Consanguinity and Dysmorphology in Arabs

Lihadh Al-Gazali^a Hanan Hamamy^b

^aDepartment of Pediatrics, College of Medicine and Health Sciences, UAE University, Al Ain, United Arab Emirates;

^bDepartment of Genetic Medicine and Development, Geneva University, Geneva, Switzerland

Key Words

Consanguinity · Dysmorphology · Arabs

Abstract

Incidence rates of congenital disorders among the 350 million inhabitants of Arab countries could be influenced via the people's demographic and cultural characteristics. Arabs usually marry at a young age and have large families. They share certain core cultural values and beliefs, with the family accepted as the central structure of society. Consanguineous marriage is favored and respected in most if not all Arab communities, and intrafamilial unions currently account for 20–50% of all marriages. First-cousin unions are especially popular and constitute almost one quarter of all marriages in many Arab countries. Consequently, autosomal recessive (AR) dysmorphic syndromes constitute a considerable proportion of all birth defects among Arabs. Arab geneticists, with their persistent commitment to advancing research, have contributed to the description of a number of rare and new AR syndromes with the identification of novel genes. The collaboration with research teams in high-income countries resulted in a plethora of data on pathogenic variants and their function in causing dysmorphic syndromes. There could still be a considerable number of rare dysmorphic syn-

dromes that prevail among Arabs which are not hitherto described and whose underlying molecular pathologies are not yet defined. Arab countries should thus strive to deploy DNA diagnostics and to build research capability around local priorities. Furthermore, a characterization of the prevailing genetic disorders in each geographic location, together with their mutations, is needed to plan for appropriate screening and testing protocols. An overview of consanguinity in Arab countries and examples of dysmorphology syndromes associated with consanguinity with their available molecular bases will be discussed.

© 2014 S. Karger AG, Basel

Introduction

Arab countries comprise the 22 states and territories of the Arab League, stretching from the Atlantic Ocean in the West to the Arabian Sea in the East, and from the Mediterranean Sea in the North to the Horn of Africa and the Indian Ocean in the Southeast (fig. 1). Arab countries can be classified – according to their global human development levels – into low-, medium- and high-income countries, with huge social inequalities and health inequities between and within the individual states. Economic

Fig. 1. Map of the Arab countries.

deficits in some Arab countries impede human development with evident paucity of scientific research and health services in such countries.

Incidence rates of congenital disorders among the 350 million inhabitants of Arab countries could be influenced via the people's demographic and cultural characteristics. Arabs usually marry at a young age and have large families, with advanced maternal and paternal ages. Consanguineous marriage is favored and respected in most if not all Arab communities, and intrafamilial unions currently account for 20–50% of all marriages. First-cousin unions are especially popular and constitute almost one quarter of all marriages in many Arab countries [1, 2].

All Arabs share certain core cultural values and beliefs, with the family accepted as the central structure of society. A strong sense of community and interdependence among family members makes the Arab culture more collectivistic (group-oriented) than individualistic [3]. Marriage is primarily regarded as a family matter, and arranged marriage is still practiced within some Arab societies. The frequency of arranged marriages may have been declining in recent years due to an increasing number of females reaching university level education which gives them a broader choice of marriage partners. The

practice of arranged marriage does not entail a union contracted against the will of the partners but essentially reflects the fact that the marriage has been mutually agreed by both sets of families based on family and traditional grounds [4]. Among 1,983 marriages contracted from 1969 to 1979 in Jordan, 73.3% were arranged through the parents' agreement first and then through the couples' consent, while 18.6% were arranged through the couples' agreement first and then through the parents' consent [5].

In clinical genetics, a consanguineous marriage means the union between partners who are related as second cousins or closer [6]. Among Arabs, this would include double first cousins, first cousins, first cousins once removed, and second cousins. Uncle-niece marriage is prohibited in Islam and therefore not seen among Arabs. In population genetics, consanguinity may also refer to unions of individuals with at least one common ancestor such as those occurring within population isolates, small towns, and tribes, intracommunity or endogamous marriages. The custom of endogamy among individuals belonging to the same tribe has been and is still strongly favored among Arabs, with the consequence of an unequal distribution of founder mutations among the population [7]. Among the consanguineous marriages, the pa-

ternal parallel first-cousin marriages are usually the most common [2]. Isolated subpopulations with a high level of inbreeding also exist among Arabs. Furthermore, in many parts of the Arab world, the society is still tribal. This has further complicated the epidemiology of genetic disorders, as many families and tribal groups descend from a limited number of ancestors and some conditions are confined to specific villages, families, and tribal groups, leading to an unusual burden of genetic diseases – especially rare autosomal recessive (AR) conditions – in these communities [8].

Due to the high consanguinity rates among Arabs, many rare abnormal AR genes that cause dysmorphic syndromes have been defined. Novel technologies, including exome sequencing and array-comparative genomic hybridization – as well as updated perceptions of developmental and functional genomics currently need to be applied in order to characterize the still unknown pathogenic AR variants [9].

An overview of consanguinity in Arab countries and examples of dysmorphology syndromes associated with consanguinity with their available molecular bases will be discussed.

Consanguineous Marriages in Arab Countries

Consanguineous marriage is customary in most if not all Arab communities, but the rates may differ between and within countries. Intrafamilial unions currently account for about 20–50% of all marriages, with first-cousin marriages being the most common, especially marriages where the couple's fathers are brothers (table 1). For a comparison of consanguinity rates among populations, 2 parameters are best used: the mean inbreeding coefficient and the rates of first-cousin marriages.

Although consanguineous marriages among Arabs are still favored, their rates have been decreasing in some countries including Jordan [10], Lebanon [11], Bahrain [12, 13], and among Palestinians [14–16]. This drop in consanguinity rates may be related to the increasing higher education levels in females, the declining fertility rates resulting in lower numbers of suitable relatives to marry, more mobility from rural to urban settings, and the improving economic status of families. Moreover, awareness among the public of the possible role of consanguinity in increasing the risk of having an affected child is on the increase. On the other hand, social, religious, cultural, political and economic factors still play their roles in favoring consanguineous marriages among the new gen-

Table 1. Consanguinity rates in Arab countries

Country	First-cousin marriage rates ¹ , %	Overall consanguinity rates, %	Reference
Algeria	11.3	22.6–34	7
Bahrain	7–24.5	10.9–45.5	7, 12, 13
Egypt	14.3–47.2	20.9–80.4	7, 122, 123
Iraq	29–35.6	47–60	7, 124
Jordan	19.5–39	28.5–63.7	7, 35
Kuwait	16.9–31.7	22.5–64.3	7
Lebanon	6.7–31.6	12.8–42	7, 125
Libya	ND	48.4	7
Mauritania	ND	47.2	7
Morocco	8.6–10	19.9–28	7, 20, 21
Oman	24.1–34	56.3–58	126, 127
Palestine	13.6–34.2	17.5–66.3	7
Qatar	34.8	54	17
Saudi Arabia	24.6–42.3	42.1–66.7	7
Sudan	44.2–49.5	44.2–63.3	7
Syria	28.7	30.3–39.8	128
Tunisia	17.4–23	20.1–39.3	129–131
UAE	20.7–29.7	39–54.2	19, 132
Yemen	32–34	40–44.7	133, 134

Values are the reported minimum and maximum rates [7].
ND = Not determined. ¹ Including double first cousins.

erations – just as strongly as they did among the older generations in some countries such as in Qatar [17], Yemen [18], and the United Arab Emirates (UAE) [19]. In Morocco, one study has indicated an increasing consanguinity rate from the previous (21.5%) to the present (25.4%) generation [20], while another study showed a decreasing consanguinity rate [21]. For some, the social advantages of consanguinity could outweigh the disadvantages, especially in rural areas [22], and consanguinity is still regarded as a deeply rooted cultural trend [23–25].

The deleterious effect of inbreeding in populations with a long-standing practice of consanguineous mating is known to be reducible through the progressive elimination of lethal equivalents [26]. However, it seems that recessive alleles in populations with a high incidence of recessive disorders are maintained through reproductive compensation. If child loss is due to genetic disorders, then the surviving 'replacement' is more likely to be a carrier (chance of 66%) than a noncarrier, hence maintaining the recessive mutation in the population. Studies have demonstrated that reproductive compensation can effectively counteract the rate at which deleterious alleles are eliminated from the gene pool of consanguineous populations [23, 27].

The image displays two pedigree charts, labeled Family 1 and Family 2, showing the inheritance of a trait across five generations (I to V). The charts use standard symbols: squares for males and circles for females. Shaded symbols indicate affected individuals.

Family 1:

- Generation I:** Unaffected male (I-1) and Unaffected female (I-2).
- Generation II:** Unaffected male (II-1) and Unaffected female (II-2).
- Generation III:** Unaffected male (III-1) and Unaffected female (III-2).
- Generation IV:** Unaffected male (IV-1) and Unaffected female (IV-2).
- Generation V:** Affected male (V-1), Affected male (V-2), Unaffected female (V-3), and Affected female (V-4).

Family 2:

- Generation I:** Unaffected male (I-1) and Unaffected female (I-2).
- Generation II:** Unaffected male (II-1) and Unaffected female (II-2).
- Generation III:** Unaffected male (III-1) and Unaffected female (III-2).
- Generation IV:** Unaffected male (IV-1) and Unaffected female (IV-2).
- Generation V:** Unaffected male (V-1) and Unaffected female (V-2).
- Generation VI:** Affected male (VI-1), Affected male (VI-2), Unaffected female (VI-3), and Affected female (VI-4).
- Generation VII:** Unaffected male (VII-1), Affected female (VII-2), Unaffected male (VII-3), and Affected female (VII-4).

Carrier frequency	Homozygote birth rates		Multiplication factor
	Population A	Population B	
0.1%	0	0.0093	×37
0.5%	0.0062	0.053	×8.5
1%	0.025	0.119	×4.8
5%	0.63	1.1	×1.7
10%	2.5	3.44	×1.4
16%	6.4	7.91	×1.23

The high consanguinity rates among Arabs, coupled with the large family sizes, have triggered the expression of a large number of AR diseases, including very rare or new syndromes (fig. 2). Genetic counseling clinics in Arab countries encounter a considerable proportion of families with AR conditions. For example, among 660 patients referred to the genetic clinic in Alexandria, 33.6%

In this paper, we are going to discuss 3 categories of syndromes which are prevalent in Arabs: (1) AR syndromes which cluster in Arab communities or isolates;

Table 3. New entries in the OMIM for AR disorders reported among Arabs from January 2011 to December 2013

Disorder	OMIM No.	Gene	Family origin
Mental retardation; MRT39	615541	TTI2	Algeria
Parkinson disease, juvenile onset; PARK19	615528	DNAJC6	Palestine
Deafness; DFNB76	615540	SYNE4	Iraqi Jews
Candidiasis familial; CANDF8	615527	TRAF3IP2	Algeria
Alacrima, achalasia and mental retardation; AAMR	615510	GMPPA	Palestine, Morocco
Congenital erythroderma with palmoplantar keratoderma, hypotrichosis and hyper-IgE; EPKHE	615508	DSG1	Arab Muslims
Early infantile epileptic encephalopathy; EIEE18	615476	SZT2	Iraqi Jews
Mitochondrial DNA depletion syndrome 13, encephalomyopathic; MTDPS13	615471	FBXL4	Saudi Arabia
Immunodeficiency 12; IMD12	615468	MALT1	Lebanon
Microcornea, myopic chorioretinal atrophy and telecanthus; MMCAT	615458	ADAMTS18	Saudi Arabia
Mitochondrial complex III deficiency, nuclear type 6; MC3DN6	615453	CYC1	Lebanon
Epidermolysis bullosa simplex; EBSB2	615425	DST (BPAG1)	Kuwait
Retinitis pigmentosa with and without situs inversus	615434	ARL2BP	Arabs
Myopia 23; MYP23	615431	LRPAP1	Saudi Arabia
Infantile hypotonia with psychomotor retardation and characteristic facies; IHPRF	615419	NALCN	Saudi Arabia
Microcephaly 11; MCPH11	615414	PHC1	Saudi Arabia
Immunodeficiency 8; IMD8	615401	CORO1A	Morocco
Meckel 11; MKS11	615397	TMEM231	Arabs
Epilepsy familial adult myoclonic 5; FAME5	615400	CNTN2	Egypt
Spiniocerebellar ataxia 14; SCAR14	615386	SPTBN2	Egypt
Muscular dystrophy, limb girdle type 2S; LGMD2S	615356	TRAPPC11	Syria
Charcot Marie Tooth; CMTRIC	615376	PLEKHG5	Morocco
Shaheen syndrome; SHNS	615328	COG6	Saudi Arabia
Mental retardation 36; MRT36	615286	ADAT3	Saudi Arabia
Multiple mitochondrial dysfunctions 3; MMDS3	615330	IBA57	Morocco
Severe congenital neutropenia 5; SCN5	615285	VPS45	Palestine, Morocco
Perrault syndrome 4; PRLTS4	615300	LARS2	Palestine
Adams-Oliver syndrome 4; AOS4	615297	EOGT	Saudi Arabia
Cataract 19; CTRCT19	615277	LIM2	Iraqi Jews
Smith-McCort dysplasia 2; SMC2	615222	RAB33B	Saudi Arabia
Nonsyndromic hydrocephalus; HYC2	615219	MPDZ	Saudi Arabia
Immunodeficiency 11; IMD11	615206	CARD11	Palestine
Ataxia-oculomotor apraxia 3; AOA3	615217	PIK3R5	Saudi Arabia
Immunodeficiency; IL21R	615207	IL21R	Lebanon
Lissencephaly 5; LIS5	615191	LAMB1	Egypt
Mental retardation 35; MRT35	615162	<i>17q21.31-q22</i>	Saudi Arabia
Microphthalmia isolated with coloboma 9; MCOPCB9	615145	ODZ3	Saudi Arabia
Lymphoproliferative syndrome 2; LPFS2	615122	CD27	Morocco, Lebanon
Primary microcephaly 10; MCPH10	615095	ZNF335	Israeli Arabs
Mitochondrial DNA depletion syndrome 11; MTDPS11	615084	MGME1	Lebanon
Osteopetrosis 8; OPTB8	615085	SNX10	Palestine
AlAzami syndrome; ALAZS	615071	LARP7	Saudi Arabia
Osteogenesis imperfecta, type XIV; OI14	615066	TMEM38B	Saudi Arabia
Spastic paraplegia 56; SPG56	615030	CYP2U1	Egypt, Saudi Arabia
Spastic paraplegia 54; SPG54	615033	DDHD2	UAE of Omani origin
Epidermolysis bullosa nonspecific; EBNS	615028	EXPH5	Iraq
Congenital ichthyosis 7; ARCI7	615022	<i>12p11.2-q13.1</i>	Israeli Arabs
Early infantile epileptic encephalopathy 7; EIEE15	615006	ST3GAL3	Palestine
Combined oxidative phosphorylation deficiency 14; COXPD14	614946	FARS2	Saudi Arabia
Combined oxidative phosphorylation deficiency 13; COXPD13	614932	PNPT1	Morocco
Deafness 70; DFNB70	614934	PNPT1	Morocco
Combined oxidative phosphorylation deficiency 11; COXPD11	614922	RMND1	Saudi Arabia
Branched chain ketoacid dehydrogenase kinase deficiency; BCKDKD	614923	BCKDK	Egypt, Libya
Lethal congenital contracture 4; LCCS4	614915	LCCS4	Bedouin tribes in Israel
Spastic paraplegia 53; SPG53	614898	VPS37A	Arab Muslims in Israel
Spinal muscular atrophy distal 5; DSMA5	614881	DNAJB2	Moroccan Jews in Israel

Table 3 (continued)

Disorder	OMIM No.	Gene	Family origin
Osteogenesis imperfecta, type XIII; OI13	614856	BMP1	Egypt
Nephronophthisis 15; NPHP15	614845	CEP164	Saudi Arabia
Amelogenesis imperfecta, hypomaturation type, IIA4; AI2A4	614832	C4orf26	Oman
Short stature, onychodysplasia, facial dysmorphism and hypotrichosis; SOFT	614813	POC1A	Saudi Arabia
Heterotaxy visceral 6; HTX6	614779	CCDC11	Arab Muslims in Israel
Microphthalmia syndromic 11; MCOPS11	614402	VAX1	Egypt
Interstitial lung disease, nephrotic syndrome and epidermolysis bullosa congenital	614748	ITGA3	Palestine
Mitochondrial pyruvate carrier deficiency; MPYCD	614741	BRP44L	Algeria
Brown-Vialetto-Van Laere syndrome-2 (BVVLS2)	614707	SLC52A2	Lebanon
Immunodeficiency, common variable, 8, with autoimmunity; CVID8	614700	LRBA	Saudi Arabia
Cataract congenital 5; CATC5	614691	AGK	Saudi Arabia
Hypertelorism and other facial dysmorphism, brachydactyly, genital abnormalities, mental retardation and recurrent inflammation episodes	614684	COQ6	Arab Muslims in Israel
Meconium ileus	614665	GUC2	Bedouins in Israel
Coenzyme Q10 deficiency, primary, 6; COQ10D6	614650	COQ6	Lebanon
Coenzyme Q10 deficiency, primary, 2; COQ10D2	614651	PDSS1	Morocco
Hyperplexia 2; HKPX2	614619	GLRB	Saudi Arabia
Congenital disorder of glycosylation, type III; CDG2L	614576	COG6	Morocco
Trichohepatoenteric syndrome 2; THES2	614602	SKIV2L	North Africa
Night blindness, congenital stationary (complete), 1E; CSNB1E	614565	GPR179	Lebanon
Infantile cerebellar-retinal degeneration; ICRD	614559	ACO2	Arab Muslims in Israel
Fibrochondrogenesis 2; FBCG2	614524	COL11A2	UAE, Saudi Arabia
Wiskott-Aldrich syndrome 2; WAS2	614493	WIPF1	Morocco
Hypertriglyceridemia, transient infantile; HTGTI	614480	GPD1	Israeli Arabs
Congenital cataracts, hearing loss, and neurodegeneration; CCHLND	614482	SLC33A1	Arabs
Thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type); THMD5	614458	TPK1	Iraq
Ichthyosis, spastic quadriplegia, and mental retardation; ISQMR	614457	ELOVL4	Saudi Arabia
Joubert syndrome 15; JBTS15	614464	CEP41	Egypt
Joubert syndrome 16; JBTS16	614465	TMEM138	UAE, Egypt
Cutis laxa, autosomal recessive, type IB; ARCL1B	614437	EFEMP2	Iraq
Hypertrophic osteoarthropathy, primary, autosomal recessive 2; PHOAR2	614441	SLCO2A1	Morocco
Febrile seizures, familial, 11; FEB11	614418	CPA6	Morocco
Systemic lupus erythematosus 16; SLEB16	614420	DNASE1L3	Saudi Arabians in Oman
Spastic paraplegia 46, autosomal recessive; SPG46	614409	GBA2	Tunisia
Microcephaly, cerebellar hypoplasia and cardiac conduction defect; Zaki-Gleeson syndrome; MCHCCD	614407	–	Egypt
Myopathy, areflexia, respiratory distress, and dysphagia, early-onset; EMARDD	614399	MEGF10	Qatar
Amyotrophic lateral sclerosis 16, juvenile; ALS16	614373	SIGMAR1	Saudi Arabia
Nephronophthisis 13; NPHP13	614377	WDR19	Morocco
Mental retardation, autosomal recessive 29; MRT29	614333	4q27-q28.2	Syria
Mental retardation, autosomal recessive 27; MRT27	614340	15q24.1-q26.1	Syria
Mental retardation, autosomal recessive 30; MRT30	614342	6q12-q15	Syria
Mental retardation, autosomal recessive 19; MRT19	614343	18p11.3	Syria
Mental retardation, autosomal recessive 23; MRT23	614344	11p13-q14.1	Syria
Mental retardation, autosomal recessive 24; MRT24	614345	6p12.2-q12	Syria
Mental retardation, autosomal recessive 25; MRT25	614346	12q13.11-q15	Syria
Mental retardation, autosomal recessive 28; MRT28	614347	6q26-q27	Syria
Inflammatory skin and bowel disease, neonatal; NISBD	614328	ADAM17	Lebanon
Ovarian dysgenesis 3; ODG3	614324	PSMC3IP	Palestine
Spinocerebellar ataxia 12; SCAR12	614322	16q21-q23	Saudi Arabia
Myopia, high, with cataract and vitreoretinal degeneration; MCVD	614292	LEPREL1	Israeli Bedouins
Arthrogryposis, Perthes disease and upward gaze palsy; APUG	614262	–	Saudi Arabia
Mental retardation, autosomal recessive 18; MRT18	614249	MED23	Algeria
Microcephaly, epilepsy, and diabetes syndrome; MEDS	614231	IER3IP1	Morocco
Retinal arterial macroaneurysm with supraaortic pulmonic stenosis; RAMSVPS	614224	IGFBP7	Saudi Arabia
Adams-Oliver syndrome 2; AOS2	614219	DOCK6	Saudi Arabia, Egypt
Hyperphosphatasia with mental retardation syndrome 3; HPMRS3	614207	PGAP2	Syria

Table 3 (continued)

Disorder	OMIM No.	Gene	Family origin
Psoriasis, generalized pustular; DITRA	614204	IL36RN	Tunisia
Hydroletharus syndrome 2; HLS2	614120	KIF7	Algeria
Stickler syndrome, type IV; SLT4	614134	COL9A1	Morocco
Cranioectodermal dysplasia 3; CED3	614099	IFT43	Morocco
Multiple congenital anomalies-hypotonia-seizures syndrome 1; MCAHS1	614080	PIGN	Arabs in Israel
Spastic paraplegia 47, autosomal recessive; SPG47	614066	AP4B1	Arabs in Israel
Spastic paraplegia 52, autosomal recessive; SPG52	614067	AP4S1	Syria
Hermansky-Pudlak syndrome 6; HPS6	614075	HPS6	Israeli Bedouins
Congenital disorder of glycosylation, type IIa, AlKuraya syndrome; CDG2A	212066	MGAT2	Saudi Arabia
Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2; MC5DN2	614052	TMEM70	Arab Muslims
Ciliary dyskinesia, primary, 16; CILD16	614017	DNAL1	Bedouins
Ventricular tachycardia, catecholaminergic polymorphic, 3; CPVT3	614021	?	Sudan
Osteogenesis imperfecta, type VI; OI6	613982	SERPINF1	Saudi Arabia
Ichthyosis, congenital 8; ARCI8	613943	LIPN	Arab Muslims
Meckel syndrome 8; MKS8	613885	TCTN2	Saudi Arabia
Retinitis pigmentosa 38; RP38	613862	MERTK	Morocco
Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis	613845	SARS2	Palestine
Osteogenesis imperfecta, type X; OI10	613848	SERPINH1	Saudi Arabia
Osteogenesis imperfecta, type XII; OI12	613849	SP7	Egypt
Leber congenital amaurosis 15; LCA15	613843	TULP1	Algeria
Pontocerebellar hypoplasia type 2D; PCH2D	613811	SEPSECS	Iraqi and Moroccan Jews
Nephronophthisis 12; NPHP12	613820	TTC21B	Egypt
Ciliary dyskinesia, primary, 14; CILD14	613807	CCDC39	Algeria, Tunisia, Egypt
Retinitis pigmentosa 39; RP39	613809	USH2A	Iraqi Jews
Retinitis pigmentosa 40; RP40	613801	PDE6B	Tunisia
Meier-Gorlin syndrome 4; MGORS4	613804	CDT1	Saudi Arabia
C3 deficiency; C3D	613779	C3	Palestine-Lebanon
Spastic paraplegia 51, autosomal recessive; SPG51	613744	AP4E1	Palestinians in Jordan
Cataract posterior polar; CTPP2	613763	CRYAB	Saudi Arabia
Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase	613752	AHCY	Tunisia
Thiamine metabolism dysfunction syndrome 4 (progressive polyneuropathy type); THMD4	613710	SLC25A19	Arab Muslims
Adrenal insufficiency, congenital, with 46XY sex reversal, partial or complete	613743	CYP11A1	Saudi Arabia
Epileptic encephalopathy, early infantile, 12; EIEE12	613722	PLCB1	Palestine
Hemorrhagic destruction of the brain, subependymal calcification, and cataracts; HDBSCC	613730	JAM3	UAE (Baluchi origin), Saudi Arabians in Morocco
Deafness, autosomal recessive 83; DFNB83	613685	?	Palestine

There are a total of 147 entries, 55 of them are dysmorphic syndromes or include facial dysmorphism in their features [39].

(2) AR syndromes which are highly prevalent in Arab populations, and (3) AR syndromes first described in Arab families.

AR Syndromes Which Cluster in Arab Communities or Isolates

In specific villages, families and tribal groups, the high level of consanguinity and the tribal trend have led to a concentration or confinement of some syndromes with the presence of founder mutations [35, 40]. There are sev-

eral reports in the literature of these founder mutations causing a specific syndrome to be common among certain tribes or villages. Here we present some examples of such syndromes.

Sanjad-Sakati Syndrome (Hypoparathyroidism-Retardation Dysmorphism)

This syndrome is common among Arabs although the exact incidence rate is not known. It is particularly widespread among Bedouins of the gulf region, but it has also been reported in Palestine, Egypt and Jordan [41–43]. It is caused by mutations in *TBCE* gene [44, 45]. All affected

Arab patients who have been studied at the molecular level have a single 12-bp deletion in the second coding exon of the *TBCE* gene [41, 45; Al-Gazali, unpubl. data]. A relationship between the Israeli Arab patients and the Saudi patients has been suggested, since the Bedouins in Neg- ev (Southern part of Israel) came to this region from the Western part of Arabia 400–500 years ago [46]. This might have led to the spread of the mutation to other parts of the Arabian Peninsula.

AR Faciodigitogenital Syndrome (Kuwait-Type Faciodigitogenital Syndrome)

Teebi et al. [47] described a Kuwaiti Bedouin family with normal consanguineous parents and 5 children (3 males and 2 females) with some features of Aarskog syndrome in addition to unusual hair changes. Teebi and al Awadi [48] later reported on another sibship from the same Kuwaiti Bedouin tribe, with 2 affected males who were double first cousins to the first reported cases. In addition, they detected 3 further distantly related sibships with 9 affected members who could all be traced back to a common ancestor. None of the 16 cases showed physical disability or mental retardation. The molecular basis of this syndrome has not been identified yet.

Stuve-Wiedemann Syndrome

This rare AR syndrome is frequent in 2 tribes in the UAE [49], but has not been reported in other Arab countries. Fifty cases in 28 families from the UAE have been evaluated at the clinical and molecular level. Most of these families were originally from Oman and Yemen. The molecular analysis revealed a founder mutation in the Leukemia Inhibitory Factor Receptor gene (*LIFR*; 653_654 insT at exon 6) in these families [50, 51].

Ehlers-Danlos Syndrome VIA

This AR connective tissue disorder is caused by a deficiency of collagen lysyl hydroxylase due to mutations in the *PLOD1* gene. Twenty children from 15 Bedouin families have been identified in the UAE as having this syndrome. Some of them were initially diagnosed as suffering from Nevo syndrome [52]. However, a molecular study showed that Nevo syndrome and Ehlers-Danlos syndrome VIA are allelic [53]. A founder mutation in the *PLOD1* gene was found in these families (p.R313X non-sense mutation) [53; Al-Gazali, unpubl. data].

Arterial Tortuosity Syndrome

This syndrome has initially been reported in 32 patients from several sibships within a large Qatari tribe

with a high degree of inbreeding [54]. More patients have later been identified from the same tribe [53]. Molecular studies of 15 affected individuals from 10 families showed a founder mutation in the *SLC2A10* gene (p.Ser81Arg) [55].

Robinow Syndrome

This syndrome has been reported in Kuwait, Oman, Saudi Arabia, the UAE and Jordan, but there are no prevalence data available [56–59; Hamamy, unpubl. data]. However, a study conducted in Oman on the prevalence of commonly diagnosed AR disorders from 1993–2002 revealed a prevalence of 1 in 35,000 births [60]. In 14 patients with recessive Robinow syndrome from 7 families originating from Oman, a founder nonsense mutation in exon 9 of the *ROR2* gene [gln502-to-ter (Q502X)] was identified [61].

AR Syndromes Which Are Highly Prevalent in Arab Populations

Several malformation syndromes are much more common throughout the Arab populations than elsewhere. During the last few years, many of these syndromes have been studied at the molecular level. Genetic and allelic heterogeneity has been shown in affected Arab families and several novel mutations have been described. Of note, most of the disorders described here belong to a group of ‘ciliary disorders’. However, it is not known whether other types of ciliopathies are also generally more common in Arabs than other populations, and further studies on their prevalence rates are needed. Examples of such syndromes are shown below.

Bardet-Biedl Syndrome

The prevalence of this syndrome among Arabs, particularly Arab Bedouins, in Kuwait is relatively high: Bardet-Biedl syndrome (BBS) affects 1 in 13,500 individuals [62] compared to 1 in 150,000 individuals in North America and Europe. A study on the prevalence of commonly diagnosed AR disorders in Oman from a hospital-based register in the years 1993–2002 revealed 14 cases of BBS, giving it a prevalence of 1 in 30,000 births [60].

BBS is common in almost all Arab countries. However, it was found to be genetically heterogeneous in those Arab countries where a molecular study of the *BBS* genes was done. Homozygosity mapping of a large Lebanese family identified a new BBS locus (BBS10) with a mutation (S311A) in the *FLJ23650* gene in affected individuals

[63]. A molecular study on 19 Tunisian families with 34 affected BBS individuals revealed 7 different homozygous mutations, 5 of them were new [64]. In Jordan, 20 families with multiple affected BBS individuals were seen at the genetic counseling clinic in Amman over a period of 5 years. A molecular diagnosis was reached in only one patient who had a mutation in the *BBS4* gene [Hamamy, unpubl. data].

Among 29 families with BBS, Abu-Safieh et al. [65] analyzed all 14 *BBS* genes as well as the MGC1203 modifier. A total of 20 mutations were found, 12 of them were novel. In addition, 2 trans-mutations in a *BBS* gene were identified in each of these families. The authors did neither observe the 2 mutations in any unaffected member of a given family, nor observe the presence of a third allele that acted as a modifier of a large set of *BBS* mutations. Abu-Safieh et al. [65] argued that BBS is inherited in a straightforward AR pattern in most cases.

Meckel Syndrome

This AR syndrome is regularly seen in Arabs. Meckel syndrome (MKS) has a prevalence of 1 in 3,500 live births in Kuwait and of 1 in 5,000 live births in the UAE [66, 67]. It is also quite common in Palestinian Arabs, with a prevalence of 1 in 2,000 [67]. The prevalence in Oman was estimated to be 1 in 50,000 births [60]. MKS has also been reported in Saudi Arabia and Tunisia [68, 69]. Shaheen et al. [70] studied 18 Arab families with MKS using autozygome-guided mutation analysis and exome sequencing. Their study revealed genetic and allelic heterogeneity of this syndrome in Arab families. They identified diverse mutations in 10 different genes including 3 novel genes (*C5orf42*, *EVC2*, *SEC8*). Shaheen et al.'s study [70] is the largest and most comprehensive genomic study of MKS in Arabs.

Joubert Syndrome

This AR developmental brain disorder is commonly seen in Arabs with an estimated birth prevalence in the UAE of 1 in 5,000 [66]. Studies from the UAE and Saudi Arabia have shown genetic and allelic heterogeneity of this syndrome in Arabs. Eighteen Arab families (Omani, Palestinian or Jordanian in addition to Emirati) living in the UAE with Joubert syndrome have been studied at the molecular level. Different mutations in 6 genes have been identified (in *TMEM*, *INPP5E*, *CEP290*, *CC2D2A*, *TMEM237*, and *AHI1*) [71–73; Al-Gazali, unpubl. data]. The gene most commonly involved was *CEP290*. A molecular analysis of 12 Saudi Arabian families with Joubert syndrome showed mutations in 6 genes (*CEP290*,

RPGRIP1L, *AHI1*, *TMEM237*, *C5ORF42*, and *TCTN1*). *CEP290* and *C5ORF42* were the 2 most frequently involved genes in that series [74].

Ellis-van-Creveld Syndrome

This AR syndrome is frequently seen in Arabs. It has been reported in Egypt, Jordan, Saudi Arabia [75, 76], Oman, and the UAE. In 2005, Rajab et al. [60] estimated its prevalence in Oman to be 1 in 25,000 births. A similar figure was obtained from the UAE: 0.52 in 10,000 births (= 1.3 in 25,000) [77]. Five children with this syndrome from 4 families in the UAE have been studied at the clinical and molecular level. A molecular study revealed a homozygous mutation in exon 13 (Q605X) of the *EVC1* gene in one family, a homozygous deletion (c.981delG) in exon 8 of the *EVC2* gene in a second family, and a splice site homozygous change (IVS13-1G>T) in exon 14 of the *EVC2* gene in the third family; there were no mutations identified in the fourth family [78].

AR Syndromes First Described in Arab Families

There has been a considerable increase in the number of new syndromes and variants reported in Arab families in the last few years (table 3). In many of these syndromes the molecular basis has been studied and identified. The following are some examples of these syndromes.

Woodhouse-Sakati Syndrome

This rare AR syndrome was first described in 1983 by Woodhouse and Sakati. They reported on 2 inbred Saudi Arabian families with 7 affected individuals suffering from a combination of hypogonadism, sparse hair, diabetes mellitus, mental retardation, and mild deafness [79]. Subsequently, several other families of different ethnic origins, including a Jordanian family from Kuwait, have been described [79–81]. Around 54 cases have been reported in the literature so far. The condition was mapped to 2q33–q35, and mutations in *C2orf37* were identified in affected patients [82]. A 1-bp deletion in *C2orf37* was found in all patients from the Arabian Peninsula. A SNP-based haplotype analysis confirmed a founder effect; the deletion likely arose approximately 55 generations ago [82].

Limb/Pelvis/Hypoplasia/Aplasia Syndrome

This syndrome has originally been reported in a non-Bedouin Palestinian family from Kuwait [83], followed by a more complete report on a second Arab family [84].

Mutations in the *WNT7A* gene were seen in 2 families with this syndrome, one of Pakistani origin and the other of Syrian Bedouin origin [85]. Subsequently, several different mutations in the *WNT7A* gene have been identified in families of different ethnic origins, including a family from Saudi Arabia [86–88].

Bifid Nose Associated with Renal Agenesis and Anorectal Malformations

In 2002, Al-Gazali et al. [89] reported on a consanguineous Arab family from Egypt in which 4 siblings had a bifid nose associated with renal and anorectal anomalies (BNAR). Two more families, one of Pakistani origin and one of Afghani origin, have been identified, and a molecular study identified homozygous mutations in the *FREM1* gene in all 3 families [90]. Manitoba-oculotricho-anal syndrome (MOTA) is a rare AR syndrome originally described in 6 siblings of Manitoba Indian origin. Features of this syndrome overlap with BNAR, and MOTA is also caused by mutations in the *FREM1* gene [91]. In 2013, Nathanson et al. [92] suggested that a disruption of the *FREM1* gene can produce a spectrum of clinical manifestation that include both MOTA and BNAR and that features of both syndromes can be seen in the same individual.

Agenesis of Corpus-Callosum-Coloboma-Mental Retardation (Temtamy Syndrome)

Temtamy et al. [93] reported on 2 siblings from a consanguineous Egyptian family with macrodolicephaly, with dysmorphic features associated with agenesis of the corpus callosum and dilatation of the fourth ventricle. Other similar cases have been reported [94, 95]. Zahrani et al. [96] identified a homozygous mutation in the *C12ORF57* gene (1A>G) in 4 siblings of Saudi Arabian origin with a similar phenotype. Akizu et al. [97] identified the same mutation in 10 unrelated families of Arab decent, including the family reported by Li et al. [95], and a haplotype analysis indicated a founder effect.

Spondylometaepiphyseal Dysplasia, Short-Limb-Abnormal-Calcification Type

The short-limb-abnormal-calcification-type spondylometaepiphyseal dysplasia (SMED) is a rare AR type of SMED which was initially reported by Borochowitz et al. in 1993 in Arab patients from Israel [98]. Many children with this disorder die in childhood due to respiratory and neurological complications [99]. SMED is caused by mutations in the *DDR2* gene [100]. Most patients reported with this disorder so far have been Arabs from Egypt and

Palestine and Middle Eastern Jews from Iraq and Egypt. There has been one family from Algeria [100].

One mutation was identified in all Palestinian families and 1 Egyptian family: c.2254C>T [R752]. The Algerian family had a different mutation: c.2177T>G [1726R] [100]. In 2010, Ali et al. [101] reported on the same mutation in a family from Egypt as originally reported by al-Gazali et al. in 1996 [99] and on a novel mutation in a family from Pakistan who had a milder phenotype.

Spondyloepiphyseal Dysplasia, Omani Type

A new type of spondyloepiphyseal dysplasia was reported in 9 patients from 2 Omani families originating from the same tribe [102]. Thiele et al. [103] identified the gene and mutation in these patients, a missense mutation (R304Q) in the chondroitin-6-O-sulfotransferase gene (*CHST3*). Mutations in the same gene have also been identified in patients diagnosed as suffering from AR Larsen syndrome and spondylo-humeral dysostosis; making these 3 conditions allelic [104].

AR Cutis Laxa, Type IIB (Cutis Laxa with Progeroid Features)

In 2001, Al-Gazali et al. [105] reported on 2 families, one from Palestine and one from Syria, with 5 children affected with a disorder overlapping with geroderma osteodysplastica and Wrinkly Skin syndrome. In 2005, Hamamy et al. [106] reported on a Palestinian child with similar features. Nanda et al. [107] reported on 3 children from 3 unrelated consanguineous Kuwaiti families with the same disorder. In addition, one of the families reported by Rajab et al. [108] as having typical geroderma osteodysplastica was found to have the same disorder. Two more families, one of Bahraini origin and one of Qatari origin, have been identified by Reversade et al. [109]. In 2009, they sequenced the *PYCR1* gene and found different mutations in all the above-mentioned families in addition to other families of different ethnic origins [109].

Congenital Disorder of Glycosylation Type1q

In 2008, Al-Gazali et al. [110] reported on a consanguineous Emirati family of Baluchi origin with ocular colobomas, ichthyosis, and mental retardation associated with endocrine abnormalities and midline brain malformations. Six additional families with the same phenotype have later been identified [111]. Cantagrel et al. [111] demonstrated a type 1 glycosylation defect in the affected individuals of the original family. A biochemical analysis of the original and other affected families showed that the metabolic block occurred early in the N-glycosylation

pathway, altering the synthesis or transfer of the glycan part of the lipid-linked oligosaccharide to the recipient proteins. In vitro assays indicated that the amount of the lipid carrier dolichol-phosphate was limited. Using linkage analysis and candidate gene sequencing of the original family, Cantagrel et al. [111] identified a homozygous mutation in the *SRD5A3* gene. Six other mutations were identified in 7 families with a similar phenotype.

Conclusions and Future Prospects

AR dysmorphic syndromes constitute a considerable proportion of the pool of birth defects among Arabs. Arab geneticists, with their persistent commitment to advancing research, have contributed to the description of a number of rare and new AR syndromes [38] with the identification of novel genes. A molecular analysis of a large number of previously undiagnosed dysmorphic syndromes has been achieved through the successful collaboration between Arab clinical geneticists and research teams in high-income countries. This collaboration resulted in a plethora of data on pathogenic variants and their function in causing dysmorphic syndromes.

Recent advances in high throughput sequencing have enhanced the capability of identifying pathogenic variants in the coding regions of genes. Research teams worldwide are currently employing this technology to identify unknown genes causing dysmorphic syndromes including AR syndromes in consanguineous families [112]. Exome sequencing facilitated the identification of novel AR pathogenic genes in small consanguineous nuclear families [97]. The high rate of consanguinity in Arab countries coupled with the large family sizes will provide the material for exploring the still unknown AR genes causing dysmorphic syndromes. The OMIM lists 1,977 AR syndromes with known molecular basis and 539 AR phenotypes with currently unknown molecular basis [46]. These unknown pathogenic variants will probably be identified through exome sequencing of affected individuals from consanguineous families over the next years.

In general terms, however, the provision of genetic services in Arab communities at all population levels is still inadequate, given the prevalence and burden of genetic diseases including dysmorphic syndromes, due to the major impediments of paucity of resources and trained health professionals in the area of medical genetics. Furthermore, genetic diagnosis is often difficult given the potential diversity of the conditions involved, and the dearth of appropriately qualified clinical geneticists in the Arab

world imposes a heavy responsibility on the few trained staff. Improving this situation calls for major educational efforts that include increasing the genetic literacy of the general public, comprehensive courses, and campaigns to familiarize primary healthcare workers with counseling needs and skills specifically focusing on consanguineous marriages. As in non-Arab societies, meeting the needs of individuals and communities in a culture-sensitive manner and understanding and respecting the ethical, moral, cultural, social, and religious beliefs of clients are essential prerequisites for the successful delivery of genetic services [2].

Since the majority of dysmorphic syndromes among Arabs tend to cluster in certain tribes and families, the most appropriate and perhaps the most effective approach to prevent genetic disorders in these communities is to use the family-oriented approach. In this approach, carrier screening and counseling of the extended family members are initiated after the diagnosis is established in the presenting individual [8]. The aim is to inform families of the implications of a carrier status, and where the carrier status cannot be diagnosed, to inform them of the possibility that future affected pregnancies could be circumvented by avoiding marriage with close biological relatives. It is still unusual for consanguineous Arab couples to learn of a major genetic risk before marriage or before starting a family, and most clinic sessions are retrospective with couples learning of the risks to future pregnancies after the birth of an affected child. As the Arab culture favors large families with many offspring, if the affected infant is the first or second child, most couples plan to have further children; the molecular diagnosis of the condition could offer them the option of acceptable preventive measures. The identification of these mutations at an unprecedented scale has the potential to significantly reshape the practice of clinical genetics in these populations and to offer opportunities for innovative public health policies [113].

Although still uncommon, the choice of prenatal diagnosis with selective termination of an affected fetus is a slowly evolving option in most Arab countries. Tunisia is at present the only clear example of an Islamic Arab country where selective abortion of an affected fetus is permissible under civil law [114, 115]. There is a diversity of opinions among Islamic institutions on the issue of pregnancy termination, ranging from an absolute prohibition of abortion at any time to the permission for pregnancy termination before the 120th day of gestation under specific circumstances [116, 117]. Preimplantation genetic diagnosis is now emerging in some Arab countries as an

additional alternative reproductive choice for high-risk couples who do not favor prenatal genetic diagnosis and selective abortion of an affected fetus [118].

There could be a considerable number of rare dysmorphic syndromes that prevail among Arabs, many of which are not hitherto described and whose underlying molecular pathologies are not yet defined. Arab countries should thus strive to deploy DNA diagnostics and to build research capability around local priorities [119]. The Editorial in *Nature Genetics* from October 2007 emphasizes the importance of attracting international collaborators,

while at the same time Arab countries should put their own priorities first, so that international collaborators must commit to return benefits, training and information to the developing region as the price of collaboration and, ideally, DNA should be genotyped and sequenced locally [120].

Furthermore, a characterization of the prevailing genetic disorders in each geographic location, together with their mutations, is needed to plan for appropriate screening and testing protocols [121].

References

- Bittles AH: The global prevalence of consanguinity. Global Patterns and Tables of Consanguinity. <http://www.consang.net/> (accessed May 1, 2013).
- Hamamy H, Bittles AH: Genetic clinics in Arab communities: meeting individual, family and community needs. *Public Health Genomics* 2008;12:30–40.
- Awad R, Veach PM, Bartels DM, LeRoy BS: Culture and acculturation influences on Palestinian perceptions of prenatal genetic counseling. *J Genet Couns* 2008;17:101–116.
- Bittles AH, Hamamy HA: Endogamy and consanguineous marriage in Arab populations; in Teebi AS (ed): *Genetic Disorders among Arab Populations*, ed 2. Berlin, Springer, 2010, pp 85–108.
- Khoury SA, Massad D: Consanguineous marriage in Jordan. *Am J Med Genet* 1992;43:769–775.
- Modell B, Darr A: Science and society: genetic counselling and customary consanguineous marriage. *Nat Rev Genet* 2002;3:225–229.
- Tadmouri GO, Nair P, Obeid T, Al Ali MT, Al Khaja N, Hamamy HA: Consanguinity and reproductive health among Arabs. *Reprod Health* 2009;6:17.
- Al-Gazali L, Hamamy H, Al-Arrayad S: Genetic disorders in the Arab world. *BMJ* 2006;333:831–834.
- Hamamy H, Antonarakis SE, Cavalli-Sforza LL, et al: Consanguineous marriages, pearls and perils: Geneva International Consanguinity Workshop Report. *Genet Med* 2011;13:841–847.
- Hamamy H, Jamhawi L, Al-Darawsheh J, Ajlouni K: Consanguineous marriages in Jordan: why is the rate changing with time? *Clin Genet* 2005;67:511–516.
- Khlat M: Consanguineous marriages in Beirut: time trends, spatial distribution. *Soc Biol* 1988;35:324–330.
- Al-Arrayed S: Genetic diseases in Bahrain; in: Tadmouri GO, Taleb Al Ali M, Al Khaja N (eds): *Genetic Disorders in the Arab World: Bahrain*. Centre for Arab Genomic Studies, Dubai, 2006.
- Al-Arrayed S, Hamamy H: The changing profile of consanguinity rates in Bahrain, 1990–2009. *J Biosoc Sci* 2012;44:313–319.
- Jaber L, Halpern GJ, Shohat T: Trends in the frequencies of consanguineous marriages in the Israeli Arab community. *Clin Genet* 2000;58:106–110.
- Sharkia R, Zaid M, Athamna A, Cohen D, Azem A, Zalan A: The changing pattern of consanguinity in a selected region of the Israeli Arab community. *Am J Hum Biol* 2008;20:72–77.
- Assaf S, Khawaja M: Consanguinity trends and correlates in the Palestinian Territories. *J Biosoc Sci* 2009;41:107–124.
- Bener A, Alali KA: Consanguineous marriage in a newly developed country: the Qatari population. *J Biosoc Sci* 2006;38:239–246.
- Jurdi R, Saxena PC: The prevalence and correlates of consanguineous marriages in Yemen: similarities and contrasts with other Arab countries. *J Biosoc Sci* 2003;35:1–13.
- al-Gazali LI, Bener A, Abdulrazzaq YM, Micallef R, al-Khayat AI, Gaber T: Consanguineous marriages in the United Arab Emirates. *J Biosoc Sci* 1997;29:491–497.
- Talbi J, Khadmaou A, Soulaymani A, Chafik A: Etude de la consanguinité dans la population marocaine. Impact sur le profil de la santé. *Antropo* 2007;15:1–11.
- Lamdouar BN: Consanguinity and public health in Morocco (in French). *Bull Acad Natl Med* 1994;178:1013–1025.
- Jaber L, Halpern GJ, Shohat M: The impact of consanguinity worldwide. *Community Genet* 1998;1:12–17.
- Bittles A: Consanguinity and its relevance to clinical genetics. *Clin Genet* 2001;60:89–98.
- Bittles AH: Endogamy, consanguinity and community genetics. *J Genet* 2002;81:91–98.
- Bittles AH: A community genetics perspective on consanguineous marriage. *Community Genet* 2008;11:324–330.
- Rittler M, Liascovich R, Lopez-Camelo J, Castilla EE: Parental consanguinity in specific types of congenital anomalies. *Am J Med Genet* 2001;102:36–43.
- Alfonso-Sanchez MA, Pena JA: Effects of consanguinity on pre-reproductive mortality: does demographic transition matter? *Am J Hum Biol* 2005;17:773–786.
- Christianson A, Howson CP, Modell B: *Global Report on Birth Defects. The Hidden Toll of Dying and Disabled Children*. March of Dimes Birth Defects Foundation, White Plains, 2009.
- Bittles AH, Black ML: The impact of consanguinity on neonatal and infant health. *Early Hum Dev* 2010;86:737–741.
- Alwan A, Modell B: *Community control of genetic and congenital disorders*. EMRO Technical Publication Series 24. WHO Regional Office for the Eastern Mediterranean Region, Alexandria, 1997.
- Mokhtar MM, Kotb SM, Ismail, SR: Autosomal recessive disorders among patients attending the genetic clinic in Alexandria. *East Mediterr Health J* 1998;4:470–479.
- Tadmouri GO: Genetic disorders in Arab populations; in: Tadmouri GO, Taleb Al Ali M, Al Khaja N (eds): *Genetic Disorders in the Arab World: United Arab Emirates*. Centre for Arab Genomic Studies, Dubai, 2004.
- Tadmouri GO: Genetic disorders in Arab populations: a 2006 update; in: Tadmouri GO, Taleb Al Ali M, Al Khaja N (eds): *Genetic Disorders in the Arab World: Bahrain*. Centre for Arab Genomic Studies, Dubai, 2006.
- Tadmouri GO: Genetic disorders in Arab populations: a 2008 update; in: Tadmouri GO, Taleb Al Ali M, Al Khaja N (eds): *Genetic Disorders in the Arab World: Oman*. Centre for Arab Genomic Studies, Dubai, 2008.

- 35 Hamamy HA, Masri AT, Al-Hadidy AM, Ajlouni KM: Consanguinity and genetic disorders. Profile from Jordan. *Saudi Med J* 2007; 28:1015–1017.
- 36 Romdhane L, Abdelhak S: Genetic diseases in the Tunisian population. *Am J Med Genet A* 2011;155A:238–267.
- 37 Romdhane L, Kefi R, Azaiez H, Ben HN, Delagi K, Abdelhak S: Founder mutations in Tunisia: implications for diagnosis in North Africa and Middle East. *Orphanet J Rare Dis* 2012;7:52.
- 38 Teebi AS: Genetic Disorders among Arab Populations, ed 2. Berlin, Springer, 2010.
- 39 Online Mendelian Inheritance in Man: OMIM Update List. <http://omim.org/statistics/update> (accessed December 12, 2013).
- 40 al-Gazali LI, Alwash R, Abdulrazzaq YM: United Arab Emirates: communities and community genetics. *Community Genet* 2005; 8:186–196.
- 41 Albaramki J, Akl K, Al-Muhtaseb A, Al-Shboul M, Mahmoud T, El-Khateeb M, Hamamy H: Sanjad Sakati syndrome: a case series from Jordan. *East Mediterr Health J* 2012; 18:527–531.
- 42 Draz S: Sanjad Sakati syndrome. *Palestinian Med J* 2006;1:57–59.
- 43 El-Sawy MA, El-Kholy MS, El-Sefdy HH, Sleem MN: Sanjad-Sakati syndrome. A case report. *Egypt J Med Hum Genet* 2004;5:61–65.
- 44 Parvari R, Hershkovitz E, Grossman N, et al: Mutation of TBCE causes hypoparathyroidism-retardation-dysmorphism and autosomal recessive Kenny-Caffey syndrome. *Nat Genet* 2002;32:448–452.
- 45 Hershkovitz E, Parvari R, Diaz GA, Gorodischer R: Hypoparathyroidism-retardation-dysmorphism (HRD) syndrome – a review. *J Pediatr Endocrinol Metab* 2004;17:1583–1590.
- 46 McKusick's Online Mendelian Inheritance in Man (OMIM). (accessed May 1, 2013).
- 47 Teebi AS, Naguib KK, Al-Awadi S, Al-Saleh QA: New autosomal recessive faciodigitogenital syndrome. *J Med Genet* 1988;25:400–406.
- 48 Teebi AS, al Awadi SA: Kuwait type faciodigitogenital syndrome. *J Med Genet* 1991;28:805.
- 49 al-Gazali LI, Varghese M, Varady E, Al Talabani J, Scorer J, Bakalinova D: Neonatal Schwartz-Jampel syndrome: a common autosomal recessive syndrome in the United Arab Emirates. *J Med Genet* 1996;33:203–211.
- 50 Dagoneau N, Scheffer D, Huber C, Al-Gazali LI, Di Rocco M, Godard A, Martinovic J, Raas-Rothschild A, Sigaudy S, Unger S, Nicole S, Fontaine B, Taupin JL, Moreau JF, Superti-Furga A, Le Merrer M, Bonaventure J, Munnich A, Legeai-Mallet L, Cormier-Daire V: Null leukemia inhibitory factor receptor (LIFR) mutations in Stuve-Wiedemann/Schwartz-Jampel type 2 syndrome. *Am J Hum Genet* 2004;74:298–305.
- 51 Akawi NA, Ali BR, Al-Gazali L: Stuve-Wiedemann syndrome and related bent bone dysplasias. *Clin Genet* 2012;82:12–21.
- 52 al-Gazali LI, Bakalinova D, Varady E, Scorer J, Nork M: Further delineation of Nevo syndrome. *J Med Genet* 1997;34:366–370.
- 53 Giunta C, Randolph A, al-Gazali LI, Brunner HG, Kraenzlin ME, Steinmann B: Nevo syndrome is allelic to the kyphoscoliotic type of the Ehlers-Danlos syndrome (EDS VIA). *Am J Med Genet A* 2005;133A:158–164.
- 54 Abdul Wahab A, Janahi IA, Eltohami A, Zeid A, Faiyaz Ul Hague M, Teebi AS: A new type of Ehlers-Danlos syndrome associated with tortuous systemic arteries in a large kindred from Qatar. *Acta Paediatr* 2003;92:456–462.
- 55 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;74:189–193.
- 56 Teebi AS: Autosomal recessive Robinow syndrome. *Am J Med Genet* 1990;35:64–68.
- 57 Soliman AT, Rajab A, Alsalmi I, Bedair SM: Recessive Robinow syndrome: with emphasis on endocrine functions. *Metabolism* 1998;47: 1337–1343.
- 58 Nazer H, Gunasekaran TS, Sakati NA, Nyhan WL: Concurrence of Robinow syndrome and Crigler-Najar syndrome in two offspring of first cousins. *Am J Med Genet* 1990;37:516–518.
- 59 al Talabani J, Shubbar AI, Mustafa KE: Major congenital malformations in United Arab Emirates (UAE): need for genetic counselling. *Ann Hum Genet* 1998;62:411–418.
- 60 Rajab A, Bappal B, Al-Shaikh H, Al-Khusaibi S, Mohammed AJ: Common autosomal recessive diseases in Oman derived from a hospital-based registry. *Community Genet* 2005; 8:27–30.
- 61 Afzal AR, Rajab A, Fenske CD, Oldridge M, Elanko N, Ternes-Pereira E, Tuysuz B, Murday VA, Patton MA, Wilkie AO, Jeffery S: Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of ROR2. *Nat Genet* 2000;25:419–422.
- 62 Farag TI, Teebi AS: High incidence of Bardet Biedl syndrome among the Bedouin. *Clin Genet* 1989;36:463–464.
- 63 Stoetzel C, Laurier V, Davis EE, et al: BBS10 encodes a vertebrate-specific chaperonin-like protein and is a major BBS locus. *Nat Genet* 2006;38:521–524.
- 64 Smaoui N, Chaabouni M, Sergeev YV, Kallel H, Li S, Mahfoudh N, Maazoul F, Kammoun H, Gandoura N, Bouaziz A, Nouiri E, M'Rad R, Chaabouni H, Hejtmancik JF: Screening of the eight BBS genes in Tunisian families: no evidence of triallelism. *Invest Ophthalmol Vis Sci* 2006;47:3487–3495.
- 65 Abu-Safieh L, Al-Anazi S, Al-Abdi L, Hashem M, Alkuraya H, Alamr M, Sirelkhatim MO, Al-Hassnan Z, Alkuraya B, Mohamed JY, Al-Salem A, Alrashed M, Faqih E, Softah A, Al-Hashem A, Wali S, Rahbeeni Z, Alsayed M, Khan AO, Al-Gazali L, Taschner PE, Al-Hazzaa S, Alkuraya FS: In search of triallelism in Bardet-Biedl syndrome. *Eur J Hum Genet* 2012;20:420–427.
- 66 al-Gazali LI, Sztriha L, Dawodu A, Bakir M, Varghese M, Varady E, Scorer J, Abdulrazzaq YM, Bener A, Padmanabhan R: Pattern of central nervous system anomalies in a population with a high rate of consanguineous marriages. *Clin Genet* 1999;55:95–102.
- 67 Teebi AS, Teebi SA: Genetic diversity among the Arabs. *Community Genet* 2005;8:21–26.
- 68 Ramadan HM, Nasrat HA: Prenatal diagnosis of recurrent Meckel syndrome. *Int J Gynaecol Obstet* 1992;39:327–332.
- 69 Boutheina BR, Aida M, Lamia S, Ali M, Med-Badis C, Samy J, Issam L, Ezzeddine S, Raouf C, Zohra M, Faouzia Z, Hedi R, Naima K, Hela C, Soumeia GS: Lethal uropathies: prenatal diagnosis and fetopathologic aspects (in French). *Tunis Med* 2000;78:120–124.
- 70 Shaheen R, Faqih E, Alshammari MJ, Swaid A, Al-Gazali L, Mardawi E, Ansari S, Sogaty S, Seidahmed MZ, Almotairi MI, Farra C, Kurdi W, Al-Rasheed S, Alkuraya FS: Genomic analysis of Meckel-Gruber syndrome in Arabs reveals marked genetic heterogeneity and novel candidate genes. *Eur J Hum Genet* 2013;21:762–768.
- 71 Dixon-Salazar T, Silhavy JL, Marsh SE, Louie CM, Scott LC, Gururaj A, Al-Gazali L, Al-Tawari AA, Kayserili H, Sztriha L, Gleeson JG: Mutations in the AHI1 gene, encoding joubertin, cause Joubert syndrome with cortical polymicrogyria. *Am J Hum Genet* 2004;75: 979–987.
- 72 Valente EM, Silhavy JL, Brancati F, Barrano G, Krishnaswami SR, Castori M, Lancaster MA, Boltshauser E, Boccone L, Al-Gazali L, Fazzi E, Signorini S, Louie CM, Bellacchio E, Bertini E, Dallapiccola B, Gleeson JG: Mutations in CEP290, which encodes a centrosomal protein, cause pleiotropic forms of Joubert syndrome. *Nat Genet* 2006;38:623–625.
- 73 Bielas SL, Silhavy JL, Brancati F, Kisseleva MV, Al-Gazali L, Sztriha L, Bayoumi RA, Zaki MS, Abdel-Aleem A, Rosti RO, Kayserili H, Swistun D, Scott LC, Bertini E, Boltshauser E, Fazzi E, Travaglini L, Field SJ, Gayral S, Jacoby M, Schurmans S, Dallapiccola B, Majerus PW, Valente EM, Gleeson JG: Mutations in INPP5E, encoding inositol polyphosphate-5-phosphatase E, link phosphatidylinositol signaling to the ciliopathies. *Nat Genet* 2009; 41:1032–1036.
- 74 Alazami AM, Alshammari MJ, Salih MA, Al-zahrani F, Hijazi H, Seidahmed MZ, Abu SL, Aldasary M, Khan AO, Alkuraya FS: Molecular characterization of Joubert syndrome in Saudi Arabia. *Hum Mutat* 2012;33:1423–1428.

- 75 Mostafa MI, Temtamy SA, el-Gammal MA, Mazen IM: Unusual pattern of inheritance and orodental changes in the Ellis-van Creveld syndrome. *Genet Couns* 2005;16:75–83.
- 76 Reddy DV, Madenlioglu M: Chondroectodermal dysplasia (Ellis-van Creveld syndrome). Report of two cases from Saudi Arabia. *Clin Pediatr (Phila)* 1967;6:51–56.
- 77 Al-Gazali LI, Bakir M, Hamid Z, Varady E, Varghes M, Haas D, Bener A, Padmanabhan R, Abdulrazzaq YM, Dawadu A: Birth prevalence and pattern of osteochondrodysplasias in an inbred high risk population. *Birth Defects Res A Clin Mol Teratol* 2003;67:125–132.
- 78 Ali BR, Akawi NA, Chedid F, Bakir M, Ur Rehman M, Rahmani A, Al-Gazali L: Molecular and clinical analysis of Ellis-van Creveld syndrome in the United Arab Emirates. *BMC Med Genet* 2010;11:33.
- 79 Al-Awadi SA, Farag TI, Teebi AS, Naguib K, el-Khalifa MY, Kelani Y, Al-Ansari A, Schimke RN: Primary hypogonadism and partial alopecia in three sibs with mullerian hypoplasia in the affected females. *Am J Med Genet* 1985;22:619–622.
- 80 Oerter KE, Friedman TC, Anderson HC, Cas-sorla FG: Familial syndrome of endocrine and neuroectodermal abnormalities. *Am J Med Genet* 1992;44:487–491.
- 81 Gul D, Ozata M, Mergen H, Odabasi Z, Mergen M: Woodhouse and Sakati syndrome (MIM 241080): report of a new patient. *Clin Dysmorphol* 2000;9:123–125.
- 82 Alazami AM, Al-Saif A, Al-Semari A, Bohlega S, Zlitni S, Alzahrani F, Bavi P, Kaya N, Colak D, Khalak H, Baltus A, Peterlin B, Danda S, Bhatia KP, Schneider SA, Sakati N, Walsh CA, Al-Mohanna F, Meyer B, Alkuraya FS: Mutations in C2orf37, encoding a nucleolar protein, cause hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome. *Am J Hum Genet* 2008;83:684–691.
- 83 Al-Awadi SA, Teebi AS, Farag TI, Naguib KM, el-Khalifa MY: Profound limb deficiency, thoracic dystrophy, unusual facies, and normal intelligence: a new syndrome. *J Med Genet* 1985;22:36–38.
- 84 Raas-Rothschild A, Goodman RM, Meyer S, Katznelson MB, Winter ST, Gross E, Tamarin M, Ben-Ami T, Nebel L, Mashiah S: Pathological features and prenatal diagnosis in the newly recognised limb/pelvis-hypoplasia/aplasia syndrome. *J Med Genet* 1988;25:687–697.
- 85 Woods CG, Stricker S, Seemann P, Stern R, Cox J, Sherridan E, Roberts E, Springell K, Scott S, Karbani G, Sharif SM, Toomes C, Bond J, Kumar D, Al-Gazali L, Mundlos S: Mutations in WNT7A cause a range of limb malformations, including Fuhrmann syndrome and Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome. *Am J Hum Genet* 2006;79:402–408.
- 86 Kantaputra PN, Mundlos S, Sripathomsawat W: A novel homozygous Arg222Trp missense mutation in WNT7A in two sisters with severe Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome. *Am J Med Genet A* 2010;152A:2832–2837.
- 87 Eyaid W, Al-Qattan MM, Al Abdulkareem I, Fetaini N, Al Balwi M: A novel homozygous missense mutation (c.610G>A, p.Gly204Ser) in the WNT7A gene causes tetra-amelia in two Saudi families. *Am J Med Genet A* 2011;155A:599–604.
- 88 Garavelli L, Wischmeijer A, Rosato S, Gelmini C, Reverberi S, Sassi S, Ferrari A, Mari F, Zabel B, Lausch E, Unger S, Superti-Furga A: Al-Awadi-Raas-Rothschild (limb/pelvis/uterus-hypoplasia/aplasia) syndrome and WNT7A mutations: genetic homogeneity and nosological delineation. *Am J Med Genet A* 2011;155A:332–336.
- 89 Al-Gazali LI, Bakir M, Hamud OA, Gerami S: An autosomal recessive syndrome of nasal anomalies associated with renal and anorectal malformations. *Clin Dysmorphol* 2002;11:33–38.
- 90 Alazami AM, Shaheen R, Alzahrani F, Snape K, Sagar A, Brinkmann B, Bavi P, Al-Gazali LI, Alkuraya FS: FREM1 mutations cause bifid nose, renal agenesis, and anorectal malformations syndrome. *Am J Hum Genet* 2009;85:414–418.
- 91 Slavotinek AM, Baranzini SE, Schanze D, Labelle-Dumais C, Short KM, Chao R, Yahyavi M, Bijlsma EK, Chu C, Musone S, Wheatley A, Kwok PY, Marles S, Fryns JP, Maga AM, Hassan MG, Gould DB, Madireddy L, Li C, Cox TC, Smyth I, Chudley AE, Zenker M: Manitoba-oculo-tricho-anal (MOTA) syndrome is caused by mutations in FREM1. *J Med Genet* 2011;48:375–382.
- 92 Nathanson J, Swarr DT, Singer A, Liu M, Chinn A, Jones W, Hurst J, Khalek N, Zackai E, Slavotinek A: Novel FREM1 mutations expand the phenotypic spectrum associated with Manitoba-oculo-tricho-anal (MOTA) syndrome and bifid nose renal agenesis anorectal malformations (BNAR) syndrome. *Am J Med Genet A* 2013;161:473–478.
- 93 Temtamy SA, Salam MA, Aboul-Ezz EH, Hussein HA, Helmy SA, Shalash BA: New autosomal recessive multiple congenital abnormalities/mental retardation syndrome with craniofacial dysmorphism absent corpus callosum, iris colobomas and connective tissue dysplasia. *Clin Dysmorphol* 1996;5:231–240.
- 94 Chan AK, Levin AV, Teebi AS: Craniofacial dysmorphism, agenesis of the corpus callosum and ocular colobomas: Temtamy syndrome? *Clin Dysmorphol* 2000;9:223–226.
- 95 Li J, Shivakumar S, Wakahiro M, Mukherjee P, Barkovich AJ, Slavotinek A, Sherr EH: Agenesis of the corpus callosum, optic coloboma, intractable seizures, craniofacial and skeletal dysmorphisms: an autosomal recessive disorder similar to Temtamy syndrome. *Am J Med Genet A* 2007;143A:1900–1905.
- 96 Zahrani F, Aldahmesh MA, Alshammari MJ, Al-Hazzaa SA, Alkuraya FS: Mutations in c12orf57 cause a syndromic form of colobomatous microphthalmia. *Am J Hum Genet* 2013;92:387–391.
- 97 Akizu N, Shembesh NM, Ben-Omran T, Bastaki L, Al-Tawari A, Zaki MS, Koul R, Spencer E, Rosti RO, Scott E, Nickerson E, Gabriel S, da Gente G, Li J, Deardorff MA, Conlin LK, Horton MA, Zackai EH, Sherr EH, Gleeson JG: Whole-exome sequencing identifies mutated c12orf57 in recessive corpus callosum hypoplasia. *Am J Hum Genet* 2013;92:392–400.
- 98 Borochowitz Z, Langer LO Jr, Gruber HE, Lachman R, Katznelson MB, Rimoin DL: Spondylo-meta-epiphyseal dysplasia (SMED), short limb-hand type: a congenital familial skeletal dysplasia with distinctive features and histopathology. *Am J Med Genet* 1993;45:320–326.
- 99 al-Gazali LI, Bakalnova D, Sztriha L: Spondylo-meta-epiphyseal dysplasia, short limb, abnormal calcification type. *Clin Dysmorphol* 1996;5:197–206.
- 100 Bargal R, Cormier-Daire V, Ben-Neriah Z, Le Merrer M, Sosna J, Melki J, Zangen DH, Smithson SF, Borochowitz Z, Belostotsky R, Raas-Rothschild A: Mutations in DDR2 gene cause SMED with short limbs and abnormal calcifications. *Am J Hum Genet* 2009;84:80–84.
- 101 Ali BR, Xu H, Akawi NA, John A, Karuvan-tevida NS, Langer R, Al-Gazali L, Leitingner B: Trafficking defects and loss of ligand binding are the underlying causes of all reported DDR2 missense mutations found in SMED-SL patients. *Hum Mol Genet* 2010;19:2239–2250.
- 102 Rajab A, Kunze J, Mundlos S: Spondylo-epiphyseal dysplasia Omani type: a new recessive type of SED with progressive spinal involvement. *Am J Med Genet A* 2004;126A:413–419.
- 103 Thiele H, Sakano M, Kitagawa H, Sugahara K, Rajab A, Hohne W, Ritter H, Leschik G, Nurnberg P, Mundlos S: Loss of chondroitin 6-O-sulfotransferase-1 function results in severe human chondrodysplasia with progressive spinal involvement. *Proc Natl Acad Sci USA* 2004;101:10155–10160.
- 104 Hermanns P, Unger S, Rossi A, Perez-Aytes A, Cortina H, Bonafe L, Boccone L, Setzu V, Dutoit M, Sangiorgi L, Pecora F, Reicherter K, Nishimura G, Spranger J, Zabel B, Superti-Furga A: Congenital joint dislocations caused by carbohydrate sulfotransferase 3 deficiency in recessive Larsen syndrome and humero-spinal dysostosis. *Am J Hum Genet* 2008;82:1368–1374.
- 105 Al-Gazali LI, Sztriha L, Sakaff F, Haas D: Geroderma osteodysplastica and wrinkly skin syndrome: are they the same? *Am J Med Genet* 2001;101:213–220.

- 106 Hamamy H, Masri A, Ajlouni K: Wrinkly skin syndrome. *Clin Exp Dermatol* 2005;30: 590–592.
- 107 Nanda A, Alsaleh QA, Al-Sabah H, Marzouk EE, Salam AM, Nanda M, Anim JT: Gero-dermia osteodysplastica/wrinkly skin syn-drome: report of three patients and brief re-view of the literature. *Pediatr Dermatol* 2008;25:66–71.
- 108 Rajab A, Kornak U, Budde BS, Hoffmann K, Jaeken J, Nurnberg P, Mundlos S: Geroder-ma osteodysplasticum hereditaria and wrin-kly skin syndrome in 22 patients from Oman. *Am J Med Genet A* 2008;146A:965–976.
- 109 Reversade B, Escande-Beillard N, Dimopou-lou A, et al: Mutations in PYCR1 cause cutis laxa with progeroid features. *Nat Genet* 2009;41:1016–1021.
- 110 Al-Gazali L, Hertecant J, Algawi K, El Teraifi H, Dattani M: A new autosomal recessive syndrome of ocular colobomas, ichthyosis, brain malformations and endocrine abnor-malities in an inbred Emirati family. *Am J Med Genet A* 2008;146:813–819.
- 111 Cantagrel V, Lefeber DJ, Ng BG, et al: SR-D5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder. *Cell* 2010;142:203–217.
- 112 Dixon-Salazar TJ, Silhavy JL, Udpa N, et al: Exome sequencing can improve diagnosis and alter patient management. *Sci Transl Med* 2012;4:138ra78.
- 113 Alkuraya F: Impact of new genomic tools on the practice of clinical genetics in consan-guineous populations: the Saudi experience. *Clin Genet* 2013;84:203–208.
- 114 Chaabouni-Bouhamed H: Tunisia: commu-nities and community genetics. *Community Genet* 2008;11:313–323.
- 115 Chaabouni H, Chaabouni M, Maazoul F, M’Rad R, Jemaa LB, Smaoui N, Terras K, Kammoun H, Belghith N, Ridene H, Ouesla-ti B, Zouari F: Prenatal diagnosis of chromo-some disorders in Tunisian population. *Ann Genet* 2001;44:99–104.
- 116 Al Aqeel AI: Islamic ethical framework for research into and prevention of genetic dis-eases. *Nat Genet* 2007;39:1293–1298.
- 117 Alkuraya FS, Kilani RA: Attitude of Saudi families affected with hemoglobinopathies towards prenatal screening and abortion and the influence of religious ruling (Fatwa). *Prenat Diagn* 2001;21:448–451.
- 118 Qubbaj W, Al-Swaid A, Al-Hassan S, Awar-tani K, Deek H, Coskun S: First successful application of preimplantation genetic diag-nosis and haplotyping for congenital hyper-insulinism. *Reprod Biomed Online* 2011;22: 72–79.
- 119 Alwan A, Modell B: Recommendations for introducing genetics services in developing countries. *Nat Rev Genet* 2003;4:61–68.
- 120 Editorial: Developing genetics for develop-ing countries. *Nat Genet* 2007;39:1287.
- 121 Al-Gazali L, Eapen V: Genetics: global chal-lenge, regional focus. *Advances in commu-nity and preventive genetics. Community Genet* 2005;8:5–6.
- 122 Badr FM: Genetic studies of Egyptian Nu-bian populations. I. Frequency and types of consanguineous marriages. *Hum Hered* 1972;22:387–398.
- 123 Yamamah G, Abdel-Raouf E, Talaat A, Saad-Hussein A, Hamamy H, Meguid NA: Prevalence of consanguineous marriages in South Sinai, Egypt. *J Biosoc Sci* 2013;45:31–39.
- 124 Al-Ani ZR: Association of consanguinity with congenital heart diseases in a teaching hospital in Western Iraq. *Saudi Med J* 2010; 31:1021–1027.
- 125 El-Khesheh G, Saadat M: Prevalence of con-sanguineous marriages among shi’a popula-tions of Lebanon. *J Biosoc Sci* 2013;1–8.
- 126 Al-Riyami A, Ebrahim GJ: Genetic Blood Disorders Survey in the Sultanate of Oman. *J Trop Pediatr* 2003;49(suppl 1):i1–i20.
- 127 Rajab A, Patton MA: A study of consanguin-ity in the Sultanate of Oman. *Ann Hum Biol* 2000;27:321–326.
- 128 Othman H, Saadat M: Prevalence of consan-guineous marriages in Syria. *J Biosoc Sci* 2009;41:685–692.
- 129 Ben Arab S, Masmoudi S, Beltaief N, Hachi-cha S, Ayadi H: Consanguinity and endoga-my in Northern Tunisia and its impact on non-syndromic deafness. *Genet Epidemiol* 2004;27:74–79.
- 130 Riou S, el Younsi C, Chaabouni H: Consan-guinity in the population of northern Tuni-sia (in French). *Tunis Med* 1989;67:167–172.
- 131 Kerkeni E, Monastiri K, Saket B, Rudan D, Zgaga L, Ben CH: Association among educa-tion level, occupation status, and consan-guinity in Tunisia and Croatia. *Croat Med J* 2006;47:656–661.
- 132 al-Gazali LI, Dawodu AH, Sabarinathan K, Varghese M: The profile of major congenital abnormalities in the United Arab Emirates (UAE) population. *J Med Genet* 1995;32:7–13.
- 133 Gunaid AA, Hummad NA, Tamim KA: Consanguineous marriage in the capital city Sana’a, Yemen. *J Biosoc Sci* 2004;36:111–121.
- 134 Jurdi R, Saxena PC: The prevalence and cor-relates of consanguineous marriages in Ye-men: similarities and contrasts with other Arab countries. *J Biosoc Sci* 2003;35:1–13.