Chapter 5

Genetic Disorders in the United Arab Emirates, Bahrain, and Oman: Lessons Learned

Ghazi Omar Tadmouri, Pratibha Nair, Tasneem Obeid
Centre for Arab Genomic Studies, 22252 Dubai, United Arab Emirates

Introduction

Ever since its initiation, the Catalogue for Transmission Genetics in Arabs (CTGA) database has endeavored to index reports of genetic disorders among Arab patients. This is a daunting task, compounded by the fact that the Arabs not only constitute a huge population of close to 340 million people, but are also spread over 23 countries covering 14 million square km in two continents within their homeland itself. Add to this the Arab diaspora spread around the world, and a picture of truly massive proportions emerges. The CTGA Database Development Team realized earlier on that this enormous undertaking would need to be managed in a systematic manner. To this end, the Team works on the database in a targeted fashion, focusing on a single Arab country at a time. This strategy, initiated with the United Arab Emirates, has enabled the complete coverage of genetic disorders in two more countries (Kingdom of Bahrain and Sultanate of Oman), while maintaining a basal amount of information in the remaining Arab countries.

The completion of surveys in the three countries mentioned above is important in many respects. Firstly, being countries small in population size, they allowed for fine tuning of the search strategy and information collection and curation processes. Secondly, since these countries are located in close proximity to each other, an analysis of data can be expected to reveal the spectrum of genetic disorders within this region (Figure 5.1), as well as shed some light on the genetic characteristics of the population.

Demographic Characteristics

The three countries, Bahrain, Oman, and the UAE, share several distinctive demographic features. Like all other countries of the Gulf Cooperation Council (GCC), their population is marked by a distinct expatriate bias. Thus, in Oman about 24% of the population is made up of expatriates (Ministry of National Economy, 2003), whereas in Bahrain the migrant worker population accounts for 49% of the total population (Central Bank of Bahrain, 2007). However, nowhere is this skewed demography more apparent than in UAE where expatriates make up to 80% of the population (HSBC Bank Middle East, 2004). In fact, with the possible exception of Qatar, UAE may have the highest percentage of expatriates among any country in the world. This high influx of migrant workers has resulted in a high population growth rate and a distorted sex ratio in these countries. The total population has grown in Bahrain from 0.67 million in 2002 to 1.04 million in

2007 (Central Bank of Bahrain, 2007), and up almost 66% in UAE from 2.4 million in 1995 to 4.04 million in 2003 (UAE Census, 2005). The Omani population has remained relatively stable over the past few years, only increasing from 2 million in 1993 to 2.5 million in 2007 (Ministry of National Economy, 2003; Ministry of Health, 2007). The total population in all three countries also shows an abnormally high male to female sex ratio ranging from 1.27 in Oman to 2.08 in the UAE (Ministry of National Economy, 2003; UAE Census, 2005).

Human Health Indicators

The governments in all three countries have given considerable priority to health care. Previous volumes of this book as well as Chapter 2 of this volume provide detailed accounts of the improved health care systems in these countries. The impact of these enhancements in the health care policies and delivery in the region has reflected in considerably better health statistics in all three countries over a period of years. In fact, these countries show some of the best values for health care indicators among Arab States (Please see Table 1.2).

Over the past couple of years, UAE has taken several additional efforts in the health care sector. Most important of these is the plan to provide compulsory health insurance to all nationals and expatriate residents and their families. This ambitious plan has already been partially implemented by way of extending this facility to all government employees in Dubai as well as all UAE nationals residing in Abu Dhabi. The Bahraini Ministry of Health has similarly also announced plans for introducing compulsory health insurance for non-Bahrainis in few months. In October, 2008, the UAE Ministry of Health announced

Figure 5.1. Kingdom of Bahrain, the United Arab Emirates, Sultanate of Oman, and neighbouring countries.

the implementation of a Hospital Information System (HIS), known as Wareed, to provide both physicians and patients with equal access to health files maintained in public and private hospitals countrywide through a unified health database. Once implemented in full, this system will play a major role in improving patient care in the country. UAE's efforts in maintaining safety standards in the health care sector have also been commendable. Recently, the World Health Organization applauded the country for its efforts in successfully implementing a completely disease-free voluntary blood donation scheme (World Health Organization, 2008).

The private health care sector is also burgeoning in the region. Dubai Health Care City has been recently set up with a long-term vision for providing for high-quality health care, medical education, and research in the region. In a similar vein, plans are underway in Bahrain to develop an island solely dedicated to health care. This Health Island is being built on reclaimed land with an aim to provide cutting edge medical facilities and services and tap the growing health tourism industry.

Genetic Research and Related Services

As a part of the main activities of the Centre for Arab Genomic Studies, the Second Pan Arab Human Genetics Conference was organized in November, 2007 in order to continue its role in providing a common platform to bring together regional and international geneticists to share their knowledge and to discuss common issues. Besides the scientific program, the conference was preceded by a one day public forum on the ethical perspectives of genetic research. This forum saw religious leaders as well as genetic researchers discussing this important issue. Additionally, genetic and related fields have been the major subject for the topics of the international awards of Sheikh Hamdan Award for Medical Sciences since its establishment in 1988. Recently, the UAE Genetic Diseases Association was established as a non-profit organization under Dubai's Islamic Affairs and Charitable Activities Department, Dubai. The main aim of this organization is to control and prevent population-specific genetic disorders prevalent in the United Arab Emirates through promoting health education, screening for genetic disorders, premarital screening and providing genetic counseling. It also facilitates communication and publication of scientific knowledge, to promote education and research in genetics, and encourages interaction between workers in genetics and those in related sciences. The first project of this organization is called 'Emirates free of Thalassemia by the year 2012'. This project aims to identify the beta-thalassemia and sickle-cell carriers in the UAE premarital population in order to make the country free from the new births of children with thalassemia major by the year 2012.

Recently, Bahrain made a breakthrough in genetic research. In 2008, a scientific team from Al Jawhara Center for Molecular Medicine, Genetics, and Inherited Disorders at Arabian Gulf University isolated a new protein called ISRAA (Immune System Released Activating Agent) which is now officially registered with International Gene Bank. This protein is the first

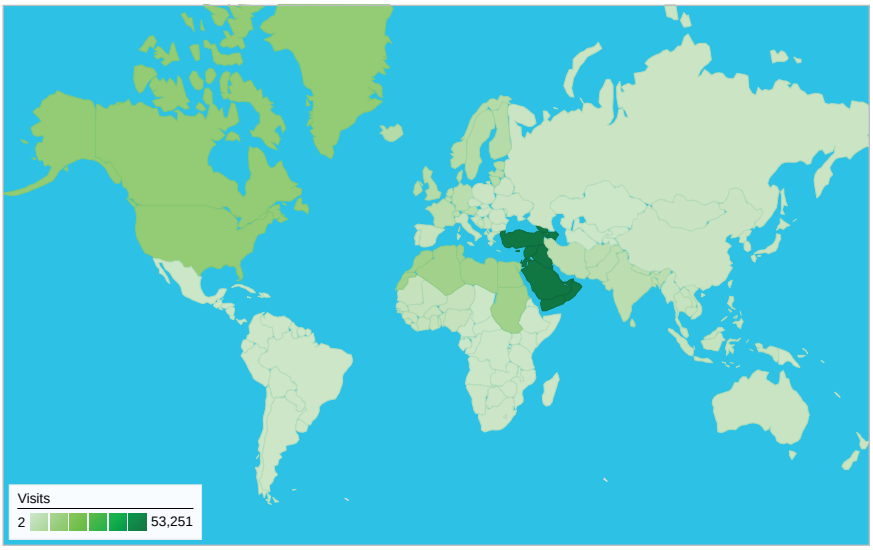
molecule that acts as a mediator between the central nervous system and the immune system. This protein is produced in the spleen when the host is infected. It then activates the immune system and gives it the capability to fight against the infection. This unprecedented discovery may help to find a possible cure for killer diseases including AIDS and cancer (Bakhiet and Taha, 2008).

In Oman, Sultan Qaboos University with collaboration with several international institutions established a research program called "Oman Family Study". The aim of this program was 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 (Hassan *et al.*, 2005; Bayoumi *et al.*, 2007; Hassan *et al.*, 2007; Please see Chapter 4).

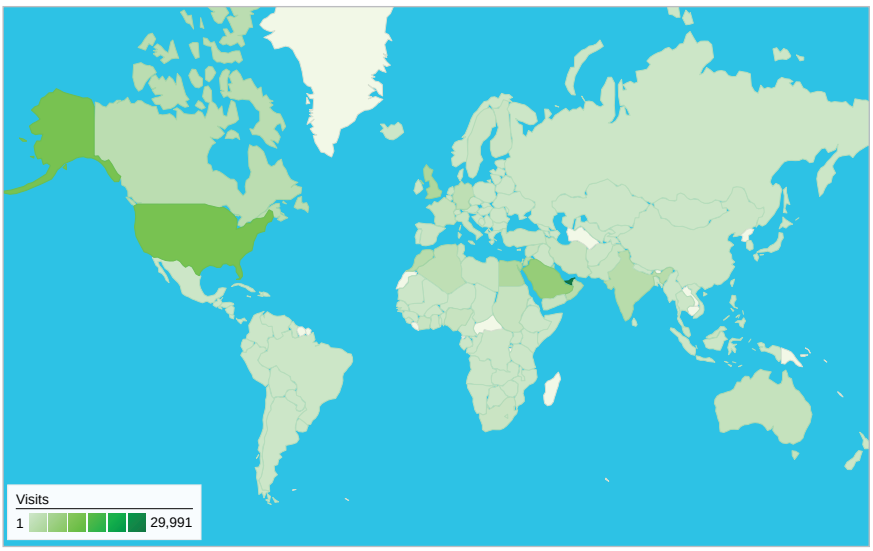
Significance of the CTGA Database

The Centre for Arab Genomic Studies adopted the proposal to launch a database on genetic disorders in the Arab World early in 2003 as a main requirement to initiate research directed towards the control of genetic disorders in Arab populations. The CTGA Database turned online on the 30th of November 2004 and since then it served nearly half a million online users. Statistics indicate that most of the visitors come from Western Asia, North America, North Africa, North Europe, and South Asia (Figure 5.2). By monitoring the CTGA Database user behaviors and by combining personal observations made throughout the last few years, users are easily grouped according to the purpose of accessing the CTGA Database as follows:

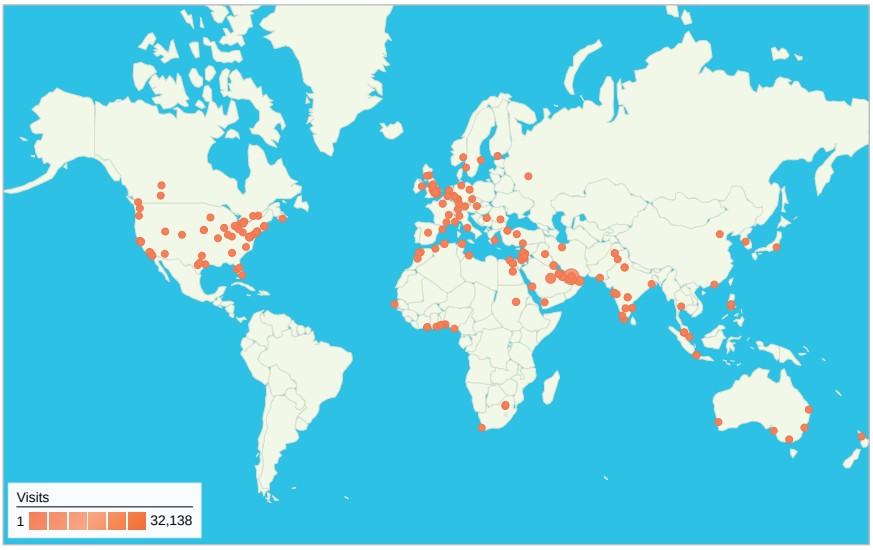
1. **Strategists and decision-makers:** This group of users interprets the CTGA Database content as an important tool for authorities to decide on future health-related strategies and to propose research directions on disorders for which information is still scant.
2. **Local information seekers:** The full-text of the majority of peer-reviewed medical journals published in the region is not available online or in other electronic formats. Thus, by accessing summarized local scientific information on genetic disorders in the CTGA Database the user is exposed to valuable local records that are otherwise hardly accessible.
3. **Intra-Arab and international collaborators:** The extended consanguineous family structure, commonly present in Arab societies, is an important factor that offers great opportunities to depict the genetic nature of disease predispositions. In view of this, the wealth of information that the CTGA Database is accumulating is an indispensable tool for Arab scientists to recognize other Arab colleagues working on similar domains and decide on possible collaborations or exchange of expertise. Similarly, international researchers use the CTGA Database to locate possible Arab collaborators in order to coordinate common global efforts.
4. **Knowledge disseminators:** CTGA Database users also encompass



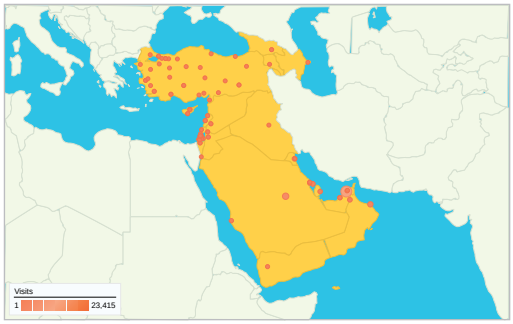
World: Subcontinents



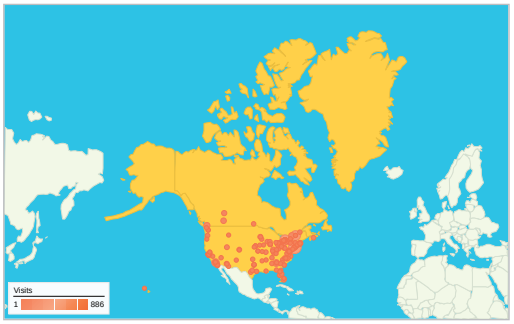
World: Countries



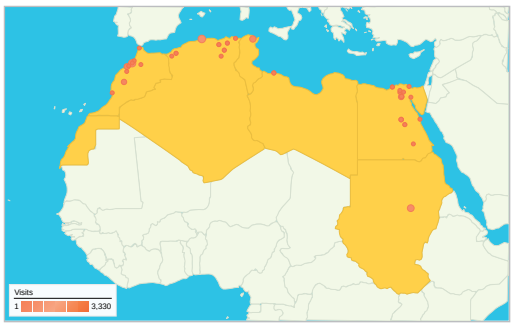
Cities: Global



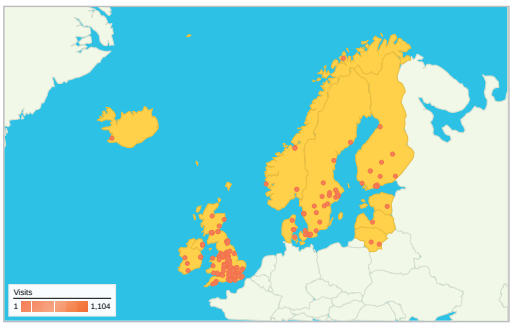
Cities: West Asia



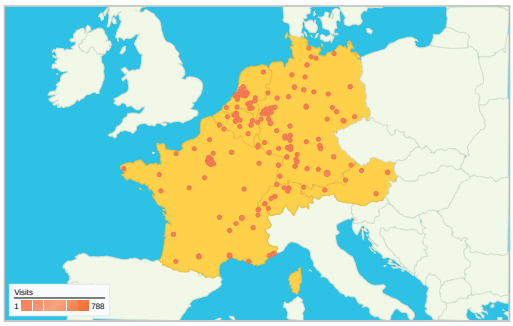
Cities: North America



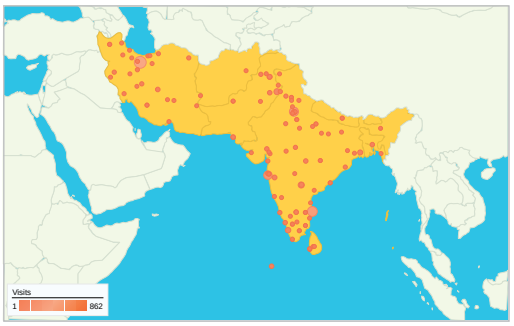
Cities: North Africa



Cities: North Europe



Cities: Central Europe



Cities: South Asia

Figure 5.2. Geographical distribution of CTGA Database users for the period between January 2005 and December 2008.

academicians, students, health care professionals, and patients who are seeking in depth information regarding all aspects of genetic disorders in Arab populations. Accordingly, the database plays an important role in disseminating this type of knowledge, which is definitely an important step towards establishing the notion of "genetic literacy" in the region (Please see 'Preventive Aspects of Genetic Disorders' in Chapter 1).

5. **Diagnosticians:** Part of users in this category utilize the CTGA Database for a more direct objective, which is to facilitate laboratory manipulations aimed at depicting a molecular diagnosis for a specific disease. In this aspect, the CTGA Database proved effective in providing local

mutation data rather than global data (mainly from Europe and the Americas), thus, enabling scientists to decide on the gene locations to target while screening for local gene changes in their populations. Similarly, at the clinical level geneticists use the CTGA Database as a "what is this syndrome" tool when facing rare cases of genetic disorders. In this regard, proper use of keywords extracted from the phenotypic description of the patients could sort out the most highly probable diagnoses that could further be refined by implementing professional skills. In year 2008, disorders that attract most of the attention include: congenital insensitivity to pain with anhidrosis, wrinkly skin syndrome, systemic lupus erythematosus, pilonidal sinus, idopathic intracranial hypertension, Down syndrome, and many others.

The Lessons Learned

The CTGA Database is not only a source of reliable statistical figures on the occurrence or geographical distribution of genetic disorders in Arab population, but also a powerful resource for a variety of other types of related information as well. This assumption comes from the concept that a database is accessed by groups of users to help them resolve varieties of subjects. Accordingly, the strength of a database is measured by its capacity to address the largest group of users with all possible interests.

In order to give the reader a concise glimpse on what could be learned from the CTGA Database, the authors attempted to tackle specific subjects dealing with a range of aspects related to genetic disease in the Arab World including: statistics regarding numbers of genetic disorders, the extent of molecular genetic analysis in the region, clinical classification of genetic disorders, consanguinity as a driving force for autosomal recessive disorders in Arab populations, clinical and genetic diversity in genetic disorders observed, the impact of genetic disorders on morbidity and mortality in Arab populations, consequences of comorbidity of genetic disorders, amniotic fluid size variation and disease associations, and the status of cooperativeness among at-risk populations with genetic counseling and the acceptance of medical advise. Definitely, this list may grow as large as the reader's imagination could reach. It could not be surprising to see contributions from independent scientists who used the CTGA Database to tackle subjects of their own interest in future editions of this publication!

Distribution of Genetic Disorders in Three Gulf States

CTGA Database records indicate the presence of 451 genetic disorders in the combined Arab populations of Bahrain, Oman, and the UAE (Table 5.1). This number is by any standards extremely high, considering the small populations involved. Among these three countries however, the number of genetic disorders surveyed seems to follow a recognizable trend. Oman, with the highest Arab population reports the largest number of disorders, followed by UAE. The Bahraini population reports the presence of the least number

of genetic disorders. Using a three set area-proportional Venn diagram, it becomes obvious that each of the three countries shares many common disorders with its neighbours (Figure 5.3). The close proximity of the countries could be a major explanation for this result. However, each of these countries has also reported several diseases exclusive to itself. Major explanations to this observation include: (1) the high heterogeneity of the populations due to the residence of many Arab expatriate populations in the region and (2) the diverse historical relations that took place between the national populations of Bahrain, Oman, and the UAE on one side with Iran, East Africa, and the Indian Subcontinent, respectively, on the other side through trade routes and immigration flows.

Nearly 30 disorders have been commonly reported in the three countries, indicating their wide-spread nature in this region. These conditions include blood disorders (thalassemia, sickle cell anemia, and G6PD deficiency), chromosomal defects (Down syndrome), developmental defects (tetralogy of Fallot and neural tube defects), cancerous conditions (breast cancer and prostate cancer), metabolic disorders (maple syrup urine disease, phenylketonuria, and propionic acidemia), and simple (cystic fibrosis) and complex (systemic lupus erythematosus, diabetes mellitus, and Noonan syndrome) gene defects.

In spite of the high number of genetic disorders reported in these countries, very limited studies have been performed here on the genes involved in these diseases (Table 5.2; also see 'Challenging Irregularities' in Chapter 1). Most studies are clinical in nature, without major effort being made to understand the molecular basis of the condition. This situation is most evident in Bahrain, where in spite of the hundred or so genetic disorders reported, only a handful of genetic studies have been conducted. Oman fares relatively better in this aspect.

Table 5.1. Genetic disorders in the Arab populations of Bahrain, UAE and Oman indexed in the CTGA Database (October, 2008).

OMIM #	Genetic Disease	Bahrain	UAE	Oman
100100	Abdominal Muscles, Absence of, with Urinary Tract Abnormality and Cryptorchidism		+	+
100300	Adams-Oliver Syndrome		+	
100800	Achondroplasia		+	
101000	Neurofibromatosis, Type II			+
101400	Saethre-Chotzen Syndrome		+	
101600	Pfeiffer Syndrome			+
104290	Alternating Hemiplegia of Childhood			+
105250	Amyloidosis, Primary Cutaneous			+
105830	Angelman Syndrome		+	
106100	Angioedema, Hereditary		+	
106300	Spondyloarthropathy, Susceptibility to, 1	+	+	+
106700	Total Anomalous Pulmonary Venous Return 1		+	+
107320	Antiphospholipid Syndrome	+		+
107600	Aplasia Cutis Congenita		+	+
108110	Arthrogryposis Multiplex Congenita		+	+
108120	Arthrogryposis, Distal, Type 1		+	+
108300	Stickler Syndrome, Type I		+	
108800	Atrial Septal Defect 1		+	+
109650	Behcet Syndrome	+		+
113600	Branchial Cleft Anomalies			+
114290	Campomelic Dysplasia		+	+
114480	Breast Cancer	+	+	+
114500	Colorectal Cancer		+	
114900	Carcinoid Tumors, Intestinal			+
115200	Cardiomyopathy, Dilated, 1A		+	+

OMIM #	Genetic Disease	Bahrain	UAE	Oman
115210	Cardiomyopathy, Familial Restrictive, 1		+	
115430	Carpal Tunnel Syndrome			+
117550	Sotos Syndrome		+	
117650	Cerebrocostomandibular Syndrome		+	
118650	Chondrodysplasia Punctata, Autosomal Dominant		+	
118800	Paroxysmal Nonkinesigenic Dyskinesia 1			+
119100	Split-Hand/Foot Malformation with Long Bone Deficiency 1		+	
119530	Orofacial Cleft 1		+	+
120000	Coarctation of Aorta		+	+
120330	Papillorenal Syndrome			+
121050	Contractural Arachnodactyly, Congenital			+
122470	Cornelia de Lange Syndrome			+
123400	Creutzfeldt-Jakob Disease			+
125851	Maturity-Onset Diabetes of the Young, Type II			+
125853	Diabetes Mellitus, Noninsulin-Dependent	+	+	+
130650	Beckwith-Wiedemann Syndrome			+
130710	Emphysema, Congenital Lobar			+
131445	Ependymoma, Familial		+	
132700	Cylindromatosis, Familial	+		
133200	Erythrokeratodermia Variabilis		+	
133450	Ewing Sarcoma Breakpoint Region 1		+	+
136760	Frontonasal Dysplasia		+	
137215	Gastric Cancer			+
137580	Gilles De La Tourette Syndrome	+		
137750	Glaucoma 1, Open Angle, A			+
137800	Glioma of Brain, Familial			+
139393	Guillain-Barre Syndrome, Familial		+	+
140300	Hashimoto Thyroiditis		+	
141200	Hematuria, Benign Familial	+	+	
141800	Hemoglobin - Alpha Locus 1	+	+	+
141900	Hemoglobin - Beta Locus	+	+	+
142250	Hemoglobin, Gamma G		+	
142340	Diaphragmatic Hernia, Congenital	+	+	+
142623	Hirschsprung Disease, Susceptibility to, 1	+	+	+
142900	Holt-Oram Syndrome	+	+	+
143100	Huntington Disease	+	+	
143400	Multicystic Renal Dysplasia, Bilateral	+	+	+
143465	Attention Deficit-Hyperactivity Disorder			+
143890	Hypercholesterolemia, Autosomal Dominant	+	+	
145500	Hypertension, Essential		+	+
145600	Malignant Hyperthermia, Susceptibility To, 1	+		
146000	Hypochondroplasia		+	
146110	Hypogonadotropic Hypogonadism			+
146390	Chromosome 18p Deletion Syndrome		+	
146450	Hypospadias, Autosomal	+		+
147050	IgE Responsiveness, Atopic	+		
147710	Intussusception	+		+
148000	Kaposi Sarcoma			+
148900	Segmentation Syndrome 1		+	
150600	Legg-Calve-Perthes Disease	+		

OMIM #	Genetic Disease	Bahrain	UAE	Oman
150800	Leiomyoma, Hereditary Multiple, of Skin		+	
151600	Leukonychia Totalis			+
152700	Systemic Lupus Erythematosus	+	+	+
153600	Macroglobulinemia, Waldenstrom, Susceptibility To, 1	+		
154500	Treacher Collins-Franceschetti Syndrome			+
154700	Marfan Syndrome			+
155600	Melanoma, Cutaneous Malignant			+
156240	Mesothelioma, Malignant			+
156810	Microgastria-Limb Reduction Defects Association		+	
158330	Mullerian Aplasia			+
160700	Myopia 2			+
160900	Dystrophia Myotonica 1		+	
161550	Nasopharyngeal Carcinoma	+		+
162091	Schwannomatosis	+		+
162200	Neurofibromatosis, Type I		+	+
163950	Noonan Syndrome 1	+	+	+
164210	Hemifacial Microsomia	+		
164400	Spinocerebellar Ataxia 1			+
164750	Omphalocele		+	
166000	Enchondromatosis, Multiple			+
166200	Osteogenesis Imperfecta, Type I		+	
166210	Osteogenesis Imperfecta, Type IIA		+	+
167000	Suppressor of Tumorigenicity 8	+	+	
167100	Pachydermoperiostosis		+	
167750	Pancreas, Annular		+	+
168900	Patella, Chondromalacia Of	+		
173000	Pilonidal Sinus	+		
173800	Poland Syndrome		+	
173900	Polycystic Kidneys	+		
174400	Polydactyly, Preaxial I			+
174800	McCune-Albright Syndrome		+	
175100	Adenomatous Polyposis of the Colon	+		
175200	Peutz-Jeghers Syndrome	+		
176000	Porphyria, Acute Intermittent	+		+
176270	Prader-Willi Syndrome		+	
176670	Hutchinson-Gilford Progeria Syndrome		+	
176807	Prostate Cancer	+	+	+
176860	Protein C Deficiency, Congenital Thrombotic Disease due to			+
176880	Protein S, Alpha		+	+
178550	Pulmonary Hemosiderosis			+
178600	Pulmonary Hypertension, Primary		+	+
179010	Pyloric Stenosis, Infantile Hypertrophic 1	+		+
179800	Renal Tubular Acidosis, Distal, Autosomal Dominant		+	
179850	Dowling-Degos Disease		+	
180200	Retinoblastoma			+
180300	Rheumatoid Arthritis		+	+
180849	Rubinstein-Taybi Syndrome		+	
182212	Shprintzen-Goldberg Craniosynostosis Syndrome	+		
182260	Slipped Femoral Capital Epiphyses	+		
182940	Neural Tube Defects		+	+

OMIM #	Genetic Disease	Bahrain	UAE	Oman
184700	Polycystic Ovary Syndrome 1	+	+	
185100	Strabismus, Susceptibility to			+
185300	Sturge-Weber Syndrome		+	+
185900	Syndactyly, Type I	+		
187300	Telangiectasia, Hereditary Hemorrhagic, of Rendu, Osler, and Weber	+		
187400	Testicular Torsion	+		
187500	Tetralogy of Fallot	+	+	+
187600	Thanatophoric Dysplasia, Type I		+	+
188030	Thrombocytopenic Purpura, Autoimmune			+
188400	DiGeorge Syndrome		+	
188470	Thyroid Carcinoma, Follicular	+	+	
188550	Thyroid Carcinoma, Papillary			+
188580	Thyrotoxic Periodic Paralysis	+		+
189800	Preeclampsia/Eclampsia 1			+
189960	Tracheoesophageal Fistula with or without Esophageal Atresia		+	+
190685	Down Syndrome	+	+	+
191100	Tuberous Sclerosis			+
191390	Ulcerative Colitis, Susceptibility to	+		+
192350	VATER Association			+
192500	Long QT Syndrome 1			+
193000	Vesicoureteral Reflux 1		+	+
193200	Vitiligo		+	+
194070	Wilms Tumor 1		+	
194200	Wolff-Parkinson-White Syndrome			+
200400	Achalasia, Familial Esophageal			+
200700	Chondrodysplasia, Grebe Type		+	+
201000	Carpenter Syndrome	+		
201450	Acyl-CoA Dehydrogenase, Medium-Chain, Deficiency of	+		
201460	Acyl-CoA Dehydrogenase, Long-Chain, Deficiency of			+
201910	Adrenal Hyperplasia, Congenital, due to 21-Hydroxylase Deficiency		+	+
203100	Oculocutaneous Albinism, Type IA	+		+
203655	Alopecia Universalis Congenita			+
206500	Anencephaly	+	+	+
207600	Takayasu Arteritis	+		
207900	Argininosuccinic Aciduria	+		+
208150	Pena-Shokeir Syndrome, Type I			+
208300	Ascites, Chylous			+
208500	Asphyxiating Thoracic Dystrophy 1		+	+
209500	Atrichia with Papular Lesions			+
209880	Autonomic Control, Congenital Failure of		+	
209900	Bardet-Biedl Syndrome	+		+
210600	Seckel Syndrome 1			+
211450	Bronchomalacia			+
211530	Bulbar Palsy, Progressive, with Sensorineural Deafness			+
211980	Lung Cancer	+		+
212065	Congenital Disorder of Glycosylation, Type Ia			+
212140	Carnitine Deficiency, Systemic Primary	+		
212750	Celiac Disease			+
213300	Joubert Syndrome 1		+	+
214100	Zellweger Syndrome			+
214150	Cerebrooculofacioskeletal Syndrome			+

OMIM #	Genetic Disease	Bahrain	UAE	Oman
214300	Klippel-Feil Syndrome, Autosomal Recessive	+		
214500	Chediak-Higashi Syndrome	+		
214800	CHARGE Syndrome			+
215100	Rhizomelic Chondrodysplasia Punctata, Type 1		+	
215700	Citrullinemia, Classic			+
216550	Cohen Syndrome		+	+
217095	Conotruncal Heart Malformations		+	
217990	Corpus Callosum, Agenesis of			+
218030	Cortisol 11-Beta-Ketoreductase Deficiency			+
218700	Hypothyroidism, Congenital, Nongoitrous, 2			+
219050	Cryptorchidism, Unilateral or Bilateral			+
219200	Cutis Laxa, Autosomal Recessive, Type II			+
219250	Cutis Marmorata Telangiectatica Congenita			+
219700	Cystic Fibrosis	+	+	+
219730	Cystic Kidney Disease with Ventriculomegaly			+
219800	Cystinosis, Nephropathic		+	
220200	Dandy-Walker Syndrome		+	+
220400	Jervell and Lange-Nielsen Syndrome	+		
220500	Deafness, Congenital, and Onychodystrophy, Recessive Form			+
222100	Diabetes Mellitus, Insulin-Dependent	+	+	+
222300	Wolfram Syndrome			+
222448	Donnai-Barrow Syndrome		+	
222765	Rhizomelic Chondrodysplasia Punctata, Type 2		+	
223000	Lactase Deficiency, Congenital			+
223400	Duodenal Atresia		+	
224700	Ebstein Anomaly	+		
224900	Ectodermal Dysplasia, Anhidrotic		+	
225500	Ellis-van Creveld Syndrome		+	+
225750	Aicardi-Goutieres Syndrome 1			+
226650	Epidermolysis Bullosa, Generalized Atrophic Benign		+	+
226700	Epidermolysis Bullosa Letalis		+	
226730	Epidermolysis Bullosa with Pyloric Atresia		+	
226980	Epiphyseal Dysplasia, Multiple, with Early-Onset Diabetes Mellitus		+	+
227090	Erythroderma, Lethal Congenital			+
227260	Facial Ectodermal Dysplasia		+	+
227600	Factor X Deficiency		+	+
227650	Fanconi Anemia		+	+
228520	Fibrochondrogenesis		+	+
228550	Fibromatosis, Congenital Generalized	+		
229400	Frontofacionasal Dysostosis		+	+
229850	Fryns Syndrome	+		
230400	Galactosemia		+	+
230500	GM1-Gangliosidosis, Type I		+	+
230750	Gastroschisis			+
230800	Gaucher Disease, Type I		+	+
231070	Geroderma Osteodysplastica		+	+
231300	Glaucoma 3, Primary Infantile, A		+	
231670	Glutaric Acidemia I		+	+
231680	Multiple Acyl-CoA Dehydrogenation Deficiency		+	+
232200	Glycogen Storage Disease I	+	+	+

OMIM #	Genetic Disease	Bahrain	UAE	Oman
232300	Glycogen Storage Disease II			+
232400	Glycogen Storage Disease III			+
232500	Glycogen Storage Disease IV			+
234820	Hemangiopericytoma, Malignant	+		
235400	Hemolytic Uremic Syndrome, Atypical		+	
235510	Hennekam Lymphangiectasia-Lymphedema Syndrome		+	+
235730	Mowat-Wilson Syndrome		+	
236000	Hodgkin Lymphoma	+	+	
236100	Holoprosencephaly		+	+
236200	Homocystinuria		+	+
236250	Homocystinuria due to Deficiency of N(5,10)-Methylenetetrahydrofolate Reductase Activity	+		
236600	Hydrocephalus		+	+
236680	Hydrolethalus Syndrome 1			+
237500	Dubin-Johnson Syndrome	+		
238320	Hypergonadotropic Hypogonadism			+
238600	Hyperlipoproteinemia, Type I		+	
241410	Hypoparathyroidism-Retardation-Dysmorphism Syndrome			+
241550	Hypoplastic Left Heart Syndrome			+
242300	Ichthyosis, Lamellar, 1		+	+
242650	Primary Ciliary Dyskinesia		+	
243150	Intestinal Atresia, Multiple		+	
243200	Intracranial Hypertension, Idiopathic		+	+
243310	Iris Coloboma with Ptosis, Hypertelorism, and Mental Retardation			+
243500	Isovaleric Acidemia	+		+
243600	Jejunal Atresia		+	+
243700	Hyperimmunoglobulin E-Recurrent Infection Syndrome, Autosomal Recessive			+
245200	Krabbe Disease		+	
245600	Larsen Syndrome, Recessive		+	
245800	Laurence-Moon Syndrome	+	+	+
246200	Donohue Syndrome		+	
246450	3-@Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency			+
248250	Hypomagnesemia 3, Renal			+
248300	Mal de Meleda		+	
248600	Maple Syrup Urine Disease	+	+	+
248950	McDonough Syndrome		+	
249000	Meckel Syndrome, Type 1		+	+
249100	Familial Mediterranean Fever	+	+	
249270	Thiamine-Responsive Megaloblastic Anemia Syndrome			+
250100	Metachromatic Leukodystrophy			+
250220	Spondylometaphyseal Dysplasia, Sedaghatian Type		+	
250950	3-@Methylglutaconic Aciduria, Type I	+		+
251000	Methylmalonic Aciduria due to Methylmalonyl-CoA Mutase Deficiency	+		+
251170	Mevalonate Kinase		+	
251200	Microcephaly, Primary Autosomal Recessive, 1			+
251260	Nijmegen Breakage Syndrome		+	
251450	Desbuquois Syndrome		+	
252350	Moyamoya Disease 1		+	
252500	Mucolipidosis II Alpha/Beta		+	
252600	Mucolipidosis III Alpha/Beta		+	

OMIM #	Genetic Disease	Bahrain	UAE	Oman
252900	Mucopolysaccharidosis Type IIIA			+
252920	Mucopolysaccharidosis Type IIIB		+	
253000	Mucopolysaccharidosis Type IVA			+
253200	Mucopolysaccharidosis Type VI		+	+
253220	Mucopolysaccharidosis Type VII			+
253300	Spinal Muscular Atrophy, Type I	+	+	+
253400	Spinal Muscular Atrophy, Type III	+		+
253550	Spinal Muscular Atrophy, Type II	+		+
254200	Myasthenia Gravis		+	+
254500	Myeloma, Multiple		+	
255120	Carnitine Palmitoyltransferase I Deficiency			+
255800	Schwartz-Jampel Syndrome, Type 1		+	+
256100	Nephronophthisis 1		+	
256300	Nephrosis 1, Congenital, Finnish Type		+	+
256450	Hyperinsulinemic Hypoglycemia, Familial, 1			+
256500	Netherton Syndrome		+	
256520	Neu-Laxova Syndrome			+
256540	Neuraminidase Deficiency with Beta-Galactosidase Deficiency			+
256550	Neuraminidase Deficiency			+
256700	Neuroblastoma		+	
256800	Insensitivity to Pain, Congenital, with Anhidrosis		+	
257220	Niemann-Pick Disease, Type C1		+	
257350	Nuchal Bleb, Familial			+
257920	Oculopalatoskeletal Syndrome		+	
258315	Omodysplasia, Generalized Form		+	
259420	Osteogenesis Imperfecta, Type III		+	
259700	Osteopetrosis, Autosomal Recessive 1	+	+	
259775	Raine Syndrome		+	
259900	Hyperoxaluria, Primary, Type I	+	+	+
260350	Pancreatic Carcinoma			+
260500	Papilloma of Choroid Plexus			+
261100	Megaloblastic Anemia 1	+		
261550	Persistent Mullerian Duct Syndrome, Types I and II		+	+
261600	Phenylketonuria	+	+	+
261800	Pierre Robin Syndrome		+	+
263200	Polycystic Kidney Disease, Autosomal Recessive		+	+
263510	Short Rib-Polydactyly Syndrome, Type III		+	
263610	Polyhydramnios, Chronic Idiopathic	+		
263630	Polysyndactyly with Cardiac Malformation			+
263650	Popliteal Pterygium Syndrome, Lethal Type		+	
264350	Pseudohypoaldosteronism, Type I, Autosomal Recessive			+
264480	Pseudotrisomy 13 Syndrome		+	
264600	Pseudovaginal Perineoscrotal Hypospadias		+	+
265000	Multiple Pterygium Syndrome, Escobar Variant		+	+
265430	Pulmonary Hypoplasia, Primary		+	+
265800	Pycnodysostosis			+
265950	Pyloric Atresia		+	
266130	Glutathione Synthetase Deficiency		+	+
266600	Inflammatory Bowel Disease 1	+		
267450	Respiratory Distress Syndrome in Premature Infants			+

OMIM #	Genetic Disease	Bahrain	UAE	Oman
267500	Reticular Dysgenesia		+	
268130	Revesz Syndrome		+	
268210	Rhabdomyosarcoma 1	+		+
268310	Robinow Syndrome, Autosomal Recessive		+	+
268800	Sandhoff Disease		+	+
269000	SC Phocomelia Syndrome		+	
269160	Schizencephaly		+	+
269250	Schneckenbecken Dysplasia		+	
269700	Lipodystrophy, Congenital Generalized, Type 2			+
270400	Smith-Lemli-Opitz Syndrome			+
270800	Spastic Paraplegia 5A, Autosomal Recessive			+
271665	Spondylometaepiphyseal Dysplasia, Short Limb-Hand Type		+	
272800	Tay-Sachs Disease		+	+
273300	Testicular Tumors	+		
273800	Thrombasthenia of Glanzmann and Naegeli			+
274150	Thrombotic Thrombocytopenic Purpura, Congenital			+
274600	Pendred Syndrome		+	
275000	Graves Disease			+
275200	Hypothyroidism, Congenital, Nongoitrous, 1		+	+
275355	Squamous Cell Carcinoma, Head and Neck			+
276300	Mismatch Repair Cancer Syndrome		+	
276700	Tyrosinemia, Type I			+
277000	Rokitansky-Kuster-Hauser Syndrome	+		+
277170	Varadi-Papp Syndrome		+	
277300	Spondylocostal Dysostosis, Autosomal Recessive, 1		+	
277440	Vitamin D-Dependent Rickets, Type II	+		+
277580	Waardenburg-Shah Syndrome		+	+
277900	Wilson Disease			+
278000	Wolman Disease	+		
278250	Wrinkly Skin Syndrome		+	+
278700	Xeroderma Pigmentosum, Complementation Group A		+	
300000	Opitz Syndrome	+		
300068	Androgen Insensitivity Syndrome			+
300388	Polymicrogyria, Bilateral Perisylvian	+		
300530	Kawasaki Disease	+		+
300624	Fragile X Mental Retardation Syndrome	+		+
301220	Pigmentary Disorder, Reticulate, with Systemic Manifestations		+	
301500	Fabry Disease		+	
301800	Anus, Imperforate		+	
302960	Chondrodysplasia Punctata 2, X-Linked Dominant		+	
303350	MASA Syndrome		+	
304050	Aicardi Syndrome			+
304100	Corpus Callosum, Partial Agenesis of, X-Linked			+
305000	Dyskeratosis Congenita, X-linked		+	
305600	Focal Dermal Hypoplasia			+
305800	Membranoproliferative Glomerulonephritis, X-Linked	+	+	+
305900	Glucose-6-Phosphate Dehydrogenase	+	+	+
306700	Hemophilia A	+		
307000	Hydrocephalus due to Congenital Stenosis of Aqueduct of Sylvius		+	
307030	Hyperglycerolemia			+
308240	Lymphoproliferative Syndrome, X-Linked	+		
308350	Infantile Spasm Syndrome, X-Linked		+	+
309400	Menkes Disease		+	
309550	Fragile Site Mental Retardation 1 Gene		+	
310400	Myotubular Myopathy 1			+
311250	Ornithine Transcarbamylase Deficiency, Hyperammonemia due to			+
312750	Rett Syndrome			+
600309	Atrioventricular Septal Defect			+
600631	Enuresis, Nocturnal 1		+	
600669	Epilepsy, Idiopathic Generalized			+
600807	Asthma, Susceptibility To		+	+
600995	Nephrotic Syndrome, Steroid-Resistant, Autosomal Recessive		+	+
601161	Trisomy 18-Like Syndrome		+	
601170	Muscular Dystrophy, Congenital, with Severe Central Nervous System Atrophy and Absence of Large Myelinated Fibers		+	
601367	Stroke, Ischemic			+
601446	Right Pelvic Kidney		+	
601451	Nevo Syndrome		+	
601559	Stuve-Wiedemann Syndrome		+	+
601626	Leukemia, Acute Myeloid			+
601634	Neural Tube Defects, Folate-Sensitive	+	+	+
602089	Hemangioma, Capillary Infantile		+	
602400	Ichthyosis, Follicular Atrophoderma, Hypotrichosis, and Hypohidrosis		+	
602722	Renal Tubular Acidosis, Distal, Autosomal Recessive			+
603003	Bile Duct Cysts	+		
603165	Dermatitis, Atopic		+	+
603278	Focal Segmental Glomerulosclerosis 1	+	+	
603513	Cerebral Palsy, Spastic, Symmetric, Autosomal Recessive			+
603553	Hemophagocytic Lymphohistiocytosis, Familial, 2			+
603671	Acromelic Frontonasal Dysostosis		+	
603802	Microcephaly with Simplified Gyral Pattern		+	+
603903	Sickle Cell Anemia	+	+	+
603933	Diabetic Nephropathy, Susceptibility to	+	+	+
604370	Ovarian Cancer, Epithelial			+
604498	Amegakaryocytic Thrombocytopenia, Congenital		+	
604801	Muscular Dystrophy, Congenital, 1B		+	
605027	Lymphoma, Non-Hodgkin, Familial	+	+	+
605074	Renal Cell Carcinoma, Papillary	+		
605552	Abdominal Obesity-Metabolic Syndrome			+
605818	Deafness, Autosomal Recessive 27		+	
605899	Glycine Encephalopathy			+
606054	Propionic Acidemia	+	+	+
606072	Rippling Muscle Disease			+
606176	Diabetes Mellitus, Permanent Neonatal			+
606369	Epileptic Encephalopathy, Lennox-Gastaut Type			+
606545	Ichthyosis, Lamellar, 5		+	
606788	Anorexia Nervosa, Susceptibility to, 1		+	+
606812	Fumarase Deficiency		+	

OMIM #	Genetic Disease	Bahrain	UAE	Oman
606854	Polymicrogyria, Bilateral Frontoparietal		+	
606893	Vascular Malformation, Primary Intraosseous			+
607014	Hurler Syndrome			+
607088	Spinal Muscular Atrophy, Distal, Autosomal Recessive		+	
607131	Macrocephaly with Multiple Epiphyseal Dysplasia and Distinctive Facies		+	+
607154	Allergic Rhinitis	+		+
607364	Bartter Syndrome, Type 3		+	
607398	Glucocorticoid Deficiency 2		+	
607411	Patent Ductus Arteriosus		+	
607432	Lissencephaly I		+	+
607483	Basal Ganglia Disease, Biotin-Responsive			+
607499	Bulimia Nervosa, Susceptibility to, 1			+
607572	Leprosy, Susceptibility to, 2		+	
607847	Neutropenia, Nonimmune Chronic Idiopathic, of Adults			+
607907	Dermatofibrosarcoma Protuberans			+
608027	Cerebellar Atrophy with Progressive Microcephaly			+
608091	Joubert Syndrome 2		+	
608154	Lipodystrophy, Generalized, with Mental Retardation, Deafness, Short Stature, and Slender Bones			+
608232	Leukemia, Chronic Myeloid			+
608594	Lipodystrophy, Congenital Generalized, Type 1		+	+
608637	Spondyloepiphyseal Dysplasia, Omani Type			+
608710	Wegener Granulomatosis	+		+
608808	Transposition of the Great Arteries, Dextro-Looped			+
608836	Carnitine Palmitoyltransferase II Deficiency, Lethal Neonatal	+		+
608911	Choanal Atresia, Posterior		+	+
608980	Bifid Nose, Renal Agenesis, and Anorectal Malformations		+	
609222	Cephalocele, Atretic			+
609465	Al-Gazali Syndrome		+	
610685	Split-Hand/Foot Malformation with Long Bone Deficiency 2		+	+

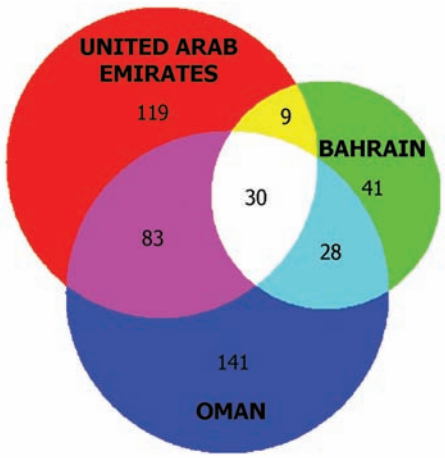


Figure 5.3. Three set area-proportional Venn diagram representing data in Table 5.1.

A comparatively higher portion of the genetic research conducted in the country includes studies at the molecular level, involving analysis of genetic or chromosomal defects in the patients studied.

Clinical Classification and Molecular Complexity

According to the WHO ICD-10 classification of diseases, the most prominent category of disorders seen in the three countries in which data collection has been completed is the category of congenital malformations and chromosomal abnormalities. This is especially true of UAE, where 52% of the total disorders reported belong to this sole category. Although congenital disorders constitute the largest category of genetic disorders in both Oman and Bahrain too, the percentage is significantly lower at 37% and 27%, respectively. Endocrine, nutritional, and metabolic disorders form another major category in these countries, with 24% of disorders in both Oman and Bahrain reported to fall under it. Only in the UAE is the percentage of disorders in this category (18%) lower than the average value for all Arab countries. Diseases of the nervous system and neoplasms are other categories seen fairly commonly in Oman (9% each). Neoplasms are also fairly common in Bahrain (12%). Bahrain also shows very high number of disorders of the blood and immune mechanism, musculoskeletal, digestive, and genitourinary systems (Figure 5.4).

These differences could be due to genuine differences in the

disease profile of these three countries. However, considering their geographical and ethnic characteristics, this seems to be unlikely, especially with regard to the populations of UAE and Oman. On the other hand, it is more likely that professionals in certain specialized medical fields are more or less active in each of these countries, giving rise to the differences in the disease profile apparent in the CTGA Database.

Interestingly, in all three countries, more than 50% of disorders reported in the database are due to single-gene defects (Figure 5.5). This should offer some comfort to researchers, since single gene disorders are expected to be easier to study than complex

Table 5.2. Gene loci studied in Arab individuals from Bahrain, UAE and Oman indexed in the CTGA Database (October, 2008).

OMIM #	Genetic Disease	Bahrain	UAE	Oman
100730	Cholinergic Receptor, Nicotinic, Gamma Polypeptide		+	+
106150	Angiotensin I		+	
106180	Angiotensin I-Converting Enzyme	+	+	+
107680	Apolipoprotein A-I		+	+
107730	Apolipoprotein B		+	
108780	Natriuretic Peptide Precursor A		+	
110300	ABO Blood Group	+		
111680	Rhesus Blood Group, D Antigen	+		+
113705	Breast Cancer 1 Gene		+	
116899	Cyclin-Dependent Kinase Inhibitor 1A			+
120700	Complement Component 3			+
120810	Complement Component 4A			+
121011	Gap Junction Protein, Beta-2			+
124092	Interleukin 10			+
126455	Solute Carrier Family 6 (Neurotransmitter Transporter, Dopamine), Member 3			+
134637	Tumor Necrosis Factor Receptor Superfamily, Member 6			+
134934	Fibroblast Growth Factor Receptor 3		+	+
139130	Guanine Nucleotide-Binding Protein, Beta-3		+	
141850	Hemoglobin--Alpha Locus 2	+	+	
142800	Major Histocompatibility Complex, Class I, A			+
142830	Major Histocompatibility Complex, Class I, B			+
142840	Major Histocompatibility Complex, Class I, C			+
142860	Major Histocompatibility Complex, Class II, DR Alpha			+
146930	Interleukin 8			+
147570	Interferon, Gamma		+	+
147620	Interleukin 6			+
147670	Insulin Receptor		+	
147679	Interleukin 1 Receptor Antagonist			+
147680	Interleukin 2			+
147720	Interleukin 1-Beta			+
147730	Interleukin 2 Receptor, Alpha		+	
147760	Interleukin 1-Alpha			+
147780	Interleukin 4			+
151443	Leukemia Inhibitory Factor Receptor		+	+
153440	Lymphotoxin-Alpha			+
153454	Procollagen-Lysine, 2-Oxoglutarate 5-Dioxygenase		+	
163890	Synuclein, Alpha		+	
164870	V-ERB-B2 Avian Erythroblastic Leukemia Viral Oncogene Homolog 2			+
170280	Perforin 1			+
176741	Proliferation-Related Ki-67 Antigen			+
176930	Coagulation Factor II	+		
179820	Renin		+	
182205	Sex Hormone-Binding Globulin			+
187011	Chemokine, CC Motif, Ligand 5	+	+	
190180	Transforming Growth Factor, Beta-1		+	
191160	Tumor Necrosis Factor			+
191170	Tumor Protein p53			+
191315	Neurotrophic Tyrosine Kinase, Receptor, Type 1		+	
227400	Factor V Deficiency	+		
243400	Isoniazid Inactivation		+	+
300126	Dyskerin		+	
300371	ATP-Binding Cassette, Subfamily D, Member 1		+	
300415	Myotubularin			+
308840	L1 Cell Adhesion Molecule		+	
400003	Deleted in Azoospermia			+
600073	Low Density Lipoprotein Receptor-Related Protein2		+	
600185	BRCA2 Gene		+	
600354	Survival of Motor Neuron 1, Telomeric	+		+
600355	Baculoviral IAP Repeat-Containing Protein 1	+		+
600778	Cyclin-Dependent Kinase Inhibitor 1B			+
601146	Growth/Differentiation Factor 5			+
601627	Survival of Motor Neuron 2, Centromeric	+		+
602302	Hairless, Mouse, Homolog of			+
602337	Receptor Tyrosine Kinase-Like Orphan Receptor 2			+
602421	Cystic Fibrosis Transmembrane Conductance Regulator	+	+	+
602744	Glyceronephosphate O-Acyltransferase		+	
603100	1-@Acylglycerol-3-Phosphate O-Acyltransferase 2		+	+
603681	Otoferlin		+	
603799	Carbohydrate Sulfotransferase 3			+
604032	Eukaryotic Translation Initiation Factor 2-Alpha Kinase 3		+	+
604945	Killer Cell Immunoglobulin-Like Receptor, Two Domains, Long Cytoplasmic Tail, 4			+
605802	Zinc Finger E Box-Binding Homeobox 2		+	
605925	Pericentrin 2			+
606119	Secreted LY6/PLAUR Domain-Containing Protein 1		+	
606154	Mucin 16	+		
606158	BSCL2 Gene			+
606945	Low Density Lipoprotein Receptor	+		
607093	5,10-@Methylenetetrahydrofolate Reductase	+	+	+
607817	COH1 Gene		+	+
607900	Kindlin 1			+
609023	Myofibrillogenesis Regulator 1			+
609884	Transmembrane Protein 67			+
610148	BBS10 Gene			+
611458	Galactosidase, Beta-1		+	
611716	ATPase, H+ Transporting, Lysosomal, V0 Subunit A2			+

disorders. In addition, such disorders are also more amenable to screening programs.

Consanguinity as a Driving Force for Autosomal Recessive Disorders

Theoretically, recessive traits are expected to be less available than dominant traits in any randomly mating population. This is attributed to the fact that while a recessive gene could be inherited by 75% of the population, it will manifest only in 25% of the population, compared to 50% in dominant traits. In Arab populations, however, 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 (El-Shafei *et al.*, 1986; Abdulrazzaq *et al.*, 1997; Kerkeni *et al.*, 2007; El Mouzan *et al.*, 2008). An analysis of data in the CTGA Database indicates that of the 451 genetic disorders reported in the three Arab countries, 36.6% document the presence of patients resulting from consanguineous marriages, mostly among first cousins. Undoubtedly, this is a high frequency, and researchers looking at this figure in isolation can easily be inflenced in concluding that consanguinity is a direct cause of most of these disorders.

In mathematical terms, consanguinity does not alter the allele frequencies of common disorders, but increases the probability of a mating between two individual heterozygotes for the same recessive mutant allele. In this regard, the risk for birth defects in the offspring

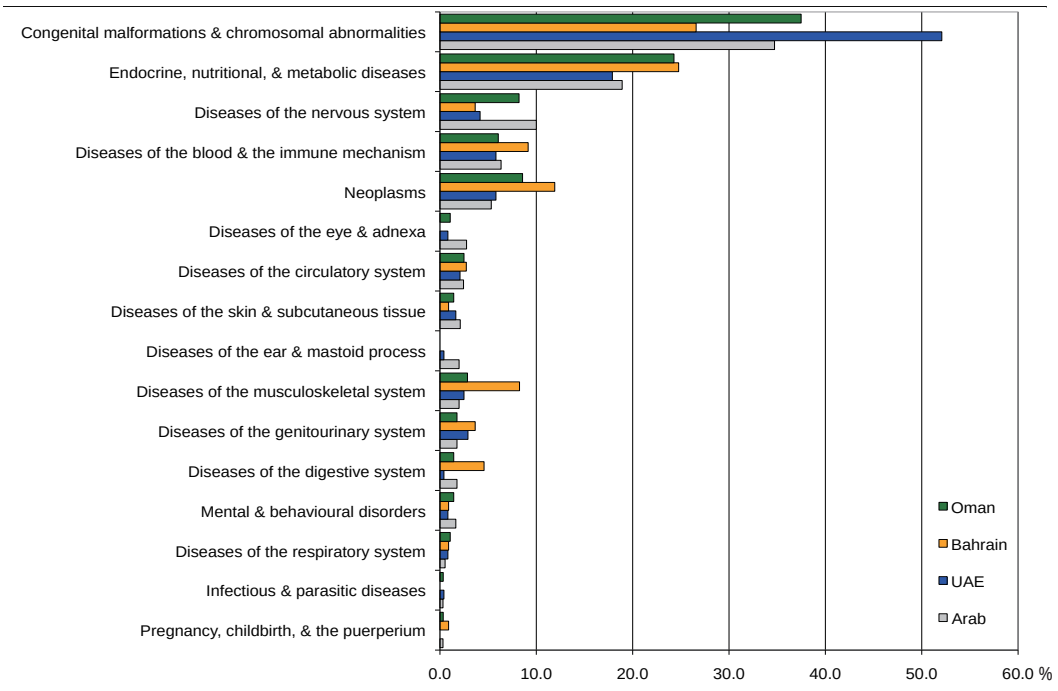


Figure 5.4. Classification of genetic disorders in the Arab populations of Bahrain, Oman, and the UAE compared to rates recorded in the Arab World using the WHO ICD-10 system (October, 2008).

of first-cousin marriage is expected to increase sharply compared to non-consanguineous marriages. While spouses share 1/8 of their genes inherited from a common ancestor, their progeny become homozygous (i.e., autozygous) at 1/16 of all loci. Accordingly, the progeny are predicted to inherit identical gene copies from each parent at 6.25% of all gene loci, over and above the baseline level of homozygosity in the general population, hence leading to an increased exposure of rare recessive traits (Gelehrter *et al.*, 1998). This is exemplified by the report of several rare autosomal recessive genetic disorders in multiply consanguineous families within the CTGA Database (Rajab *et al.*, 2004; Naveed *et al.*, 2006). Additionally, the database has several reports of higher rates of consanguinity among parents of children with genetic disorders compared to the general population (Rajab *et al.*, 1997; Al-Talabani *et al.*, 1998; Rajab and Thomas, 2001). However, consanguinity has very little role to play in the transmission of common autosomal recessive diseases such as thalassemia (Baysal, 2005) since an unrelated couple would have a similar chance of having an affected child as a related couple due to the frequent occurrence of carriers in the population.

Figure 5.6 shows the comparative profile of patterns of inheritance of genetic diseases in the three Gulf countries studied. It is obvious that in all three countries, recessive disorders are more in number than the dominant ones. As explained above, given the high rates of consanguinity in the countries, this pattern is not entirely surprising. Data from Bahrain indicate that autosomal recessive and dominant disorders comprise 45% and 40%, respectively of all genetic disorders in the country.

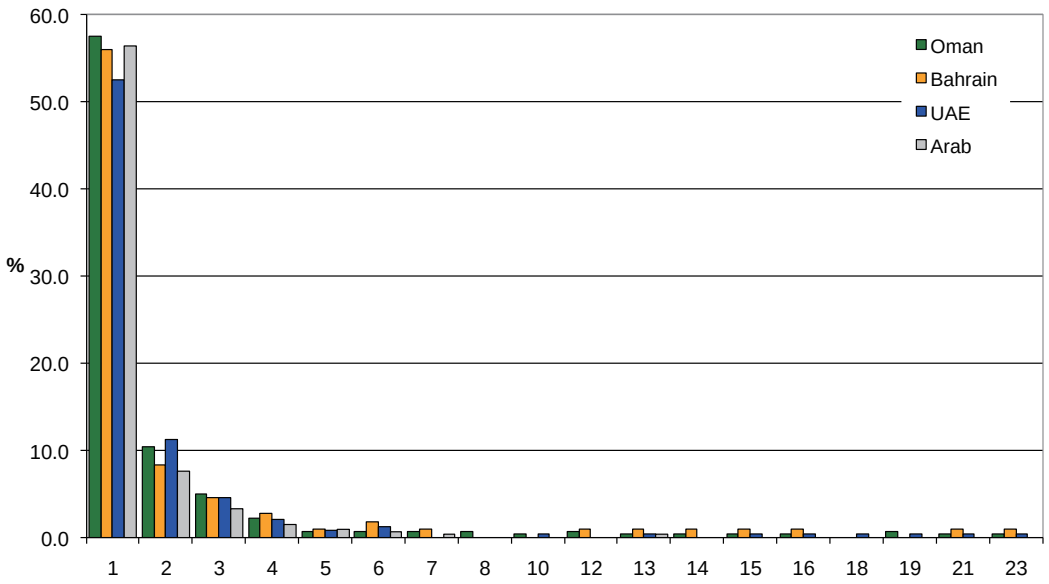


Figure 5.5. Distribution of genetic disorders in the Arab populations of Bahrain, Oman, and the UAE according to number of causative gene loci (October, 2008).

The frequency gap between autosomal recessive and dominant disorders increases in Oman and increases further more in the United Arab Emirates (Figure 5.7). Despite the preliminary nature of disease records from Saudi Arabia, data from this country further support this observation with the widest difference between frequencies of autosomal recessive (63%) and autosomal dominant (25%) accompanied with an elevated rate of consanguineous marriages (51%). These indicators clearly reveal the strength of the CTGA Database as a population-based information hub with a capacity to draw direct relations between variables that could influence the type of genetic disorders common in the region. The completion of other surveys on genetic disorders in Arab populations accompanied with a continuous surveillance of this pattern shall provide further insights on this subject.

Clinical and Genetic Variability in the Region

As mentioned earlier in this chapter, the CTGA Database records indicate the presence of 451 genetic disorders in the combined Arab populations of Bahrain, Oman, and the UAE. This diversity is further exemplified at three inter-related levels that give altogether an unparalleled heterogeneity in the Arab World at the clinical and the molecular pathologies as well. The first level of complexity is derived from the fact that many genetic disorders are occurring at epidemic levels that make them occur in many individuals with a variety 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 Arab patients from the region especially with major

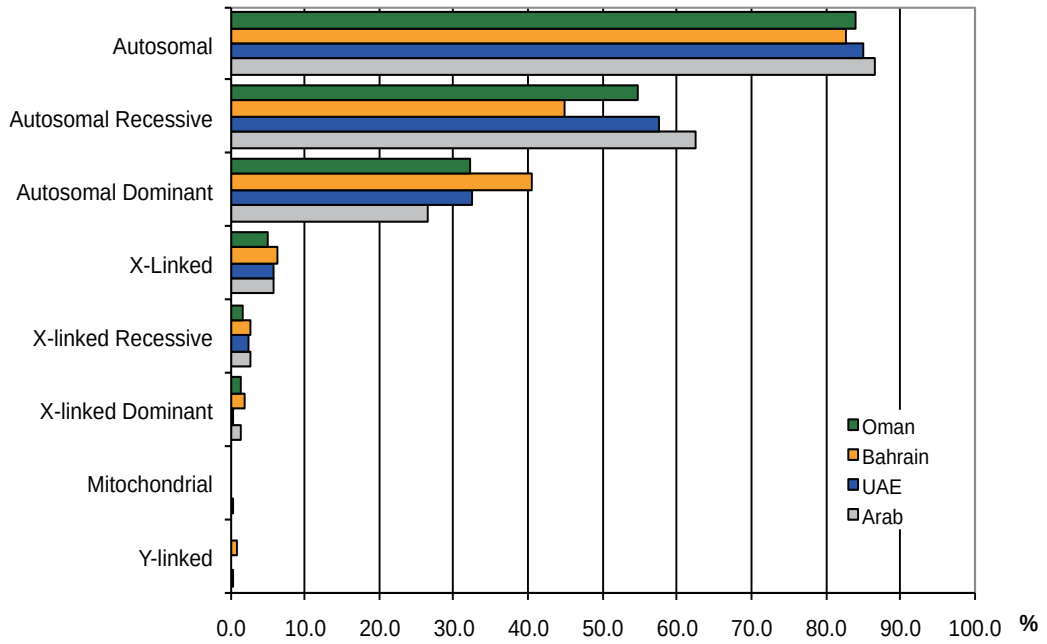


Figure 5.6. Classification of genetic disorders in the Arab population of Oman, Bahrain, and the UAE compared to rates recorded in the Arab World according to their mode of inheritance (October, 2008).

disorders including thalassemias, sickle cell disease, cystic fibrosis, Down syndrome, G6PD deficiency, and many others (Table 5.3). 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 the 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 for cystic fibrosis during a 17 years 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%. Certainly, the systemic study of comorbidity would represent a main approach to study clinical complexity in Arab patients. 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.

At another level, many of the broad groupings of genetic disorders are fur-

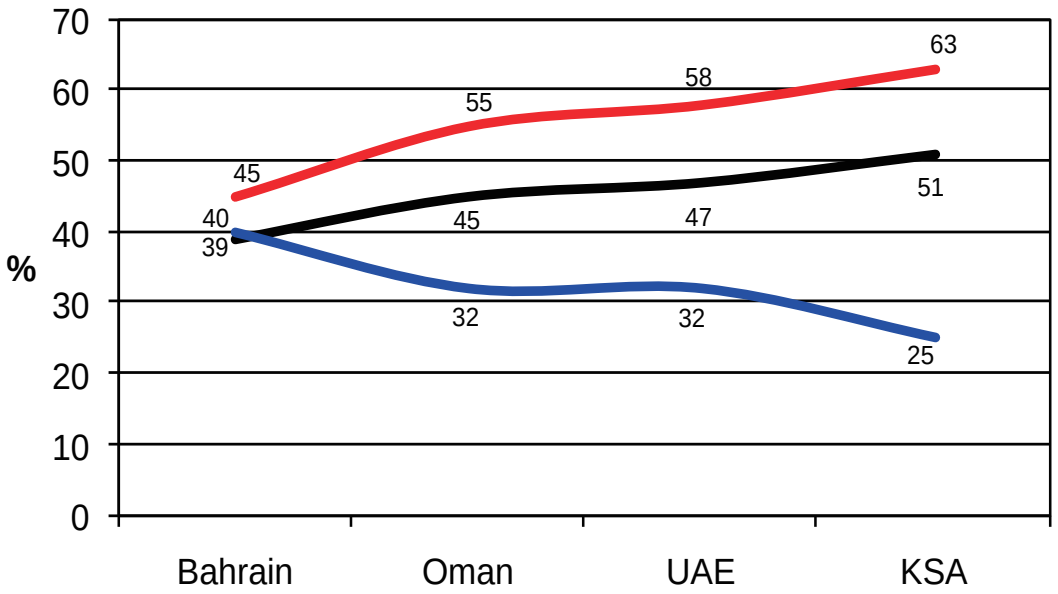


Figure 5.7. A comparison between per cent consanguinity rates (black line) and frequency of recessive (red line) and dominant (blue line) disorders in Bahrain, Oman, the UAE, and Saudi Arabia.

ther classified into types and subtypes within the CTGA Database indicating a heterogreneity in the features associated with these disorders in the corresponding populations. For example, glycogen storage disease and mucopolysaccharidosis are both reported into four distinct types in the Omani population whereas spinal muscular atrophy is associated with three types. This latter disease also occurs in three variants in the Bahraini population. In the UAE population, three variants do occur for epidermolysis bullosa as well as osteognesis imperfecta. Other disorders that do occur in Arabs with multiple variants includes: Bartter syndrome, Charcot-Marie-Tooth disease, Ehlers-Danlos syndrome, lamellar ichthyosis, Meckel syndrome, multiple pterygium syndrome, limb-girdle muscular dystrophy, spinocerebellar ataxia, Usher syndrome, and many others.

At the molecular level, this diversity is further expressed. In contrast to many world populations, 50 mutations are responsible for the molecular etiology of beta-thalassemia in the UAE population, making it one of the most heterogenous populations in the world with regard to mutations in the beta-globin gene (Baysal, 2005). Besides that, many novel mutations have been identified in common genetic disorders in the region. In cystic fibrosis, worldwide studies indicate that more than 70% of patients with cystic fibrosis show a single mutation that involves the deletion of three nucleotides of exon 10, within the first nucleotide binding domain, resulting in the deletion of phenylalanine at position 508 in the protein product; the delta F508. In the region, this picture seems to be different. In Bahrain, the disease is associated with eight mutations includ-

Table 5.3. Examples of disease comorbidities as recorded in the CTGA Database (October. 2008).

Disease	Comorbidity
Alpha-thalassemia	Wolman disease
Beta-thalassemia	Alpha-thalassemia
	Dyskeratosis Congenita, X-linked
	G6PD deficiency
	Pycnodysostosis
Cystic fibrosis	Beta-thalassemia
	Ehlers-Danlos syndrome type III
	G6PD deficiency
	Glioblastoma multiforme
	Infantile hypertrophic pyloric stenosis 1
	Sickle cell disease
	Sickle/beta-thalassemia
Down syndrome	Absence of abdominal muscles with urinary tract abnormality and cryptorchidism
	Choanal Atresia, Posterior
	Moyamoya syndrome
	Tetralogy of Fallot
G6PD deficiency	Dyskeratosis Congenita, X-linked
	Pycnodysostosis
Sickle cell disease	Alpha-thalassemia
	Beta-thalassemia
	Blepharophimosis, Ptosis, and Epicanthus Inversus
	G6PD deficiency
Tetralogy of Fallot	Chromosome 18p deletion syndrome
	Down syndrome
	Frontonasal dysplasia
	Holt-Oram syndrome

ing 2043delG (30.8%) and delta F508 (7.7%). This latter mutation occurs in Bahrain in families of Persian families (Eskandarani, 2002). In Oman and the UAE, the picture seems to be different with the S549R (T-G) mutation being most common and the delta F508 occurring at relatively low frequencies, but exclusively in patients of Baluch descent (Frossard *et al*., 2000; Dawson and Frossard, 2000). Dawson and Frossard (2001) also concluded that patients homozygous for the mutations delta F508 and S549R (T-G) have a severe clinical presentation and illness and are indistinguishable on clinical grounds, hence, emphasizing the importance of gene testing to explain the processes converting distinct genotypes into highly severe and similar phenotypes. On the other hand, in a comprehensive molecular study in Omani patients with familial hemophagocytic lymphohistocytosis, seven distinct mutations were identified in the coding region of the Perforin gene, of which five were novel (Muralitharan *et al*., 2007). This molecular heterogeneity is also expressed in linkage analyses that excluded classical gene loci known to be involved in the pathogenesis of certain genetic disorders and indicated the possibility of other genes to be modeling the disease in Arab patients (Al-Yahyaee *et al*., 2006; Bayoumi *et al*., 2006).

Morbidity and Mortality

As mentioned earlier in Chapter 1, genetic disorders place a huge financial burden on the health care system of a country. For an individual affected patient and his/her family, the problems are of a more personal nature. There is a physical disorder to contend with, complicated by the financial aspects of managing the disease, and to top it all, there is increased emotional burden on the primary care giver. The situation is much more complicated if the disorder is lethal. According to the CTGA Database, about 20% of the genetic disorders reported in the UAE, Bahrain and Oman resulted in the death of the affected individual(s) early in their lives. More distressingly, a number of these disorders have high incidence rates in this region (Table 5.4). Therefore, it is possible to say that the mortality associated with genetic disorders is fairly high in Arab populations.

Of late, more and more emphasis is being provided to prenatal screening for the early identification of genetic disorders in this region. Advocates for the use of this strategy in diagnosing genetic disorders argue that gene defects bound to lead to mortality in utero or in early infancy or childhood are best diagnosed early. In the case of disorders that are both lethal and common, therefore, it would seem that the health care system would give a priority to the early detection of such disorders. However, there are questions raised on the usefulness of a prenatal diagnostic test for lethal disorders. In the UAE and Oman, fetal impairment is not a legally justifiable reason for termination of pregnancy. Although Bahraini laws are comparatively more relaxed, clinical abortion after the first trimester is rare. In fact, even in Western countries, in the event of a prenatal diagnosis of a lethal disorder being made, it has been seen that most

parents prefer to continue with the pregnancy knowing that with nature taking its course, they will not have an indefinite period of caring for the sick child (McEwan, 2007). The importance of early diagnosis of lethal disorders in such a scenario is, therefore, highly suspected. On a related note, studies have shown that parents with a prenatal knowledge of a sub-lethal disorder in their child have increased emotional burden and grief even after a year when compared to those who did not have any prenatal knowledge of their children's disorder (Hunfeld *et al.*, 1999). Interestingly, a recent study in the Islamic Republic of Iran found that about 50 percent of affected couples decided to separate upon being informed of their carrier status, and births with severe non-lethal defects fell to about 30 percent of those expected (Samavat and Modell, 2004). The reasons for this remarkable observation require further investigation and may be due to an increased attention in Muslim populations to comply with a genetic advice when the information is properly conveyed (see 'preventive aspects of genetic disorders' in Chapter 1).

Amniotic Fluid Size Variation and Genetic Disease Associations

Amniotic fluid is an important part of pregnancy and fetal development (Spong, 2001). Normal amounts may vary, but, generally, women carry about 1,000 ml of amniotic fluid. The fluid is produced by the fetal lungs and kidneys and is taken up with fetal swallowing and sent across the placenta to the mother's circulation. Too much amniotic fluid (polyhydramnios or hydramnios) or too little (oligohydramnios) can be a

Table 5.4. List of the most common disorders leading to mortality in the UAE, Oman and Bahrain according to the CTGA Database (October, 2008).

Disease	Incidence*
Alpha Thalassemia	Epidemic
Breast Cancer	Epidemic
Down Syndrome	Epidemic
Hypertension, Essential	Epidemic
Neural Tube Defects	Epidemic
Pyloric Stenosis, Infantile Hypertrophic 1	Epidemic
Aplasia Cutis Congenita, Nonsyndromic	Common
Arthritis, Aacroiliac	Common
Cardiomyopathy, Dilated	Common
Choanal Atresia, Posterior	Common
Cystic Fibrosis	Common
Fibrochondrogenesis	Common
Gastric Cacer	Common
Head and Neck Cancer	Common
Hirschsprung Disease	Common
Hydrocephalus	Common
Hyperinsulinemic Hypoglycemia, Familial	Common
Hypoplastic Left Heart Syndrome	Common
Long QT Syndrome	Common
Neurofibromatosis, Type I	Common
Prostate Cancer	Common
Pulmonary Hypertension, Primary	Common
Spinal Muscular Atrophy I	Common
Systemic Lupus Erythematosus	Common
Total Anomalous Pulmoary Venous Return	Common
Transposition of the Great Arteries, Dextro-looped	Common

*Epidemic indicates an occurrence rate of more than 100 cases per 100,000 live births. Common indicates an occurrence rate of 51-100 cases per 100,000 live births.

cause or an indicator of abnormalities in fetal development, still birth, and maternal complications (Aagaard-Tillery *et al*., 2006).

Polyhydramnios, also known as hydramnios, is a condition in which there is too much amniotic fluid around the fetus (over 2,000 ml). It occurs in about 2 to 4 percent of all pregnancies (Bundgaard *et al*., 2007). About 20% of polyhydramnios cases are due to maternal diabetes mellitus, which causes fetal hyperglycemia and resulting polyuria. About another 20% of cases are associated with fetal anomalies that impair the ability of the fetus to swallow the amniotic fluid (Gaxiola Castro *et al*., 1995). These include: intrinsic or extrinsic obstruction of the gastrointestinal tract (esophageal atresia, duodenal atresia, facial cleft, and tracheoesophageal fistula), neurological or neuromuscular congenital anomalies impairing swallowing (anencephaly, neural tube defects) or chromosomal abnormalities (Down syndrome), twin-to-twin transfusion syndrome, high-output congestive cardiac failure, acquired congenital infection, and skeletal dysplasias (Orhan *et al*., 2005; Touboul *et al*., 2007). The remaining cases are usually not associated with any of the above-mentioned factors and are known as idiopathic polyhydramnios. Although it is the most common, this latter type is the least studied type of polyhydramnios with a severe lack of worldwide consensus in monitoring related afflicted pregnancies (Magann *et al*., 2007).

On the other hand, oligohydramnios is a condition in which there is too little amniotic fluid around the fetus. It occurs in about 4 percent of all pregnancies. Generally, it is caused by conditions that prevent or reduce amniotic fluid production (premature rupture of membranes, intrauterine growth restriction, post-term pregnancy, birth defects, especially kidney and urinary tract malformations, and twin-to-twin transfusion syndrome). As a rule, oligohydramnios has been implemented as a sign of potential fetal compromise and associated with an increased incidence of adverse perinatal morbidity and mortality (Sherer, 2002). At the fetal level, oligohydramnios causes the fetus to develop contractures of the limbs, clubbing of the feet and hands, and also develop a life threatening condition called hypoplastic lungs leading to not fully formed lungs (Christianson *et al*., 1999).

Studying hydramnios as a possible factor associated with perinatal mortality is not common in the region. To our knowledge, a study has been conducted in Kuwait in the context of analyzing several medical factors among which hydramnios could be linked to perinatal mortality in Al-Jahra district (Morsy *et al*., 2000). In Tunisia, the etiology of hydramnios is dominated by renal malformations, obstructive myopathies, and polymalformatives syndromes (Chanoufi *et al*., 2000).

More recently, Malas and colleages (2005) studied 2,142 deliveries in Bahrain during a period of 16 months to determine if idiopathic polyhydramnios was associated with an increased hazard to the fetus. Among all deliveries, 4.8% were found to have poly-

hydramnios and 67% of those cases were idiopathic with a high incidence of macrosomia and three times more the rate of Cesarean section. Malas and colleagues (2005) concluded that polyhydramnios is more common in Bahraini community than what was shown in other communities and that idiopathic polyhydramnios does not seem to have adverse perinatal outcome. Interestingly, in a very recent study from Oman polyhydramnios occurred in 7.8% of deliveries recorded in Sultan Qaboos University Hospital for years 2005 and 2006 (Mathew *et al*., 2008). These alarming rates could probably be linked to genetic susceptibility to develop the feature or to the widespread occurrence of various genetic or congenital disorders in many of the fetuses (Stoll *et al*., 1998).

Throughout the process of updating the CTGA Database a noticeable amount of observations on poly- and oligo- hydramnios were noted. Searching available records of the database indicate the occurrence of these features with nearly 19 genetic disorders (Table 5.5). Interestingly, almost all cases of polyhydramnios in Arab patients presented with non-bilious vomiting immediately after birth.

Knowing that this list is of highly conservative nature, the real extent of associations between poly- and oligo-hydramnios and genetic disease could be more than what is revealed at this time. Further analysis of this subject using information from the CTGA Database may considerably help shedding light on this peculiar clinical trait.

The Familial and Social Facet

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 is 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 not necessarily restricts to, the perception of family history and compliance to medical and genetic advice.

Family History: Close to 40% of diseases in the database from the three GCC countries document a family history of the condition. Interestingly, within this group, 72% of the diseases also 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 can not 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 of 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 16 cases of non compliance within the patient population of the three 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

Table 5.5. Associations of poly- and oligo-hydramnios with genetic disorders according to the CTGA Database (October, 2008).

Disease	Polyhydramnios	Oligohydramnios
Aplasia Cutis Congenita	+	
Apparent Mineralocorticoid Excess Syndrome	+	
Bartter Syndrome, Infantile, with Sensorineural Deafness	+	
Bifid Nose, Renal Agenesis, and Anorectal Malformations		+
Choanal Atresia, Posterior	+	
Contractural Arachnodactyly, Congenital		+
Dyssegmental Dysplasia, Silverman-Handmaker Type		+
Epidermolysis Bullosa with Pyloric Atresia	+	
Fibrochondrogenesis	+	
Jejunal Atresia with Down Syndrome	+	
Microgastria-Limb Reduction Defects Association	+	
Mucopolysaccharidosis Type VII	+	
Nephronophthisis 2		+
Orofaciodigital Syndrome, Type IV		+
Pulmonary Hypoplasia, Primary		+
Pyloric Atresia	+	
Pyloric Stenosis, Infantile Hypertrophic 1	+	
Raine Syndrome	+	
Skeletal Dysplasia, Rhizomelic, with Retinitis Pigmentosa	+	

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 advise, 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).

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 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).

A direct correlation has been demonstrated between the level of education and awareness and early detection and better management of genetic disorders in these 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.

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