

Genetic Diseases in the Sultanate of Oman: Public Health Perspective

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General Information about Oman

Oman is situated in the South East of the Arabian Peninsula along the eastern coast of the Arabian Gulf and its territory 309,500 sq km. It has its borders with the United Arab Emirates to the North, Saudi Arabia to the West, and Yemen to the South West.

After the accession of H. M. Sultan Qaboos Bin Said in 1970, Oman opened the doors wide to the modern world. Since 1970, progress has been extremely rapid. Schools, roads, hospitals, electricity, and telecommunications have been brought to the most remote regions. Main sources of Oman’s income are

oil, gas, fisheries, agriculture, industry, and tourism.

There are eight main geographical areas in Oman, referred to as *Manateq*, each of which is further divided into Districts, referred to as *Welayat* (Figure 3.1).

Oman’s History

The earliest archeological evidence of settlements in Oman dates back to about 12000 BC, towards the end of the Ice Age. The ancient burial mounds of Northern Oman (“beehive tombs”) contained pottery, weapons, and jewelry dated from about 3000

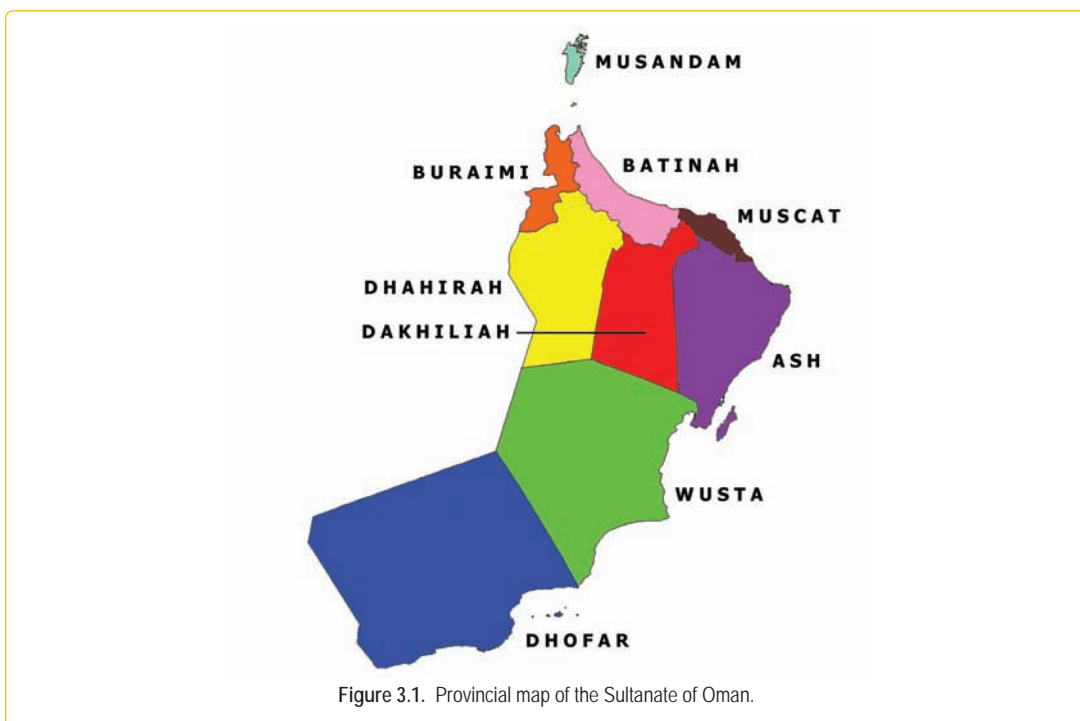


Figure 3.1. Provincial map of the Sultanate of Oman.

BC. A few settlements and burial grounds have been discovered which date from 4000 BC near Buraimi and Ibri which closely resemble the Temdet Nasr in Mesopotamia 3000-2800 BC. The most valuable metal of the ancient world, copper, was brought from Magan (Mountainous central Oman) to Mesopotamia by ships in the 2400 BC. Open-cast Copper mining pits over 30 meters deep have been found in Oman which were dug over 2,500 years ago. Oman's sailors and merchants traded from one end of the monsoon to the other, from China to East Africa as far back as the 8th century CE and forged their ways in ancient times to the markets of India and the distant shores of China. For centuries, Muscat was an important place of trade with India, the Red Sea, and East Africa. As Oman lies on the cross-roads between East and West, mixing with populations from neighbouring Asian and African countries occurred due to immigration, trade, introduction of slaves, and mercenaries.

The tribes that took possession of Arabia in the beginning of the New Era were composed of two main stocks. One of these stocks was Kahtan (Bani Hina), who colonized Yemen and moved up North into Oman territories after the collapse of the Mareb Dam in Yemen in the 5th century CE. The other was Adnan (Bani Ghafir) who descended from Ismael and occupied the Northern part of Arabian Peninsula (Carter, 1982). Bani Hina and Bani Ghafir were opponents and competed for the territories as pastures and watering places. Later, more Arab tribes (Northern Arabs) came from Iraq and settled in the North of Oman.

Community Structure: Past and Present

The Interior of Oman in the past had a tradition of a closed, isolated, self-sufficient community, tribal in its organisation, governed by an elected *Imam* (religious leader; Antony, 1976; Wilkinson, 1987). A part of the community was sedentary and the other part included Bedouin tribal units.

Bedouins in Oman in the past represented not only the most numerous, but also politically and economically the most important group of autonomous population. They were believed to be the indigenous inhabitants of the country. The way of life and economy of the Bedouins is characterized by a mobility which allows them to change their dwelling place frequently and to cover great distances to look for fresh pastures. The nomadic group in the past represented an optimal adaptation to the prevailing ecological condition, where pastures were rapidly consumed by livestock, thereby necessitating a frequent change of location. Largely members of nomadic tribes have settled now in permanent housing.

Ancient settlers of Oman possessed the vital skills and the knowledge of how to make the underground water channels "falages". The water conduits enabled huge tracks of barren land to be cultivated facilitating sedentary life.

There were several important sedentary tribes in central Oman where traditionally each one controlled the territory of the *Wadi* (valley) and may take its name. For its members a tribe represents the supreme cultural, political and social unit. All those belonging to a tribe

derive their descent from a common ancestor who cannot be accurately traced in genealogical terms, but who lived a very long time ago, possibly in pre-Islamic days. Historically, the common characteristics of a tribal unit were the existence of a leader (*sheikh*), a well defined territory of pastures and water places, political and military autonomy, and identification element in the tribal brand mark for camels. The tribal entity, however, could not be thought to be a static as it can change with time. A tradition of tribal organization and a Sheikh's leadership of the tribe is still preserved in Oman, but became directed towards justice and care of those in need rather than historical inter-tribal politics.

Consanguinity

The Omani society has a long tradition of consanguinity which goes back to pre-Islamic times. The preferred type of marriage is still among tribal members. Consanguinity levels in a health survey conducted in 1995, as part of the Gulf Family Health Project, was 53% in urban and 57% in rural communities (Sulaiman *et al.*, 1995). Large consanguinity data collected in

1995 representing 20% of the national child-bearing age population was retrieved from delivery book records in 1993 for 60,895 Omani couples (Rajab and Patton, 2000). In this large survey, which included all sections of the community, the inbreeding coefficient (F) was 0.0176. Almost quarter (24.1%) of marriages observed were between first cousins, 11.8% among second cousins, and further 20.4% within members of the same tribe; thus, making a total of 56.5%. In order to obtain more specific figures of consanguinity (like percentages of double first cousins, first cousins once removed, and others), 500 pedigrees were studied in detail with calculated inbreeding coefficient (F) of 0.0204. Significant reduction of consanguinity would be expected in the next generation due to high level of literacy and urbanization.

Health Services in the Sultanate of Oman

In the past thirty years Oman has witnessed remarkable social and economic growth which is best reflected in the well-organized and efficient healthy care system. With

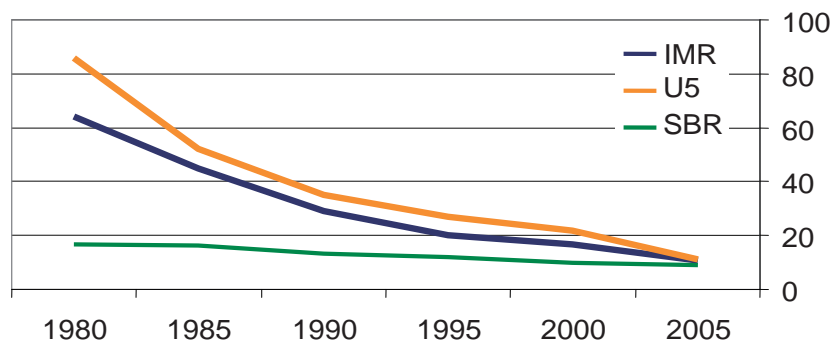


Figure 3.2. Changes in infant mortality rates (IMR), mortality under 5 years (U5) and stillbirth (SBR) at 5 year intervals observed in the past 25 years (1980-2005) from Ministry of Health Information System data.

these achievements the country has witnessed an epidemiologic shift in the disease pattern. There has been a significant decrease in the incidence of communicable diseases and in the mortality and morbidity rates of infants and children under 5 years (Figure 3.2). The national incidence of stillbirths and of congenital anomalies is recorded as 0.9% and 16.9% respectively (Modell, 2003). The figures are astoundingly high when the incidence of congenital malformations, deformations and chromosomal abnormalities are considered together (73/1000 births). The estimated incidence of children born with congenital and genetic disorders is 7% as compared to 4.4% in Europe (EUROCAT, 2002; Modell, 2003). The difference is suggested to be due to the high prevalence of inherited red cell disorders, advanced maternal age, and customary consanguineous marriages (Alwan and Modell, 1997).

In the past the scale of the problem of congenital/genetic disorders was hidden in the high infant mortality because most affected infants died without being diagnosed. Now the majority are diagnosed and provided with best possible treatment. As a result the number of surviving affected children increases by the annual birth cohort. The cumulative number of patients requiring care is therefore rising rapidly.

Genetic Services in the Sultanate of Oman

The need for Genetic Services and Genetic Technologies as means for controlling Genetic Diseases in the Sultanate has been recognized as a priority. The provision of genetic

services is expected to ensure high standard medical care in the era of rapidly expanding Genetic Science and Biotechnology.

Emphasis in Oman is on community genetic services which combine the skills of community medicine and medical genetics. The community approach is an accepted policy in the Sultanate of Oman and the approaches for early identification and prevention of genetic risk are aimed to be applied for the whole population and empower individuals to apply knowledge of genetics for their own benefit. Genetic Services in The Sultanate of Oman are in the process of being incorporated into primary health care. Involvement of the primary health care system is essential if genetic services are to reach the general population. Educational packages and advocacy sessions are delivered regularly to increase population genetic literacy.

National Program for the Control of Genetic Blood Disorders: The first Community Genetic service in the Sultanate was established in 1999 as the national Program for the Control of Genetic Blood Disorders. It is an integrated strategy combining the best possible patient care, as a first objective, coupled with community education, high-risk population screening and genetic counseling. Regional teams with administrative set up have been formed to carry out the program in the regions of Oman. Regional teams have been trained to provide modern care, premarital screening, counseling, health education, and data collection. Recently, the National Program for the Control of Genetic Blood Disorders was strengthened with HPLC facilities in regional hospitals and central labo-

ratory facility for molecular diagnosis of genetic blood disorders.

National Cytogenetic Services: The National Cytogenetic Laboratory Services were built and expanded in the Sultanate from the year 2000. High resolution banding, chromosomal fragility tests, and fluorescent *in situ* hybridization assist in providing care to patients affected by genetic diseases, cancer, and infertile couples.

Ethical, Social and Religious Considerations: The Ministry of Health is aware of the new ethical, legal, social, and economic issues emerging with the development of new genetic technologies. The National Guidelines on Medical Genetics were adopted in the Sultanate of Oman in 1999 on the basis of WHO guidelines. Treatment and prevention remain complementary aspects of a holistic service aiming to help families with a genetic problem (caring for affected children and helping parents to avoid a recurrence). It was observed that informed at-risk couples usually try all means they find acceptable to maximize their chances of having healthy children. The core ethical principles of genetic counseling have been observed such as respect to the autonomy of the individual or couple, their right to full information, and strict confidentiality and exclusion of coercive approaches.

Current Data on Genetic Diseases in the Sultanate of Oman

Hospital-based data on genetic disease were collected in Oman from 1990. The number of diagnosed conditions was growing over years parallel to an improvement in diagnostic expertise

and growth of diagnostic capacity. It is understood that before comprehensive genetic diagnoses became available, the illness and death of many children may have been attributed to other causes. As an example, limited access to mitochondrial and glycosylation studies may be the cause of undiagnosed and may not be a reflection of disease rarity. The following types of inherited disorders were ascertained in the Sultanate:

Chromosomal Rearrangements: Population-based figures of chromosomal rearrangements in Oman are still to be determined. National Cytogenetic Service data for years 2000-2006 indicate a Down syndrome birth prevalence of 1:350 livebirth (Rajab *et al.*, 2008). The rate of chromosomal rearrangements in 1800 pediatric samples referred to the National Cytogenetic Laboratory is 28.3% (Goud *et al.*, 2005). Trisomies, tetrasomies and monosomies, translocations, autosomal aneuploidies, and other structural rearrangements are also detected.

Autosomal Dominant Conditions: Commonly ascertained in hospital practice are conditions of adult polycystic kidney disease (OMIM 601313), congenital non-syndromic sensoryneural deafness (OMIM 600965), various types of craniosynostoses, mainly acrocephalosyndactily (OMIM 101400), tuberous sclerosis (OMIM 191100), neurofibromatosis (OMIM 162200), Sotos syndrome (OMIM 117550), Huntington's chorea (OMIM 143100), achondroplasia (OMIM 100800), Hyper-IgE syndrome (OMIM 147060), hereditary angioedema (OMIM 106100), epidermolysis

bullosa simplex (OMIM 131800), spinocerebellar ataxia (OMIM117360), Allagille syndrome (OMIM 118450), Fanconi renotubular syndrome (OMIM 134600).

X-Linked Conditions: G6PD deficiency is found in 28% of males and 12% females in Oman (Daar *et al.*, 2004). In a majority of Omanis, G6PD deficiency is benign (White *et al.*, 1993; Daar *et al.*, 1996), thus, suggesting that the asymptomatic forms A+ and B+ G6PD types predominate in the Sultanate of Oman. Neonatal jaundice and hemolytic crises are seen in a small proportion of patients, mainly in Northern parts of Oman. Other common X-linked disorders seen are hemophilia A and B (OMIM 306700 and 306900), various forms of X-linked forms of mental retardation, Bruton agammaglobulinaemia (OMIM 300300), Alport syndrome (OMIM 301050), testicular feminization syndrome (OMIM 300068), anhydrotic ectodermal dysplasia (OMIM 305100), Duchenne muscular dystrophy (OMIM 310200), and OTC deficiency (OMIM 311250).

Autosomal Recessive Disorders: Recessive diseases are by far the commonest type and remain the major contributors to childhood morbidity, mortality, and handicap. The complexity of dealing with autosomal recessive disorders is that it sums to a large number when a variety of rare disorders are put together. There is no possibility to present individual disorders because of space limitation. Autosomal recessive disorders observed in the Sultanate could be broadly grouped as follows:

- **Hemoglobin Disorders:** In the Sultanate of Oman the estimated

birth prevalence of infants with hemoglobin disorders is 3.5-4.7/1,000 (White *et al.*, 1993; Rajab and Patton, 1997; Daar *et al.*, 1998; Rajab and Patton., 1999). Around 10% of Omani nationals are carriers of the gene of sickle cell disease (OMIM 603903), 3% carry a mutation of beta-thalassemia (OMIM 141900) and 45% are found to have alpha-thalassemia (OMIM 141800). Hemoglobin disorders can be successfully managed. Currently, about 400 patients with thalassemia major are thought to be living in Oman, approximately 290 are treated in Muscat and Sohar and over 100 are treated in the UAE. It is thought there are at least 3,000 patients with sickle cell disorders.

- **Inborn errors of metabolism:**
 - (A) Metabolic endocrinopathies: Congenital adrenal hyperplasia (OMIM 201910, 202110 and 107910), metabolic rickets (OMIM 277440, 264700, 600785, and 241520), apparent mineralocorticoids excess (OMIM 218030) and nesidioblastosis (OMIM 256450).
 - (B) Disorders of aminoacid metabolism commonly ascertained in hospital practice include: maple syrup urine disease (OMIM 248600), tyrosinemia (OMIM 276700), dihydropterin synthetase deficiency (OMIM 261640), homocystinuria (OMIM 236200), and glutaric aciduria (OMIM 231670 and 231680).
 - (C) Organic acidurias include propionic (OMIM 606054) and isovaleric acidurias (OMIM 243500).
 - (D) Lysosomal storage disorders: Mucopolysaccharidoses (OMIM 607014, 607015, and 252300), multiple sulphatase deficiency (OMIM 272200), mucopolipidosis

- I and II (OMIM 256500 and 256550), glycogen storage diseases (OMIM 232200, 230800, 232400, 232300, and 232700), galactosialidosis (OMIM 256540), and GM1-gangliosidosis (OMIM 230500). (E) Long-chain fatty acid oxidation defects: Zellweger syndrome (OMIM 214100) and Refsum disease (OMIM 266500). (F) Mitochondrial diseases: Kearns-Sayre syndrome (OMIM 530000), congenital lactic acidosis (Bappal *et al.*, 2001), Pyruvate carboxylase deficiency (OMIM 266150), and pyruvate dehydrogenase deficiency (OMIM 208800). (G) Abnormality of fatty alcohol metabolism Sjogren-Larsen syndrome (OMIM 270200).
- **Congenital Syndromes with Mental Retardation:** (A) Primary Microcephaly of various types: Microcephaly (OMIM 608716 and 251200), lethal microcephaly (Rajab *et al.*, 2007), microcephaly with pontocerebellar hypoplasia (Rajab *et al.*, 2003), and Cohen microcephaly (OMIM 216550). (B) Congenital malformations syndrome with brain structural anomalies and poor outcome: Walker-Warburg syndrome (OMIM 236670), Pena-Shokeir syndrome (OMIM 214150), Meckel-Gruber syndrome (OMIM 249000), and Fryns syndrome (OMIM 229850). (C) Non-syndromic mental retardation (OMIM 249500).
 - **Conditions with Regression and Neurologic Deficit:** Joubert syndrome (OMIM 213300), Batten's disease (OMIM 256730), Tay-Sach's disease (OMIM 272800), Niemann-Pick's disease (OMIM 257220), leukodystrophies (OMIM 251100, 254200, and 264090), progressive myoclonic epilepsy (OMIM 310370), hereditary spastic paraplegia (OMIM 270800), hyperekplexia (OMIM 149400), and the genetic form of cerebral palsy (Rajab *et al.*, 2006).
 - **Neuromuscular Disorders:** Spinal muscular dystrophies (OMIM 253300, 253400, and 253900), congenital myopathies (OMIM 255310, 161100, and 601462), Charcot-Marie-Tooth neuropathy (OMIM 214400), facioscapulohumeral (OMIM 158900), and limb girdle muscular dystrophies (OMIM 608099, 160500, and 253601).
 - **Skeletal Dysplasias:** Asphyxiating thoracic dystrophy (OMIM 208500), Ellis Van-Creveld syndrome (OMIM 225500), Robinow syndrome (OMIM 268310), three M dwarfism (OMIM 273750), Omani type spondyloepiphyseal dysplasia (OMIM 608637), Grebe chondrodysplasia (OMIM 200700), and hypochondrogenesis (OMIM 200610).
 - **Diseases with Abnormal Bone Fragility/Density:** Osteogenesis imperfecta (OMIM 610195), pycnodysostosis (OMIM 265800), Bamatter syndrome (OMIM 231070), and osteopetrosis (OMIM 259700).
 - **Diseases Affecting Kidneys and Liver:** Infantile polycystic kidneys (OMIM 263200), focal segmental glomerulosclerosis (OMIM 603278), Finnish form congenital nephrosis (OMIM 256300), steroid-resistant nephrotic syndrome (OMIM 600995), nephronophytosis (OMIM 256100 and 602088), cystinosis (OMIM 219800), hyperoxaluria (OMIM 259900), distal renal tubular

acidosis (OMIM 602722), Bartter syndrome (OMIM 607364), familial intrahepatic cholestasis (OMIM 211600), Crigler-Najjar syndrome type I (OMIM 218800), and Wilson disease (OMIM 277900).

- **Immunodeficiencies and Chromosomal Instability:**

Chronic granulomatous disease (OMIM 233700), common variable immunodeficiency (OMIM 240500), SCID (OMIM 102700), cyclic neutropenia (OMIM 610738), hemophagocytic lymphohistiocytosis type 1 (OMIM 267700), Fanconi anemia (OMIM 227650), Nijmegen syndrome (OMIM 251260), ataxia-telangiectasia (OMIM 208900), Bloom syndrome (OMIM 210900), and xeroderma pigmentosum (OMIM 278700).

- **Dermatological Disorders:** Epidermolysis bullosa (OMIM 226700 and 226670), hypohydrotic ectodermal dysplasia (OMIM 224900), lamellar ichthyosis (OMIM 242300), and ichthyosis congenita (OMIM 242500).

- **Blindness and Deafness:** Usher syndrome (OMIM 276900), leber congenital amaurosis (OMIM 204000), congenital optic atrophy (OMIM 258500), and various types of congenital non-syndromic sensoryneural deafness (OMIM 220290).

- **Other Conditions and Syndromes:** Oculocutaneous albinism (OMIM 606952), Bardet-Biedl syndrome (OMIM 209900), Escobar syndrome (OMIM 265000), Schwartz-Jampel syndrome (OMIM 255800), congenital generalized lipodystrophy (OMIM 269700, 608594, and 608154), apple-peel syndrome (OMIM 243600), cystic

fibrosis (OMIM 219700), cutis laxa with growth and developmental delay (OMIM 219200), long Q-T syndrome (OMIM 152427), neonatal progeroid syndrome (OMIM 271900), and congenital insensitivity to pain with anhidrosis (OMIM 256800).

Future Plans and Challenges

The Ministry of Health in the Sultanate of Oman is wishing to promote the potential benefits of the genomic advances for the health of the Omani population, considering the context of the added value of the genetic technology to health care delivery and recognizing the urgent need for the application of genomics in the Sultanate of Oman. The Specialized National Genetic Health Centre is under construction in the Capital city of Muscat.

As children with handicapping genetic disorders now survive, the population of patients on long term therapy has steadily expanded causing a considerable burden on the health care and social services. National strategies for the prevention and management of genetic and congenital disorders can be defined according to the epidemiological situation, local needs and priorities, as well as available resources. The challenge faced by public health geneticists is to define novel prevention strategies ethically compatible with the cultural and social make up and religious beliefs of the population, and the legal system of the country. The objective of a Genetic Service is to maximize the chances for every couple to have a healthy child and to offer early and

proper management for the affected. A prevention program can be credible and will enlist the confidence of the people only if accompanied by visible commitment to the care of affected people.

Few important adjustments in health care delivery are needed in order to structure efficient prevention programs for prevention of genetic diseases. These should be based on availability of medical genetic expertise, comprehensive genetic diagnostic laboratory services and research. In addition, integrated support to the families affected by genetic illness, education in genetic health and continuous medical education on medical genetics and ethics would be required.

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