



GENETIC DISORDERS IN QATAR

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Introduction

Qatar is ranked as the wealthiest country in the world with the highest GDP per capita, derived from the production and export of oil and natural gas. A monarchy, Qatar has been ruled by the Al-Thani family since the mid-1800s and has since transformed itself from a poor British protectorate, noted mainly for pearling, into an independent state with Islam as the official religion, *Sharia* as the prime source of legislation and Arabic as the official language.

The genetic singularity of Qatari population, quite similar to the UAE group, a slight genetic differentiation with Syria and Egypt and a particular genetic affinity with sub-Saharan African populations, was shown by microsatellites diversity (Pérez-Miranda *et al.*, 2006). Microsatellites, tend to occur in non-coding DNA, are short segments of DNA that have a repeated sequence. Typically neutral and co-dominant, Microsatellites can be used as molecular markers in genetics, for kinship, population and other studies. Increased microsatellite homozygotes over heterozygotes is likely a consequence of the high consanguinity rates in Qatar due to its geographic position close to major migratory routes between Eurasia and Africa. Qatari population genetics is a unique demographic case which can provide information on the evolution of modern humans as well as contribute important and useful data of a highly inbred human society which may be helpful for understanding the relationship between genetics and diseases.

Currently in Qatar, genetic information is being used for genetic counseling and prenatal diagnosis. In order to strengthen the field of genetic medicine in Qatar, additional attempts are being made to set up a complete database of Qatari-specific genetic information and to use these data to formulate standard indexes and protocols.

The Geography and Ethnography of Qatar

Qatar is an independent state, occupying 11,427 km² of the Qatar Peninsula. It extends northward from the eastern coast of Arabian Peninsula into the Arabian Gulf and is bordered by Saudi Arabia to the south. A strait of the Arabian Gulf separates Qatar from the relatively nearby island nation of Bahrain. Qatar is located in a desert land of tropical climate as it is littoral and low lying and is frequently humid. According to the Statistics

Authority, on Sept. 30 2010, there were 1,642,235 Qatari residents, approximately 350,000 of who are Qatari citizens and primarily Sunni “Wahhabi” Muslims. The remaining residents are expatriates chiefly from South Asia and from non-oil-rich Arab states. In recent years, due to the current surge in construction development, the number of expatriates of working age has been increasing exaggeratedly. Doha is both the capital of Qatar and its largest city.

Prior to 1920, the ancestries in Qatar were made up of several distinct ethnicities: Bedouin, Persian and African and “other”. The Bedouins were from the Najd Plateau of the Arabian Peninsula and were the earliest denizens in Qatar. Most Qataris are from nomadic, Bedouin backgrounds and settled in Qatar in the late 20th century with the discovery of oil and natural gas. The Persians migrated along the coast of the Arabian Gulf in when this happened and were attracted to the region by the fishing and pearl diving in the nearby gulf. The Africans were mostly Arabic-speaking Sunni Muslims brought in as slaves through Zanzibar and Oman before the 20th century. The “other” group likely obtained citizenship based on service to, and residence in, Qatar. This group does not tend to intermarry and therefore, their distinct ethnicities have generally remained intact.

Genetic Services and Neonatal Screening Centers in Qatar

Consequent founder effects are responsible for the high prevalence and unusual burden of inherited disorders in Qatar. Established by the Emiri decree in 1979, Hamad Medical Corporation (HMC) is the premier non-profit health care provider in Doha, Qatar. HMC manages four highly specialized hospitals: Hamad General Hospital, Rumailah Hospital, Women’s Hospital, Psychiatric Hospital and the Primary Health Care Centers. These hospitals are quite sophisticated and have many patients affected by genetic disorders.

Biochemical neonatal screening programs in Qatar have started as research projects that have provided valuable information on the incidence of hemoglobin disorders, glucose-6-phosphate dehydrogenase deficiency (G6PD), congenital hypothyroidism, phenylketonuria, and cystic fibrosis. Newborn screening is coordinated in the capital city of Doha by the HMC, the largest medical center in the country. In 2003, HMC decided to introduce screening

by MS/MS, a tandem mass spec method of screening the amino acids profiling of metabolic and endocrine disorder, although it did not have the laboratory facilities to implement such expansion. As a result, HMC partnered with the University Children's Hospital of Heidelberg, Germany and from December 2003 through July 2006, roughly 25,000 newborns were screened (*Lindner et al., 2007*). Population-wide newborn screening commenced within six months. Qatar's guidelines for newborn screening were based on the initial recommendations for the German program, although in total twenty-eight disorders (Table 5.1) were screened for which was substantially more than in Germany. The decision to screen for so many neonatal diseases was based on several factors: although disease prevalence for the country were unknown, it was believed that due to high rates of consanguinity and centuries-long genetic isolation, disorders that are quite rare in Germany might be more common in Qatar. Neonatologists and nurses provided information to mothers verbally and also provided a written brochure prior to blood sampling. The results were striking: a newborn in Qatar is twice as likely to suffer from one of the 28 diseases than a baby born in Germany. This panel of disorders will be maintained; pending the outcome of a retrospective study, sickle cell disease may be added.

Table 5.1. Disorders integrated into the extended neonatal screening program in Qatar.

Group	Disorders
Endocrinopathies	Congenital hyperthyroidism Congenital adrenal hyperplasia Phenyl ketonuria (PKU) Benign hyperphenylalaninemia (HPA) Defects of bipterin cofactor biosynthesis (BS) Maple syrup disease (MSUD)
Aminoacidopathies and urea cycle disorders	Homocystinuria (HCY) Tyrosinemia type 1 Citrullinemia Argininosuccinic aciduria
Organic acidurias	Methylmalonic aciduria CBI-disorders Propionic aciduria Glutaric aciduria type I Isovaleric aciduria, 3-methylcrotonulglycinuria Multiple acyl CoA dehydrogenase (MAD) deficiency Isobutryl-CoA dehydrogenase (IBDH) deficiency
Fatty acid oxidation disorders, carnitine cycle defects and disorders of ketogenesis	Medium chain dehydrogenase (MCAD) deficiency Very long chain acyl CoA dehydrogenase (VLCAD) deficiency LCHAD deficiency Short chain acyl CoA dehydrogenase (SCAD) deficiency Carnitine transporter deficiency Carnitine palmitoyltransferase I (CPT I) deficiency Carnitine palmitoyltransferase (CPT II) deficiency 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) lyase deficiency
Others	Ketothiolase deficiencies Classical galactosidase Biotinidase deficiency

To prevent genetic disorders, medical genetic education and research assumes particular importance. More recently, a major American university, Weill Cornell Medical College in Qatar (WCMC-Q), has opened a branch campus in Education City, Doha and Sidra Medical and Research Center is set to open in 2012. Together with WCMC-Q, Sidra will form an academic medical center of world-class standards within Education City.

Consanguinity

Based on the statistical results of the responses from 876 female participants, the rate of consanguinity in the present Qatari generation was 51% with a coefficient of inbreeding of 0.023724 (*Bener et al., 2007*). The inbreeding coefficient of Qatar is higher than in the Kuwait population and the UAE because of the higher level of double first cousin marriages (34.8%; *Bener and Al-Ali, 2006*). They also showed a significant increase of the effects of consanguinity in the Qatari population on common adult diseases including cancer, mental disorders, heart diseases, gastro-intestinal disorders, hypertension, and hearing defects. A more detailed cross-sectional study was conducted among 362 Qataris to estimate the prevalence of consanguinity from March 2007 to March 2008 (*Sandridge et al., 2010*). Twenty-two percent of participants reported a cousin relationship between their parents and an even greater percentage, 35%, of participants married consanguineously. *Jaber et al. (1998)* detailed strategies for reducing the burden of consanguinity, which could be applicable in a population with common consanguineous marriages.

Genetic and Congenital Disorders

Red Cell Genetic Disorders

Hemoglobin abnormality: A new type of abnormal hemoglobin, Hb Doha, was identified in a Qatari woman and two of her relatives (*Kamel et al., 1985*). The position 1 (NA1) of the β -chain leads to a Val→Glu replacement. The glutamic acid residue can prevent the removal of the methionyl N-terminal, but the Hb Doha heterozygote showed no apparent clinical consequences.

β -Thalassemia (OMIM 141900): β -thalassemia is common among populations of the Arabian Peninsula. *Al-Obaidli et al. (2007)* analyzed the molecular basis of β -thalassemia in Qatar. They found the most common mutant alleles were IVS-I-5 (G>C) and codon 8/9 (+G), representing 35.4% and 26.1% of the total, respectively. Most of these two mutations are homozygous, likely because of the high rate of consanguinity in Qatar. The frequencies of another three common mutant alleles, IVS-II-1 (G>A), 25bp deletion and IVS-I-110 (G>A) are higher in surrounding locations, such as Southern Iran, Kuwait, eastern Saudi Arabia and Bahrain. There are also seven other rare mutations including: codon 8 (-AA), codon 15 (G>A), codon 44 (-C), codon 30 (G>C), codon 39 (C>T),

IVS-I-1 (G>A) and undefined alleles, of which the codon 39 (C>T) allele was found at high frequencies in Bahrain (24%) and the east of Saudi Arabia (20.3%). Recently, a novel β -thalassemia deletional variant allele in an ethnic Qatari patient was reported (*Al-Obaidli et al., 2009*). The deletion spans exon 1, the entire intron 1 and the first two bases of exon 2 causing a frameshift and the premature appearance of a stop codon. The presence of this novel deletional allele in a compound heterozygous state with a non-deletional allele is alarming in a diagnostic setting, especially in the absence of family studies.

Sickle cell disease (OMIM 603903): Most mild Sickle Cell Anemia cases are from the Middle Eastern. A study of patients in Qatar showed α -thalassemia was not a contributing factor because the phenotype of a patient with α -thal-2 homozygosity ($-\alpha/\alpha$; the 3.7-kb deletion) is similar to other patients with four α genes (*Bakioglu et al., 1985*). All of the patients were determined to have the same haplotype #19 through family studies. By analyzing the respective hemoglobin A gene mutation in 6000 dried blood spots collected between April 2004 to April 2005, a recent retrospective study suggests that sickle cell disease should be added to the neonatal screening panel in Qatar (*Lindner et al., 2007*).

Bleeding Disorders

Hemophilia A (OMIM 306700): A study in Shafallah Medical Genetics Center, Doha showed FVIII mutation spectrum in severe Arabic hemophilia A patients (*Abu-Amero, 2008*). The results of full FVIII gene sequencing demonstrated intron 22 inversion was common (55%), eight base substitutions (six of which are novel) in the remaining (45%) patients and none of insertions and deletions were detected. Of the eight base substitutions, six were potentially pathologic. These are promising data but a larger study with more patients is needed to establish a solid conclusion about the prevalence of various mutations.

Chromosomal Disorders

Down syndrome (OMIM 190685): According to a 6-year study of 146 Down Syndrome (DS) children cases in Qatar, the prevalence rate is 19.5 per 10,000 live births (*Abdul Wahab et al., 2006*). Of the DS cases, 40.4% were of Qatari ancestry and 52.7% were males. Interestingly, Qatari males present a significantly lower incidence of DS than females (32.5% vs. 49.3%). Among 146 patients, regular trisomy dominates the types of chromosomal anomalies as a frequency of 98% in Qataris, and mosaicism and non-classical types are found in 0.7% and 1.4%, respectively.

X-Linked Disorders

G6PD is the relatively common x-linked disorders in Qatar (*Al-Jawadi and Al-Hilali, 1998*). The frequency is about 5% in Qatar, but in Oman and Bahrain the frequency among males is about 27% (*White et al.,*

1986). Other X-linked disorders diagnosed in Qataris include incontinentia pigmenti, Lenz microphthalmia syndrome, ichthyosis, hemophilia, color blindness, and hypophosphatemic rickets (*Teebi and Ben-Omran, 2010*).

Genetic Endocrine Disorders

Cystic fibrosis (OMIM 219700): Cystic fibrosis (CF) is an inherited autosomal recessive disorder. CF is not uncommon in Qatar. A large series of CF cases was reported in the same tribe and the rate of consanguineous marriage among 26 related Arab Bedouin families belonging to the same tribe was 98% (*Abdul Wahab et al., 2000*). Of the patients in this tribe, the homogenous mutation I1234V of the cystic fibrosis transmembrane conductance regulator (CFTR) on exon 19 is the main genotype (*Abdul Wahab et al., 2001*). In another report, a 36-year-old Qatari woman, which is the oldest CF case ever published in Qatar, also showed a mutation I1234V, which suggests CF mutation I1234V has a long survival (*Abdul Wahab, 2003*). Thirty-six patients with CFTR I1234V mutation were reported in a following study on the pattern of microbiological agents responsible for chronic pulmonary infection, which shows a high incidence of CF in Qatar (*Abdul Wahab et al., 2004*).

Metabolic and Nutritional Diseases

Homocystinuria (OMIM 236200): The incidence of homocystinuria in Qatari population is 1:1,800, the highest in the world and about 6% of the population are carriers for this condition (*Zschocke et al., 2009*). Mutations in the cystathionine beta-synthase (CBS) gene are associated with homocystinuria. A new tandem mass spectrometric method, combining a rapid method to measure total homocysteine in dried blood spots by MS/MS with genetic testing for the prevalent mutation in parallel, identified homozygosity for the mutation c.1006C→T (p.R336C) in the CBS gene in most of the patients from 31 Qatari families (*El-Said et al., 2006*). This possible recurrent mutation in the highly consanguineous Qatari population demonstrated a strong founder effect. Only a single patient was homozygous for mutation c.700G→A (p.D234N) in the CBS gene. Subsequently, in the following studies involving the screening of 46,406 neonates born in Qatar over a period of 3 years, 14 affected neonates were detected and they were all of Qatari origins (*Zschocke et al., 2009; Gan-Schreier et al., 2010*). By screening the two mutations of CBS gene, 13 of the 14 identified infants were homozygous carriers for the common Qatari mutation p.R336C. Only one affected child detected through biochemical screening was homozygous for a known homocystinuria mutation p.G347S (c.1039 G>A) in exon 9, previously unidentified in Qatar. For the allele frequency of the mutation p.R336C, approximately 1% displayed a significant deviation from Hardy Weinberg equilibrium. However, molecular neonatal screening is technically feasible for early detection of homocystinuria in this population. *El-Said et al. (2007)* demonstrated significantly lower levels of folic acid and B12 in

heterozygotes for CBS deficiency. This study correlated heterozygosity for CBS deficiency with thromboembolic diseases and morbidity and mortality.

Hydronephrosis (OMIM 604916): Intrauterine ultrasonography imaging is a well approved approach to identify hydronephrosis. If it is recognized early by ultrasonography, renal damage may be minimized. Previous studies showed the incidence of congenital hydronephrosis was very high in Qatar. A retrospective study of 311 congenital hydronephrosis patients in a 10 year period between 1987 and 1996 shows an overall incidence of 1:330 live births and the male to female ratio was 3.78:1 in Qatar (*Saad et al., 1999*). Fortunately, the incidence dropped to 1:186 and 1:149 in 1995 and 1996 respectively due to the awareness of the problem and greater expertise in diagnoses. According to ultrasound data, the patients were stratified as severe (6%), moderate (30%), and mild (64%). On follow-up, 45(14.4%) patients needed an operation and the remaining patients (85.6%) either spontaneously improved or remained stable.

Hydrocephalus (OMIM 236600): A retrospective study showed that hydrocephalus has an incidence of 157/100,100 live births and meningomyelocele has a lower incidence of 41/100,100 in Qatar (*Nogueira, 1992*). Chromosomal studies showed one abnormal from 10 cases. Hydrocephalus is reasonably easy to diagnose but quite difficult to explain and treat. Therefore, the discovery the hypothesized “genetically privileged” mothers and in-depth genetic evaluation are better ways to identify high-risk pregnancies.

Noninsulin-dependent diabetes mellitus (OMIM 125853): During this past decade, diabetes prevalence in Qatar has been dramatically increasing and the diabetes is significantly more common among the consanguineous marriages of the first degree relatives (33.1%) compared with the control group (24.6%; *Bener et al., 2005*). The Pro12Ala polymorphism in the PPAR- γ 2 gene has been shown to influence the risk for T2D and obesity in various ethnic populations worldwide (*Moriet et al., 2001; Frederiksen et al., 2002; Bener et al., 2005; Tavares et al., 2005*). However, *Badii et al. (2008)* showed that the allele frequency of Pro12Ala polymorphism in PPAR- γ 2 gene among Qataris is lower than that in many Caucasian ethnic groups. No association is seen between the Pro12Ala and type 2 Diabetes (0.055 vs 0.059). Therefore, further studies are required to identify whether there are genetic factors that contribute to the dramatic increase in diabetic patients due to the interaction between genetic and environmental factors.

Connective Tissue Disorders

Ehlers-Danlos syndrome (OMIM 604327): Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders. *Abdul Wahab et al. (2003)* had studied an apparently new type of EDS in a large Qatari extended family. The results showed there

was a well-defined parental consanguinity and family history of EDS in 30 patients (93.8%). Linkage analysis showed there was no evidence for genetic linkage to any of mutant loci implicated in EDS. Intragenic and flanking microsatellite markers suggested the disease in this family is unique because no mutation found in known EDS or other connective tissue disorders was detected in this family. *Faiyaz-Ul-Haque et al. (2004)* described two similar patients from a large consanguineous family from Qatar. They showed D5S469 and D5S2111, which were markers for galatyltransferase-I (B4GALT7) located on chromosome 5q35.2, of the patients were homozygous. And also, a homozygous mutant allele (C→T) at nucleotide residue 808 of the coding sequence was discovered in affected individuals. Parents of these two children were heterozygous for this mutation. Healthy siblings are either heterozygous or didn't carry the mutation. Ethnically matched controls are all wild types, which demonstrated it isn't a rare polymorphic site. These homozygous mutation carriers exhibited milder abnormalities than previously reported mutation carriers. Therefore, different mutations in the B4GLAT7 gene indicated different phenotypes of variable severity among the progeroid type of EDS. Recently, a p.S81R (c.243C>G) encoding mutation in SLC2A10 gene was identified in EDS patients with arterial tortuosity syndrome from ten Qatari families (*Faiyaz-Ul-Haque et al., 2008*). The c.243C>G mutation has previously been identified in two families of Middle Eastern origin (*Coucke et al., 2006*). Subsequently, a recurrent mutation of c.243C>G in the SLC2A10 gene has been found in a Saudi Arabian family (*Faiyaz-Ul-Haque et al., 2008*). These data suggest that the c.243C>G mutation in the Middle Eastern families may have a common origin and shared ancestry.

Dermatological Disorders

Xeroderma pigmentosum (OMIM 278700): Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by pigmentary abnormalities and malignancies on sunlight-exposed areas. But XP patients exist frequently in Qatari families due to strong sunshine and common consanguinity in Qatar. In a case of 28-year-old Qatari woman (*Fathy and Khafagy, 1986*), the family history is interesting: her parents are first cousins; and her brother, one cousin, and her grandfather have XP. Although XP is often fatal before the age of 10 years, this woman survived to 28. It is possible that women in the Gulf area usually stay indoors and are covered when they go out and their cars are screened, which contribute the decrease of her sun exposure and limitation the risk of damage.

Epidermolysis bullosa, junctional type (OMIM 226700): Five affected children from five related families, which belonged to the same Bedouin tribe, were diagnosed with epidermolysis bullosa, junctional type. A homozygous splice mutation c.3609+1G>A of the LAMA3 gene has been found in two of the families (*Teebi and Ben-Omran, 2010*).

Eye Disorders

Ectopia lentis (OMIM 225100): Shafallah Medical Genetics Center, Doha described an isolated form of ectopia lentis in a large inbred family that shows autosomal recessive inheritance (Ahram *et al.*, 2009). The ectopia lentis locus of this family was mapped to the pericentromeric region on chromosome 1 (1p13.2-q21.1). In this region, a homozygous nonsense mutation in exon 11 of ADAMTSL4 (p.Y595X; c.1785T>G) was revealed in all affected individuals. The mutation would result in a truncated protein of half the original length. The results suggest mutations in ADAMTSL4 are responsible for autosomal recessive simple ectopia lentis.

Blindness: According to a clinic survey in Rumeliah General Hospital, congenital malformations accounted for 17.01% in blinding children below 10-year-old (Hosni, 1977). However, it showed consanguinity could only partially account for these cases of blindness.

Nonsyndromic microphthalmia/anophthalmia (OMIM 251600): Through the investigation on four families with nonsyndromic microphthalmia, a homozygous mutation c.599G>C (p. R200P) in exon 4 of CHX gene has been found in six affected siblings from two families (Faiyaz-Ul-Haque *et al.*, 2007). The two families belonged to the same Bedouin tribe. Recently, two more families from the same tribe have been proved to present the same mutation (Teebi and Ben-Omran, 2010).

Teebi-Shaltout syndrome (OMIM 272950): To date, four affected siblings from three families in the same tribe were diagnosed with Teebi-Shaltout syndrome. The candidate gene is being mapped and cloned from the reported families (Teebi and Ben-Omran, 2010).

Cancer

Qatar has witnessed rapid changes in socioeconomic status during the last two decades. The brisk growth and changing environmental and social conditions has influenced the prevalence and pattern of cancer in Qatar. A retrospective study of 5825 cancer cases registered in Qatar from 1991 to 2006 showed incidence rates per 100,000 population in Qatar (63.1) is remarkably lower than in the United States, Europe and the other Middle East countries, such as Egypt (143.0) and Jordan (113.3; Bener *et al.*, 2008). Nevertheless, cancer is also an important public health issue in Qatar, with a sharp rise in the total number of cancer cases during the period 2002-2006 of 57.1% compared to the period 1991-1996. Incidence rates were higher of women compared to men. Colorectal, liver, and lung cancers were the most frequent cancers in men while breast cancer is the most common among woman. The incidence rate per 100,000 population of breast cancer in Qatar (30.1) is significantly higher than other Middle Eastern countries in spite of the similar socioeconomic circumstances. Therefore, more genetic studies to elucidate the cancer patterns in Qatar are called for. However, the high consanguinity

rate of Qatari population seems to have no effect on the incidence of cancers overall (Bener *et al.*, 2009). The study showed that the rate of parental consanguinity was similar in both cases (29.5%) and controls (29.9%) with a higher inbreeding coefficient in controls (0.017-/+0.03), compared to cancer patients (0.0155-/+0.03). However, there was an increased risk found for leukemia and lymphoma, colorectal and prostate cancer groups (with the coefficient of inbreeding 0.018, 0.025 and 0.017, respectively), but a reduced risk in breast, skin, thyroid and female genital cancer groups (with the coefficient of inbreeding 0.014, 0.012, 0.008, and 0.014).

Multiple endocrine neoplasia type IIA (OMIM 171400): Zirie *et al.* (2000) reported a large family with MEN IIA and showed its classic mendelian autosomal dominant inheritance. Of the family members screened, 10 were positive for the RET proto-oncogene mutation (codon 634, TGC→GGC), the major mutation (87%) found in MEN IIA patients.

Childhood acute nonlymphocytic leukemia: HMC reported a case with acute nonlymphocytic leukemia (M4; Mostafavipour *et al.*, 1991). This study showed a new reciprocal apparently balanced translocation between chromosome 7 and 22, i.e., t(7;22)(p22;q13), in association inv(16)(p13q22). ANLL-M4 is a rare neoplasia in children and no genetic advantage is observed, as survival for all cases is poor. Future cytogenetic evaluation of both infants and children with ANLL-M4 would help to elucidate the pathogenesis.

Conclusion

The Qatari population has more Bedouin tribes with strong traditions, and consanguineous marriages between close relatives to guarantee the continuity of the economic unity of the family, while other gulf region countries like the UAE has a cosmopolitan population of different ethnic origins. Founder effects of deleterious mutations are apparent in some diseases. Genetic studies in populations with rather small, traditional communities are recommended to examine specific genetic questions (Wright, 1976). Furthermore, Qatar has a singular public health system. However, the rapid growth of Qatar has taken place in past 20 years. Although quantities of data have been collected, the information of genetic disorders is far from well established. Meanwhile, genetic disorders are on the rise because of the increasing rates of consanguinity. More effort needs to be made in developing public health strategies to improve the population's understanding of the cost-benefit analysis involved in contracting consanguineous marriages given the goal of healthy offspring.

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