process is largely driven by the different methods used at the Centre for Arab Genomic Studies (CAGS) to collect data and information on genetic conditions in Arab patients. Most of the data included in the database come from the United Arab Emirates, Bahrain, and Oman following systematic reviews conducted in years 2004, 2006 and 2008, respectively, of all published literature on the occurrence of genetic disorders in UAE, Bahraini, and Omani nationals and Arab expatriates residing in these countries. However, data from other Arab countries are also included, though at a slower rate, mostly owing to submissions by scientists, practitioners, and researchers working in the region. It is anticipated that exhaustive systematic reviews will be conducted in other Arab countries using several alternatives methods of data collection.

Bibliographic Indices: Over the last 20 years, a steady increase in the rate of international biomedical publications has been recorded in almost all Arab countries (Tadmouri and Bissar-Tadmouri, 2003). Overall, scientists affiliated to Arab biomedical institutes produce about 2600 scientific articles annually according to the Medline bibliographic index (unpublished observations). A similar result could also be drawn from the Index Medicus of the Eastern Mediterranean Region (EMR), which is a bibliographic index of regional health and biomedical journals. The presence of these indices has facilitated the location of articles with observations on genetic disorders in Arab patients. In fact, international bibliographic indices, such as PubMed and Index Medicus of the EMR, form the source of the major bulk of information collected by the CTGA Database Development Team at the centre. They also allow almost instantaneous search for information on specific genetic disorders in certain Arab populations using a multitude of search strategies and syntaxes (Tadmouri *et al*., 2006b). However, careful sorting and screening of search results have to be made to avoid false-positive records especially in the cases of Lebanon and Palestine (due to the fact that many cities in the world carry the names of these two countries) as well as of Jordan (also a common family name in foreign societies), Sudan (confused with Sudan dye), and Syria (confused with Syrian hamster; Tadmouri and Bissar-Tadmouri, 2004; Tadmouri, 2006a; Tadmouri, 2006b).

Regional Peer-Reviewed Medical Publications: National peer-reviewed medical publications are also monitored at CAGS. Most of these journals, however, are partially indexed or digitized. Therefore, manual search is the only method to mine information from this source. Complete full search has been successfully implemented so far in the cases of the Emirates Medical Journal, the Bahrain Medical Bulletin, the Journal of the Bahrain Medical Society, and the Oman Medical Journal. With the availability of hundreds of national peer-reviewed medical journals, manual search is time consuming and requires the involvement of a considerable number of well-trained staff to accomplish the task of data collection and curation from these sources with significant local value.

The Arab Council of CAGS as a Source of Information: Through its Arab Council, the Centre for Arab Genomic Studies works with nuclear groups of leading scientists in Arab institutes to initiate local projects of data collection. At present, countries involved include: Egypt, Jordan, Kuwait, Lebanon, Qatar, Saudi Arabia, Sudan, and Tunisia.

The CTGA Database Information Submission Form: In order to allow a better chance for geneticists working on genetic disorders in Arab individuals to contribute to the growth of the CTGA Database, the CTGA Database Development Team made available the CTGA Database Information Submission Form (downloadable from *http://www.cags.org.ae/ctgadisf.html*) to speed up the process of data submission, review, and publication in the CTGA Database (Tadmouri *et al*., 2006b). The proper utilization of the CTGA Database Information Submission Form has contributed to the successful and rapid inclusion of many disease and gene records in the database straight from the pens of their corresponding authors, who are usually major authorities in their corresponding fields.

In summary, the CTGA Database Development Team continuously updates each and every record of the database following a rigorous protocol that has been optimized following previous surveys in the United Arab Emirates and Bahrain. The current protocol, used for collecting data from Oman (see 'Methods of Data Collection for the CTGA Database' in Chapter 2), involves seven defined steps that are mainly conducted in the headquarter of the Centre for Arab Genomic Studies (Figure 1.5) except for the collection of local publications and the detailed review of their content. These steps are conducted in the country subject to the survey using satellite research assistants with the collaboration of CAGS Arab Council Members at that country. By applying such a strategy, CTGA Database curators create about 30 entries and update an equivalent number each month with an average of 5-10 new publications reviewed per day.

Since the establishment of the CTGA Database in year 2004, a total of not less than 61,000 international and national articles were surveyed. From this, nearly 4,200 articles were investigated in detail during the surveys to collect data for the United Arab Emirates (2040 international and 306 national), Bahrain (494 international and 74 national), and

Oman (1173 international and 176 national). As a result, 2097 articles (1764 international and 333 national) appear in the CTGA Database as they contained informative details about the occurrence of genetic disorders in Arab people. These papers can be broadly classified into four types according to their content:

1. **Case reports**: These are short and concise reports of individual or a handful number of cases. These reports usually include detailed descriptions of the diagnosis, treatment, and follow-up of an individual patient. They also contain some demographic information about the patient including age, gender, and ethnic origin.
2. **Linkage studies**: These are original articles that usually report the results of genetic linkage studies in a small number of families. Emphasis in these studies is more towards the genetic pathology rather than the clinical phenotype of a genetic abnormality.
3. **Retrospective studies**: These include several subtypes. Some retrospective studies may be focused on a specific disorder or a group of genetic disorders. Others may describe all patient cases reported at a medical institution during a certain period of time. This latter group of studies usually results in a considerable amount of information regarding a large number of genetic disorders in certain populations with possibilities to obtain prevalence rates of these disorders in the corresponding population as well.
4. **Newborn screening studies**: These refer to publications resulting from nationwide screening programs

Figure 1.5. The optimized workflow for data collection and processing for the CTGA Database as implemented during the recent survey in the Sultanate of Oman.

involving large numbers of cases screened within a specified period of time. This type of articles is usually an important source of information on the prevalence rates of common genetic ailments in Arab populations.

5. **Review articles**: This is the least commonly targeted type of article while collecting data for the CTGA Database. In the overwhelming majority of cases, review papers do not include clinical data for genetic disorders or the details of individual patients. However, they are good starting points to seek further details regarding specific subjects.

Challenging Irregularities

The lack of information on the ethnic origin of Arab patients with genetic disorders continues to be a problem in many articles utilized to compile the CTGA Database. Although these inconsistencies occur in both national and international reports, they tend to occur more in the latter group. In this aspect, it is important to adapt a unified system of clinical or molecular reporting that includes vital data necessary for population geneticists and ethnic database curators.

Science in the Arab World is generally suffering from serious lack of funds. For this reason, science groups working in the highly demanding field of human genetics conduct very limited studies that mostly result in clinical reports rather than molecular analyses (Tadmouri and Bissar-Tadmouri, 2003). In fact, gene-related records constitute only 28% of the total number of records in the CTGA Database. Maghreb countries (Algeria, Tunisia, and Morocco) seem to be leading in terms of molecular genetic studies (Figure 1.6). However, careful investigation of corresponding research articles indicate the significant role of French science groups in diagnosing disorders in Algerian, Tunisian, or Moroccan patients living in France (Tadmouri and Bissar-Tadmouri, 1999). While, at present, this remark could be preliminary, solid results could be pronounced for countries in which exhaustive surveys have been conducted (United Arab Emirates: 13%, Bahrain: 11%, and Oman: 17%). In general, the majority of molecular studies included in the CTGA Database are the fruits of collaborations with international groups that usually cover the needed expenses and provide the sophisticated equipment (Selamnia and Tali-Maamar, 2003; Dakik *et al.*, 2006). Accordingly, large-scale data production of DNA or protein sequences, mutations, and single nucleotide polymorphisms (SNPs) is seriously lacking in the region and cannot be foreseen in the near future.

Self-plagiarism, which is the reuse of significant portions of one's own work without acknowledging the original work, is an observation that was first encountered by the CTGA Database Development Team while reviewing articles originating from Oman. Two such cases have been observed and they consisted of exactly identical multiple publications appearing in different journals almost with little difference in their dates of publications. Considering the total number of citations included in the CTGA Database at the time, this

results in a minute fraction that does not exceed 0.0009%. This number is far less than the frequency (0.4%) reported by the Deja vu database, a publicly available database of highly similar Medline citations (Errami *et al*., 2008). While duplicate publication is considered by some as useful in providing wider access to the scientific community, publications that simply reproduce a previous work with virtually identical results and conclusions often lack the novelty to justify additional publication. This type of duplicate publication is considered unethical because they undermine the public confidence in scientific integrity (Benos *et al*., 2005; Marcovitch, 2007).

The CTGA Database Growth

Overall, all methods of data collection adapted by the CTGA Database Development Team have resulted in a steady increase in the rate of total record numbers in the CTGA Database since it was released late in 2004. Three important soars mark the progress of data growth (Figure 1.7); these coincide with extensive efforts to thoroughly examine the genetic disorders observed in the Arab populations of the United Arab Emirates (2004), Bahrain (2006), and Oman (2008).

In order to cope with the growing numbers of records in the CTGA Database, major enhancements were introduced to its search engine to allow the users to perform elaborate queries and obtain focused results without sacrificing the simplicity. Further enhancements were also introduced to the core of the database to meet future expected demands and to allow additional ramifications in the database. Detailed explanations and examples of how to use the search modes at CTGA are available in a devoted guide available in electronic and hard copy formats (Tadmouri *et al*., 2006b).

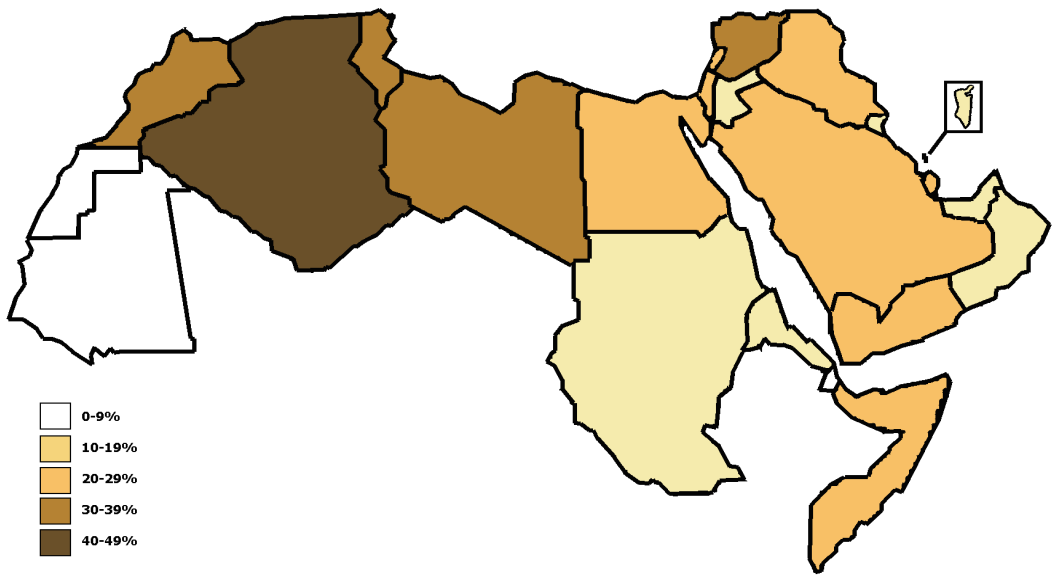


Figure 1.6. Schematic representation of the per cent gene-related records of the total number of CTGA Database records for each Arab country (August, 2008).

Genetic Disorders in Arab Populations

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 health care standards in many Arab countries decreased the impact of such disorders in favor of an increased understanding of the molecular basis of heredity, hence, the better recognition of genetically transmitted conditions as a major cause of morbidity and mortality (Tadmouri, 2006b). In accordance to this, the public release of the CTGA Database in 2004 helped in the proper collection of data and analysis of genetic conditions in Arab patients.

As of June 2008, the CTGA Database has recorded the presence of 897 phenotype/disease entries in Arab individuals (Appendix 1). However, data on only about 344 related genes are available in the CTGA Database reflecting the dominance of clinical observation over molecular analysis in most of the research conducted in the region (Appendix 2).

In the initial release of the CTGA Database in 2004, most of the records came from the Maghreb region (Tunisia, Morocco, and Algeria) as well as Lebanon and Saudi Arabia (Tadmouri, 2004). Along with the completion of data collection from the United Arab Emirates and Bahrain in 2006, this distribution has changed in favor of the United Arab Emirates, Palestine, Saudi Arabia, Lebanon, Tunisia, Bahrain, and Morocco (Tadmouri 2006b). At present, this distribution seems to shift in favor of Oman, United Arab Emirates, Saudi Arabia, Lebanon, Palestine, Tunisia, and Egypt (Figure 1.8). Factors that contributed to this change include the extensive surveys that the Centre for Arab Genomic Studies has conducted in the United Arab Emirates, Bahrain, and Oman. Additionally, during the

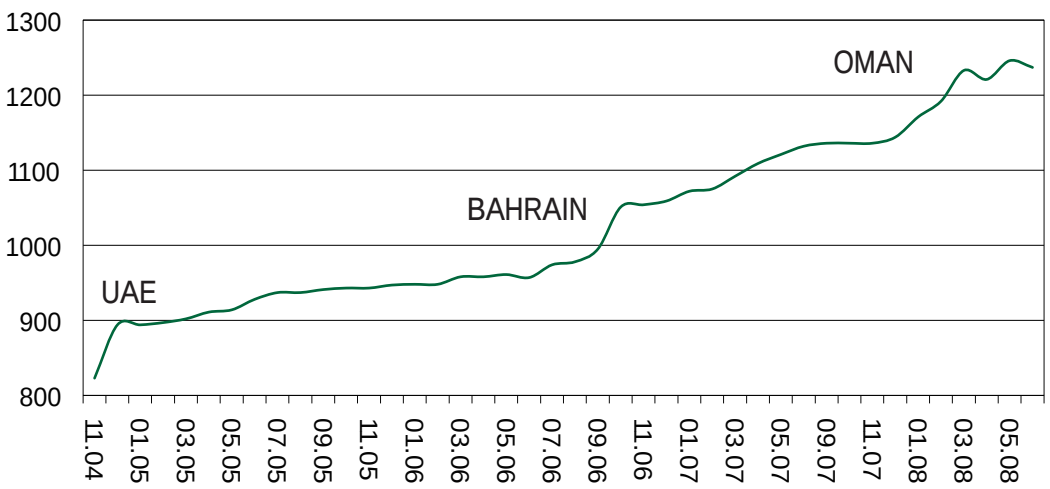


Figure 1.7. Total growth of CTGA Database records from December 2004 until June 2008.

review process, articles from Saudi Arabia, Lebanon, Palestine, Tunisia, and Egypt were either frequently encountered at international bibliographic indices or directly submitted by scholars from these countries. It is anticipated that in the coming five to ten years major surveys will be conducted in other Arab countries to accomplish a more realistic perception of the extent of genetic disorders in the Arab World.

Classification and Molecular Complexity of Genetic Disorders in Arabs

By employing the World Health Organization International Classification of Disease version 10 (WHO ICD-10), it is possible to categorize the distribution of genetic disorders in Arab people according to disease taxonomies. Nearly, one-third of genetic disorders in Arab individuals result from congenital malformations and chromosomal abnormalities (34.7%). They are then followed by endocrine and metabolic disorders (18.9%) and diseases of the nervous system (10.0%). Other types of disorders seem to occur at lower frequencies in the Arab population (Figure 1.9); this finding may be due to the lack of specific regional research or expertise in these entities (Tadmouri, 2006b; see also Chapters 2 and 3).

The overwhelming proportion of genetically transmitted diseases in Arab patients is inherited through autosomal recessive modes (approximately 63%). These are followed by autosomal dominant (27%) and X-linked traits (6%; Figure 1.10). High consanguinity rates and the extended family structure, commonly present in Arab

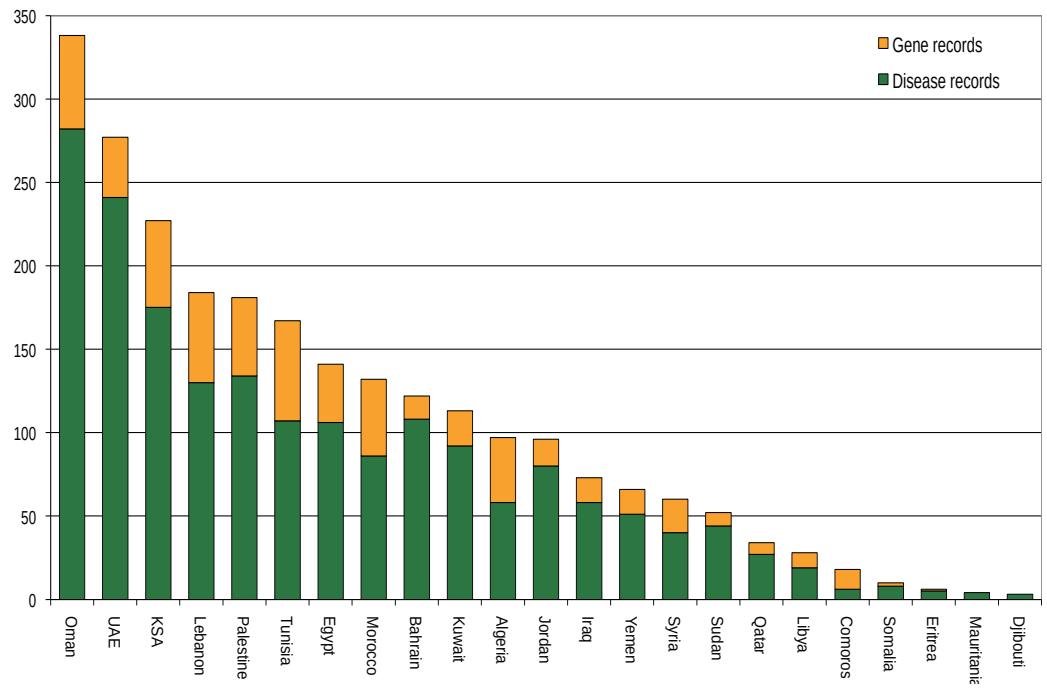


Figure 1.8. Disease and gene records in Arab countries according to the CTGA Database (June 2008).

societies, are likely explanations for these observations (Tadmouri, 2006b; see also 'Consanguinity as a Driving Force for Autosomal Recessive Disorders' in Chapter 5).

The Spectrum of Genetic Disorders in Arab Populations

A recent introduction to the CTGA Database is the possibility to classify genetic disorders according to their incidence rates in the Arab World. Noteworthy are two groups of disorders:

1. Genetic disorders that have reached epidemic values and occur at annual incidences (> 100 cases/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, hypercholesterolemia, orofacial cleft, pyloric stenosis, and others.
2. Many other disorders do occur in the Arab World at higher incidence rates when compared to world data, these include: Tetralogy of Fallot, familial Mediterranean fever, deafness, Noonan syndrome, Meckel syndrome, and spondyloarthropathy.

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.

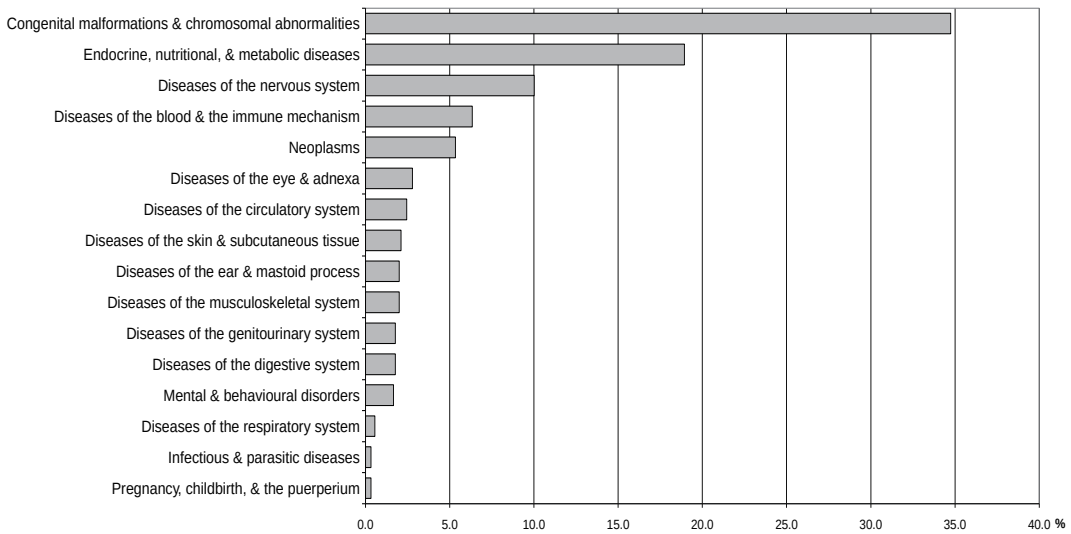


Figure 1.9. Classification of genetic disorders in Arabs according to the WHO ICD-10 (June 2008).

Other genetic disorders exhibit wide geographical distributions encompassing one or more neighboring regions, such as in the cases of the atypical hemolytic uremic syndrome (Figure 1.11a) and spondyloarthropathy (Figure 1.11b). 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 (Figure 1.11c), cystic fibrosis (Figure 1.11d), autosomal recessive polycystic kidney disease (Figure 1.11e), anencephaly (Figure 1.11f), Hirschsprung disease (Figure 1.11g), and others. On the other hand, many genetic diseases exhibit specific geographic distributions. Examples include: familial Mediterranean fever described in all Arab Mediterranean and some Gulf countries (Figure 1.11h), type 2C limb-girdle muscular dystrophy in North Africa (Figure 1.11i), susceptibility to diabetic nephropathy (Figure 1.11j), and Laurence-Moon syndrome in the Gulf region (Figure 1.11k).

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, such as: Fadhil syndrome (Fadhil *et al.*, 1983), Teebi type of hypertelorism (Teebi, 1987), Teebi-Shaltout syndrome (Teebi and Shaltout, 1989), Sanjad-Sakati syndrome (Sanjad *et al.*, 1991), Al-Gazali syndrome (Al Gazali *et al.*, 1994), Al Aqeel-Al Sewairi syndrome (Al Aqeel *et al.*, 2000), and Megarbane syndrome (Megarbane *et al.*, 2001). Also, some genetic disorders seem to be specific to Arab populations, such as: the Lebanese type of mannose 6-phosphate receptor recognition defect (Alexander *et al.*, 1984), the Algerian type of spondylometaphyseal dysplasia

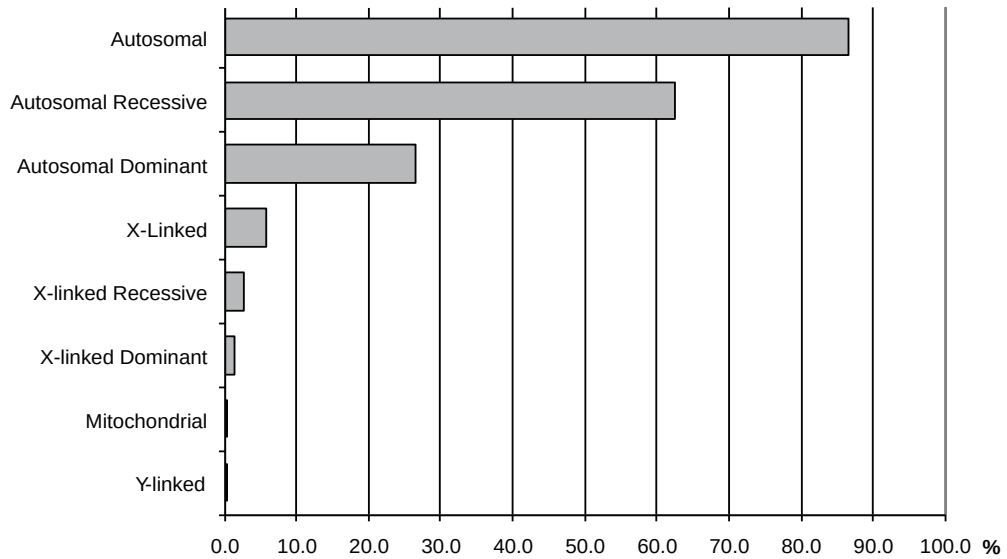
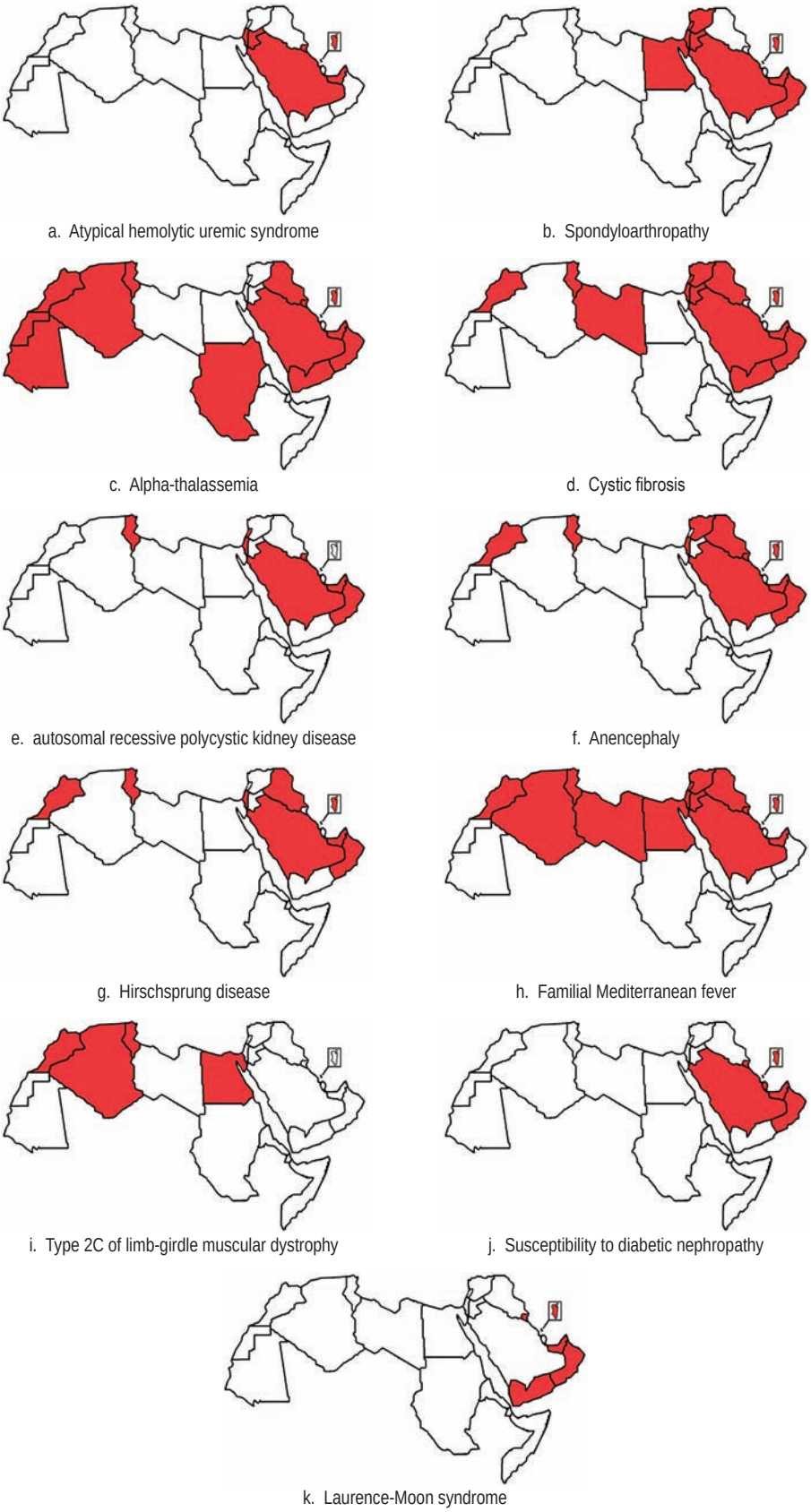


Figure 1.10. Classification of genetic disorders in Arabs according to mode of inheritance (June 2008).



a. Atypical hemolytic uremic syndrome

b. Spondyloarthropathy

c. Alpha-thalassemia

d. Cystic fibrosis

e. autosomal recessive polycystic kidney disease

f. Anencephaly

g. Hirschsprung disease

h. Familial Mediterranean fever

i. Type 2C of limb-girdle muscular dystrophy

j. Susceptibility to diabetic nephropathy

k. Laurence-Moon syndrome

Figure 1.11. Computer generated maps indicating the relative geographic distribution of some genetic disorders in the Arab World according to the CTGA Database (June 2008).

(Kozlowski *et al.*, 1988), the Kuwait type faciodigitogenital syndrome (Teebi *et al.*, 1988), the Kuwaiti type of cardioskeletal syndrome (Reardon *et al.*, 1990), the Yemenite deaf-blind hypopigmentation syndrome (Warburg *et al.*, 1990), the Nablus mask-like facial syndrome (Teebi, 2000), the Jerash type of the distal hereditary motor neuropathy (Christodoulou *et al.*, 2000), Karak syndrome (Mubaidin *et al.*, 2003), and the Omani type of spondylo-epiphyseal dysplasia (Rajab *et al.*, 2004).

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 economic impact of each of these disorders differs according to their severity, many of which involve medical, surgical, or cosmetic interventions. Generally, these conditions are a leading cause of spontaneous abortion, neonatal death, and increased morbidity and mortality in both children and adults. They are a significant health care and psychosocial burden for the patient, the family, the health care system and the community as a whole (El-Hazmi, 1999).

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 other patients (Carnevale *et al.*, 1985; McCandless *et al.*, 2004). Additionally, the total costs paid by patients with genetic conditions are slightly greater (Hall *et al.*, 1978) and these patients often must travel significant distances to get specialized treatment (Carnevale *et al.*, 1985).

In recent years, heath 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 annual 'cost of illness' estimates per patient for all common genetic conditions including: Down syndrome (US$ 36,000; Boulet *et al.*, 2008), cystic fibrosis (US$ 9,400; Nielsen *et al.*, 2002; Schreyogg *et al.*, 2006), beta-thalassemia (US $7,000; Karnon *et al.*, 1999), diabetes mellitus (US$ 6,900; Hogan *et al.*, 2003), sickle cell disease (US$ 6,300; Davis *et al.*, 1997), hemophilia (US$ 1000; Meyers *et al.*, 1972), and atopic dermatitis (US$ 1000; Fowler *et al.*, 2007).

In 1995, a study estimated 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 as $10.8 billion (2004 normalized data) for a single year's cohort (Waitzman *et al.*, 1995). This total cost comprises $2.8 billion in direct health care 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 States, and ignore the fact that many of these 18 birth defects occur more frequently in the region than elsewhere, then the cost of these problems in Arab countries is about $13 billion per year.

Preventive Aspects of Genetic Disorders

A detailed analysis of the molecular basis of defined genetic diseases indicates that approximately half of the genetic disorders described in Arabs (56%) result from single-gene or gene loci alterations (Figure 1.12). Hence, in the presence of the necessary technical infrastructure, diagnostic services may well be available for people at risk and preventive programs may be successfully applied in many Arab communities.

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 (WHO, 1996). 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 (Al-Odaib *et al.*, 2003). 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

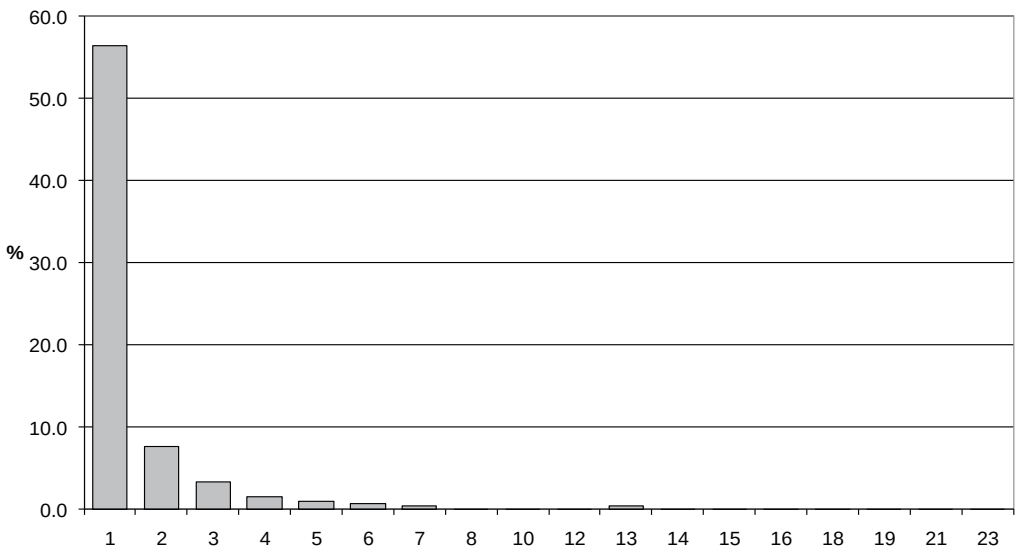


Figure 1.12. Distribution of genetic disorders in Arabs according to the number of causative gene loci (June 2008).

disorders. However, having the technology and resources alone are not enough. To start an effective program it has to be orchestrated by different strata of the society including patient representatives, medical geneticists, physicians, public health physicians, sociologues, ethicists, pharmaceutical industries, policy commentators, and policy makers within governments. Moreover, distinct policy areas have to be defined when dealing with a prevention program for genetic disorders, these include:

1. **The science base**: through which disease conditions could be defined according to their attributed burden, prevalence of the genetic trait, and natural history in the target population from susceptibility, to latent, and to overt disease. Experts have to also evaluate the safety and effectiveness of possible tests involved. Most important, population screening should be performed only if the abnormal finding in question can change the clinical management, and that this management will improve the prognosis.
2. **Educational strategies**: should be built based on the concept of "genetic literacy". This could be best achieved by applying interactive processes of dialogue and discussion in educational processes. For this, new biology has to be integrated as a necessary component of general education as well as in the education and training of all health professionals. In this framework, medical geneticists, genetic counselors, and clinical psychologists have a crucial role in making the prevention program acceptable by the target population by clear explanation of associated risks, proper parental consenting, and councelling (Khalifa, 1999).
3. **Regulatory framework**: have to be directed to resolve the wide-spread misunderstanding about genetics, especially the concept of genetic risk to a disease. In this area, scientists and the media have a great role. Politicians also have a responsibility in leading the public debate and making available ad-equate infrastructures, surveillance policies, and supportive financing mechanisms.
4. **Cultural sensitivity**: is a required safeguard to protect the public from premature and inappropriate use of genetic information, stigmatization, and discrimination, and to avoid coercion or manipulation (Meyer, 2005).
5. **Financial framework**: is a vital factor in securing the continuity of a preventive program. In most of the cases, the annual cost of a nationwide disease prevention program would not exceed the cost of treating one annual birth cohort of patients with a genetic condition for one year (WHO, 1996).

Several Arab States have initiated systematic cost effective prevention programs for certain common genetic conditions using a variety of approaches:

1. **Neonatal screening**: This involves the establishement of national or hospital based registries for congenital abnormalities (e.g., Oman and the United Arab Emirates) and the implementation of biochemical technologies to depict the incidence of many inherited disorders. Currently, Egypt, Oman,

Palestine, Qatar, Saudi Arabia, and the United Arab Emirates execute national newborn screening programs varying from one disease to 23. With an estimated 10 million newborns per year, a wide coverage of such programs in the Arab World becomes an important challenge (reviewed in Saadallah and Rashed, 2007).

2. **Family screening**: In Arab countries, this proves to be more effective than a population screening program due to the high level of consanguinity and the relative clustering of genetic diseases in specific population groups (Defesche *et al*., 2004).
3. **Premarital screening**: Several Arab countries have introduced premarital screening, especially for hemoglobin disorders as in Bahrain (Al Arrayed, 2005), Jordan (Hamamy *et al*., 2007), Lebanon, Saudi Arabia (Al-Suliman, 2006; Alhamdan *et al*., 2007), Tunisia (Al-Gazali *et al*., 2006), and the United Arab Emirates (Al-Gazali *et al*., 2005).
4. **Prenatal diagnosis**: This is an important component that requires an extensive social framework and without which a prevention program is practically gagged (Figure 1.13). In most Arab countries, except Tunisia, selective termination of pregnancy is not legally available (Chaabouni-Bouhamed, 2008).
5. **Preimplantation genetic diagnosis**: This is a more welcomed approach since it allows the avoidance of termination. Succesful applications of this approach have been reported in Jordan (Kilani and Haj Hassan, 2002; Abdelhadi *et al*., 2003) and Saudi Arabia (Ozand *et al*., 2005). A recent study from the United Arab Emirates found that most people favour this mode of prevention (Al-Gazali, 2005).

Figure 1.13. The social framework of prenatal genetic testing.

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 (Hamamy and Alwan, 1994). Additionally, in most Arab populations the birth prevalence of severe recessively inherited disorders may approach that of congenital malformations (Alwan and Modell, 1994).

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 lead to the loss of important information that can be used for research, and potential cures for genetically transmitted conditions (Editorial, 2006). 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 mostly exerted by medical practitioners and clinical geneticists who have developed a particular interest or have specialized in molecular studies (Naveed *et al.*, 2006; Naveed *et al.*, 2007). 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 the modern medical applications of genetics.

Databasing prevalence data as well as the molecular pathologies leading to genetic disorders in Arabs offers a solid groundwork to promote proper 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.

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