4 GENETIC DISORDERS IN ARAB POPULATIONS: QATAR

Tawfeg Ben-Omran, Atqah Abdul Wahab
Department of Pediatrics, Hamad Medical Corporation, P.O. Box 3050 Doha, Qatar

Introduction

Qatar is a peninsula bordering the Arabian Gulf and Saudi Arabia. The country occupies an area of 11,437 square kilometers that roughly stretches 160 kilometers long and 70 kilometers wide. Doha is the capital of the country and the major administrative, commercial, and population center. The population of Qatar according to recent census was as high as 1,700,000 and the total number of live births were around 16,000. The country's population has been roughly split with 20% native Qatari, largely tribal, and 25% other Arabs from Egypt, Syria, Iraq, Lebanon, Yemen, Palestine, and Jordan. The rest of the population (55%) consists of expatriate workers from the East and the West. Generally, Qatar is witnessing a rapid population growth and family units are large with more than five children per family.

Historical Background

Qatar's history is very rich indicating the various phases that led to the ultimate development of the present State. The first trace of human settlements was found in the Qatar peninsula around 4000 BCE. The strategic location of Qatar is responsible for the inflow of Arab tribes from the Arabian Peninsula and especially from the Nejd Desert. Its people embraced Islam in the seventh century CE and Later on, however, Qatar played a significant role in spreading this religion to various parts of the world. In the beginning of the 16th century Qatar fell under the control of the Portuguese who were successful in establishing their control in many parts of the Arabian Peninsula. The Portuguese also efficiently controlled the trade and navigation. Later on in 1538 CE the Portuguese were overthrown by the Ottomans. The Ottomans ruled Qatar for four centuries. Sheikh Muhammad ibn Thani Al-Thani, head of a leading Qatari family, was installed as the region's ruler. Qatar is a member of the Gulf Cooperation Council (GCC) that also includes Bahrain, Kuwait, Oman, Saudi Arabia, and the UAE.

Current Genetic Facilities in Qatar

Medical genetic services are well-established sub-specialties within the Pediatric Department at Hamad Medical Corporation (HMC). In addition, there are cytogenetic and molecular diagnostic laboratories within HMC performing wide range of cytogenetic and molecular studies. In 2003, an expanded national newborn screening program for metabolic and endocrine disorders was established in collaboration with the University Children's Hospital of Heidelberg, Germany. The screening involves over than 30 disorders and includes all live births in the country. More recently, the National Premarital Screening and Counseling program was established in Qatar. Additional participation comes from the involvement of Weill Cornell Medical College in Qatar and the Shafallah Medical Genetics Center.

Consanguineous Marriages and their Implications in Qatar

Consanguinity rate in the Qatari population is about 54%, the majority of marriages being among first cousins (*Bener and Al Ali, 2006*). Generally, genetic disorders and birth defects are relatively high given the small population size. Apparently, not only, autosomal recessive disorders are increased due to consanguinity, but also common, multifactorial disorders such as diabetes mellitus type 2, obesity, psychosis, and congenital malformations are seen in excess (*Bener and Alali, 2006*; *Bener et al., 2007*).

Reported Genetic Disorders in Qatar

Chromosomal disorders: The incidence of Trisomy 21 (Down syndrome) was found to be 1:513 live births (*AbdulWahab et al., 2006a*). The most common abnormality was regular trisomy 21(98.3%). Advanced maternal age was partly attributed to the relatively high incidence with the median age being 36 years, and 48.5 % of mothers were above 36 years. In another study a total of 146 cases out of 74,980 babies were diagnosed with Down syndrome and born during six-year period from 1st January 2000 to 31st December 2005. The prevalence rate was 19.5:10,000 live births. Table 4.1 shows the chromosomal findings in 146 cases with Down syndrome from Qatar (*AbdulWahab et al., 2006b*). Furthermore, rare chromosomal disorders were also diagnosed especially after the introduction of array CGH studies in the cytogenetic laboratory (*unpublished data*).

Multifactorial birth defects: Congenital heart disease was diagnosed in 610 of 49,887 live-born children between 1984 and 1994, making an incidence of 12.23:1000 live births (*Robida et al., 1997*). Congenital heart diseases were detected in 44 cases of 97 of Down syndrome

Table 4.1. Chromosome findings in 146 cases with Down syndrome from Qatar.

Karyotype	*n*	Qatari	Non-Qatari
Regular triosomy 21			
47, xy, +21	74	31	43
47, xx, +21	69	29	40
Mosaicism			
47, xy, /46, xy + 21	1	-	1
Non-classical karyotypes			
47,xy,t(Y,9)(p10;q10) + 21	2	-	2
Total	**146**	**60**	**86**

(45.4%) born between January 2000 and December 2003 at Hamad Medical Corporation (*AbdulWahab et al., 2006c*). In the period 1986-1989, 34 cases of hydrocephalus were diagnosed prenatally and 31 after delivery (*Nogueira, 1992*). Among them 17 cases had meningomyelocele and in 12 others malformations outside the nervous system were observed. The incidence of hydrocephalus in this study was 157:100,000 live births and for meningomyelocele the incidence was 41:100,000 live-births.

Monogenic disorders (autosomal dominant): Numerous autosomal dominant disorders are diagnosed including Marfan syndrome, neurofibromatosis type 1, tuberous sclerosis, familial dilated cardiomyopathy, achondroplasia and hypochodroplasia, and multiple exostosis syndrome. Various craniosynostosis syndromes including Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, Saethrae Chotzon syndrome, and FGFR3-related craniosynostosis (Muenke syndrome) were also diagnosed. Multiple endocrine neoplasia type IIA was reported in a 3-generation family (*Zirie et al., 2001*). Other disorders seen include autosomal dominant Robinow syndrome, ulnar mammary syndrome, Cornelia de Lange's syndrome, Rubinstein-Taybi syndrome, Beckwith-Wiedemann syndrome, and von Hippel-Lindau syndrome.

Monogenic disorders (X-linked): In Qatar, the frequency of glucose-6-phosphate dehydrogenase deficiency (G6PD) is around 5% (*Al-Jawadi and Al-Hilali, 1998*). Other disorders diagnosed include incontinentia pigmenti and X-linked recessive hypophosphatemic rickets (*El-Benhawi and George, 1988*).

Monogenic disorders (autosomal recessive): High consanguinity rate, similar to other parts of the Arab World, contributed to the increased frequency of autosomal recessive disorders. In addition, we have observed several consanguineous families having affected children with more than one autosomal recessive condition in one child or in the same sibship. The following disorders are more commonly encountered due to inbreeding and founder effect including: classical homocystinuria, cystic fibrosis, arterial tortuosity syndrome, nonsyndromic microphthalmia/anophthalmia, van den Ende-Gupta syndrome, Woodhouse-Sakati syndrome, epidermolysis bullosa (junctional type), Sandhoff disease, and primary ciliary dyskinesia. These disorders are discussed below in detail.

Monogenic Disorders

Classical homocystinuria (OMIM 236200): Classical homocystinuria is caused by the lack of an enzyme called cystathionine beta-synthase (thus, the name CBS deficiency). This is the most common metabolic disease in Qatar with an estimated incidence of 1:3000 (*El-Said et al., 2006*). In this study, 64 patients with clinical and biochemical diagnosis of classical homocystinuria from 31 nuclear families were ascertained over a period of more than 4 years (2001-2005). Molecular studies were performed on all patients. Results showed that 53 patients from a single tribe (tribe 1) and three patients from another tribe (tribe 2) were homozygous for the mutation p.R336C of the CBS gene. There were additional seven patients resulting from mixed marriages between tribe 1 and tribe 2. Only one patient from tribe 3 was found to have another mutation p.D234N in the CBS gene.

In order to facilitate reliable early diagnosis of this treatable disease, a novel combined metabolic and molecular testing strategy for newborn screening of CBS deficiency in the Qatari population was established. This has demonstrated a disease incidence of 1:1800, the highest incidence in the world (*Zschocke et al., 2009*; *Gan-Schreier et al., 2010*). However, from our observation, the incidence of homocystinuria is at least 1:1400 live births. Classical homocystinuria provides a clear example of the founder effect in Qatar where the bulk of cases with a single mutation were present in a single endogamous tribe. It is one of the diseases with carrier status screening now included in the National Premarital Screening and Counseling Program in Qatar.

Cystic fibrosis (OMIM 219700, 602421): Cystic fibrosis (CF) provides another example of the founder effect in Qatar. *Abdul Wahab et al.* (*2000*) reported on 45 patients with CF diagnosed between 1987 and 1999 in the main hospital in Qatar. Twenty six of the 32 families ascertained to have CF belonged to the same Arab Bedouin tribe. The parents of 98% of the patients were consanguineous. The patient's manifestations were mild to moderate. Homozygous I1234V mutation in exon 9 of CFTR gene was identified in all 29 patients belonging to the same Arab tribe, thus, illustrating the founder effect in this tribe (*Abdul Wahab et al., 2001a*). A multiparous Qatari woman with chronic lung disease was found to have the same homozygous mutation (*Abdul Wahab, 2003*). The pattern of microbiological agents responsible for chronic pulmonary infection was studied in 36 patients with the CFTR I1234V mutation from Qatar (*Abdul Wahab et al., 2004b*; *Abdul Wahab et al., 2004d*). Cystic fibrosis with homozygous CFTR I1234V mutation is associated with pancreatic sufficiency by measuring fecal elastase-1 (*Abdel Rahman et al., 2006*). The current number of cases ascertained with this mutation is close to 65 from Qatar reflecting a very high incidence of CF in this tribe. There are examples of other mutations seen in the expatriates in Qatar (*Abdul Wahab et al., 2002b*; *Abdul Wahab et al., 2004a*; *Abdul Wahab et al., 2004c*).

Arterial tortuosity syndrome (OMIM 208050): A new type of Ehlers-Danlos syndrome associated with tortuous systemic arteries was described in 32 patients in several sibships from a large Qatari tribe with many intermarriages (*Abdul Wahab et al., 2003*). A distinctive elongated face with epicanthic folds, full flat and saggy cheeks and micrognathia was present in 30 patients (93.8%; Figure 4.1). Moderate to severe hyperextensibility of the skin was noted in all patients (Figure 4.2). Moderate to severe laxity of small joints was a feature in all patients (Figure 4.3). Echocardiography and HRCT revealed an elongated aortic arch and tortuosity of the brachiocephalic arteries in 30 patients (93.8%). Subsequently, more patients were identified to have the same disorder from the same tribe in Qatar (*Abdul Wahab et al., 2003*; *Zaidi et al., 2009*).

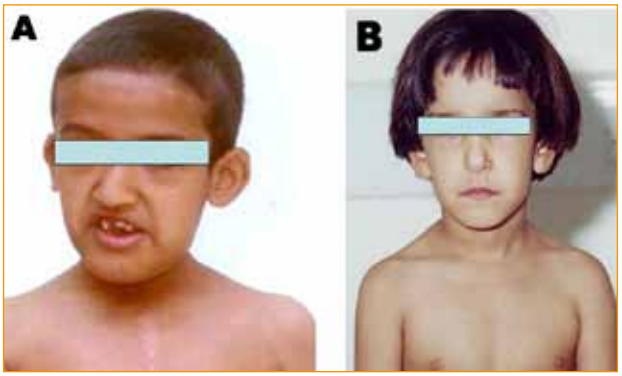

Figure 4.1. The distinctive facial features of an elongated face, epicanthic folds, flat, and saggy cheek.

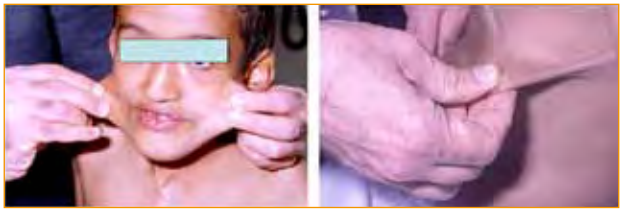

Figure 4.2. Moderate to severe hyperextensibility of the skin.

Figure 4.3. Moderate to severe laxity of the large joints.

Molecular studies of 15 affected individuals from 10 families have identified a p.Ser81Arg encoding mutation in SLC2A10 gene (*Faiyaz-Ul-Haque et al., 2008*). From the near-by Saudi Arabia, two unrelated families with similar phenotype have been found to have a novel missense mutation (p.Arg105Cys) and a recurrent mutation (p.Ser81Arg) in the SLC2A10 gene (*Faiyaz-Ul-Haque et al., 2009*).

Nonsyndromic microphthalmia/anophthalmia (OMIM 251600, 610092, 6200930): In 2004, we investigated four families ascertained to have non-syndromic microphthalmia. Patients were recruited from the school of blind. Two of the families with total six affected siblings had a homozygous mutation c.599G>C in exon 4 of the CHX10 gene. This mutation produces a p.Arg200Pro substitution (*Faiyaz-Ul-Haque et al., 2007*). The two families belonged to the same Arab Bedouin tribe. Recently, two more families from the same tribe presented with similarly affected individuals and presented the same mutation. Carriers were identified and premarital counseling within the same tribe was highly recommended. Two families affected with this disorder had a successful preimplantation genetic diagnosis (PGD).

Van den Ende-Gupta syndrome (OMIM 600920): Van Den Ende-Gupta syndrome (VDEGS) is an infrequently described disorder characterized by arachnodactyly, camptodactyly, blepharophimosis, malar hypoplasia, narrow nasal bridge, convex nasal ridge, and everted lower lip. Patients show normal growth and cognition. We reported on three male and three female cases from four consanguineous families, of which three belong to the same highly inbred tribe from Qatar (*Ali et al., 2010*). Molecular studies indicated that mutations in SCARF2 are responsible for Van Den Ende-Gupta syndrome. Sequencing of this gene identified a missense change, c.773G>A (p.C258Y), in exon 4 in the two patients and a 2 bp deletion in exon 8, c.1328_1329delTG (p.V443DfsX83), in two other patients (*Anastasio et al., 2010*).

Woodhouse-Sakati syndrome (OMIM 241080): Woodhouse-Sakati syndrome (WSS) is a rare autosomal recessive neuroendocrine ectodermal disorder characterized by hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome. The syndrome was first described by Woodhouse and Sakati in 1983 and reports thus far include 36 patients from 18 families mainly from Saudi Arabia. We report additional six patients (3 girls and 3 boys) from the same highly inbred tribe from Qatar. These cases presented with a mild phenotype of WSS and mutations in the C2orf37 gene (*unpublished data*).

Epidermolysis bullosa, junctional type (OMIM 226650): To date, six related families with six affected children (3 females and 3 males) were diagnosed. The families belonged to the same Bedouin tribe. Two of the families had homozygous splice mutation c.3609+1G>A of the LAMA3 gene.

Sandhoff disease (OMIM 268800): A patient was reported with a rare and unusual presentation of intrauterine growth retardation, premature delivery, and bronchopulmonary dysplasia. The clue for diagnosis was the fundoscopy examination (*Abdul Wahab et al., 2002a*).

Primary ciliary dyskinesia (OMIM 244400): Two cases of primary ciliary dyskinesia (PCD) in two siblings were

observed for the first time in the Arabian Gulf region. The appearance of respiratory symptoms within the first month of life in these two siblings together with a history of recurrent persistent rhinitis are the cardinal features of PCD (*Abdul Wahab et al., 2001b*).

Inborn Errors of Metabolism (IEM)

Qatar is the first Arab Country to establish a national expanded newborn screening program for IEM. The program is conducted in collaboration with the University Children's Hospital of Heidelberg since December 2003, with a laboratory situated in Germany. This program replaced the screening for congenital hypothyroidism from cord blood that has been in operation since 1996. In less than three years, between December 2003 and July 2006, 25,214 neonates in the State of Qatar were investigated for inborn errors of metabolism and endocrine disorders with the incidence of metabolic disorders (26 disorders) found to be 1:1327 (in Germany 1:2517; *Linder et al., 2007*). Among them, aminoacidopathies, fatty acid oxidation defects, organic acidurias, and biotinidase deficiency, are prevalent.

Follow-up data (December 2003-June 2010), out of 71,861 newborns born in Qatar, confirmed the presence of 144 neonates with positive screening results (101 metabolic and 43 endocrine disorders). Estimated incidences of metabolic and endocrine disorders were 1:711 and 1:1671, respectively. Thirty-four infants were diagnosed with congenital hypothyroidism and nine with congenital adrenal hyperplasia. Twenty-two were diagnosed with classical homocystinuria, 12 with other aminoacidopathies and urea cycle disorders, 18 with fatty acid oxidation disorders, eight with organic acidaemias, 35 with cobalamin factor defects, three with biotinidase deficiency, and three with galactosemia. Individual disorders diagnosed and confirmed through the neonatal screening programs as well as those ascertained in the metabolic clinic are included in Table 4.2.

Table 4.2. Confirmed cases by NBS and disorders ascertained in the Clinical and Metabolic Genetic Clinic.

Diseases
3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC)
Arginosuccinate lyase deficiency (ASL)
Beta-ketothiolase deficiency
Biotinidase
Carnithine palmityl transferase I (CPTI) deficiency
Citrullinemia
Classical homocystinuria
Ethylmalonic encephalopathy
Familial hypertriglyceridemia
Galactosemia
Gaucher disease
Glutaric aciduria types I and II
Glycogen storage disease types I and III
GM1 gangliosidosis
HMG-CoA lyase deficiency
Hyperinsulinism–hyperammonemia syndrome
Maple syrup urine disease (MSUD)
Medium chain acyl-CoA dehydrogenase deficiency
Metachromatic leukodystrophy
Methylmalonic aciduria
Mitochondrial diseases
Mucolipidosis type II (I cell disease)
Mucopolysaccharidosis types I H, IH/S, II, III, IV, and VI
Niemann-Pick disease (types B and C)
Oculocutaneous albinism
Phenylketonuria (PKU)
Primary carnitine deficiency
Propionic aciduria
Tetrahydrobiopterin deficiency
Very long chain acyl-CoA carboxylase deficiency

Endocrine Disorders

According to the neonatal screening program, incidence of endocrine disorders which include congenital hypothyroidism (CH) and congenital adrenal hyperplasia was found to be 1:2,801 which is similar to that in Germany (1:2,784; *Linder et al., 2007*).

Hemoglobinopathies

Thalassemias, in particular beta-thalassemia, are frequently diagnosed in Qatar. In the main pediatric department at HMC in Doha, at least 60 patients with thalassemia major are seen on regular basis. Adult patients are seen elsewhere by hematologists. The frequency of heterozygotes is estimated to be 2-3%. Recently, *Al-Obaidli et al.* (*2007*) studied, at molecular level, 31 clinically recognized patients with beta-thalassemia including three with sickle cell disease and beta-thalassemia, and additional six cases referred because of unexplained microcytic anemia. They found 12 different beta-thalassemia alleles and two undefined alleles which highlights ethnic diversity in the small population of Qatar.

Sickle cell disease is also relatively common in Qatar. At least 70 patients are followed up by the pediatric department of HMC. The frequency of sickle cell trait is estimated to be 3%. Sickle cell is amongst the disorders that are included recently in the neonatal screening program, and both sickle cell and thalassemias are included in the National Premarital Screening and Counseling Program in Qatar.

Miscellaneous Disorders/Syndromes

Many disorders/syndromes either reported or diagnosed by our group are included in Table 4.3. This reflects the wide variety of patients we see in the Clinical and Metabolic Genetic Clinic, as well as the appropriate and high quality services offered by the section at HMC.

Table 4.3. Disorders/syndromes either reported or diagnosed by the research group at Hamad Medical Corporation.

OMIM #	Disease/Syndrome	Reference
276820	Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome	
208900	Ataxia-telangiectasia	*Osundwa and Dawod, 1994; Ehlayel et al., 2008*
225100	Autosmal-recessive isolated ectopia lentis	*Ahram et al., 2009*
263650	Bartsocas-Papas syndrome	*Masssoud et al., 1998*
204200	Batten's disease	
130650	Beckwith-Wiedemann syndrome	
254940	Carey-Fineman-Ziter syndrome	
216550	Cohen syndrome	
122470	Cornelia de Lange's syndrome	
222448	Donnai-Barrow syndrome	*Kantarci et al., 2007*
225500	Ellis-van Creveld syndrome	
208250	Familial hypertrophic synovitis	*Hammoudeh and Siam, 1993*
-	Galactosyltransferase-I deficiency (facioskeletal anomalies and Ehlers-Danlos syndrome resembling the progeroid type with the B4GALT7 mutation)	*Faiyaz-Ul-Haque et al., 2004*
308300	Incontinentia pigmenti	*El-Benhawi and George, 1988*
243800	Johanson-Blizzad syndrome	
262500	Larone syndrome	
246200	Leprechaunism	*Hone et al., 1995*
249000	Meckel-Gruber syndrome	
-	Myofibrillar myopathy	*El-Menyar et al., 2004*
300183	Noncompaction cardiomyopathy	*El-Menyar et al., 2007*
261540	Peters-Plus syndrome	
180700	Robinow syndrome	
180849	Rubinstein-Taybi syndrome	
268800	Sandhoff disease	*Abdul-Wahab et al., 2002a*
-	Severe childhood autosomal recessive muscular dystrophy	*Salih et al., 1984; Salih et al., 1996*
193300	von Hippel-Lindau syndrome	
236670	Walker-Warburg syndrome	*Fawzi et al., 2000*
277590	Weaver syndrome	
226980	Wolcott-Rallison syndrome	*Engelmann et al., 2008*
241080	Woodhouse-Sakati syndrome	
300554	X-linked recessive hypophosphatemic rickets	

References

Abdel Rahman H, Abdul Wahab A, Abdel Rahman MO, Mostafa OA. Faecal elastase-1 concentration in cystic fibrosis patients with CFTR I1234V mutation. *Acta Paediatr*. 2006; 95(9):1066-9.

Abdul Wahab A, Al Thani G, Dawod ST, Kambouris M, Al Hamed M. Heterogeneity of the cystic fibrosis phenotype in a large kindred family in Qatar with cystic fibrosis mutation (I1234V). *J Trop Pediatr*. 2001a; 47(2):110-2.

Abdul Wahab A, Al Thani G, Dawod ST, Kambouris M, Al Hamed M. Rare CFTR mutation 1525-1G>A in a Pakistani patient. *J Trop Pediatr*. 2004a; 50(2):120-2.

Abdul Wahab A, Bener A, Sandridge AL, Hoffmann GF. The pattern of Down syndrome among children in Qatar: a population-based study. *Birth Defects Res A Clin Mol Teratol*. 2006b; 76(8):609-12.

Abdul Wahab A, Bener A, Teebi AS. The incidence patterns of Down syndrome in Qatar. *Clin Genet*. 2006a; 69(4):360-2.

Abdul Wahab A, Bessisso MS, Elsaid MF. Sandhoff disease (GM2 Gangliosidoses) in a premature patient with bronchopulmonary dysplasia. *Saudi Med J*. 2002a; 23(5):602-5.

Abdul Wahab A, Dawod ST, al Thani G. Cystic fibrosis in a large kindred family in Qatar. *Ann Trop Paediatr*. 2000; 20(3):203-7.

Abdul Wahab A, Janahi IA, Al-Rawi F, Mostafa OA. Diagnostic role of pediatric flexible bronchoscopy in Down's syndrome associated with congenital heart disease. *Saudi Med J*. 2006c; 27(9):1431-3.

Abdul Wahab A, Janahi IA, El-Shafie SS. Achromobacter xylosoxidans isolated from the sputum of a patient with cystic fibrosis mutation I1234V with Pseudomonas aeruginosa. *Saudi Med J*. 2004b; 25(6):810-1.

Abdul Wahab A, Janahi IA, Eltohami A, Zeid A, Ul Haque MF, Teebi AS. A new type of Ehlers-Danlos syndrome associated with tortuous systemic arteries in a large kindred from Qatar. *Acta Paediatr*. 2003; 92(4):456-62.

Abdul Wahab A, Janahi IA, Hebi S, Al-Hamed M, Kambouris M. Cystic fibrosis in a child from Syria. *Ann Trop Paediatr*. 2002b; 22(1):53-5.

Abdul Wahab A, Janahi IA, Marafia MM, El-Shafie S. Microbiological identification in cystic fibrosis patients with CFTR I1234V mutation. *J Trop Pediatr*. 2004d; 50(4):229-33.

Abdul Wahab A, Janahi IA, Marafia MM. Pseudo-Bartter's syndrome in an Egyptian infant with cystic fibrosis mutation N1303K. *J Trop Pediatr*. 2004c; 50(4):242-4.

Abdul Wahab A, Rosenthal M, Dawod ST. Cilial Aplasia of the Respiratory Tract-The First Report in a Qatari Family. *Emirates Med J*. 2001b; 19:175-177.

Abdul Wahab A. Cystic fibrosis mutation I1234V in a Qatari lady. *J Trop Pediatr*. 2003; 49(1):54-5.

Ahram D, Sato TS, Kohilan A, Tayeh M, Chen S, Leal S, Al-Salem M, El-Shanti H. A homozygous mutation in ADAMTSL4 causes autosomal-recessive isolated ectopia

lentis. *Am J Hum Genet*. 2009; 84(2):274-8.
Ali R, Almureikhi M, Al-Musaifri F, Bhat V, Teebi A, Ben-Omran T.. Further Delineation of the Van den Ende-Gupta Syndrome. *Am J Med Genet A*. 2010; 152A(12):3095-100.
Al-Jawadi O, Al-Hilali A. Haemoglobin A2 concentration in glucose-6-phosphate dehydrogenase-deficient patients. *Acta Haematol*. 1998; 100(2):99-100.
Al-Obaidli A, Hamodat M, Fawzi Z, Abu-Laban M, Gerard N, Krishnamoorthy R. Molecular basis of thalassemia in Qatar. *Hemoglobin*. 2007; 31(2):121-7.
Anastasio N, Ben-Omran T, Teebi A, Ha KC, Lalonde E, Ali R, Almureikhi M, Der Kaloustian VM, Liu J, Rosenblatt DS, Majewski J, Jerome-Majewska LA. Mutations in SCARF2 are responsible for Van Den Ende-Gupta syndrome. *Am J Hum Genet*. 2010; 87(4):553-9.
Bener A, Alali KA. Consanguineous marriage in a newly developed country: the Qatari population. *J Biosoc Sci*. 2006; 38(2):239-46.
Bener A, Hussain R, Teebi AS. Consanguineous marriages and their effects on common adult diseases: studies from an endogamous population. *Med Princ Pract*. 2007; 16(4):262-7.
Bener A, Hussain R. Consanguineous unions and child health in the State of Qatar. *Paediatr Perinat Epidemiol*. 2006; 20(5):372-8.
Ehlayel M, de Beaucoudrey L, Fike F, Nahas SA, Feinberg J, Casanova JL, Gatti RA. Simultaneous presentation of 2 rare hereditary immunodeficiencies: IL-12 receptor beta1 deficiency and ataxia-telangiectasia. *J Allergy Clin Immunol*. 2008; 122(6):1217-9.
El Menyar AA, Bener A, Al Suwaidi J. Cardiovascular manifestations of myofibrillar myopathy. *Anadolu Kardiyol Derg*. 2004; 4(4):336-8.
El-Benhawi MO, George WM. Incontinentia pigmenti: a review. *Cutis*. 1988; 41(4):259-62.
El-Menyar AA, Gendi SM, Numan MT. Noncompaction cardiomyopathy in the State of Qatar. *Saudi Med J*. 2007; 28(3):429-34.
El-Said MF, Badii R, Bessisso MS, Shahbek N, El-Ali MG, El-Marikhie M, El-Zyoid M, Salem MS, Bener A, Hoffmann GF, Zschocke J. A common mutation in the CBS gene explains a high incidence of homocystinuria in the Qatari population. *Hum Mutat*. 2006; 27(7):719.
Engelmann G, Meyburg J, Shahbek N, Al-Ali M, Hairetis MH, Baker AJ, Rodenburg RJ, Wenning D, Flechtenmacher C, Ellard S, Smeitink JA, Hoffmann GF, Buchanan CR. Recurrent acute liver failure and mitochondriopathy in a case of Wolcott-Rallison syndrome. *J Inherit Metab Dis*. 2008; 31(4):540-6.
Faiyaz-Ul-Haque M, Zaidi SH, Al-Ali M, Al-Mureikhi MS, Kennedy S, Al-Thani G, Tsui LC, Teebi AS. A novel missense mutation in the galactosyltransferase-I (B4GALT7) gene in a family exhibiting facioskeletal anomalies and Ehlers-Danlos syndrome resembling the progeroid type. *Am J Med Genet A*. 2004; 128A(1):39-45.
Faiyaz-Ul-Haque M, Zaidi SH, Al-Mureikhi MS, Peltekova I, Tsui LC, Teebi AS. Mutations in the CHX10 gene in non-syndromic microphthalmia/anophthalmia patients from Qatar. *Clin Genet*. 2007; 72(2):164-6.
Faiyaz-Ul-Haque M, Zaidi SH, Al-Sanna N, Alswaid A, Momenah T, Kaya N, Al-Dayel F, Bouhoaigah I, Saliem M, Tsui LC, Teebi AS. A novel missense and a recurrent mutation in SLC2A10 gene of patients affected with arterial tortuosity syndrome. *Atherosclerosis*. 2009; 203(2):466-71.
Faiyaz-Ul-Haque M, Zaidi SH, Wahab AA, Eltohami A, Al-Mureikhi MS, Al-Thani G, Peltekova VD, Tsui LC, Teebi AS. Identification of a p.Ser81Arg encoding mutation in SLC2A10 gene of arterial tortuosity syndrome patients from 10 Qatari families. *Clin Genet*. 2008; 74(2):189-93.
Fawzi M, Bessisso M, Omar F. Walker-Warburg Syndrome: A Case Report of a Qatari Patient. *Qatar Med J*. 2000; 9(2): 66-7.
Gan-Schreier H, Kebbewar M, Fang-Hoffmann J, Wilrich J, Abdoh G, Ben-Omran T, Shahbek N, Bener A, Al Rifai H, Al Khal AL, Lindner M, Zschocke J, Hoffmann GF. Newborn population screening for classic homocystinuria by determination of total homocysteine from Guthrie cards. *J Pediatr*. 2010; 156(3):427-32.
Hammoudeh M, Siam AR. Familial hypertrophic synovitis. *Clin Rheumatol*. 1993; 12(3):401-4.
Hone J, Accili D, Psiachou H, Alghband-Zadeh J, Mitton S, Wertheimer E, Sinclair L, Taylor SI. Homozygosity for a null allele of the insulin receptor gene in a patient with leprechaunism. *Hum Mutat*. 1995; 6(1):17-22.
Kantarci S, Al-Gazali L, Hill RS, Donnai D, Black GC, Bieth E, Chassaing N, Lacombe D, Devriendt K, Teebi A, Loscertales M, Robson C, Liu T, MacLaughlin DT, Noonan KM, Russell MK, Walsh CA, Donahoe PK, Pober BR. Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow and facio-oculo-acoustico-renal syndromes. *Nat Genet*. 2007; 39(8):957-9.
Lindner M, Abdoh G, Fang-Hoffmann J, Shabeck N, Al-Sayrafi M, Al-Janahi M, Ho S, Abdelrahman MO, Ben-Omran T, Bener A, Schulze A, Al-Rifai H, Al-Thani G, Hoffmann GF. Implementation of extended neonatal screening and a metabolic unit in the State of Qatar: developing and optimizing strategies in cooperation with the Neonatal Screening Center in Heidelberg. *J Inherit Metab Dis*. 2007; 30(4):522-9.
Massoud AA, Ammaari AN, Khan AS, ven Katraman B, Teebi AS. Bartsocas-Papas syndrome in an Arab family with four affected sibs: further characterization. *Am J Med Genet*. 1998; 79(1):16-21.
Nogueira GJ. Pre- and neonatal hydrocephalus in the Middle East: experience in Qatar. *Childs Nerv Syst*. 1992; 8(1):40-4.
Osundwa VM, Dawod ST. The occurrence of ataxia-telangiectasia and common variable immunodeficiency in siblings: case report. *Ann Trop Paediatr*. 1994; 14(1):71-3.
Robida A, Folger GM, Hajar HA. Incidence of congenital heart disease in Qatari children. *Int J Cardiol*. 1997; 60(1):19-22.
Salih MA, Ekmejian A, Ibrahim M, Omer A. Respiratory insufficiency in a severe autosomal recessive form of muscular dystrophy. *Ann Trop Paediatr*. 1984; 4(1):45-8.
Salih MA, Mahdi AH, al-Rikabi AC, al-Bunyan M, Roberds SL, Anderson RD, Campbell KP. Clinical and molecular pathological features of severe childhood autosomal recessive muscular dystrophy in Saudi Arabia. *Dev Med Child Neurol*. 1996; 38(3):262-70.
Woodhouse NJ, Sakati NA. A syndrome of hypogonadism, alopecia, diabetes mellitus, mental retardation, deafness, and ECG abnormalities. *J Med Genet*. 1983; 20(3):216-9.
Zaidi SH, Meyer S, Peltekova VD, Lindinger A, Teebi AS, Faiyaz-Ul-Haque M. A novel non-sense mutation in the SLC2A10 gene of an arterial tortuosity syndrome patient of Kurdish origin. *Eur J Pediatr*. 2009; 168(7):867-70.
Zirie M, Mohammed I, El-Emadi M, Haider A. Multiple endocrine neoplasia type IIA: report of a family with a study of three generations in Qatar. *Endocr Pract*. 2001; 7(1):19-27.
Zschocke J, Kebbewar M, Gan-Schreier H, Fischer C, Fang-Hoffmann J, Wilrich J, Abdoh G, Ben-Omran T, Shahbek N, Lindner M, Al Rifai H, Al Khal AL, Hoffmann GF. Molecular neonatal screening for homocystinuria in the Qatari population. *Hum Mutat*. 2009; 30(6):1021-2.