Medical genetics around the world

Autosomal recessive disorders among Arabs: an overview from Kuwait

Ahmad S Teebi

Abstract
Kuwait has a cosmopolitan population of 1.7 million, mostly Arabs. This population is a mosaic of large and small minorities representing most Arab communities. In general, Kuwait's population is characterised by a rapid rate of growth, large family size, high rates of consanguineous marriages within the Arab communities with low frequency of intermarriage between them, and the presence of genetic isolates and semi-isolates in some extended families and Bedouin tribes. Genetic services have been available in Kuwait for over a decade. During this time it has become clear that Arabs have a high frequency of genetic disorders, and in particular autosomal recessive traits. Their pattern is unique and some disorders are relatively common. Examples are Bardet-Biedl and Meckel syndromes, phenylketonuria, and familial Mediterranean fever. A relatively large number of new syndromes and variants have been delineated in Kuwait's population, many being the result of homozygosity for autosomal recessive genes that occurred because of inbreeding. Some of these syndromes have subsequently been found in other parts of the world, negating the concept of the private syndrome. This paper provides an overview of autosomal recessive disorders among the Arabs in Kuwait from a personal perspective and published studies, and highlights the need for genetic services in Arab countries with the goal of prevention and treatment of genetic disorders.

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In contrast to the genetically well studied populations of North America and Europe, particularly communities such as the Amish, French Canadians, and Jews, many communities within the Arab world remained unstudied. However, previous efforts have been made to study genetic disorders in some Arabian countries such as Lebanon, Saudi Arabia, and Egypt. I present here a geneticist's experience in Kuwait and review pertinent published reports in order to give an overview of autosomal recessive disorders, which are the most common category of genetic disorders among Arabs in Kuwait.

The country and population
Kuwait is a small Arab country situated in the north east of the Persian Gulf. It is bounded on the north and north east by Iraq and on the south by Saudi Arabia. The country's total area (6880 square miles) is barren desert that is rich in oil which is the source of Kuwaiti wealth. The population is cosmopolitan and comprised of large and small minorities. Until August 1990 (Iraqi invasion), its 1.7 million people, according to a 1985 census, were made up of 40% Kuwaiti natives and Bedouin, and 60% immigrants, the majority of whom were Arabs. These immigrants were mostly from Arabian Middle Eastern countries; however, small minorities from North Africa are also present. One of the large minorities before the invasion of Kuwait were the Palestinians who formed about 22% of the total population at that time. Those considered to be Kuwaiti natives are the early settlers of the urban centres originating mostly from neighbouring Arab countries, while the Bedouin are the nomadic Arabs of the desert who live on the fringes of the Arabian peninsula which includes parts of Kuwait, Saudi Arabia, Qatar, United Arab Emirates, Oman, Iraq, Jordan, and Syria as well as Negev and Sinai desert. Over the past three to four decades, they have settled in urban centres and have acquired the citizenship of the countries that host them. Those who lived in Kuwait have acquired Kuwaiti nationality and some of them became indistinguishable from natives. However, Bedouins form tribal communities which are quite isolated. It is very likely that individual people from the same tribe or kindred have settled in different Arab countries and acquired their nationalities.

Also, the Kuwaiti population has one of the highest growth rates in the world (approximately 50,000 live births/year) and large family size with five children being an average number of offspring per family. The rate of consanguineous marriage is high, with high inbreeding coefficients not only within the Kuwaiti native population but also within other Arab communities, according to studies conducted in Kuwait or in their countries of origin (table 1). The most frequent form of
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### Table 1 Frequencies of consanguineous marriages among Arabs

<table>
<thead>
<tr>
<th>Population</th>
<th>Frequency (%)</th>
<th>Ref</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuwait</td>
<td>54.3</td>
<td>9</td>
<td>Higher rates among Bedouin tribes</td>
</tr>
<tr>
<td>Egyptian</td>
<td>37.8</td>
<td>10</td>
<td>Sample from Kuwait</td>
</tr>
<tr>
<td>Iraqi</td>
<td>28-96</td>
<td>11</td>
<td>Higher rates in rural areas</td>
</tr>
<tr>
<td>Jordanian</td>
<td>57-87</td>
<td>12</td>
<td>Sample from Kuwait</td>
</tr>
<tr>
<td>Lebanese</td>
<td>36-2</td>
<td>13</td>
<td>Lower rates among Christians</td>
</tr>
<tr>
<td>Palestinian</td>
<td>26-0</td>
<td>14</td>
<td>Lower rates among Christians</td>
</tr>
<tr>
<td></td>
<td>39-0</td>
<td>15</td>
<td>Arabs in Israel</td>
</tr>
<tr>
<td></td>
<td>38-7</td>
<td>16</td>
<td>Arab village in Israel</td>
</tr>
</tbody>
</table>

Consanguineous marriage is between first cousins, particularly paternal first cousins. Double first cousin marriages also exist. The frequency of intermarriage between different Arab communities is low, which is also the case for some extended families and tribes within the community. This has resulted in sustained isolation, particularly for the Bedouins and some wealthy families.

**Religion, culture, and genetic issues**

Islam is the predominant religion among Kuwaitis, the majority being Sunnite Muslims who are generally described as being modest with a strong faith in Islam. Despite the westernisation of a significant sector of the population, many still maintain their cultural ties and religious principles. Although Islam, according to many religious scholars, discourages consanguineous marriages, such marriages have been traditionally practised over many generations because of social, economic, and geographical factors. Because they are forbidden by Islam, uncle-niece/aunt-nephew marriages are virtually non-existent. Prenatal diagnosis is acceptable for purposes of reassurance or of therapy. Termination of pregnancy, however, at any stage is absolutely forbidden (haram), unless the mother’s life is endangered. Under Islamic law, according to some interpretations, termination of pregnancy is considered a crime. However, couples may avoid pregnancy if they are at an unacceptably high risk of having a child with a certain genetic defect. On the other hand, artificial insemination using the husband’s sperm (AIIH) and in vitro fertilisation (IVF) using the husband’s sperm is acceptable, but using donor sperm is absolutely forbidden. In general, assisted reproduction using the husband’s and wife’s gametes is acceptable. Adoption has been practised since the early ages of Islam. However, “legal” adoption is not allowed.

**Genetic disorders in Kuwait**

At birth, the incidence of major defects is slightly higher than the 2 to 3% found in the world’s major surveys. However, if other disorders that manifest later in life are included, the figure would be substantially higher than in other parts of the world and the profile is distinctive. In the virtual absence of prenatal diagnosis and termination of pregnancy, and the long reproductive period, patients with chromosomal anomalies, particularly trisomy 21, constitute approximately 28% of patients seen at the genetic clinic (unpublished data on 1300 new patients seen at the Al-Amiri satellite clinic and Farwania community genetic programme over a seven year period from 1983 to 1990). Although the incidence of aneuploidies among live births is higher than other parts of the world, the pattern of chromosomal abnormalities in general does not appear to be significantly different. On the other hand, birth defects as a result of known teratogens form only 1 to 2% of patients, partly because of restricted use of drugs and chemicals, prohibition of alcohol, and the fact that the vast majority of females are naturally immune to rubella before childbearing age. The remaining 70% of patients seen in genetic clinics can be divided as follows. (1) Known autosomal recessive (AR) disorders or unknown disorders with a family pattern suggestive of AR inheritance (approximately 45%). (2) Known multifactorial and polygenic disorders (18%). (3) Known and unknown autosomal dominant disorders (12%). (4) Unknown disorders without suggestive family pattern (22%). (5) X linked disorders (2 to 3%).

In addition to data from the survey (personal observation), sources of information about AR phenotypes include personal communications, published studies, and case reports (general reviews and abstracts are available).

Apart from the extreme rarity of Huntington’s disease, the pattern and apparent frequencies of autosomal dominant disorders in Kuwait are not remarkably different from those in western countries. In contrast, several AR disorders are reported to be highly prevalent (table 2). Autosomal recessive disorders among Arabs in clinical, cytogenetic, and genetic counselling services, to teach medical genetics to medical residents and other health professionals, and to conduct research directed towards understanding genetic problems in the community. Genetic services have subsequently been expanded to involve satellite clinics at the Al-Amiri Hospital in Kuwait City and satellite community genetic programmes at three regional hospitals in the governorates of Farwania, Jahra, and Al-Ahmadi. Services in these regions were furnished on a weekly or twice weekly basis and on demand. The centre in the years 1985 to 1990 was staffed by three trained geneticists at the consultant level, three others at the registrar or senior registrar level, two nurses, and two social workers, and a reasonably equipped and staffed cytogenetics laboratory.
Kuwait will be discussed according to their conspicuous features and McKusick’s entry numbers for the defined entities are included.

**Relatively common autosomal recessive disorders**

**FAMILIAL MEDITERRANEAN FEVER (FMF) OR RECURRENT HEREDITARY POLYSEYOSITIS**

This is a multisystem disease characterised by recurrent, painful, self-limiting, episodes of peritonitis, pleuritis, arthritis, or erysipelas-like erythema usually accompanied by fever. This condition was diagnosed in 88 children and 151 adults from Kuwait. More than 70% of these patients were Palestinians or Jordanians. Accordingly, the prevalence of FMF in this community is at least 1:2000. Similar observations have been noted in Jordan (H A Majeed, personal communication). This disorder is also common among Sephardic Jews and Armenians and to a lesser degree in Turks, Greeks, Italians, and Arabs (other than Palestinians). In earlier studies from Lebanon, FMF was found in most ethnic groups but particularly in Armenians.

**BARDET-BIELD SYNDROME (BBS) AND LAURENCE-MOON SYNDROME (LMS)**

Laurence-Moon-Barret-Biedl syndrome (LMBBS) was a common designation. However, nosological splitting of LMBBS into BBS and LMS has become widely accepted. As from 1986, 20 cases were diagnosed with BBS, including monozygotic twins, and six with LMS among a mixed Arab population in Kuwait. The combined minimum prevalence was 1 in 50,000 among the general population which is more than three times the prevalence in Switzerland. Many of these cases were Palestinians, confirming the observations among Arabs from Israel. Subsequent studies documented more cases of BBS among the Bedouin with an estimated prevalence of 1:13,500 which is three times higher than that of the general population. The incidence of BBS among the Bedouin in Jahra district was estimated to be 1:6900 livebirths. Parental consanguinity was 87% among patients from the general population while it was 100% among Bedouin patients. BBS is also not rare among Jews.

**MECKEL SYNDROME (MS)**

MS is a frequently diagnosed malformation syndrome among neonates in Kuwait. The incidence is unusually high for a malformation syndrome (1:3530 livebirths) and most ascertained cases are of Bedouin ancestry. A similarly high incidence is also seen among ‘Tartars’ in the former Soviet Union and among Gujarati Indians. A Bedouin family with five affected sibs was reported to have a variant of MS lacking polydactyly. Other cases of MS were ascertained in a study of cleft lip with or without cleft palate.

**MULTIPLE PTERYGIUM SYNDROME (MPS)**

MPS was found in 13 cases in six sibships during a genetic survey in the Farwania district (1/3 of Kuwait’s Arab population). The estimated minimum prevalence was 1 in 31,000 in the general population. A detailed report of a Bedouin family with five affected sibs is available. A phenotypically similar but lethal condition(s) has also been reported.

**FACIODIGIOTENITAL SYNDROME, KUWAIT TYPE**

This condition, which closely resembles Aarskog syndrome, has been described in five Kuwaiti Bedouin sibs as a new syndrome. Subsequently, nine patients in four sibships from the same tribe (approximately 8000 people) have been found to have this disorder and all could be traced to a common ancestor.

The prevalence of this syndrome in this tribe is remarkably high and represents a founder effect.

**SEVERE AUTOSOMAL RECESSIVE CHILDHOOD MUSCULAR DYSTROPHY (SARCMD)**

SARCMD, or Duchenne-like MD, is a relatively common disease among Arabs particularly in Sudan and Tunisia. In Kuwait, in Farwania and Jahra districts with highly inbred populations, eight families were ascertained to have SARCMD. This number constitutes more than one third of families with MD compared to 5% as estimated from the UK and North America and 6-8% as estimated from Brazil.
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PROGRESSIVE PSEUDORHEUMATOID ARTHROPATHY OF CHILDHOOD, OR Spondyloepiphyseal dysplasia tarda with progressive arthropathy (SEDT-PA)
This is a rare disorder that was diagnosed in three families in Kuwait. Two of these families were reported in detail.50,51 A review of published reports has shown that seven out of 16 cases were Arabs.51

PHENYLKETONURIA (PKU)
PKU was found to have a frequency of between 1.6% and 1.86% among institutionalized mentally retarded patients.5253 In addition, 13 cases were detected at the genetic clinic through evaluation for mental retardation.52 Other cases were published subsequently.54 The majority of these patients have consanguineous parents. Five patients in three sibships have a common ancestry in a Kuwaiti kindred. The incidence of classical PKU was found to be 1:6479 livebirths,55 as estimated during the course of a neonatal screening project, which is higher than the average figure from the USA and Europe (1:11 000). The combined incidence of PKU and hyperphenylalaninaemia (HPA) was 1:4860 livebirths. PKU has also been ascertained in a Bedouin mother with three children who had PKU embryopathy.56

CONGENITAL CHLORIDE DIARRHOEA (CCD)
In one study over a seven year period,57 16 cases were ascertained, all of whom have consanguineous Kuwaiti parents. The estimated minimum incidence was 7-6:100 000 livebirths, similar to that in Finland.58 Twelve other children with suspected CCD died before having a confirmed diagnosis. Other cases have also been reported.58

CONGENITAL ADRENAL HYPERPLASIA
Over a decade (1978–1988), at least 60 paediatric patients with congenital adrenal hyperplasia were diagnosed.59 The majority (90%) had 21-hydroxylase deficiency while 10% had either 11-β-hydroxylase deficiency or 3-β-hydroxysteroid dehydrogenase deficiency. The estimated overall incidence ranged from 1:7000 to 1:9000 livebirths which is higher than that in Europe and Canada. Other cases were also ascertained in a study of true and pseudohermaphroditism.60

NON-KETOTIC HYPERGLYCAEMIA (NKH) AND HOMOCYSTINURIA (HC)
Seven cases of NKH and five cases of HC were ascertained at Al-Sabah Hospital within a three year period.61 Several other cases of NKH and HC were diagnosed in other hospitals to make these disorders relatively more common in Kuwait than in other parts of the world.

UREA CYCLE DEFECTS
Citrullinaemia is a commonly diagnosed disorder.6263 Cases of argininosuccinic aciduria and carbamoyl phosphate synthase deficiency (CPS) are also common.

TYROSINAEMIA
Several cases of type I tyrosinaemia have been found in a laboratory survey.64 A Kuwaiti family with several members with tyrosinaemia type II was also reported.65

OSTEOPETROSIS, SEVERE AUTOSOMAL RECESSIVE
Data from Kuwait66 and Saudi Arabia67 indicate that this form of osteopetrosis is relatively common in the Arabian peninsula. The incidence, however, is not known. Osteopetrosis with renal tubular acidosis and cerebral calcification has also been reported frequently from Kuwait68–70 and Saudi Arabia,68,69 and it seems to be relatively common also.

HAEMOGLOBINOPATHIES
The genes for sickle cell haemoglobinopathies and β0 thalassaemia are prevalent in Kuwait, and diseases resulting from homozygosity or double heterozygosity (sickle cell anaemia, β0 thalassaemia, and HB S β0 thalassaemia) are common.71 The prevalence of the sickle cell trait (McKusick no 141900-0243) may be similar to or slightly lower than the 10 to 25% estimated in the Eastern Province of Saudi Arabia.72,73 In a study from Kuwait involving 110 patients with major β chain haemoglobinopathies, 47 patients had homozygous haemoglobin S disease (Hb SS) and 21 had Hb β0 thalassaemia.70 In contrast to African-American patients with these diseases, most Kuwaiti patients have a less severe haemolytic anaemia and fewer signs and symptoms of vaso-occlusive phenomena as a result of modifying effects of high levels of Hb F. In another study,74 the incidence of α thalassaemia heterozygotes is estimated to be 4-6% by screening 345 consecutive cord blood samples (16/345). All the 16 samples contained a deletion in either one or two α globin genes. The incidence is significantly lower than in the Eastern Province of Saudi Arabia (56%).

DISORDERS FREQUENTLY DIAGNOSED IN KUWAIT BUT UNCOMMON ELSEWHERE
These include cystinuria (220100), spinal muscular atrophy or Werdnig-Hoffmann disease (226600), GM1 gangliosidosis (230500), Gaucher disease type I (230300), microcephaly (251200), clinical anopthalmia (251600), mucolipidosis type II (252500), Hurler and Hurler-Scheie syndromes (252800), Maroteaux-Lamy syndrome (253200), Nieman-Pick disease type B (257200), Sandhoff disease (264800), multiple sulphatases (272200), Wilson's disease (277900), wrinkly skin syndrome (278250), organic acidemias, lethal chondrodystrophies, and undelineated neurodegenerative brain disorders. The above
information is not published and is based on personal experience and personal communications.

**New autosomal recessive syndromes**

Out of 22 new syndromes and variants that were described in Kuwait in the period from 1985 to 1992, three were autosomal dominant,15-17 one was X linked,18 and 18 were autosomal recessive. Of the 18 AR syndromes and variants, 11 had new entries in McKusick's catalogue25 which constitutes approximately 5% of all new entries during that period (11/211). The remaining seven disorders either had no entries,12-14 or were included in existing AR18,27-30 or autosomal dominant30 entries (table 3).

**LIMB/PELVIS-HYPOPLASIA/APLASIA SYNDROME**

This was the first new disorder to be described from Kuwait.95 The patients were two Palestinian sibs (a male and a female) of consanguineous parents. They had severe limb deficiency, displastic hips, and minor facial anomalies. Subsequently, seven patients were described from several countries including Brazil, Israel, Italy, and again from Kuwait in a Bedouin child.96 Two of the five females hitherto reported had hypoplasia or aplasia of the uterus.99,100 Prenatal diagnosis by ultrasonography has been accomplished.101

**HYPOGONADISM SYNDROMES**

One syndrome was first described in three sibs of consanguineous Jordanian Christian parents. Anomalies included partial alopecia consisting of hair only in the centre of the scalp, primary hypogonadism, and defective Müllerian development in the sisters.84 Their brother had hormonal and histological findings consistent with germinal cell aplasia. After this description, two Kuwaiti sisters of consanguineous parents were found to have a similar condition (unpublished). Another hypogonadism syndrome was reported in three sibs of first cousin Palestinian parents.92 Anomalies included hypogonadotrophic hypogonadism, mental retardation, obesity, and minor skeletal anomalies. The two brothers also had gynaecomastia. This paper reviews seven new autosomal recessive disorders described from the Middle East, six of which were in Arabs and one was in a Yemenite Jewish family.

**FACIODIGITOTEGENITAL SYNDROME, KUWAIT TYPE**

This has been discussed under common disorders.13-14

**CARDIOSKELETAL SYNDROME, KUWAIT TYPE**

Two sibs of Kuwaiti first cousin parents were found to have congenital heart malformation and skeletal dysplasia including rhizomelic limb shortness and coronal clefting of the vertebral bodies.80

**BEDOUIN SPASTIC ATAXIA SYNDROME**

This condition was described in a highly inbred Bedouin family with affected subjects in several sibships.90 Anomalies included spastic ataxia, congenital cataracts, macular and corneal dystrophy, and non-axial myopia, in the absence of mental retardation. Immunological abnormalities were common. The authors concluded that this disorder was clinically distinct from a similar disorder described in Lebanon.103

**SPINOCEBELLAR DEGENERATION WITH SLOW EYE MOVEMENTS (SDEM)**

This condition was described in six subjects (three males and three females) in two sibships from a consanguineous Palestinian family.91 Associated manifestations included progressive intellectual impairment and extrapyramidal dysfunction as well as peripheral neuropathy and skeletal abnormalities. Muscle biopsy showed non-specific mitochondrial changes.

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Table 3 New genetic syndromes and variants reported from Kuwait

<table>
<thead>
<tr>
<th>Disorder</th>
<th>No of patients</th>
<th>Family origin</th>
<th>McKusick No</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric sneezing</td>
<td>11</td>
<td>Syrian</td>
<td>137130</td>
<td>74</td>
</tr>
<tr>
<td>Hypertelorism-Yeebi type (brachycephalofrontonasal dysplasia)</td>
<td>16</td>
<td>Syrian</td>
<td>145420</td>
<td>75, 76</td>
</tr>
<tr>
<td>Tibia, hypoplasia of, with polydactyly</td>
<td>2</td>
<td>Kuwaiti</td>
<td>188770</td>
<td>77, 78</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grebe-like chondrodysplasia</td>
<td>1</td>
<td>Palestinian</td>
<td>200700</td>
<td>81</td>
</tr>
<tr>
<td>Cardioskeletal syndrome, Kuwait type</td>
<td>2</td>
<td>Kuwaiti</td>
<td>212135</td>
<td>80</td>
</tr>
<tr>
<td>Cystic fibrosis with helicobacter gastritis, megaloblastic anaemia and subnormal mentality</td>
<td>2</td>
<td>Bedouin</td>
<td>219721</td>
<td>82</td>
</tr>
<tr>
<td>Faciodigito-genital syndrome, Kuwait type</td>
<td>5 + 9</td>
<td>Kuwaiti, Bedouin</td>
<td>227330</td>
<td>43, 44</td>
</tr>
<tr>
<td>Hypertelorism, hypoplasia, polysyndactyly syndrome</td>
<td>3</td>
<td>Pakistani (non-Arab)</td>
<td>239710</td>
<td>88, 89</td>
</tr>
<tr>
<td>Hypertelorism, hypoplasia, tetralogy of Fallot syndrome</td>
<td>4</td>
<td>Palestinian</td>
<td>239711</td>
<td>83</td>
</tr>
<tr>
<td>Hypogonadism, primary, and partial alopecia</td>
<td>3 + 2</td>
<td>Jordanian, Kuwaiti</td>
<td>241090</td>
<td>84</td>
</tr>
<tr>
<td>Macrocoma with microphthalmia, lethal</td>
<td>5</td>
<td>Palestinian</td>
<td>248110</td>
<td>85, 86</td>
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<tr>
<td>Microcephaly with normal intelligence</td>
<td>8</td>
<td>Palestinian</td>
<td>251260</td>
<td>87</td>
</tr>
<tr>
<td>Bedouin spastic ataxia syndrome</td>
<td>22</td>
<td>Bedouin</td>
<td>271320</td>
<td>90</td>
</tr>
<tr>
<td>Spinocerebellar degeneration with slow eye movements</td>
<td>6</td>
<td>Palestinian</td>
<td>271322</td>
<td>91</td>
</tr>
<tr>
<td>Spondyloepiphyseal dysplasia, a new variant</td>
<td>3</td>
<td>Syrian, Bedouin</td>
<td>271640</td>
<td>95</td>
</tr>
<tr>
<td>Trigonobrachycephaly, bulbous bifid nose, micrognathia, and abnormalities of the hands and feet</td>
<td>2</td>
<td>Palestinian</td>
<td>275595</td>
<td>97</td>
</tr>
</tbody>
</table>

| Limb/pelvis-hypoplasia/aplasia syndrome | 2 + 1 | Palestinian | 276820 | 98–101 |
| Weaver-like syndrome | 2 | Bedouin | 277590 | 96 |
| Palmo-planter keratoderma, epidermolytic recessive form | 2 | Kuwaiti | 144200 | 102 |
| Craniofacial-hair-finger-caudal syndrome | 1 | Kuwaiti | — | 93, 94 |
| Hypogonadotrophic hypogonadism, obesity, MR, and skeletal anomalies | 3 | Palestinian | — | 92 |
| X linked | 4 | Syrian | — | 79 |

*Autosomal dominant entry in McKusick’s catalogue.*
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TRIGONOBRAHYCEPHALY SYNDROME
This condition was described in a brother and sister, offspring of first cousin Palestinian parents.\textsuperscript{97} Other manifestations included a bulbous nose which was slightly bifid at the tip, micrognathia, macrostomia, relatively broad first metatarsals and phalanges, and severe psychomotor retardation.

MACROSOMIA-MICROPHTHALMIA SYNDROME
This condition was described in three females and two males from a sibship of 10 whose parents were Palestinian first cousins.\textsuperscript{98} Associated manifestations included median cleft palate in three and recurrent infections in all, with early, rapid, or sudden death.

WEAVER-LIKE SYNDROME
A brother and sister, offspring of consanguineous Bedouin parents, were reported to have manifestations resembling Weaver syndrome.\textsuperscript{99} These included accelerated growth of prenatal onset, hypotonia, variable psychomotor retardation, excess loose skin, dental dysplasia, serrated gums, joint laxity, distinctive craniofacial and digital anomalies, and a hoarse, low pitched cry. One of them had accelerated harmonic skeletal maturation.

HYPERTelorism-HYPOSpADIAS AND TETRALOgy OF FALLOT SYNDROME
This combination was found in three brothers of Palestinian parents who were first cousins once removed.\textsuperscript{100} The father had hypertelorism and his brother, who is married to a second cousin, had a daughter with hypertelorism and tetralogy of Fallot. The four affected relatives had mild or borderline developmental delay.

HYPERTelorism-HYPOSpADIAS AND POLYsyndACTLY SYNDROME
This condition was described in two brothers and a sister of Pakistani consanguineous parents (non-Arabs). Similar cases have also been reported.\textsuperscript{101}

MICROCEPHALY WITH NORMAL INTEllIGENCE
A large inbred Palestinian kindred with eight cases in five sibships was found to have this combination in addition to a characteristic facial appearance.\textsuperscript{102} This condition is probably different from that associated with immunodeficiency and increased risk of lymphoreticular malignancies.

CYSTIC FIBROSIS WITH HELICOBACTER PYLORI GASTRITIS, MEGALOBLASTIC ANAEMIA, AND SUBNORMAL MENTALITY
A brother and a sister of consanguineous Bedouin parents were found to have this association in addition to minor facial anomalies.

SPONDYLOEPIPHYSIAL DYSPLASIA, A NEW VARIANT
A Syrian-Bedouin consanguineous family was found to have three children with this bone dysplasia (two males and a female).\textsuperscript{103} The proband was a 6 year old boy with rhizomelic shortness of limbs, dwarfism, dish-like facies, cleft palate, deafness, and camptodactyly. Radiological changes were compatible with Kniest disease. Two similarly affected sibs died in early life.

CRANIOFACIAL-HAIR-FINGER-CAUDAL SYNDROME
A Kuwaiti female of parents who were first cousins once removed was described with craniofacial anomalies, abnormally slow growing hair, absence of primary teeth, camptodactyly, and a caudal appendage with sacrococcygeal dimple.\textsuperscript{104} Intelligence was normal. A similarly affected female neonate was seen in the United States.\textsuperscript{105}

GREBE-LIKE CHONDRODYSPLASIA
This non-lethal severe form of short limb bone dysplasia was found in two unrelated patients.\textsuperscript{106} One of these patients was the product of first cousin Palestinian parents.\textsuperscript{107} Features included peculiar facial appearance with deafness, rib anomalies, and severe shortness and distortion of long bones, notably the humeri, tibiae, fibulae, metapodia, and phalanges with marked irregularity and asymmetry.

AUTOSOMAL RECESSIVE EPIDERMOlyTIC PALMOPLANTER KERATODERMA
Two male sibs of first cousin Kuwaiti parents were described as having this condition,\textsuperscript{108} which is known to be inherited as an autosomal dominant trait (144200). Parents presented with patchy eczematous skin lesions followed by palmoplantar keratoderma and raised serum levels of IgE. Although gonadal mosaicism cannot be excluded, it is more likely that an autosomal recessive variant of the disease exists in this inbred population.

Disorders with unknown frequencies

CYSTIC FIBROSIS (CF)
CF (219700), a well known and studied disease in Europe and North America, was not reported in Kuwait until 1981 when two patients (Kuwaiti and Syrian) presented with meconium ileus.\textsuperscript{109} One of them died postoperatively and the other had recurrent respiratory infections and died at the age of 1 year. At necropsy, clinical findings of CF were noted. Subsequently, CF was reported in several Kuwaiti and Palestinian patients.\textsuperscript{105-107} A questionnaire survey showed that 40 patients were diagnosed with CF in all hospitals in Kuwait from 1979 to 1979 (approximately 500 000 livebirths).\textsuperscript{110} Manifestations were variable and occasionally atypical. Several infants presented initially with hyponatraemia, hypo-
chloreaemia, and metabolic alkalosis owing to excessive sweating in Kuwait's very hot and humid weather. These patients had minimal manifestations of pulmonary and pancreatic exocrine deficiency. CF among Arabs from Lebanon, Iraq, and Israel has been reported. It has been suggested that the incidence is high among Arabs of Israel, in the Bedouin as well as in the city dwellers. This was supported by a recent study from Jordan. Our experience from Kuwait suggests that the frequency of CF may be less than that in western countries with mild allelic variants prevailing.

**CONGENITAL DEAFNESS, TYPE 1 (220700)**

In a large inbred Palestinian family, 13 subjects in several sibships were reported to have uncomplicated profound deafness from early infancy. The family originated from a small village (El-Sawiah) on the West bank near Nablus. Eight cases in three other families from the same village (apparently not related to each other or the reported family) were ascertained to have a clinically similar disorder (unpublished data). At the Farwania genetic clinic, at least nine more patients from four Kuwaiti or Syrian families were found. It is difficult, however, to conclude that this disorder is highly prevalent in Kuwait because of the remarkable genetic heterogeneity of deafness. Certainly, it has a very high frequency in the people of the Palestinian village whose affected members live in several countries including the West Bank, Jordan, and Kuwait. The population of this village tends to inbreeding even outside their homeland.

**Table 4 Other autosomal recessive disorders reported among Arabs in Kuwait**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>McKusick No</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrodactylis enteropathica</td>
<td>201100</td>
<td>116</td>
</tr>
<tr>
<td>3-B-hydroxysteroid dehydrogenase deficiency</td>
<td>201810</td>
<td>99</td>
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<tr>
<td>3-B-hydroxysteroid deficiency</td>
<td>202010</td>
<td>99</td>
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<tr>
<td>Congenital hypoplastic anemia of Blackfan and Diamond</td>
<td>205900</td>
<td>117</td>
</tr>
<tr>
<td>Anencephaly, AR</td>
<td>206500</td>
<td>118</td>
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<tr>
<td>Costello syndrome</td>
<td>218400</td>
<td>119</td>
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<tr>
<td>Cystathioninuria</td>
<td>219500</td>
<td>53</td>
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<tr>
<td>Cystinuria</td>
<td>220100</td>
<td>54</td>
</tr>
<tr>
<td>Dyserythropoietic anemia, type I</td>
<td>224120</td>
<td>120</td>
</tr>
<tr>
<td>Torson dystonia, AR</td>
<td>224500</td>
<td>121</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome type VI</td>
<td>225400</td>
<td>122</td>
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<tr>
<td>Fucosidosis</td>
<td>230000</td>
<td>123</td>
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<tr>
<td>Galactosaemia</td>
<td>230400</td>
<td>21,39</td>
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<tr>
<td>Hallermann-Streiff syndrome</td>
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<td>124</td>
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<tr>
<td>Histidinemia</td>
<td>235800</td>
<td>21</td>
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<tr>
<td>Hydrocephalus, AR</td>
<td>236600</td>
<td>125</td>
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<tr>
<td>Urophelial syndrome</td>
<td>236730</td>
<td>126,127</td>
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<tr>
<td>Hyperlysinuria</td>
<td>238750</td>
<td>53</td>
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<tr>
<td>Hyperprolinemia</td>
<td>239700</td>
<td>54</td>
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<tr>
<td>Intestinal atresia, multiple</td>
<td>243150</td>
<td>128</td>
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<tr>
<td>Apple peel syndrome (jejunal atresia)</td>
<td>243600</td>
<td>129,130</td>
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<tr>
<td>Primary hypomagnesaemia</td>
<td>248250</td>
<td>131</td>
</tr>
<tr>
<td>Mandibulocutaneous dysplasia</td>
<td>248370</td>
<td>132</td>
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<tr>
<td>Maple syrup urine disease (MSUD)</td>
<td>248600</td>
<td>54</td>
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<tr>
<td>Metaphyseal chondrodysplasia, Spaher type</td>
<td>250400</td>
<td>133</td>
</tr>
<tr>
<td>Clinical anophthalmia</td>
<td>251600</td>
<td>134</td>
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<tr>
<td>Multiple pterygium syndrome, lethal</td>
<td>253290</td>
<td>42</td>
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<tr>
<td>Schwartz-Jampel syndrome</td>
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<tr>
<td>Osteoporosis-pseudoglioma syndrome</td>
<td>259770</td>
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<tr>
<td>Persistent Müllerian duct syndrome</td>
<td>261550</td>
<td>60,137</td>
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<tr>
<td>Congenital hepatic fibrosis</td>
<td>262300</td>
<td>138</td>
</tr>
<tr>
<td>Porphyrin, congenital erythropoietic</td>
<td>263700</td>
<td>139</td>
</tr>
<tr>
<td>Pseudohermaphrodism, male, with gynaecomastia</td>
<td>264300</td>
<td>60</td>
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<tr>
<td>Pseudovaginal perineourethral hypoplasia</td>
<td>264600</td>
<td>60</td>
</tr>
<tr>
<td>Vitamin D dependent rickets type I</td>
<td>264700</td>
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</tr>
<tr>
<td>Renal tubular acidosis with nerve deafness</td>
<td>267300</td>
<td>141</td>
</tr>
<tr>
<td>Erythropagocytic lymphohistiocytosis, familial</td>
<td>267700</td>
<td>142</td>
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<tr>
<td>Robinow syndrome</td>
<td>268310</td>
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<tr>
<td>Russell-Silver syndrome</td>
<td>270050</td>
<td>144</td>
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<tr>
<td>Skin peeling, familial, continuous</td>
<td>270300</td>
<td>145</td>
</tr>
<tr>
<td>Spastic paraplegia</td>
<td>270800</td>
<td>146</td>
</tr>
<tr>
<td>Thyroid hormonogenesis, genetic defect</td>
<td>274300</td>
<td>147</td>
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<tr>
<td>Tyrosinaemia type II</td>
<td>276600</td>
<td>148</td>
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<tr>
<td>Spondylothoric dysplasia</td>
<td>277300</td>
<td>149</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>277900</td>
<td>148</td>
</tr>
<tr>
<td>Xanthinuria</td>
<td>278100</td>
<td>149</td>
</tr>
<tr>
<td>XX male syndrome</td>
<td>278550</td>
<td>150</td>
</tr>
<tr>
<td>Brachmann-de Lange syndrome, AR</td>
<td>122470*</td>
<td>151</td>
</tr>
<tr>
<td>Central Cogcock-like cataract</td>
<td>123470*</td>
<td>152</td>
</tr>
</tbody>
</table>

*Autosomal dominant entry in McKusick's catalogue.

**Genetic predisposition to non-disjunction (257300)**

Following the suggestion of Penrose that a recessive gene in man may cause non-disjunction of chromosome 21 in the ova of homozygous females, similar to the gene in *Drosophila melanogaster*, a study from Kuwait showed that Down’s syndrome (DS) was four times more frequent among the children of closely related parents than among those of unrelated parents (p < 0.005). Another study also suggested an association between consanguinity and the occurrence of non-disjunction after correcting for maternal and paternal ages, but a single gene effect was not observed. Recent data from a community genetic survey at Farwania and Jahra districts containing 15% and 80% Bedouin respectively have shown an incidence of DS of 1/7 and 4/5/1000 livebirths respectively. The incidence of DS correlates very well with the inbreeding coefficient. A remarkably higher incidence of DS was noted in the inbred Bedouin community in the Jahra district, two families had sibs with recurrent aneuploides, one of these families had two sibs with trisomy 21 and the other had sibs with trisomy 21 and trisomy 18. Comparable high frequencies of DS were also reported from West Jerusalem and among the Negev Bedouin.

**Other disorders reported from Kuwait**

In addition to the aforementioned, there are a number of AR disorders that have been reported among Arabs from this country (table 4). Although it may not be an exhaustive list, it includes a number of case reports of unusual associations, case series studies, and informative pedigrees. Some of the case reports served as early delineation of disorders. Examples are the urofacial syndrome (Ochoa syndrome), metaphyseal chondrodysplasia, Spaher type, and the Costello syndrome. A number of unusual associations have also been reported which may not be fortuitous if found in several members of the family, such as the association of osteoporosis-pseudo-glioma syndrome and ventricular septal defect in three sibs of consanguineous parents, and the association of the AR congenital dyserythropoietic anemia (CDA) with recurrent multifocal osteomyelitis and Sweet syndrome (unknown aetiology) in two male sibs of first cousin Palestinian parents and the occurrence of CDA and Sweet syndrome in their female cousin.
Homozgyosity for two AR syndromes in the same sibship is not rare. In an inbred Palestinian family, three out of eight sibs had AR microcephaly with typical facial appearance and mental retardation. Two of these also had glycogen storage type I, and another sib had only glycogen storage disease (unpublished data). A Kuwaiti brother and sister with consanguineous parents had the phenotype of Ehlers-Danlos syndrome with aortic regurgitation and mitral valve prolapse in addition to peripheral polyneuropathy. Although this may be a new form of Ehlers-Danlos syndrome, it is more likely that the sibs had inherited different recessive traits.

Although some case series studies provide no incidence data, the number of cases included indicates that certain disorders are probably not rare, such as congenital hypoplastic anaemia of Blackfan and Diamond and vitamin dependent rickets type I.

Among cases diagnosed in Kuwait’s population, a number are commonly encountered among Jews. Examples are the Palestinian family with erythrophagocytic lymphohistiocytosis, another with torsion dystonia, and two Kuwaiti families with Tay-Sachs disease (unpublished data). A number of informative pedigrees for other diseases have been found. Examples are the Robinow syndrome pedigree, Russell-Silver syndrome with six affected sibs and normal consanguineous parents, AR hydrocephalus, apple peel syndrome, and the extended pedigrees suggestive of an autosomal recessive form of anencephaly. Since then, AR inheritance of anencephaly in some families has been accepted by McKusick. In an inbred Syrian-Bedouin family, three sibs were found to have cyclops or alobar holoprosencephaly (unpublished data).

The paucity of neurodegenerative disorders and other metabolic disorders may not reflect a low frequency among Arabs but rather the underlying difficulties in establishing or confirming the diagnosis of such disorders. However, the pattern is somewhat similar to that reported from Saudi Arabia.

Comments
In McKusick’s 1992 edition, the number of asterisked and non-asterisked autosomal dominant entries is more than twice the number of AR entries (3711 versus 1631). While the autosomal dominant phenotype manifests as a result of a single dose of an autosomal allele, either inherited or freshly mutated, the AR phenotype manifests as a result of a double dose of an autosomal allele which requires both parents to be heterozygotes and to have a 25% chance of both transmitting the allele(s) to their offspring in each pregnancy. The chance of having an affected homozygous child in a family is increased by increasing the number of children. In a family with four or five children, one of them would be expected to be affected. In Kuwait and other Arab countries, owing to the high rates of consanguinity and the large family size, conditions are optimal for the expression of AR disorders, as seen by the large number of newly recognised AR disorders. A number of new syndromes described from Kuwait have now been recognised elsewhere, suggesting that the private syndrome does not exist.

The frequencies of AR disorders in Kuwait may reflect those of the Arabs at large since the population is mixed with significant representation from most Arab nations. It may not be mere chance that Arabs, particularly Palestinians, share with Jews several common recessive genes. Being hitherto unstudied populations, the Arab countries will continue to be a source of new information about genetic disorders for the whole world. For these communities with special religious and cultural backgrounds, more work should be done in planning and implementing ways of prevention and treatment of genetic disorders.


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A S Teebi

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