Historical Primer

Genetic and inherited disorders have accompanied humanity since its earliest existence. Many prehistoric and historic sites have revealed archeological remains with pathologies suggestive of inherited disorders. Paleopathology studies - the identification of pathological conditions in ancient skeletal remains - from many world sites revealed the presence of various hereditary or congenital conditions including Paget’s disease, neurofibromatosis, cleft lip and cleft palate, juvenile kyphosis (Scheuermann’s disease), scoliosis, spina bifida, achondroplasia, Hurler syndrome (mucopolysaccharidosis type I), Hunter’s syndrome, (mucopolysaccharidosis type II), Morquio’s syndrome (mucopolysaccharidosis type IV), osteogenesis imperfecta (types III and IV), cleidocranial dysostosis, osteopetrosis, diaphyseal sclerosis (Camurati-Engelmann disease), osteopoikilosis, and many others (reviewed in Ortner, 2003). One of the oldest of such records includes a 1.5 million year old fossil of a 2-year-old Homo erectus child with amelogenesis imperfecta (Zilberman et al., 2004). In Indonesia, the skeleton of a 25-30 year-old Homo floresiensis, discovered in 2003 on the island of Flores, featured a small skull that could be due to microcephaly (Jacob et al., 2006). 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 high frequencies in populations of the “Middle Kingdom” (2050-1750 BCE; Nerlich et al., 2002). In addition, bizarre physical features were shared by many members of Egypt’s 18th Dynasty, including the Pharaoh Akhenaten, suggestive of possible familial disorders possibly including the aromatase excess syndrome, the sagittal craniosynostosis syndrome, or a variant of the Antley-Bixler syndrome (Braverman et al., 2009). Interestingly, ancient DNA analysis revealed a β-thalassemia mutation in the skeletal remains of an Ottoman child with severe porotic hyperostosis (Filon et al., 1995).

Concomitantly, almost all prehistoric and ancient civilizations suffered from the severe consequences of many infectious diseases. In fact, many of these diseases played major roles in the development of human civilization, impacting and altering the course of wars, migrations, population growth, and urbanization. In many world countries, including Arab States, breakthroughs in managing such diseases only happened few decades ago with the clinical availability of specific drugs and vaccines. This progress decreased the impact of such disorders in favor of an increased understanding of the molecular basis of heredity, hence, a better recognition of genetically transmitted conditions as a major cause of morbidity and mortality (Tadmouri, 2008).

Genetic Disorders in World Populations

To date, records for more than 6500 inherited disorders, known to afflict world populations, are indexed and maintained at the Online Mendelian Inheritance in Man (OMIM) database, which is a comprehensive compendium of human genes and genetic phenotypes (McKusick, 2007). Many of these disorders are rare entities that occur at higher frequencies in particular ethnic, racial, or demographic groups. More common disorders show a worldwide spread supported by natural selective forces or stimulated by socially-oriented reproductive choices.

Systematic attempts to catalogue genetic disorders in world populations are almost non-existent. The only available examples include the Finnish Disease Database (www.findis.org; 35 disorders) and Rare Diseases Sweden database (www.sallsyntadiagnoser.nu; 68 disorders) that represent national efforts to highlight the disease heritage of their respective populations. Hence, to try to give an approximate visualization of the number of genetic disorders in various world populations the only comprehensive source that could be utilized would be the OMIM database. Using proper search syntaxes it is possible to deduce the populations in which most of the genetic disorders were described; these include: the Japanese (~750), Italian (~550), German (~450), Turkish (~400), Chinese (~350), Canadian (~300), French (~300), Finnish (~300), Pakistani (~300), and many other populations. 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 (reviewed in Tadmouri, 2008).

Arab Populations: A Definition

Defining the term Arab is a challenging task. Arabs are a panethnicity of peoples of various ancestral origins, religious backgrounds, and historic identities. 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 southeast of Asia Minor, East Africa, 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 (UAE), and Yemen. Yet, this geocultural unit is the largest in the world after Russia and Anglo-America, with a population exceeding 360 million and spanning more than 14,000,000 square kilometers (Appendix 1).

Major Prehistoric Events

Archeological excavations and historical records provided considerable information regarding early evolutionary history of modern humans in this vast geographical region. However, the application of DNA molecular anthropology methods allowed scientists to high resolution information that go as far as depicting similarities and dissimilarities between the population histories of males and females by analyzing unique non-recombining regions of uniparental Y-chromosome and mitochondrial DNA (mtDNA), respectively.

DNA evidence indicates that modern humans originated in East Africa about 100,000-200,000 years ago (Li et al., 2006) then established regional populations throughout the continent. Archeological artifacts excavated from Taforalt in Morocco indicate that human inhabitation of modern day’s Maghreb region (modern day Morocco, Algeria, Tunisia, and Libya) date back to some 82,000 years ago (Ferembach, 1959). At that time, settlements in the region were characterized by developed cultural manifestations that could only exist in Europe 40 millennia later (Bouzouggar et al., 2007). According to the Recent Out-of-Africa model, members of one branch of anatomically modern humans left Africa to the Near East some 60,000-70,000 years ago (Relethford, 2008). Phylogenetic studies based on the bimodal comparisons are indicative for two possible migration routes in this episode of human history:

(1) One route laid across Bab-el-Mandeb straits in the Red Sea linking modern day Eritrea and Djibouti in Africa to eastern Yemen in the Arabian Peninsula (Bailey et al., 2007; Cerny et al., 2008). Supportive evidence comes from Y-chromosome diversity studies that show a pool typical of African biogeographic ancestry among 14% of modern Saudi males (Abu-Amero et al., 2009). High diversity in the Y-haplogroup substructure in samples from the region extends the geography of this active route to include Yemen, southern Arabia, South Iran, and South Pakistan. This route maintained its important role in influencing gene flow from Africa along the coastal crescent-shaped corridor of the Gulf of Oman facilitating human dispersals into the region until nearly 2500 years ago (Cadenas et al., 2008).

(2) Another route followed the Nile from East Africa, heading northwards and crossing through the Sinai Peninsula into the Levant resulting in a marked gene flow especially during the Upper Paleolithic and Mesolithic periods between 14,000-40,000 years ago (Cann et al., 1987; Ingman et al., 2000; Luis et al., 2004). Human populations in the Near East then branched in several directions, some moving into Europe and others heading east into Asia (Ke et al., 2001; Maca-Meyer et al., 2001; Underhill et al., 2001; Lahr and Field, 2005). Y-chromosome analysis support this view and demonstrate the absence of any significant genetic barrier in the eastern part of the Mediterranean area, where a remarkable genetic variation was attained and gene flow followed the “isolation-by-distance” model. This is in contrast to a strong north-south genetic barrier, for both male and female gene flow, in the western Mediterranean basin, defined by the Gibraltar Strait (Manni et al., 2002; Ennafaa et al., 2009).

Paleoanthropological evidence and mtDNA variation analysis indicate that both the Horn of Africa and, possibly more importantly, the Levantine corridor served, repeatedly, as migratory passageways between Africa and Eurasia (Luis et al., 2004; Rowold et al., 2007). Some studies also support the view that regions near, but external to northeast Africa, like the Levant or the southern-Arabian Peninsula could have served as incubators for the early diversification of non-African lineages (Abu-Amero et al., 2009).

The Early Farmers

Around 12,000 years ago, Neolithic human populations adopted agricultural technologies that allowed them to establish permanent sizeable settlements and to adapt a far-reaching shift in subsistence and lifestyle. Undoubtedly, improvement of the climatic conditions in the area along with the practice of agriculture helped in the establishment of major historical settlements with sizeable densities that could have contributed enormously to the genetic makeup of modern Arab populations. Yet, farming was almost always associated with settlements near mosquito-infested soft and marshy soil causing large malarial outbreaks (Grmek, 1994; de Zulueta, 1994; Joy et al., 2003). These outbreaks imposed selective pressure on the human genome and amplified the frequencies of several genetic disorders including sickle cell disease, β-thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency (Angel, 1966; Carter and Mendis, 2002; Kwiatkowski, 2005).

In the Arabian Peninsula, Levantine, Sub-Saharan African and Iranian lineages have participated in the building of the primitive Arabian population. Approximately 62-69% of today’s Y-chromosome and mtDNA haplogroups in Saudi Arabia share common structures with those in the near east and demonstrate an important role for the Levant in shaping the Neolithic dispersal of human settlements in the Gulf. Male lineage estimates for these prominent Levantine haplogroups indicate a north to south influence with a history of almost 12,000 years in Saudi Arabia,
11,000 years in Yemen, mainly in the western region, and only at nearly 7,000 years in Qatar and the UAE (Abu-Amero et al., 2008; Cerny et al., 2008; Abu-Amero et al., 2009). Detailed analyses hint to a terrestrial more than to a maritime colonization for the eastern Arabian Peninsula that was followed by subsequent population isolation from the western Arabian Peninsula which demonstrates significant genetic affinities to near-eastern populations (Alshamli et al., 2009). On the other hand, studies of mtDNA variability confirm a notable sub-Saharan African and, to a lesser extent, Iranian female-driven flow in the Arabian Peninsula (Rowold et al., 2007; Cerny et al., 2008).

Analysis of the pattern of Y-chromosome and mtDNA variations in North Africa provides evidence of the relatively young population history of North Africa mainly formed through a strong demographic expansion of Neolithic pastoralists from the Levant (Arredi et al., 2004; Kujanova et al., 2009). Some of these earliest civilizations in the Maghreb region include immigrant Berbers who originated from the Sahara 10,000 years ago and left considerable gene imprints in the gene pool of modern day Mauritania, Morocco, Algeria, Tunisia, Libya, and southern Egypt (Lucotte et al., 2000; Lucotte and Mercier, 2003). The Berbers were followed by the Mesolithic Capsians who settled in the area 2,000 years later (Irish, 2000).

Major Events in Ancient and Medieval History

In the Arabian Peninsula, Semitic-speaking peoples of Arabian origin migrated into the valley of the Tigris and Euphrates rivers in Mesopotamia some 7,000-5,500 years ago (Beech et al., 2005). Archeological evidence further indicates that another group of Semites left Arabia around 4,500 years ago during the Early Bronze Age and settled along the Levant mixing in with the local populations there. Some 3,500 years ago, the Phoenician civilization of Lebanon became a developed enterprising maritime trading culture. Subsequently, Phoenician traders spread across the Mediterranean and established major cities and colonies that harbored their pathologic or polymorphic gene variations (Walter et al., 2001; Tadmouri et al., 2001; Gerard et al., 2006; Zalloua et al., 2008a). Results of the Genographic Consortium from Y-chromosome variations indicate that as many as 1 in 17 men living today on the coasts of North Africa and southern Europe may have a Phoenician direct male-lineage ancestry (Zalloua et al., 2008b). The genetic pool was further enriched in Mesopotamia through Persians while Romans gained a 600 year-long period of settlements throughout most of the region and were subsequently replaced by the Byzantines (Zahed et al., 2002).

Soon after the rise of Islam 1,400 years ago, the Arab Caliphates unified the entire region as a distinct territory and amalgamated the dominant ethnic identity that persists today in the Levant and extends as far as the Maghreb Region in North Africa as well as Andalusia in the Iberian Peninsula (Fattoum and Abbès, 1985; Ben Abdeladhim et al., 1987; Zalloua et al., 2008a). Similarly, the Arabian Peninsula linked distant populations of China and India to communities of the Mediterranean and beyond. During this period, demographic dynamics were predominantly governed by cultural change in endogenous populations rather than demic influences with significant gene flow (Labie et al., 1994). This view is strongly supported by Y-chromosome analysis of Muslim expansion in India and mtDNA haplogroups in the Sinai Peninsula and North Africa (Saleh et al., 1996; Gutala et al., 2006; Ennafaa et al., 2009).

On the contrary, the eastern Mediterranean region witnessed major Crusader settlements during the 11th-13th centuries CE that could have caused remarkable genetic drifts and bottlenecks and introduced western European lineages into the Levant affecting a considerable portion of today’s gene pool (Zalloua et al., 2008a). The impact of western European gene backgrounds extends to the eastern Arabian Peninsula where major parts, including Bahrain, fell under the influence of the Portuguese at the beginning of the 16th century and remained as such for the following 150 years. This presence left clear impressions in the mutational spectrum of common disorders in the eastern Arabian Peninsula as in the case of the relative high frequency of the western Mediterranean Codon 39 (C-T) β-thalassemia mutation (Gomes et al., 1988; Jassim et al., 1998; Al-Ali et al., 2005; reviewed in Tadmouri and Gulen, 2003). On the contrary, some other disorders spread out to geographically distant locations from the region under this Portuguese influence; for example, as demonstrated in the increasing evidence noted with regard to Machado-Joseph disease (Parday, 2004; Mittal et al., 2005).

Landmarks of Modern History

Simultaneously, Ottomans controlled much of the Mediterranean then expanded their influence to cover all the Arabian Peninsula and further contributed to the enrichment of the genetic pool in the region (Haj Khelil et al., 2004). After the 19th century, areas of the Maghreb were colonized by France, Spain and Italy while the remaining areas where colonized by France and England. Despite all this long trail of admixtures in the region, there are still localities marked by the presence of genetic isolates. Some examples include the dwellers of the Dead Sea region in Jordan (Gonzalez et al., 2008), Bedouins of Sinai (Salem et al., 1996), and inhabitants of the Island of Jerba in Tunisia (Loueslati et al., 2006).

Arab Diaspora

Throughout modern history, Arab emigrants formed many Diasporas in world continents. At present, the main countries of immigration within the Arab World are countries of the Gulf Cooperation Council that host more than two million emigrant Arabs mostly from Iraq.
(more than 4 million), Palestine (300,000), Lebanon (120,000), Egypt, and Syria. 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, the Caribbean, North America, Europe, parts of Southeast Asia, Australia, and West Africa.

In Latin America and the Caribbean, there is an estimated presence of more than 16 million people of Arab (Lebanese, Syrian, and Palestinian) descent according to statistics compiled by the Arab Federation of Latin America (Salloum, 2000; Luxner, 2001). In Brazil, the Arab community started arriving over one hundred years ago. Brazil has nearly 10-12 million Brazilians of Arab ancestry, mainly from Lebanon, Syria, Palestine, and Iraq (Luxner, 2005). Brazilians of Lebanese ancestry number nearly seven million, and some 70% of them live in Sao Paulo, while Brazilians of Syrian origin number nearly three million (Klich, 1992). In Argentina, estimates indicate a net Arab migration to Argentina that is not less than 110,000 immigrants between years 1871-1976. Today, Argentina is home for large Arab communities; including not less than 1,000,000 of Lebanese descent. In Mexico, approximately 400,000 people are from Lebanese background and represent nearly 45% of all Arab Mexicans (Guzman and Zeraoui, 2002). In addition, substantial minorities, mainly from Lebanon, Syria, and Palestine, are also found in Chile (800,000 including nearly half a million of Palestinian descent, 170,000 from Syria, 30,000-90,000 from Lebanon, and 10,000 from Jordan), Venezuela (600,000 including nearly 340,000-400,000 of Lebanese and significant communities originating from Syria, Palestine, and Iraq), Colombia (200,000 of Lebanese descent, 40,000-70,000 of Iraqi descent, and 12,000 of Palestinian descent), El Salvador (150,000 of Palestinian descent), Uruguay (55,000 of Lebanese descent), Honduras (54,000 of Palestinian descent), Puerto Rico (25,000 of Iraqi descent), Ecuador (20,000-100,000 of Lebanese descent), Haiti (4,600 mainly of Lebanese and Syrian descent), Bolivia, Costa Rica, Dominican Republic, Guatemala, Guinea, Jamaica, and Trinidad and Tobago (Salloum, 2000; Luxner, 2001).

In North America, Arabs arrived in several waves of immigrations from countries of southwestern Asia (Lebanon, Syria, and Palestine) and North Africa (Morocco, Algeria, and Egypt) since the 1880s (The Canadian Arab Federation, 1999; Zogby International, 2000). Approximately 110,000 Arab-speakers gained entry to the US prior to year 1914 and some 18,500 between years 1915 and 1940. In between years 1945 and 1952, 7,285 Arab immigrants, mainly from Palestine, Syria, Egypt, and Lebanon, were admitted (Aboud, 2002). Today, there are around 3.7 million people in the United States of Arab ancestry mostly from Lebanon, Syria, or Palestine (Zogby International, 2000). Lebanese Americans constitute a greater part of the total number of Arab Americans residing in most states (37%), except New Jersey, where Egyptian Americans are the largest Arab group (12% of all Arab Americans; The United States Census Bureau, 2000). Americans of Syrian descent make up the majority of Arab Americans in Rhode Island (12% of all Arab Americans), while the largest Palestinian (68,000) and Iraqi populations are in Illinois (6% and 3% of all Arab Americans, respectively). Other Arab groups residing in the United States come from Jordan, Morocco, Yemen, Algeria, Saudi Arabia, Tunisia, and Libya. In year 2000, 27% of the Arab population lived in the Northeast, while 26% lived in the South, 24% in the Midwest, and 22% in the West. Approximately, 70,000 people of Arab ancestry live in New York, making it the city with the largest number of Arabs, followed by Los Angeles, Chicago, Houston, Detroit, and San Diego (The United States Census Bureau, 2000). In Canada, 5,899 Syrian and Arabian immigrants were admitted up to year 1914 while approximately 2421 were admitted between years 1915 and 1940 and 1761 were admitted between years 1945 and 1955 (Aboud, 2002). Today, most of the 470,580 Arabs living in Canada reside in Quebec (42%) and Ontario (42%; Statistics Canada, 2006). Arab communities in Canada are highly urban; 69% live in Toronto, Montreal, and Ottawa-Hull alone. They mainly originate from Lebanon (250,000-400,000 people), Morocco, Algeria, Egypt, Syria, Palestine, and others (The Canadian Arab Federation, 1999).

In Europe, the history of Arab immigrations started as early as 1898 with the arrivals of Somali and Yemeni communities to the United Kingdom. Today, the United Kingdom is home for about 1 million Arabs representing 1.7% of the country’s population. The vast majority of these originate from Iraq (250,000-450,000), Yemen (70,000-80,000), Morocco (65,000-70,000), Algeria (40,000), and Egypt (some 30,000; Office for National Statistics, 2001). Yet, the European country with the largest number of Arab immigrants is France, with nearly 7 million Arabs, including a great majority of nearly 3 million from North Africa (including 1,200,000 of Moroccan origin) and around 100,000-250,000 Lebanese. The region with the largest Arab community in France is Ile de France (Paris). On the other hand, the number of Arab immigrants in Germany is 280,000-350,000 (including 150,000 Iraqis and 50,000 Lebanese) and in Belgium there are approximately 333,000 Arabs. In the Netherlands, official statistics indicate the presence of not less than 350,000 Arabs of Moroccan origin with a significant presence of many Iraqis as well (Centraal Bureau voor de Statistiek, 2010). Further to the North, Sweden hosts about 120,000 Iraqis forming the country’s second largest immigrant group. Other major groups of Arab descent in the country include Lebanese (23,000), Syrians (20,000), and Moroccans (7,000; Statistics Sweden, 2010). In Eastern Europe, Bulgaria is home for about 17,000 Arabs mainly from Lebanon, Syria, Palestine, and Iraq (Zhelyazkova et al., 2005). Other European countries with significant Arab communities include Turkey (60,000-90,000 Iraqis), Norway (26,000 Iraqis), Greece (5,000-40,000 Iraqis), Denmark (12,000-15,000 Iraqis), Belarus, Italy, Romania, and Spain.
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 Hadramaut region of Yemen and Oman. Estimates indicate that as many as 4 million Hadramis live in Indonesia and 7,000-10,000 are in Singapore (Talib, 1997). Hadramis also contributed to the strong presence of a large Arab population in Hyderabad in India, known as Chaush, who migrated to the sub-continent in the 18th century and were once the soldiers of the Nizam of Hyderabad (Minda, 2004). Similarly, many Arab traders permanently settled in southern India and in Sri Lanka between the 8th and 15th centuries. Descendants of these traders formed the bulk of today’s Sri Lankan Moors, the third largest ethnic group in the country with a population of not less than one million (Ross and Savada, 2002). In Afghanistan, Arab presence dates back to the end of the 7th century, when Umayyad armies overran the Sassanids in Nihawand. Arabs remained a minority in the conquered lands, but set up garrison towns to house regional armies and were the main force in many important urban centers. Historical references from the second half of the 18th century point out that the lineages of not less than 60,000 families trace back to Arabic tribes that came from Khorasan under the Umayyads and Abbasids (Kieffer, 2000).

In Australia, Arabic is the fourth most widely spoken second-language. Syrian and Lebanese-born immigrants started arriving to the continent as early as 1911 (1527 persons). In year 1921, the Arab population grew to 1803 individuals then in year 1933 to 2020 persons. In between years 1945 and 1955, 4,053 new settlers arrived to Australia from Lebanon, Syria, and Egypt (Aboud, 2002). Today, the Arab community in Australia includes roughly 360,000 people from Arab countries (Australian Bureau of Statistics, 2006). Some estimates place the number of Australians of Arab origin at almost one million from which more than 500,000 are from Lebanese descent. Of the Arabs who have settled in Australia, the Lebanese and Egyptian communities are generally the most established, followed by the Iraqi (nearly 80,000) and Syrian communities (Australian Government, 2003). The Lebanese in Australia are heavily concentrated in the larger cities, with Sydney being home to some 75% of Australia’s Lebanese; and nearly to 45% of Australia’s Arabs (Price, 1999). In neighboring New Zealand, Lebanese makes up a majority of Arabs in the country with a population of nearly 47,200 individuals (Akoorie, 2007).

Arab Diasporas are also noted in several countries in Central and West Africa (Handloff, 1988). Although there is debate about the exact year during which Arabs first arrived in West Africa, it is generally believed that the Lebanese might have been the earliest immigrants to arrive to the region between the 1860s and 1870s (Boumedouha, 1993). Main African countries with notable Arab communities include Ivory Coast (home to over 300,000 Lebanese and Syrians; Handloff, 1988), Senegal (roughly 30,000 Lebanese), Sierra Leone (roughly 10,000 Lebanese), Liberia, and Nigeria (Van der Laan, 1993).

**Demographic and Medico-Economic Characteristics of Arab Populations**

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:

- High fertility rates (1.7-6.4 children born/woman; Appendix 1).
- High birth rates (15-43 births/1,000 people; Appendix 1).
- High annual population growth rates of 0.6-3.6% (Appendix 1).
- Extremely high rates of birth defects (63-82/1000 live births; Christianson et al., 2006).
- High rates of inbreeding or consanguineous marriages (Tadmouri et al., 2009).
- Child bearing at either very early or old maternal ages.
- The presence of isolates (e.g., Armenians, Bedouins, Druzes, Jews, Kurds, and Nabians).
- 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 alarming 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 by the reducing rates of infant mortality below the global average of 44.1 per 1000 live births, 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 (Appendix 1). This is a natural outcome of increasing investments in healthcare systems in the region. However, these improvements will only solidify once attention is focused on basic health problems, as well as on underlying factors such as poverty. 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). To overcome these obstacles, medical genetic societies in the region have an important role to play in establishing an interactive process of dialogue and discussion to be directed towards the public and decision makers. This process should include the establishment of preventive programs acceptable by target populations as a main goal besides tackling related issues of local importance.
Medical teaching in the region is deep-rooted. Unsurprisingly, many Arab States are home to some of the oldest medical schools such as Qasr Al-Aini Medical School and Teaching Hospital in Egypt (1827), the American University of Beirut Medical Center (1867), the Syrian University (1923), the Kitchener School of Medicine in University of Khartoum (1924), and the Iraqi Royal College of Medicine (1928). Yet, that has led many schools in the past to follow classical curricula that resulted in many practitioners in the region having an incompletely assimilated understanding of heredity. This reflected in the absence of proper genetic counseling, in many communities, and in the genetic literacy at the levels of the general public and at-risk families as well. However, the leaping progress achieved in medical genetics in the past few decades transformed this science from a peripheral entity into a central innovative area with extensive interdisciplinary exchange. Over the last few decades, medical genetics established itself as a core pillar in many Arab academic medical educational systems. This has lead to an increased understanding of the molecular basis of heredity and to a better recognition of genetically transmitted conditions as a major cause of morbidity and mortality in Arab States.

Currently, genetic services in the region can be broadly grouped as: national screening programs, genetic testing laboratories, and research centers. With nearly 9 million infants estimated to be born annually, advanced national screening programs exist in almost all Arab States with the aim of routine screening for commonly occurring genetic ailments at the newborn and prematernal levels (Saadallah and Rashed, 2007). Genetic testing facilities, however, have more limited coverage and are usually maintained at private institutions with variable capacities. In research centers, mostly found within academic or semi-governmental setups, activities are usually translated into scientific peer-reviewed reporting that, so far, occupies only a small share (nearly 0.5%) of the permanent record of global scientific progress (Tadmouri and Bissar-Tadmouri, 2003). Among active research centers in the field are King Faisal Specialist Hospital and Research Centre in Saudi Arabia, the National Research Center in Egypt, the Medical Genetics Unit at Saint-Joseph University in Lebanon, the Kuwait Medical Genetics Centre, Institut Pasteur in Tunisia, the Hereditary Research Laboratory at Bethlehem University in Palestine, the UAE University, Weill Cornell Medical College in Qatar, and Al Jawhara Center for Genetics and Inherited Diseases in Bahrain, just to name a few.

Outlook of Genetic Research in the Region

Science in the Arab World is generally suffering from serious lack of funds. In many instances, 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). Despite this, the region witnessed in the last 10 years a steady increase in biomedical research outputs mainly driven by stringent academic promotion requirements, the foundation of many advanced research centers, the launch of several national and private funding agencies supporting biomedical research activities, and the “return migrations” of Arab scientists educated in world-class institutions. This category of scientists is characterized by higher publication rates, extensive contacts distributed over distant geographical locations, and the expertise to conduct advanced genetics research. Many of these observations can be benchmarked using comprehensive online bibliographies that allow mapping of complete or near-complete co-authorship networks for entire fields and provide a window on patterns of scientific collaboration in region.

Overall, there is a rising incidence of co-authorship in many academic disciplines. This is largely driven by the dynamics of internal differentiation of science into specialized disciplines and large scale investment in science enhancing multi-national collaborations (i.e., ‘big science’). At global level, biological sciences lead this trend with an average co-authorship rate of 3.75 when studying nearly 2 million papers published in years 1995-1999 (Newman, 2004). By analyzing approximately 52,000 PubMed-indexed biomedical articles published by principal investigators from Arab countries for the years 1988-2007, an average of 3.9 co-authors is observed in each published article. Sizes of co-authorship patterns in Jordan, Saudi Arabia, Egypt, and Kuwait are in the range of 3 co-authors, while these units reach sizes of 4-6 co-authors in Lebanon, Morocco, and Tunisia (unpublished results). By analyzing a subset of 566 random genetics publications indexed in the Catalogue for Transmission Genetics in Arabs (CTGA) Database for genetic disorders in Arab populations, the average co-authorship rate increases to 5.7 indicating that Arab scientific reporting in medical and molecular genetics is generally a collaborative activity due to the interdisciplinary requirements to achieve comprehensive phenotype-genotype correlations and the expense of modern molecular technologies (unpublished results).

The analysis of resulting medical genetics networks over the last two decades reveals important observations on how some Arab States, such as Tunisia, Morocco, and Lebanon, integrated themselves further close to the core of more advanced countries, namely France and the USA (Wagner and Leydesdorff, 2005). Within this group, research collaborations, mostly international, involve the implementation of advanced molecular technologies and result in papers with higher visibilities. In fact, the most recent survey conducted by the Centre for Arab Genomic Studies on articles discussing genetic disorders in Arab patients indicate that gene-pathology articles constitute only 28% of the total number of articles analyzed (Tadmouri, 2008). Maghreb countries (i.e., Algeria, Tunisia, and Morocco) are leading in terms of molecular genetic studies (Figure 1.1). In many cases, these molecular studies are the fruits of collaborations with international groups that usually cover the needed expenses...
and provide the sophisticated equipment (Selmamni and Tali-Maamar, 2003; Dakik et al., 2006). As an example, 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). Meanwhile, Eastern Mediterranean and Gulf Arab countries became more structured, but disconnected from the main grouping of more advanced countries (Wagner and Leydesdorff, 2005). This trend seems to be fuelled by collaborations at the clinical level that address endogenous needs through local capacities. For example, in countries for which the Centre for Arab Genomic Studies concluded its exhaustive surveys on genetic disorders (i.e., UAE, Bahrain, Oman, and Qatar) the percent share of molecular studies ranges only between 14-16% of the total of medical genetics. 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.

On the bright side, however, noteworthy achievements do also exist in the region. Recently, a scientific team from Al Jawhara Center for Molecular Medicine, Genetics, and Inherited Disorders at the Arabian Gulf University isolated a new protein called ISRAA (Immune System Released Activating Agent), which represents the first molecule that acts as a mediator between the central nervous system and the immune system. This protein is produced in the spleen when the host is infected. It then activates the immune system and gives it the capability to fight against the infection. This unprecedented discovery may help to find a possible cure for killer diseases including AIDS and cancer (Bakhiet and Taha, 2008). Studies are now being developed to study expression analyses of related genes as well as functional studies of possibly associated proteins (Bakhiet and Taha, 2008). In Oman, Sultan Qaboos University in collaboration with several international institutions established a research program called “Oman Family Study”. The aim of this program is to establish an Omani model for the study of the genetics of complex diseases, such as diabetes, obesity, dyslipidemia, and hypertension. Individual studies in this program resulted in identifying several loci that may be implicated in the pathogenesis of these diseases (Bayouni et al., 2008). Similarly, the Molecular Pathology Unit at the University of Kuwait specializes in studying genomic aspects of early-stage colorectal cancer and breast cancer and aims at translating its discoveries into diagnosis, screening, premarital counseling of couples, and prenatal diagnosis of offspring with biallelic cancer gene mutations (Al-Mulla et al., 2006; Marafie et al., 2009; Al-Mulla et al., 2009). In Qatar, the Shafallah Medical Genetics Center is focusing on linkage analysis and mutation spectrum definitions for common and rare disorders occurring in the Arab population of Qatar (Abu-Amero et al., 2008; Ahram et al., 2009). Likewise, in Bethlehem University genomic analyses conducted over extended consanguineous families have resulted in the determination of multiple novel alleles for inherited hearing loss in the Palestinian population (Walsh et al., 2006).

Consanguinity in Arab People

Many Arab countries display some of the highest rates of consanguineous marriages in the world (Table 1.1). Sociocultural factors, such as maintenance of family structure and property, ease of marital arrangements, better relations with in-laws, and financial advantages relating to dowry, play a crucial role in the preference of consanguinity in Arab populations (Tadmouri et al., 2009).

In Arab populations, consanguinity rates are changing in either way. In Bahrain, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Palestine, and Tunisia decreasing trends of consanguineous marriages have been recorded among previous and present generations. On the other hand, increasing consanguinity rates have been recorded among generations in Algeria, Morocco, Oman, Qatar, Saudi Arabia, Sudan, Syria, the UAE, and Yemen (reviewed in: Tadmouri et al., 2009).

In Arab populations and Diasporas, the deep-rooted norm of consanguineous marriage has been widely accused of being an important factor contributing to the preponderance of autosomal recessive genetic disorders (reviewed in: Tadmouri et al., 2009). Actual data from countries for which surveys on the occurrence of genetic disorders have been completed by the Centre for Arab Genomic Studies (Bahrain, Oman, Qatar, and the UAE) indicate that recessive disorders are greater in number than the dominant ones. Interestingly, these data demonstrate a direct correlation between the increase in consanguinity rates in a population accompanied with an increase in the share of autosomal recessive disorders and a decrease in the number of autosomal dominant disorders in the respective population (reviewed in: Tadmouri et al., 2008).

Figure 1.1. Schematic representation of the per cent gene-related articles of the total number of biomedical records surveyed at the Centre for Arab Genomic Studies (July 2010).
Table 1.1. Consanguinity rates in Arab populations. Minimum and maximum reported rates are indicated when available [reviewed in: Tadmouri et al., 2009; include updates for Bahrain (Al Arrayed, 2006), Morocco (Jaoaud et al., 2009), and Qatar (Sandridge et al., 2010)].

<table>
<thead>
<tr>
<th>Country</th>
<th>&gt;1C, 1C</th>
<th>Overall Consanguinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>11.3</td>
<td>22.5-34</td>
</tr>
<tr>
<td>Bahrain</td>
<td>11.4-24.5</td>
<td>20.4-55</td>
</tr>
<tr>
<td>Egypt</td>
<td>14.3-23.2</td>
<td>20.9-32.8</td>
</tr>
<tr>
<td>Nubia</td>
<td>39.47-2</td>
<td>60.5-80.4</td>
</tr>
<tr>
<td>Iraq</td>
<td>29-33</td>
<td>47-60</td>
</tr>
<tr>
<td>Jordan</td>
<td>19.5-39</td>
<td>28.5-63.7</td>
</tr>
<tr>
<td>Kuwait</td>
<td>16.9-31.7</td>
<td>22.5-63.4</td>
</tr>
<tr>
<td>Lebanon</td>
<td>6.7-31.6</td>
<td>12.8-42</td>
</tr>
<tr>
<td>Libya</td>
<td>-</td>
<td>48.4</td>
</tr>
<tr>
<td>Mauritania</td>
<td>-</td>
<td>47.2</td>
</tr>
<tr>
<td>Morocco</td>
<td>8.6-10</td>
<td>15.2-28</td>
</tr>
<tr>
<td>Oman</td>
<td>24.1</td>
<td>56.3</td>
</tr>
<tr>
<td>Palestine</td>
<td>13.6-34.2</td>
<td>17.5-66.3</td>
</tr>
<tr>
<td>Qatar</td>
<td>34.8</td>
<td>22-54</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>24.6-42.3</td>
<td>42.1-66.7</td>
</tr>
<tr>
<td>Sudan</td>
<td>44.2-49.5</td>
<td>44.2-63.3</td>
</tr>
<tr>
<td>Syria</td>
<td>28.7</td>
<td>30.3-39.8</td>
</tr>
<tr>
<td>Tunisia</td>
<td>17.4-23</td>
<td>20.1-39.3</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>20.7-28.2</td>
<td>40.5-42</td>
</tr>
<tr>
<td>Yemen</td>
<td>32-34</td>
<td>40-44.7</td>
</tr>
</tbody>
</table>

Abbreviations: [>1C] = Double first-cousin marriage; [1C] = First-cousin marriage.

The CTGA Database

Reporting information on genetic disorders among Arab people in printed publications is not a practical process and usually results in rapidly outdated coverage due to the continuous process of describing more genetic disorders in the region. To overcome this problem, Tadmouri and Bissar-Tadmouri (1999) initiated an early attempt to maintain offline tabular lists of 374 genetic disorders described in Arab individuals, with corresponding references, by monitoring international genetic databases and scanning bibliographic indices. The number of maintained records increased to 752 entries early in 2004 (unpublished data). 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 continuous survey (Tadmouri, 2004). Later that year, the Centre for Arab Genomic Studies (CAGS) started implementing its proposal to launch a pilot CTGA Database by constructing major software components of the Database and testing them separately. The CTGA database was then assembled and tested with limited amounts of data prior to its public release on the 30th of November 2004 (Tadmouri et al., 2006).

Today, the CTGA Database is defined as 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., 2006). Its update process is largely driven by the diverse methods used at the Centre for Arab Genomic Studies to collect data and information on genetic conditions in Arab patients including from various sources that include bibliographic indices, regional peer-reviewed medical publications, and personal submissions (Tadmouri, 2008). The size of the pool of international and national articles surveyed to collect data for the CTGA Database during the years 2004-2010 mounts to nearly 73,000 articles. From this, nearly 10,000 articles were investigated in detail during the surveys to collect data for the UAE, Bahrain, Oman, and Qatar. Of these, 2,804 articles contained informative details about the occurrence of genetically disorders in Arab populations in the region.

Genetic Disorders in Arab Populations

In December 2010, the CTGA Database hosted 955 entries for phenotypes/diseases and 373 entries for corresponding genes in Arab individuals (see: Appendix 2). These data still reflect a dominance of clinical observations over molecular analyses in most of the research conducted in the region (Figure 1.2). Yet, indications do demonstrate that a slow improvement in this situation is taking place. For example, the ratio of gene:disease records in the CTGA Database increased from 0.36:1, to 0.38:1, and to 0.39:1 for years 2006, 2008, and 2010, respectively (Tadmouri, 2006; Tadmouri, 2008).

Nearly two-third of genetically transmitted diseases in Arab patients follow an autosomal recessive mode of inheritance (approximately 61%). High consanguinity rates and the extended family structure, commonly present in Arab societies, are likely explanations for this observation (Tadmouri et al., 2009). Less common modes of inheritance include autosomal dominant (28%) and X-linked traits (6%; Figure 1.3).

The Spectrum of Disease and Gene Diversity in Arab Populations

Diversity of disease groups and affected systems: Nearly, one-third of the genetic disorders in Arabs result from congenital malformations and chromosomal abnormalities (34%) and are followed by endocrine and metabolic disorders (19%). Major affected systems include the nervous (11%) and the blood and immune systems (6%). Neoplasms account for 5% of all disorders observed in Arabs. Other groups of genetic disorders are less prevalent in the region (Figure 1.4).

Diversity of disease incidence: Several groups of genetic disorders have reached epidemic values and occur at extremely high annual incidences of > 100 cases/100,000 live births among Arab individuals. This group encompasses all hemoglobin disorders (thalassemias, sickle cell disease, and hemoglobin variants), G6PD deficiency, Down syndrome, cancers (breast, ovarian, cervical, lung), intestinal carcinoid.
Figure 1.2. Disease and gene records in Arab countries according to the CTGA Database (December 2010).

Figure 1.3. Classification of genetic disorders in Arabs according to modes of inheritance (December 2010).

Figure 1.4. Classification of genetic disorders in Arabs according to the World Health Organization International Classification of Disease version 10 (December 2010).
tumors, diabetes, obesity, achondroplasia, Alzheimer’s disease, anencephaly, atrial septal defect, attention deficit-hyperactivity, Caffey disease, celiac disease, coarctation of aorta, atopic dermatitis, febrile convulsions, Graves disease, Hashimoto thyroiditis, benign hematuria, hemochromatosis, hydrocephalus, hypercalcemia, hypercholesterolemia, essential hypertension, hypospadias, intussusceptions, myopia, neural tube defects, neutropenia, orofacial cleft, poly cystic kidneys, polyhydramnios, preeclampsia, infantile hypertrophic pyloric stenosis, Sjogren syndrome, strabismus, ischemic stroke, Takayasu arteritis, Wolff-Parkinson-White syndrome, and others. Many other disorders do occur in Arab populations at higher incidence rates when compared to world data, these include: Tetralogy of Fallot, familial Mediterranean fever, deafness, Noonan syndrome, Meckel syndrome, and spina bifida. 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, dietary traditions in the case of G6PD deficiency, and consanguineous marriages in the case of many autosomal recessive disorders.

**Diversity of disease geography:** Genetic disorders are not equally distributed over the geography of the region. Almost half (48%) of these disorders occur in a single Arab country or population such as, the Lebanese type of mannose 6-phosphate receptor recognition defect (Alexander et al., 1984), the Bedouin spastic ataxia syndrome (Mousa et al., 1986), the Algerian type of spondylometaphyseal dysplasia (Kozlowski 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 Jeraish type of distal hereditary motor neuropathy (Christodoulou et al., 2000), Karak syndrome (Mubaidin et al., 2003), and the Omani type of spondyloepiphyseal dysplasia (Rajab et al., 2004). A third of the Arab disorders are limited to two or three Arab countries (21%, and 12%, respectively). Other genetic disorders occur in four or more countries (17%). In this later group, some genetic disorders hint for specific regional occurrence, such as in the case of Laurence-Moon syndrome in the Arabian Peninsula and autosomal recessive osteopetrosis type 1 and wrinkle skin syndrome in the Arabian Peninsula and the Levant (Figure 1.5). Finally, a number of disorders have a wide geographical presence encompassing 10 or more Arab countries. This group includes glucose-6-phosphate dehydrogenase deficiency, alpha- and beta-thalassemias, insulin- and noninsulin-dependent diabetes mellitus, hydrocephalus, familial Mediterranean fever, cystic fibrosis, sickle cell anemia, hereditary multiple leiomyoma of skin, anencephaly, and protein S (Figure 1.5).

**Diversity of clinical subtypes:** Many of the broad groupings of genetic disorders are further classified into types and subtypes in Arab patients indicating a heterogeneity in the features associated with these disorders. For example, mucopolysaccharidosis occurs in at least five types in the south of the Arabian Peninsula (IIIa, IIIb, VI, and VII). In Oman, glycogen storage disease is reported into four distinct types (I, II, III, and IV) and spinal muscular atrophy is associated with three types (I, II, and III). This latter disease also occurs in three variants in the Bahraini, Saudi, and Kuwaiti populations. In the UAE population, three variants occur for epidermolysis bullosa ( Junctional Herlitz type, junctional non-Herlitz type, and junctional with pyloric atresia) as well as osteogenesis imperfecta (I, IIA, and III). Some of the disorders that occur in other Arab regions with multiple variants include: Deafness (aminoglycoside-induced, autosomal dominant nonsyndromic sensorineural 15, autosomal recessive 9, 12, 13, 14, 16, 21, 22, 27, 30, 31, 32, 33, congenital neurosensory 10, neurosensory 1, and neurosensory 2, congenital with total albinism, and with onychodystrophy osteodystrophy and mental retardation syndrome), Charcot-Marie-Tooth disease (axonal 2B1, 2H, 2K, 4A, 4B2, 4C, and 4H), renal tubular acidosis (distal autosomal dominant, distal autosomal recessive, distal with progressive nerve deafness, and distal with nephrocalcinosis, short stature, mental retardation, and distinctive facies), spastic paraplegia (autosomal recessive 5A, 5B, 20, 23, and 24, and autosomal dominant 3 and 4), Ehlers-Danlos syndrome (III, VI, VIB, and the progeroid form), limb-girdle muscular dystrophy (2A, 2B, 2C, 2D, and 21), spinocerebellar ataxia (1, 2, 7, autosomal recessive 2 and 5, and autosomal recessive with axonal neuropathy), Usher syndrome (ID, IE, IG, IIA, IIB, and III), Parkinson’s disease (2, 6, 7, and 9), arthrogryposis (type 1, 2A, multiplex congenital, and multiplex congenital neurogenic type), cardiomyopathy (dilated 1A, dilated autosomal recessive, familial restrictive 1, and congestive with hypergonadotropic hypogonadism), and many others.

**Diversity of clinical outcomes due to comorbidity:** Various genetic disorders occurring at epidemic levels appear in many individuals with an array of other distinct disorders at a rate higher than expected by chance, thus the term comorbidity. In fact, many studies reviewed in the CTGA Database reveal the presence of comorbidity in patients from the region especially with major disorders including thalassemias, sickle cell disease, cystic fibrosis, Down syndrome, G6PD deficiency, and many others (Table 1.2). In certain cases, the striking occurrences of such comorbidities motivated scientists to explore the clinical outcomes such as in the case of Mohammad and colleagues (1998) who studied the coexistence of sickle cell disease with G6PD deficiency and found out that severe G6PD deficiency occur in 47% of individuals with sickle hemoglobin in Bahrain. In an independent study of six patients with cystic fibrosis, Khan and Mohammad (1985) described a reduced G6PD enzyme activity in four of their patients. A decade later, Al Arrayed and Abdulla (1996) studied the incidence of cystic fibrosis in Bahrain retrospectively by reviewing the records of patients diagnosed with the disorder during a 17-year period in a major hospital in Bahrain. The survey included a total of 27 patients, including 25 Bahrainis, with cystic
fibrosis among whom 98% also had G6PD deficiency. The common presenting clinical picture was failure to thrive (66%), pneumonia (62%), hypochloremic alkalosis (44%), and anemia (37%) with a mortality rate of 60%.

In a study of patients with cardiomyopathy in Qatar, El-Menyar et al. (2006) noticed an array of rare associations with familial antiphospholipid syndrome, Ebstein disease, HbH disease, Crohn’s disease, and thalassemia. In the later case, comorbidity of cardiomyopathy and thalassemia was found to have the shortest period between diagnosis and death (El-Menyar et al., 2006). Certainly, the systemic study of comorbidity would represent a main approach to study the clinical complexity in Arab patients with genetic disorders. Once epidemiologically established through population or community surveys, the study of the comorbidity direction and of the chronological patterns of associated clinical entities may then be translated into enhanced care of patients, selection of initial treatment, evaluation of treatment effectiveness, and improvement of prognosis.

Diversity of novel disorders: Arab scholars and researchers contributed to the description of many new syndromes and variants, such as: Najjar syndrome (Najjar et al., 1973), Barakat syndrome (Barakat et al., 1977), Abdallat syndrome (Abdallat et al., 1980), Fadhil syndrome (Fadhil et al., 1983), Woodhouse-Sakati syndrome (Woodhouse and Sakati, 1983), Al-Awadi-Raas-Rothschild syndrome (Al-Awadi et al., 1985), Malouf syndrome (Malouf et al., 1985), the Teebi type of hypertelorism (Teebi, 1987), Jalili syndrome (Jalili and Smith, 1988), Naguib-Richieri-Costa syndrome (Naguib, 1988), Teebi Naguib Al-Awadi syndrome (Teebi et al., 1988), Majeed syndrome (Majeed et al., 1989), Teebi Al Saleh Hassoon syndrome (Teebi et al., 1989), Teebi-Shaltout syndrome (Teebi and Shaltout, 1989), Dudin-Thalji syndrome (Dudin and Thalji, 1991), Sanjad-Sakati syndrome (Sanjad et al., 1991), Al-Gazali syndrome (Al Gazali et al., 1994), Temtamy preaxial brachydactyly syndrome (Temtamy et al., 1998), Al Aqeel-Al Sewairi syndrome (Al Aqeel et al., 2000), Megarbane syndrome (Megarbane et al., 2001), El-Shanti syndrome (El-Shanti et al., 2003), Bosley-Salih-Alorainy syndrome

Figure 1.5. Computer generated maps indicating the relative geographic distribution of (a) Laurence-Moon syndrome, (b) autosomal recessive osteopetrosis type 1, (c) wrinkly skin syndrome, (d) glucose-6-phosphate dehydrogenase deficiency, and (e) hydrocephalus in the Arab World according to the CTGA Database (December 2010).
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, 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 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$ 28,000; Eidi et al., 2009), Niemann-Pick disease type C (US$ 27,000; Imrie et al., 2009), inherited leukodystrophy (US$ 22,579; Bonkowsky et al., 2010), sickle cell disease (US$ 16,668; Kauf et al., 2009), beta-thalassemia (US$ 7,000; Karron et al., 1999), diabetes mellitus (US$ 1,500; Wang et al., 2009), asthma (US$ 1250; Bahadori et al., 2009), retinal dystrophy (US$ 1,000; Porz et al., 2010), hemophilia (US$ 1000; Meyers et al., 1972), and atopic dermatitis (US$ 1000; Fowler et al., 2007). Overall, the total annual cost of the most common 20 genetic ailments in the Arab World is estimated not to be less than $13 billion per year (reviewed in Tadmouri, 2008).

### Preventive Aspects of Genetic Disorders in Arabs

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 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 1.6). Hence, in the presence of available expertise and resources preventive programs may be successfully applied in many Arab communities especially in the areas of newborn screening and carrier screening for prevalent genetic disorders. Yet, 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, sociologists, 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:

**The science base:** through which disease conditions could be defined according to their attributed burden,

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**Table 1.2.** Selected examples of genetic disease comorbidities recorded in the CTGA Database (September 2010).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-thalassemia</td>
<td>Wolman disease</td>
</tr>
<tr>
<td>Beta-thalassemia</td>
<td>Alpha-thalassemia</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Dykeratosis congenita, X-linked</td>
</tr>
<tr>
<td></td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>Pycnodysostosis</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Beta-thalassemia</td>
</tr>
<tr>
<td></td>
<td>Ehlers-Danlos syndrome type III</td>
</tr>
<tr>
<td></td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td></td>
<td>Infantile hypertrophic pyloric stenosis 1</td>
</tr>
<tr>
<td></td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td></td>
<td>Sickle/beta-thalasemia</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>Absence of abdominal muscles with urinary tract abnormality and cryptorchidism</td>
</tr>
<tr>
<td></td>
<td>Choanal atresia, posterior</td>
</tr>
<tr>
<td></td>
<td>Moyamoya syndrome</td>
</tr>
<tr>
<td></td>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Dykeratosis congenita, X-linked</td>
</tr>
<tr>
<td></td>
<td>Pycnodysostosis</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Alpha-thalassemia</td>
</tr>
<tr>
<td></td>
<td>Beta-thalassemia</td>
</tr>
<tr>
<td></td>
<td>Biopharopathosis, piosis, and epiandanthus inversus</td>
</tr>
<tr>
<td></td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>Chromosome 18p deletion syndrome</td>
</tr>
<tr>
<td></td>
<td>Down syndrome</td>
</tr>
<tr>
<td></td>
<td>Frontonasal dysplasia</td>
</tr>
<tr>
<td></td>
<td>Holt-Oram syndrome</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td></td>
<td>Ebstein disease</td>
</tr>
<tr>
<td></td>
<td>Familial antiphospholipid syndrome</td>
</tr>
<tr>
<td></td>
<td>HbH disease</td>
</tr>
</tbody>
</table>

(Tischfield et al., 2005), and Megarbane-Jalkh syndrome (Megarbane et al., 2008).

**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, G6PD 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).
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.

**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 counseling (Khalifa, 1999; Fadel, 2008).

**Regulatory framework:** has to be directed to resolve the widespread misunderstanding about genetics, especially the concept of genetic risk for 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 adequate infrastructures, surveillance policies, and supportive financing mechanisms.

**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).

**Financial framework:** is a vital factor in securing the continuity of a preventive program. In most 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).

Genetic Disorders Prevention Programs in Arab States

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

**Neonatal screening:** This involves the establishment of national or hospital based registries for congenital abnormalities (e.g., Oman and the UAE) and the implementation of biochemical technologies to depict the incidence of many inherited disorders. Currently, Bahrain, Egypt, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, and the UAE execute national and private newborn screening programs varying from one disease to 23. Pilot newborn screening programs are implemented in Jordan, Kuwait, and Tunisia. 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; Krotoski et al., 2009).

**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).

**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 (Inati et al., 2006), Palestine (Tarazi et al., 2010), Saudi Arabia (Al-Saliman, 2006; Alhamdan et al., 2007), Tunisia (Chaabouni-Bouhamed, 2008), and the UAE (Al-Gazali et al., 2005).

**Prenatal diagnosis:** Is an important component that requires an extensive social framework and without which a prevention program is practically gagged. In most Arab countries, except Tunisia, selective termination of pregnancy is not legally available (Chaabouni-Bouhamed, 2008). Yet, limited applications of prenatal diagnosis were also reported from Egypt (Elgawhary et al., 2008), Lebanon (Eldahdah et al., 2007), and Palestine (Ayesh et al., 2005).

**Preimplantation genetic diagnosis:** This is a more welcomed approach since it allows the avoidance of selective pregnancy termination. Successful 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; Hellani et al., 2009; Alsulaiman et al., 2010). A recent study from the UAE found that most people favor this mode of prevention (Al-Gazali, 2005).

![Figure 1.6. Distribution of genetic disorders in Arabs according to the number of causative gene loci (December 2010).](image-url)
Arab Family Perception of Genetic Disorders

Arab families are highly close-knit units, integrated within the mesh of the larger culture-bound socioeconomic network. Families form the centre of the Arabian society and religion as an integral part of the culture. The major involvement of the family and society on genetic disorders in the Arab World does not come, thus, as a surprise. The most important ways in which the society plays its role in the manifestation of genetic diseases includes, but is not necessarily restricted to, the perception of family history and compliance to medical and genetic advice.

**Family history:** Close to 115 diseases catalogued in the CTGA Database document a positive family history of corresponding conditions. Interestingly, within this group, a large number of records document consanguinity within the family. This could again be due to the high prevalence of consanguinity in the region, an assumption highly supported by the autosomal recessive mode of inheritance of most of these disorders. In such a scenario, traditional genetic counseling cannot be expected to be as successful as reported in other societies with lower rates of inbreeding and less emphasis on families. Instead, genetic counseling in the Arab society needs to be oriented towards families. Such family oriented counseling can have an enormous impact on multiply consanguineous kindred where rare genetic disorders are clustered (Al-Gazali et al., 2006). Unfortunately, the medical community in the Arab region demonstrates a very high turnover rate. This is especially true for the Gulf States where expatriates form the major mass of the medical community. As a result, there is a dearth of family physicians who have been involved with families for a fairly long enough time to know the genetic background of the entire family. In Western societies, family physicians routinely use their experience with the history of the family right from prenatal and newborn screening to the early recognition of individuals at risk of disease (Feder and Modell, 1998). Since such a system is lacking in the region, specialists may find it difficult to diagnose a genetic disorder from consultation with the patient in isolation.

**Non-compliance:** Therapeutic non-compliance is a feature frequently encountered by physicians. This phenomenon is characterized by a refusal of the patient to abide by the recommendations of the health care provider. Apart from the direct effect on the treatment outcome of the patient, non-compliance can also cause an indirect increase in the financial burden on the society by way of excess urgent care visits, hospitalizations and higher treatment costs (Jin et al., 2008). It has been seen that chronic diseases tend to lead to lower rates of compliance than do diseases of a short duration (Farmer et al., 1994; Gascon et al., 2004). Genetic diseases tend to require life-long treatment, and thus patients are highly susceptible to resorting to non-compliance with the treatment strategies. The CTGA Database documents 17 cases of non-compliance within the patient population of the four GCC countries studied in detail. Data on this subject may not be complete since most authors do not deem it necessary to concentrate on this seemingly non-vital aspect. CTGA Database records clearly demonstrate that non-compliance can occur in any of the phases of management of the genetic screening. Thus, there are instances of parents at-risk of having an affected child refusing to get themselves screened (Joshi et al., 2002) and of parents not complying with treatment options for their children (Al Ansari, 1984; Soliman et al., 1995). More dangerous is the practice of not only disregarding the medical advice, but also seeking the help of traditional ‘healers’, often leading to disastrous consequences (Ahmed and Farroqui, 2000). In most cases of non-compliance by parents, however, parents tend to get back to the physician and restart treatment once the symptoms in the children begin to worsen, and they see that there is no option left. Patient refusal, on the other hand, is more disturbing, since those patients who demonstrate non-compliance on their own do not generally restart treatment later, even with adequate counseling (Khandekar et al., 2005). Patients may show non-compliance by refusing invasive diagnostic methods (Bhat and Hamdi, 2005), discontinuing medication (Khandekar et al., 2005), refusing surgery (Venugopalan et al., 1997), or refusing a medically advised termination of pregnancy (Gowri and Jain, 2005).

**Genetic literacy:** A characteristic feature of the Arab society is the extremely low level of genetic literacy, which makes the role of the genetic counselor quite difficult. Instances of successful applications of genetic counseling in affected families, which have helped in the early diagnoses and management of disease conditions, can be extracted from the CTGA Database (Subramanyan and Venugopalan, 2002). However, generally, people in these populations are reluctant to refer to a genetic counselor under the erroneous assumption that counselors would advise them on personal issues, such as the choice of a marriage partner or on their reproductive options. Unfortunately, such misconceptions exist not only among the patients themselves, but also among the health care providers (Hamamy and Bittles, 2009).

**Education:** A direct correlation has been demonstrated between the level of education and awareness and early detection and better management of genetic disorders in Arab populations (Al-Mahroos, 1998; Al-Saweer et al., 2003; Al-Moosa et al., 2006). Of note is the observation that compulsory premarital screening for identifying thalassemia carriers increased public awareness on genetic diseases in general, with requests for counseling on other conditions increasing (Hamamy and Bittles, 2009). It may also be a useful strategy to integrate genetic counseling into the procedure of routine prenatal care, so that it may be better accepted by the population.

**Concluding Remarks**

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, 1997).

Approximately 27% 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.

References


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