III An Overview of Mendelian Disorders In Saudi Arabia

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نبذة مختصرة

المملكة العربية السعودية هي أكبر دولة في شبه الجزيرة العربية وهي تتبع الشريعة الإسلامية، وهي المشتقة عن المبادئ الدينية للإسلام. ترتفع نسبة زواج الأقارب في المملكة كما تنتشر اضطرابات وراثية معينة في فئات سكانية محددة. علاوة على ذلك، يلاحظ وجود مورثات خاصة بالمجتمع السعودي، خصوصاً في مناطق وقبائل محددة. كما وترتفع نسبة بعض الاضطرابات الوراثية بشكلٍ خاص، ومنها أمراض الدم، والإعاقة الذهنية، والجلوكوما الخلقية، وفقدان السمع. في عام ٢٠١٣، أعلنت المملكةَ العربية السعودية عن إطلاق برنامج الجينوم البشري السعودي الذي يهدف إلى توثيق مائة ألف جينوم في المجتمع السعودي من أجل إجراء بحوث بيولوجية طبية ذات جودة عالمية ترتكز على علم الجينوم، لتحديد الأساس الجيني للأمراض الوراثية في المجتمع السعودي والتخفيف من عبئها على أفراده. يستعرض هذا الفصل الاضطرابات الوراثية الشائعة في المملكة العربية السعودية وتأثير التقاليد الثقافية على المجتمع.

Abstract

The Kingdom of Saudi Arabia is the largest country of the Arabian Peninsula and it follows Sharia or Islamic law, which is derived from the religious precepts of Islam. Consanguinity and high incidence of population-specific disorders are well-known observations in Saudi Arabia. Furthermore, there are novel genes in the Saudi population and founder effect is observed in specific tribes or regions. On the other hand, there are commonly encountered genetic disorders in the Saudi population like hemoglobinopathies, intellectual disability, congenital glaucoma, ciliopathies, inborn errors of metabolism disorders, retinal dystrophies, hearing loss and primary microcephaly. In 2013, Saudi Arabia announced the launching of the Saudi Human Genome Program which aims to sequence 100,000 human genomes to conduct world-class, genomics-based biomedical research on the Saudi population, in order to provide a better understanding of the landscape of genetic disorders in Saudi Arabia and challenge the burden to the community of inherited disorders. This chapter reviews the genetic disorders in Saudi Arabia and the impact of cultural tradition on the community.

Introduction

The Kingdom of Saudi Arabia was established in 1932 by its founder King Abdulaziz ibn Abdulrahman Al Saud, uniting four distinct regions to their mutual benefit: Hejaz, Najd and parts of Eastern (Al-Ahsa) and Southern (‘Asir) Arabia. The Kingdom constitutes 80% of the Arabian Peninsula (the world’s largest peninsula), covering a land area of approximately 2,150,000 km2. The population of Saudi Arabia grew from 22.56 million in 2004 to an estimated 32.6 million in May 2017, of which 37% are non-nationalized immigrants (https://www.stats.gov.sa). However, the Saudi fertility rate (total births per woman) has declined significantly from 7.2 in 1960 to 2.6 in 2015 (http://www.worldbank.org). The official language of Saudi Arabia is Arabic, though English is widely spoken in hospitals, universities and the private sector. In June 2016, the Saudi Council of Ministers approved the National Transformation Program, also known as Saudi Vision 2030, to reduce Saudi Arabia’s dependence on oil, diversify the economy and develop public service sectors, such as education, infrastructure, health, recreation and tourism.

Saudi Arabia is also called the Land of the Two Holy Mosques, a reference to Al-Masjid al-Haram (in Mecca) and Al-Masjid an-Nabawi (in Medina), the two holiest places in Islam. Saudi Arabia follows Islamic law (Sharia) and the Quran. The Quran and the Sunnah (the traditions of Muhammad) are declared to be the country’s constitution.

Genetics in Saudi Arabia

High rates of consanguinity and high incidence of population-specific autosomal recessive disorders are well-known observations in Saudi Arabia. Specific, novel genes in the Saudi population and, more importantly, the founder effect in specific tribes or regions that present common disease-causing variants both demand the provision of medical services across the Kingdom. However, medical genetic services in Saudi Arabia are limited to large cities and tertiary hospitals, mainly governmental institutions, with few services in private hospitals and unclear insurance coverage. Therefore, in 2018, the Saudi Council of Cooperative Health Insurance (https://www.cchi.gov.sa) issued a unified health insurance policy that mandated coverage of genetic disorders related to birth defects.

Saudi Arabia follows *Sharia* or Islamic law, which is derived from the religious precepts of Islam, particularly the Quran and the Hadith. Islamic law considers Muslims to be one community and prescribes their practice from birth to death, including their diet, personal hygiene and daily social life. In Islamic law, ethical considerations in genetics include support for the discovery of disorders and providing of treatment: "every illness has a cure" and "taking proper care of one's health is the right of the body". Based on the practice of Prophet Muhammad (peace be upon him), treating and managing diseases will lead to strategies for their prevention, ultimately improving the health of the entire community.

In this regard, Saudi Arabia faces an enormously high incidence of genetic disorders. Many attempts have been made to challenge the burden to the community of inherited disorders, for example by establishing premarital screening for haemoglobinopathies (1), expanding medical genetics services, sponsoring physicians and scientists in the field of genetics, launching fellowship programs in clinical genetics and master's degree programs in genetic counselling, increasing awareness of inherited disorders through the media and launching the Saudi Human Genome Program (SHGP), which aims to sequence 100,000 human genomes to conduct world-class, genomics-based biomedical research on the Saudi population in order to provide a better understanding of the landscape of genetic disorders in Saudi Arabia (2). Whilst around 60 genetic disorders were first described in Saudi Arabia (3), there are commonly encountered genetic disorders in the Saudi population like thalassaemia, intellectual disability, congenital glaucoma, Bardet–Biedl syndrome, Meckel–Gruber syndrome, organic acidaemia, lysosomal storage disorders, retinal dystrophies, hearing loss and primary microcephaly.

Consanguinity, Tribal Unions and Founder Effects

Currently, an estimated one billion people globally live in communities with a preference for consanguineous marriage (4, 5), mostly in North Africa, the Middle East and Asia, where intra-familial unions collectively account for 20–50% of all marriages (6-8) . Saudi Arabia has one of the highest rates of consanguinity among Arab countries, with the overall rate estimated at 52–58% (9-11) and certain areas even reaching 80% (12). First-cousin marriages are the most frequent in Saudi Arabia, accounting for 28–40% of all marriages (9-12). The role consanguinity plays in the prevalence of genetic disorders, especially autosomal recessive disorders, is well-established. In two large, whole exome cohorts conducted in Saudi Arabia, Alfares et al. 2017 and Monies et al. 2017 (13, 14) both reported high rates (97%) of autosomal recessive disorders with homozygous disease-causing variants. Based on the calculated allele frequency of disease-causing variants, the estimated probability a first-cousin union has a child homozygous for disease-causing variants is approximately 0.7% (15). However, considering the high rate of consanguinity, the likelihood that both first cousin parents are carriers for the diseases-causing variants is nearly 1 in 8 (allowing for 100% likelihood of being a carrier for at least one disease-causing recessive disease, and 1/8 sharing of variants between first cousins), which results in 1:32 risk of having an affected child with an autosomal recessive disorder. Also, first-cousin unions lead to increased frequencies of homozygosity even for autosomal-dominant traits (16), or to unveiling novel phenotypes of dominant disorders in homozygous occurrence of disease causing alleles. The impact of consanguineous unions on the incidence of some of the genetic disorders in the Saudi population is further detailed in the following sections.

Consanguineous unions and the tribal structure of Saudi Arabia have impacted the incidence of genetic diseases in the country. The maintenance

of tribal lineage and intra-tribal marriages over many generations has retained and spread private genetic variants specific to a geographic location or tribe. Many of these founder variants of different autosomal recessive disorders were identified in Saudi patients even before the expansion of advanced technology like next-generation sequencing, demonstrating the high allele frequency of these variants in the population. Some of these founder variants are tribal-specific. For example, the c.559G>T p.(Gly187X) in *SLC26A3*, which appears to be an Arab founder pathogenic variant causing familial chloride diarrhoea, was identified and reported in 1998 (17). In another example, the homozygous deletion of 12 bp c.155-166del p.(Ser52_Gly55del) in exon 3 of the *TBCE* gene was identified and reported in 2002, in both Saudi and Kuwaiti patients, with Sanjad–Sakati syndrome present with hypoparathyroidism, retardation and delay of growth and development (18, 19). Moreover, the well-known splice junction variant in the Arabic population in *CA2* (c.297+1G>A), which is located at the 5' end of intron 2 and causes carbonic anhydrase type II deficiency leading to osteopetrosis autosomal recessive type 3, was initially reported in 1992 (20, 21). The c.436delC p.(Ala147Hisfs*9) in *DCAF17* was reported in 2008 from patients with Woodhouse–Sakati syndrome, who present with hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal signs (22). Other common disorders with founder variants include hereditary haemoglobin disorder B-thalassaemia and sickle cell disease, particularly in provinces with high rates of intermarriage and tribal unions. Furthermore, the high incidence of rare genetic and metabolic disorders in certain tribes have become clinical markers during the diagnostic and clinical evaluation of patients and individuals from those tribes. The combination of tribal societal structure, high rates of consanguinity and large family size have elevated the prevalence of specific autosomal recessive diseases to alarming levels in Saudi Arabia. For instance, some metabolic disorders in Saudi Arabia like maple syrup urine disease, very-long-chain fatty acid deficiency and propionic acidaemia are almost entirely limited to specific tribes, with prevalence rates five to ten times higher than those worldwide (23).

Other non-metabolic founder variants are also common in Saudi Arabia. The well-known ADAT3-related intellectual disability has been described in many individuals from Saudi families with the homozygous founder variant c.382G>A p.(Val128Met). These individuals often have cognitive impairment, microcephaly, epilepsy, nonspecific brain abnormalities and dysmorphic facial features. ADAT3-related intellectual disability is considered a recognizable cause of intellectual disability in Saudi Arabia (24, 25). Another commonly encountered disease-causing variant, in the well-known gene *C12ORF57* which causes Temtamy syndrome, a form of intellectual disability characterized by ocular involvement, epilepsy and dysgenesis of the corpus callosum. The founder variant occurs in the methionine ATG starting codon of the gene (c.1A>G: p.Met1?) (26) and completely abolishes gene translation. This variant alone represented around 1.5% of all positive cases in one of the large cohorts of Saudi individuals, unselected for phenotype, who underwent whole exome sequencing (13). Among disorders in Saudi Arabia with the autosomal recessive mode of inheritance, over one-third are estimated to result from founder mutations, with the remainder being private and limited to the family in which the variant was identified. The estimated percentage of disease-causing founder variants in the Saudi population is 42% (Figure 1) (13). Disease-causing founder variants, as yet unreported, are currently being discovered in many genetics clinics as well as local and international diagnostic/research laboratories. Reporting founder variants greatly benefits, not only the family, but also often the whole tribe. For example, the highest calculated carrier frequency for a single disease-causing variant in the Saudi population, 0.015, is that of a founder variant in *CYP1B1* NM_000104.3 c.182G>A p.(Gly61Glu), which causes congenital glaucoma (15). Knowing this information will improve management and treatment, in addition to genetic counselling and prevention. Aside from single gene disorders, many studies have reported that polygenic and multifactorial disorders are also very common in Saudi Arabia, attributing this to the high rates of consanguinity. For example, there is a high incidence of congenital heart disease across the country, increased rate of gastrointestinal tract anomalies in the Asir region, and in Najran regions there is a significantly high prevalence of hypothyroidism and hyperthyroidism (27). However, due to lack of national registries of complex disorders, lifestyle influence and phenocopies, as well as limited robust epidemiological statistical studies on large cohorts, the impact of consanguinity on the incidence of complex disorders is controversial. For example, *DNASE1L3* is linked to an autosomal recessive form of systemic lupus erythematosus

(SLE) which is considered as a multifactorial complex autoimmune disease (28), and *LRPAP1* was found to be associated with severe myopia (29). *GNB5, LRBA* and *TBXT* are linked to mendelian forms of neuropsychiatric disorder, inflammatory bowel disease with combined immunodeficiency and neural tube defects, respectively (30-32).

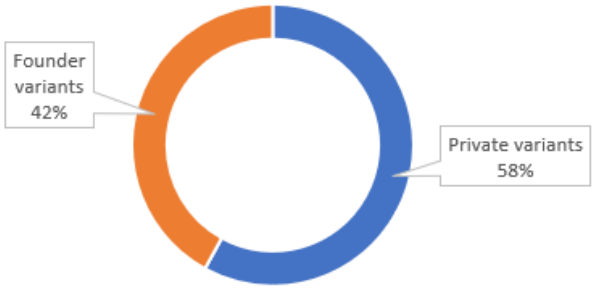

Figure 1: Representation of the distribution of disease-causing founder variants and private variants.

Zygosity and Mode of Inheritance

Previous reports have shown that, as expected, most disease-causing variants in the Saudi population are homozygous. Around 81% of all reported monogenic disorders in Saudi Arabia are autosomal recessive, and of these recessive disorders, 97% are homozygous, which is consistent with the high rate of consanguineous unions in the Saudi population. Compound heterozygous variants account for 5% of disease-causing variants. Non-recessive disorders in Saudi Arabia are less prevalent, accounting for 10–27% of autosomal dominant disorders and only 2–5% for X-linked disorders (Figure 2) (13, 14).

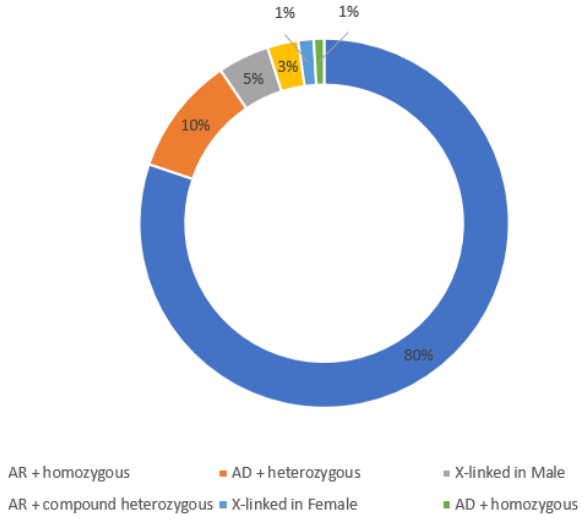

Figure 2: Distribution of genetic disorders in Saudi Arabia by mode of inheritance and allele state; AR: autosomal recessive, AD: autosomal dominant.

Dual diagnosis occurred in 3.3–6% of cases, with diagnosis established by molecular testing. This is similar to the published rate internationally and perhaps surprisingly less than expected, considering the high rate of consanguinity (13, 14).

Novel Gene Discoveries

Advances in molecular genetic testing in recent years made it possible to uncover, with reasonable time and cost, many genetic disorders in which consanguinity and a homozygous variant predispose to autosomal recessive diseases. Novel discovery of disease-causing genes in Saudi Arabia has been tremendously improved by the ability to analyse the entire set of autozygous intervals (the autozygome) in consanguineous patients (33), primarily focused on identifying homozygous variants in autosomal recessive disorders. This approach has helped increase the yield of molecular testing to identify novel candidate genes not previously associated with diseases. The following sections discuss many of these novel genes in further detail.

Commonly Encountered Genetic Disorders

Inborn error of metabolism (IEM) is one of the most common disorders in Saudi Arabia, with estimated incidence of 1:591 for all IEM including small and large molecule subtypes (34) and 1:1043 for all disorders included in newborn screening. Propionic acidaemia has the highest incidence rate, at 1:14,000, of all specific IEM disorders in Saudi Arabia (35). However, non-metabolic disorders are also very common; Table 1 lists all commonly observed genes and variants linked to disorders in descending frequency.

As many clinical geneticists have observed, there can be wide differences in the type and prevalence of genetic diseases in Saudi Arabia in comparison with the rest of the world. For example, whilst phenylalanine hydroxylase deficiency is by far the most common form of phenylketonuria in the Caucasian population, the 6-pyruvoyl tetrahydrobiopterin synthase (PTPS) deficiency is fairly common in Saudi Arabia (36) due to a *PTPS* founder variant in one large tribe in the country. Another disorder that is common due to high carrier frequency is biotin-responsive encephalopathy, which was mapped to *SLC19A3* in Saudi families (37). Among other "rare variants," are

Table 1: List of most common disease-causing variants and corresponding genes in Saudi population.

GENE	VARIANTS
HBB	c.20A>T:p.E7V and c.118C>T:p.Q40X
ABCA4	c.1633_1634insGAAA:p.N545fs
ABCC2	c.2273G>T:p.G758V
ACADM	c.254C>T:p.T85I and c.362C>T:p.T121I and c.374C>T:p.T125I and c.104C>T:p.T35I and c.461C>T:p.T154I
ACADVL	c.65C>A:p.S22X and c.203C>A:p.S68 and c.134C>A:p.S45X
ADAT3	c.430G>A:p.V144M
AGPAT2	c.335delC:p.P112fs
ALG3	c.344G>A:p.R115Q and c.188G>A:p.R63Q and c.512G>A:p.R171Q and c.407G>A:p.R136Q and c.368G>A:p.R123Q
ALG8	c.104C>T:p.T35I
ANTXR2	c.134T>C:p.L45P and c.134T>C:p.L45P
ASNS	c.962G>A:p.R321H and c.62G>A:p.R321H and c.1148G>A:p.R383H
ATP7B	c.46T>C:p.S16P and c.1556T>C:p.F519S and c.2230T>C:p.S744P and c.2230T>C:p.S744P and c.1897T>C:p.S633P
ATP8B1	c.1594G>A:p.A532T
C12ORF57	c.1A>G:p.M1V
CANT1	c.906_907insGCGCC:p.S303fs
CC2D2A	c.2936delG:p.R979fs and c.3083delG:p.R1028fs
CFTR	c.416A>T:p.H139L
CFTR	c.1911delG:p.Q637fs and c.129delG:p.Q43fs
CFTR	c.3700A>G:p.I1234V and c.1918A>G:p.I640V
CRYBB1	c.171delG:p.G57fs
CTSC	c.815G>C:p.R272P and c.371G>C:p.R124P
CYP1B1	c.182G>A:p.G61E
CYP1B1	c.1405C>T:p.R469W
CYP21A2	c.760A>G:p.M254V and c.850A>G:p.M284V
CYP2U1	c.947A>T:p.D316V and c.320A>T:p.D107V
DBT	c.360delA:p.K120fs
DCAF17	c.436delC:p.L146fs and c.436delC:p.L146fs
DHCR7	c.1A>G:p.M1V
DPYD	c.257C>T:p.P86L
DYNC2H1	c.6035C>T:p.A2012V
EPCAM	c.499dupC:p.L166fs
FAM98C	844C>T:p.R282X

FKRP	c.941C>T:p.T314M
FYCO1	c.449T>C:p.I150T
G6PD	c.653C>T:p.S218F and c.563C>T:p.S188F
G6PD	c.233T>C:p.I78T and c.143T>C:p.I48T
GEMIN4	c.2452T>C:p.W818R
GPR179	c.349G>A:p.D117N
GUSB	c.991C>T:p.R331W and c.1429C>T:p.R477W
IRAK4	c.451delT:p.S151fs and c.823delT:p.S275fs
ISCA2	c.229G>A:p.G77S
KCNV2	c.427G>T:p.E143X
LAMC3	c.1931_1932insT:p.S644fs
MC4R	c.485C>T:p.T162I
MYO18B	c.854C>A:p.S285X and c.5444C>A:p.S1815X and c.4367C>A:p.S1456X and c.6548C>A:p.S2183X and c.6551C>A:p.S2184X and c.6545C>A:p.S2182X and c.6905C>A:p.S2302X
NPHP4	c.673G>T:p.G225C
NR2E3	c.932G>A:p.R311Q
OTOF	c.1565G>A:p.R522H and c.3305G>A:p.R1102H and and c.3074G>A:p.R1025H,OTOF and c.5375G>A:p.R1792H
PEX5	c.1467T>G:p.N489K and c.1554T>G:p.N518K and c.1578T>G:p.N526K and c.1623T>G:p.N541K and c.1641T>G:p.N547K and c.1578T>G:p.N526K
PKHD1	c.4870C>T:p.R1624W
PLCE1	c.2134C>T:p.Q712X and c.3058C>T:p.Q1020X
RGS9BP	c.330_342del:p.R110fs
RP1	c.606C>A:p.D202E
RP1L1	c.5959C>T:p.Q1987X
SLC26A3	c.559G>T:p.G187X and c.454G>T:p.G152X
SLC3A1	c.260T>A:p.M87K and c.566T>A:p.M189K and c.1400T>A:p.M467K
STXBP2	c.314C>T:p.P105L and c.1430C>T:p.P477L and c.1421C>T:p.P474L and c.1463C>T:p.P488L
TANGO2	c.94C>T:p.R32X and c.217C>T:p.R73X
TBCE	c.151_162del:p.51_54del
TMEM231; *CHST5*	c.223G>A:p.V75I and c.751G>A:p.V251I and c.316G>A:p.V106I and c.664G>A:p.V222I
TULP1	c.742C>T:p.Q248X and c.901C>T:p.Q301X and c.898C>T:p.Q300X
TYR	c.230G>A:p.R77Q
TYRP1	c.1557T>G:p.Y519X
WDR19	c.1568G>TA44:C65:p.S523I and c.2297G>T:p.S766I and c.2777G>T:p.S926I

the transversion change c.722G>C p.Cys241Ser in PSAP which appears to be relatively more common in Saudi Arabia, causing sphingolipid activator protein B deficiency (38) as w well as CLN6 gene defects that lead to late infantile neuronal ceroid lipofuscinosis (39). Table 2 lists the most common metabolic disorders observed in Saudi population, in descending order.

Table 2: Diseases listed by decreasing incidence of the common metabolic disorders in Saudi Arabia with the corresponding OMIM number

Dubin-Johnson syndrome, 237500
Glycogen storage disease IIIa, 232400
Dihydropyrimidine dehydrogenase deficiency, 274270
Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency, 616277
Asparagine synthetase deficiency, 615574
Cystinuria, 220100
Wilson disease, 277900
VLCAD deficiency, 201475
Lipodystrophy, congenital generalized, type 1, 608594
Biotinidase deficiency, 253260
Cholestasis, benign recurrent intrahepatic, 243300
Acyl-CoA dehydrogenase, medium chain, deficiency of, 201450
Succinyl CoA:3-oxoacid CoA transferase deficiency, 245050
Congenital disorder of glycosylation, type Id, 601110
Congenital disorder of glycosylation, type Ih, 608104
Congenital disorder of glycosylation, type It, 614921
Smith-Lemli-Opitz syndrome, 270400
Propionic acidemia, 606054
Cholestasis, progressive familial intrahepatic 4, 615878
Multiple mitochondrial dysfunctions syndrome 4, 616370
3-Methylcrotonyl-CoA carboxylase 2 deficiency, 210210
Maple syrup urine disease, type II, 248600
Mucopolysaccharidosis Ih, 607014
Mucopolysaccharidosis VII, 253220
Peroxisome biogenesis disorder 2A (Zellweger), 214110
Gaucher disease, perinatal lethal, 608013
Niemann-Pick disease, type A, 257200
Crigler-Najjar syndrome, type I, 218800
Rhizomelic chondrodysplasia punctata, type 2, 222765
Combined oxidative phosphorylation deficiency 2, 610498
Myopathy due to myoadenylate deaminase deficiency, 615511
Chondrodysplasia punctata, X-linked recessive, 302950
Methylmalonic aciduria, mut(0) type, 251000
Hyperphenylalaninemia, non-PKU mild, 261600
Dihydrolipoamide dehydrogenase deficiency, 246900
Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation, 611105

Skeletal Dysplasia in Saudi Arabia

Most reported skeletal dysplasia disorders in Saudi Arabia are autosomal recessive. Their calculated incidence based on the carrier allele frequency is 1:397. Osteogenesis imperfecta (OI) is the most common skeletal dysplasia in Saudi Arabia (16%). Whilst OI is known to be an autosomal dominant disorder, autosomal recessive OI accounts for 64% of OI cases in Saudi Arabia, compared to the rest of the world, where 85% of cases are de novo disease-causing variants in collagen genes (40). Also, novel genes have been described in the Saudi population, which include *WNT3A, PAN2, RIN1* and *DIP2C*. Figure 3 shows the percentage of disorders classified as skeletal dysplasia identified in Saudi Arabia (41).

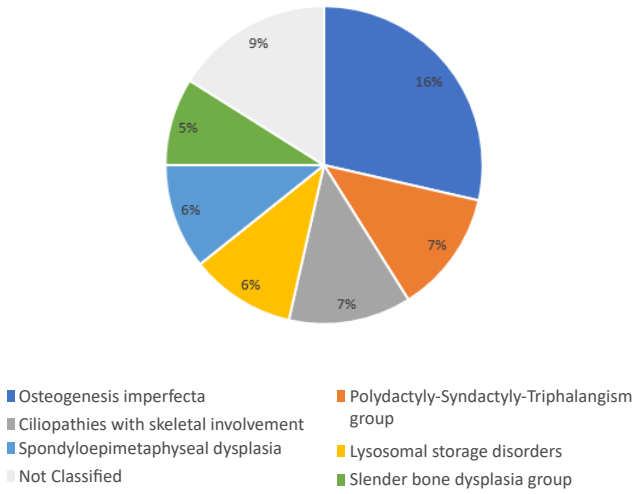

Figure 3: The percentage of skeletal dysplasia disorders identified in Saudi Arabia based on the International Skeletal Dysplasia Nosology classification.

Neurogenetic Genes in Saudi Arabia

Neurological disorders account for the largest category of Mendelian disorders in humans. Applying whole exome sequencing to patients with neurogenetic disorders from multiple consanguineous families and looking at regions of homozygosity using this approach lead to the discovery of 36 associated genes in the Saudi population that have not been previously reported *(SPDL1, TUBA3E, INO80, NID1, TSEN15, DMBX1, CLHC1,— C12orf4, WDR93, ST7, MATN4, SEC24D, PCDHB4, PTPN23, TAF6, TBCK, FAM177A1, KIAA1109, MTSS1L, XIRP1, KCTD3, CHAF1B, ARV1, ISCA2, PTRH2, GEMIN4, MYOCD, PDPR, DPH1, NUP107, TMEM92, EPB41L4A* and *FAM120AOS, DENND5A, NEMF and DNHD1)* (41, 42).

Microphthalmia

Regarding microphthalmia, or birth defects that lead to anatomic malformations of the eye, testing multiple affected Saudi patients led to the discovery of a landscape of genetic causes in the Saudi population, mainly associated with the posterior type. The reported causative genes for microphthalmia in the Saudi population are, in descending order of frequency: *PRSS56* (24%), *C12orf57, ALDH1A3* and *MFRP* (11%), *RAB3GAP1* (6%), *OTX2, PXDN* and *STRA6* (4%) and other genetic causes (24%) which occur at least in one single family (43).

Cholestatic Liver Disease

Progressive, familial intrahepatic cholestasis (PFIC) is the most common form of familial liver disorder in the Saudi population. Two genes are responsible for nearly half of all cases of PFIC: *ABCB11*, which causes PFIC2 (14, 44), and *ABCB4*, which causes PFIC3. Several other genes are linked to cholestatic liver diseases in the Saudi population, including TJP2, which typically causes familial hypercholanaemia and has rarely been reported to cause cholestatic liver disease; *UGT1A1*, which causes hereditary hyperbilirubinemias, and ATP7B, which causes Wilson's disease. The estimated carrier frequency of all cholestatic liver disease–causing variants in Saudi Arabia is 1:87, which translates to a minimum incidence of 1:7246 (44).

Retinal Dystrophies

The many causes of retinal dystrophies (RD) can be classified into syndromic and isolated, or non-syndromic. The major causes of RD in the Saudi population are isolated, non-syndromic retinitis pigmentosa (RP). In descending order of prevalence, the causative genes are: *ABCA4*, which causes Stargardt's disease 1 or juvenile macular degeneration; *TULP1*, which leads to retinitis pigmentosa 14; *MERTK*, which causes retinitis pigmentosa 38; *CRB1*, which causes retinitis pigmentosa 12; *RPE65*, which causes retinitis pigmentosa 20; *RPGRIP1*, which causes cone-rod dystrophy 13; *IMPG2*, which causes retinitis pigmentosa 56; *KCNV2*, which causes retinal cone dystrophy 3B; *NR2E3*, which causes retinitis pigmentosa 37 and *RP1*, which causes retinitis pigmentosa.

The most common causes of syndromic, non-isolated RP in the Saudi population are *ALMS1*, which leads to Alstrom syndrome, as well as BBS2 and BBS4, which lead to Bardet-Biedl syndromes 2 and 4, respectively. Other novel candidate genes identified in the Saudi population as causing RP include *AGBL5*, *CDH16* and *DNAJC17* (45). Additionally, six novel candidate disease-causing genes were identified *(C21orf2*, *EMC1, KIAA1549, GPR125 ACBD5* and *DTHD1*), two of which *(ACBD5* and *DTHD1)* were observed in the context of syndromic forms of RD described for the first time (46).

Congenital Glaucoma

CYP1B1 is the major cause of congenital glaucoma in the Saudi population, with two disease-causing variants, c.182G>A;p.(Gly61Glu) and c.1405C>T ; p.(Arg469Trp), accounting for more than 86% of all identified cases (47).

Familial Congenital Hydrocephalus

Whilst the most common cause of familial congenital hydrocephalus worldwide is the X-linked *L1CAM*, this gene is not commonly encountered in the Saudi population, perhaps due to overrepresentation of autosomal recessive disorders. Two genes account for most cases of familial congenital hydrocephalus in the Saudi population: *POMT1*, which causes muscular dystrophy-dystroglycanopathy normally present with significant elevation in serum creatine kinase, and MPDZ, which causes non-syndromic autosomal recessive hydrocephalus 2 (48). Furthermore, ciliopathies account for a considerable part of congenital hydrocephalus.

Ciliopathies

Some ciliopathies in the Saudi population are secondary to Bardet-Biedl syndromes, which account for around 30% of cases, followed by Meckel syndrome, which accounts for 24%, Joubert syndrome, which accounts for 17%, and short-rib thoracic dysplasia, which accounts for 7% of cases. Several genes, reported as novel candidate genes in the Saudi population, are shown in Figure 4 (49).

Cataract

Cataracts are divided into syndromic or isolated forms. *CRYBB1* is the leading cause of autosomal recessive type 3 cataract 17 in the Saudi population,

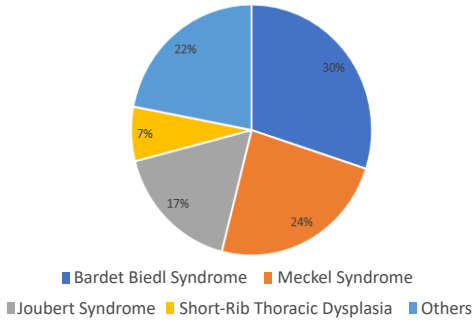

Figure 4: Distribution of the aetiology of ciliopathies in the Saudi population.

accounting for 18% of all identified cases. *LONP1* causes cerebral, ocular, dental, auricular and skeletal anomalies (CODAS), accounting for 9% of identified cases. *GEMIN4*, linked to neurodevelopmental disorder with microcephaly, cataracts and renal abnormalities, accounts for 7%. Each single gene of *CYP51A1, EPHA2, FYCO1*, *GCNT2*, *RIC1* and *SIL1* accounts for around 4% (Figure 5). Two genes were reported as novel candidate genes for cataracts, *TAF1A* (cataract with global developmental delay) and WDR87 (non-syndromic cataract), along with a founder variant in *RIC1* c.3794G>C p.(Arg1265Pro), that causes global developmental delay, microcephaly and brain atrophy with or without cleft lip and palate (50).

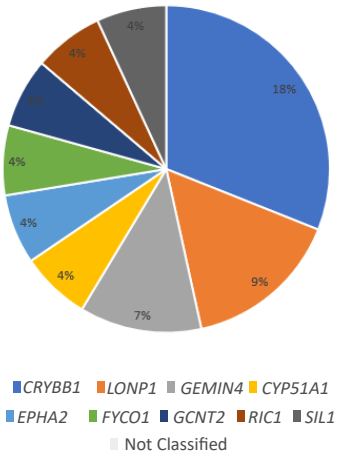

Figure 5: Distribution of the most common genes causing cataracts in the Saudi population.

Microcephaly

Microcephaly primary hereditary (MCPH) or autosomal recessive primary microcephaly is another common disorder in Saudi Arabia. Disease-causing variants were encountered in 10 genes *(MCPH1, WDR62, CDK5RAP2, ASPM, STIL, CEP135, CEP152, CENPJ, CIT, MFSD2A)* out of around 18 genes which are known to cause MCPH. These variants account for 24% of all cases

with microcephaly in Saudi population. Apart from these known MCPH genes, other genes with established phenotypes (60%) and novel or candidate genes (16%) have also been shown to cause microcephaly in the Saudi population (Alkuraya, unpublished data).

Prenatal Genetics and Prevention Genetics

Prenatal genetic testing in Saudi Arabia is constrained by ethical and cultural beliefs, in addition to Islamic law. Although many prenatal services are available across the country, the clinical utility and the impact of prenatal diagnostic modality is inadequate either due to limited availability of prenatal testing around the country or to extended turnaround time to obtain the diagnostics results. However, recent years have seen growth in chorionic villus sampling and amniocentesis, as well as non-invasive prenatal screening (NIPS or NIPT).

Pre-implantation Genetic Diagnostic (PGD) services in Saudi Arabia are not available today except in few governmental and private centres. Normally, such services are performed primarily for carriers of chromosomal structural changes, such as translocations, or those of monogenic diseases. Even though PGD offers efficient and precise results for such cases there are still many social, financial and cultural limitations in Saudi Arabia. Around 45% of couples opt for early prenatal diagnosis, compared to 35% who choose PGD (33). PGD provides an ideal solution to the challenge of terminating a pregnancy, which is constrained by Islamic law.

NIPS is also available in the country; however, there are no clear guidelines available regarding whom to test and what to test for.

Congenital and genetic disorders are responsible for a major proportion of infant mortality, morbidity and disability in Arab countries (51). Public health measures, albeit insufficient, are directed at the prevention of congenital and genetic disorders, and are coupled with inadequate health care before and during pregnancy. Services for the prevention and control of genetic disorders are restricted by certain cultural, legal and religious limitations. All of this leads to the high incidence of physically disabled children in Arab countries. Since most genetic disorders have no treatment yet, preventing severe outcomes is one of the main goals of genetics. Any treatment or procedure that could harm the foetus or mother should be avoided. The goals of prevention are to lower the incidence of genetic disorders, prevent the burdens of a chronic illness on families and the community, and minimize the economic impact of genetic disorders, which can be highly costly in terms of management and treatment. Genetic disorders can be prevented in many ways. For example, Saudi Arabia implemented premarital screening for haemoglobinopathies (thalassaemia and sickle cell disease) which is mandatory to perform. However, the decision to act based on its outcome is left for the couple to make. Also, carrier testing for well-known familial variants is available at many governmental or private laboratories. Recently, some laboratories and hospitals have started offering whole exome sequencing as a method to test for the carrier status of any lethal or chronic genetic disorder, meant primarily for consanguineous couples. Genetic counselling services are in very short supply in Saudi Arabia considering the population size. One paper estimating the impact of premarital screening on the incidence of the two haemoglobinopathies demonstrated a reduction in thalassaemia, but no change in the incidence of sickle cell disease (1).

Ethical Considerations

Saudi Arabia follows Islamic law. Fatwa number 4 of the Islamic Fiqh council of the Islamic World League, Makkah Al Mukaramah, at its 12th session (Makkah, 10–17 February 1990) contemplates the option of abortion under certain, specific conditions. Islamic bioethics emphasizes the importance of preventing illness, and any measure to prevent mental handicap in children is highly recommended by Islamic jurists (52). The *fatwa* determined that an abortion may take place only if a committee of three specialized, competent physicians has decided the foetus is grossly malformed and that its life would be a calamity for both the family and itself. The malformation must be untreatable, unmanageable and very serious, and the abortion may only be performed prior to the 120th day after conception (computed from the date of fertilization, not the last menstrual cycle) (52). Beyond 120 days, considered to be after ensoulment, abortion is only allowed if there is a danger threatening the mother's life, not her health. On the basis of this *fatwa*, abortions of foetuses with serious congenital diseases are performed in Saudi hospitals.

Adoption is not acceptable in Islamic law, though fostering children is allowed; the lineage of the child must persist to his or her natural parents. Advances in feto-maternal medicine and in vitro fertilization have led to new applications, like sperm, ovum or pre-embryo donation and other interventions. All of these practices are unacceptable in the view of Islamic teachings, which recognize procreation only within the bounds of husband and wife and exclude any third party from the process. Furthermore, no procreation is allowed after the death of a spouse or in the event of a divorce.

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