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Full Length Research Paper

Spotlight into some Abnormalities of Human Chromosome in Saudi Arabia

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Middle Eastern cultures are tribal and heavily consanguineous. Marriage between cousins has been part of the culture for millennia leading to "founder" effect and a large number of genetic diseases. Chromosomal abnormalities are the results of alterations in the number or structure of chromosomes causing significant human morbidity and mortality. They are responsible for a large proportion of miscarriages, developmental delay, and disorders of sexual development, congenital malformations and mental retardation. The aim of this study is to screen some of these frequent observed common chromosomal disorders and try to identify the significant reason behind the increase or present of these diseases in our community. Data collection and survey study into different local hospital in Riyadh and cytogenetic lab with a variety of clinical disorders; Down syndrome (DS), Turner's syndrome (TS) and Klinefelter syndrome; amenorrhea; ambiguous sex and multiple congenital malformations. The most common autosomal abnormalities were DS. Numerical abnormalities were accounted for 353 (41.0%) and structural abnormalities 18 (2.0%), respectively. Various other chromosomal anomalies were also reported. We have reviewed the incidence and distribution of chromosomal abnormalities and found higher rate of chromosomal abnormalities 43.1% in the referred cases. Our data suggest that chromosomal analysis is important tool in the evaluation of genetic disorders but lack of genetic counseling did not help to understand the high frequency of such rare genetic disorder in our community.

Keywords: Aneuploidy, Autosomes, Cytogenetic analysis, Karyotypes, Sex chromosomes

INTRODUCTION

Middle Eastern cultures are tribal and heavily consanguineous. Marriage between cousins has been part of the culture for millennia leading to "founder" effect and a large number of genetic diseases.

In Saudi Arabia like other Middle East countries first cousin marriages account for 60 -70% of all marriages, leading to uniquely common disorders which are either rare by Western standards or are unknown. The practicing physician must include these unusual disorders in his diagnostic considerations, since cybernetic trees described for European countries or USA may not be valid for the Middle East.

Many disorders have been first described/mapped in Saudi patients . Other disorders are known to exist elsewhere but are particularly common in Saudi Arabia . For some, this can easily be explained by the disease's high degree of genetic heterogeneity such that consanguinity can be an important catalyst in unmasking the recessiveness of numerous potential mutations across many loci, for example, ciliopathies, retinal dystrophies, and deafness. For others, a strong founder effect can be invoked as in many inborn errors of metabolism (1.5 in 1000 newborns are diagnosed with a metabolic disease in the Saudi newborn program) and congenital glaucoma. Geographic variation in the incidence of diseases has been suggested by some but the mobility of the population lessens the practical utility of this map especially when one considers that the geographic variation falls largely along tribal lines, which suggests that knowledge about the tribal origin can be more helpful clinically.

A study has been carried out in Riyadh to determine the incidence and distribution of Down's syndrome births during a 9-year period from July 1982 to June 1991. Down's syndrome was ascertained in 42 (23 females and 19 males) of 23,261 consecutive babies born alive to Saudi women, giving an incidence of 1 in 554 live births (1.8 per 1,000). A trend towards an increased incidence of Down's syndrome with advanced maternal age or increased maternal parity was found. Cytogenetic studies were performed on 37 cases of which all but 1 were non-disjunction trisomy 21, while the remaining infant had a translocation. This study provides the first step for further epidemiological surveys of Down's syndrome in the Kingdom of Saudi Arabia in order to prepare the ground for an effective antenatal screening program for chromosomal disorders.

Saudis in general favor a strong contribution of Government to their life in return for its control over the country's vast natural resources. The public healthcare system is mostly under the governance of the Ministry of Health (MOH) and consists of 2259 primary care centers, and 259 hospitals. The doctor/population ratio and hospital/population ratios at 24.4/10,000 and 20.7/10,000, respectively, are below that of many developed countries but newer plans have been revealed to improve this ratio. Law-enforcement personnel are entitled, in addition to MOH-run health care, to a large network of primary care centers and hospitals that are run by the Ministry of Interior. Similarly, military and National Guard personnel and their families enjoy the additional medical services that are administered by the respective agencies. The author's own institution (KFSHRC) is a general organization that is funded by the Government and offers highly specialized health care independent of MOH. The private sector consists of a vast network of private practices, usually in the form of polyclinics that fall under one administration, as well as secondary and tertiary hospitals. Although this sector represents the sole healthcare provider for noncitizens, many citizens also receive their healthcare in the private sector by choice, for example, to avoid a long wait-time in the public sector. This fragmentation of healthcare delivery has created a number of challenges towards the adoption of a national healthcare strategy equivalent to other countries with socialized medicine, for example, NHS in the UK. Mortality rate statistics are well below the global average but not yet on par with those of more developed countries. For example, mortality rate of children less than 5 is 12/1000 and maternal mortality is 7/100,000

births (global average is 44/1000 and 209.1/100,000, and Western Europe has an average of 3.9/1000 and 6.3/100,000, respectively) (Kassebaum *et al.,* 2014; Wang *et al.,* 2014). Life expectancy has also increased to 73.8 (compare to 80.3 years in Western Europe). This improvement in healthcare delivery has resulted in reduction in communicable diseases and brought non communicable diseases including genetic disorders to the forefront of national healthcare agenda.

Cytogenetic testing is widely available, usually in the form of traditional karyotyping and FISH analysis. Molecular karyotyping is only available in a few centers. The major molecular diagnostic laboratory is at KFSHRC (Saudi Diagnostic Laboratory or SDL), which tests for 66 single gene disorders. We are currently validating the "Mendeliome" assay, which uses new multiplexing methods to amplify ~3000 Mendelian genes known to cause human diseases followed by next-generation sequencing, on 3500 patients. Once validated, this test will be available for all patients with suspected genetic diseases as an intermediary test before considering whole-exome or whole-genome sequencing (details will be published elsewhere). Whole-exome and whole-genome sequencing are only available on research basis locally but SDL plans to launch these on clinical basis in the very near future.

In this study is as a part of the general project of the medical genetic unite to build up a genetic data base of genetic disorders, we reported the frequencies of number of chromosomal anomalies

MATERIAL AND METHODS

Data collection

Data were obtained from variant hospitals and cytogenetic labs who obtaining cytogenetic screening. Data collection interests of all participants were considered and balanced throughout this process, taking into considerations revising the bioethics bylaw. Through pilot testing with cognitive interview techniques, we refined the wording of certain questions, and added or deleted questions to improve the length and overall flow of the survey

Variables measured four broad domains: personal data (for example, ages, type of mirage, premarital examination); personal health (for example, family medical history, medical genetic status); familiarity with some genetic disorders , and we also personal interest for un-relative marriages.

Statistical analysis

We used descriptive statistics, which is the discipline of quantitatively describing the main features of a collection of information (Abu-Safieh *et al*., 2011), or the quantitative description itself. It is distinguished from inferential statistics (or inductive statistics), in that descriptive statistics aim to summarize a sample, rather than use the data to learn about the population that the sample of data is thought to represent. This generally means that descriptive statistics, unlike inferential statistics, are not developed on the basis of probability theory (Abu-Safieh *et al.,* 2013, Adly *et al.,* 2014). Even when a data analysis draws its main conclusions using inferential statistics, descriptive statistics are generally also presented. It also provides simple summaries about the sample and about the observations that have been made. Such summaries may be either quantitative, summary statistics or visual (Alangari *et al.,* 2012).

Bioinformatics

Bioinformatics is the application of computer technology to the management of biological information. Computers are used to gather, store, analyze and integrate biological and genetic information which can then be applied to gene-based drug discovery and development. The need for Bioinformatics capabilities has been precipitated by the explosion of publicly available genomic information resulting from the Human Genome Project.

RESULTS

Table 1. literature review, illustrate all Clinical conditions first described in Saudi Arabia:

Condition	Gene	Reference
Arthrogryposis, Perthes disease, and upward gaze palsy	*?*	
Retinal dystrophy with severe white matter changes	*ACBD5*	Abu-Safieh et al. (2013)
Weill–Marchesani-like syndrome	*ADAMTS17*	Morales et al. (2009)
Microcornea, myopic chorioretinal atrophy, and telecanthus (MMCAT)	*ADAMTS18*	Aldahmesh et al. (2013b)
Intellectual disability-strabismus syndrome	*ADAT3*	Alazami et al. (2013)
AGK-related cataract	*AGK*	Aldahmesh et al. (2012a)
Hypopituitarism, microcephaly, and visual and renal anomalies	*ARNT2*	Webb et al. (2013)
BRCA2-related primordial dwarfism	*BRCA2*	Shaheen et al. (2014a)
Microphthalmia-dysgenesis of corpus callosum-epilepsy	*C12orf57*	Zahrani et al. (2013)
C21orf2-related retinal dystrophy	*C21orf2*	Abu-Safieh et al. (2013)
Woodhouse–Sakati syndrome	*C2orf37*	Alazami et al. (2008)
Cognitive impairment, dysmorphicfacies and skeletal abnormalities syndrome	*CACNA1G*	Al-Owain et al. (2011)
CENPJ-related Seckel syndrome	*CENPJ*	Al-Dosari et al. (2010)
Intellectual disability-hypohidrosis syndrome	*COG6*	Shaheen et al. (2013a)
COLEC11-related Malpuech syndrome	*COLEC11*	Rooryck et al. (2011)
CRIPT-related primordial dwarfism	*CRIPT*	Shaheen et al. (2014a)
CSPP1-related Meckel–Gruber syndrome	*CSPP1*	Shaheen et al. (2014b)
Lethal familial hyperekplexia-brain malformation syndrome	*CTSD*	Seidahmed et al. (2012)
Myopia with dysmorphism	*CTSH*	Aldahmesh et al. (2013a)
CYP51A1-related cataract	*CYP51A1*	Aldahmesh et al. (2012b)
DDX59-related oral-facial-digital syndrome	*DDX59*	Shamseldin et al. (2013)
DNA2-related Seckel syndrome	*DNA2*	Shaheen et al. (2014a)
DNASE1L3-related SLE	*DNASE1L3*	Al-Mayouf et al. (2011)
DOCK6-related Adams-Oliver syndrome	*DOCK6*	Shaheen et al. (2011a)
Retinal dystrophy with myopathy	*DTHD1*	Abu-Safieh et al. (2013)
Ichthyosis, spastic quadriplegia, and mental retardation	*ELOVL4*	Aldahmesh et al. (2011a)
EMC1-related retinal dystrophy	*EMC1*	Abu-Safieh et al. (2013)
EOGT-related Adams-Oliver syndrome	*EOGT*	Shaheen et al. (2013b)
Pellagra-like syndrome	*ERCC5*	Hijazi et al. (2013)
ERLIN2-related complex hereditary spastic paraplegia	*ERLIN2*	Alazami et al. (2011)
EVC2-related Meckel–Gruber syndrome	*EVC2*	Shaheen et al. (2012a)
FARS2-related mitochondrial encephalomyopathy	*FARS2*	Shamseldin et al. (2012a)
FBXL4-related mitochondrial encephalomyopathy	*FBXL4*	Gai et al. (2013)
Bruck syndrome 1	*FKBP10*	Shaheen et al. (2010)
G6PC3-related cyclic neutropenia	*G6PC3*	Alangari et al. (2013)
GPR125-related retinal dystrophy	*GPR125*	Abu-Safieh et al. (2013)
IFT27-related Bardet–Biedl syndrome	*IFT27*	Aldahmesh et al. (2014)
Familial retinal artery macroaneurysm	*IGFBP7*	Abu-Safieh et al. (2011)
Congenital hyperinsulinemia with rhabdomyolysis	*KCNJ11*	Albaqumi et al. (2014)
KIAA1549-related retinal dystrophy	*KIAA1549*	Abu-Safieh et al. (2013)
KLHL41-related myopathy	*KLHL41*	Gupta et al. (2013)
Facial dysmorphism with severe growth deficiency	*LARP7*	Alazami et al. (2012)
LRBA-related Crohn's disease with immunodeficiency	*LRBA*	Alangari et al. (2012)
LRPAP1-related myopia	*LRPAP1*	Aldahmesh et al. (2013a)
MEOX1-related Klippel–Feil syndrome	*MEOX1*	Mohamed et al. (2013)
METTL23-related intellectual disability	*METTL23*	Reiff et al. (2014)
MFF-related mitochondrial encephalomyopathy	*MFF*	Shamseldin et al. (2012a)
MMP2-related multicentricosteolysis	*MMP2*	Al-Aqeel (2005)

Table 1continue

MPDZ-related hydrocephalus	*MPDZ*	Al-Dosari et al. (2013)
MRI1-related infantile epilepsy with severe cystic degeneration of the brain	*MRI1*	Sunker and Alkuraya (2013)
Bone marrow failure with facial dysmorphsim	*MYSM1*	Alsultan et al. (2013)
NECAP1-related early infantile epileptic encephalopathy	*NECAP1*	Alazami et al. (2014a)
ODZ3-related microphthalmia	*ODZ3*	Aldahmesh et al. (2012c)
OPLAH-related oxoprolinurai	*OPLAH*	Almaghlouth et al. (2012)
PHC1-related microcephaly	*PHC1*	Awad et al. (2013)
PHGDH-related Neu-Laxova syndrome	*PHGDH*	Shaheen et al. (2014c)
PITX3-related microphthalmia	*PITX3*	Aldahmesh et al. (2011b)
POC1A-related primordial dwarfism	*POC1A*	Shaheen et al. (2012b)
RAB33B-related Smith–McCort dysplasia	*RAB33B*	Alshammari et al. (2012)
CMT-microcephaly-syndactyly-intellectual disability	*SBF1*	Alazami et al. (2014b))
SCLT1-related oral-facial-digital syndrome	*SCLT1*	Adly et al. (2014)
SEC8-related Meckel–Gruber syndrome	*SEC8*	Shaheen et al. (2012a)
SIX6-related autosomal recessive microphthalmia	*SIX6*	Aldahmesh et al. (2013c)
TBC1D32-related oral-facial-digital syndrome	*TBC1D32*	Adly et al. (2014)
Congenital hypoparathyroidism, severe growth failure, and dysmorphicfacies	*TBCE*	Sanjad et al. (1991)
TCTN2-related Meckel–Gruber syndrome	*TCTN2*	Shaheen et al. (2011b)
TMEM231-related Meckel–Gruber syndrome	*TMEM231*	Shaheen et al. (2013c)
TMEM38-related osteogenesisimperfecta	*TMEM38B*	Shaheen et al. (2012c)
Osteogenesisimperfecta with profound neurological impairment	*WNT1*	Faqeih et al. (2013)
XRCC2-related Fanconi anemia	*XRCC2*	Shamseldin et al. (2012b)
XRCC4-related primordial dwarfism	*XRCC4*	Shaheen et al. (2014a)

Table 2. These illustrate types and number of cases gathered for cytogenetic screening for the last five years.

Chromosomal Abnormalities		**Total number of cases / year**					
		2012	2013	2014	2015	2016	Total
Numerical							
	Down syndrome	17	16	17	15	15	
	Patau syndrome	0	0	0	1	0	
	Edward syndrome	1	1	1	1	1	
	Turner syndrom	1	1	0	2	0	
	Klinefeltersyndrom	2	0	1	0	1	
Structural							
	karyotype: 46.XX.inv(9)(p12q13)	1					
	karyotype : 46X.i(x)(q10)	1					
	karyotype: 46.XX.t(11;22)(q23.3;q11.2)	1					
	Karyotype: 46, XY, t(7;10)(q31.3;p15)		1				
	Karyotype: 47, XY, +mar		1				
	Karyotype: 46XY, dup(15)(q13q15)		1				
	Karyotype: 46XY, del(q11.2;q13.2)		1				
	Karyotype: 46XX,t (11;22) (q23.3;q11.2)			1			
	Karyotype: 46,XY,der(a4;21)q10;q10)+21			1			
	Karyotype: 46XX,t(11;22)(q23.3;q11.2)			1			
	Karyotype: 46,XY,t(7;17)(q22;p13)			1			
	Karyotype: 45,X/46,i(x)(q10)				2		
	Karyotype: 46,XX,der(14;21)(q10;q10)+21				1		
	Karyotype: 46,XY,der(21,21)(q10;q10)					1	

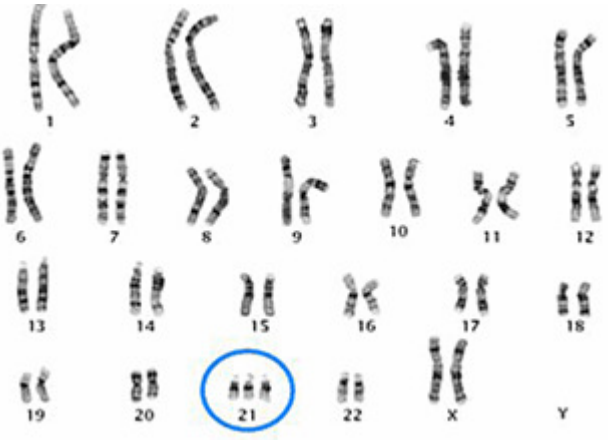

Figure 1. Down syndrome

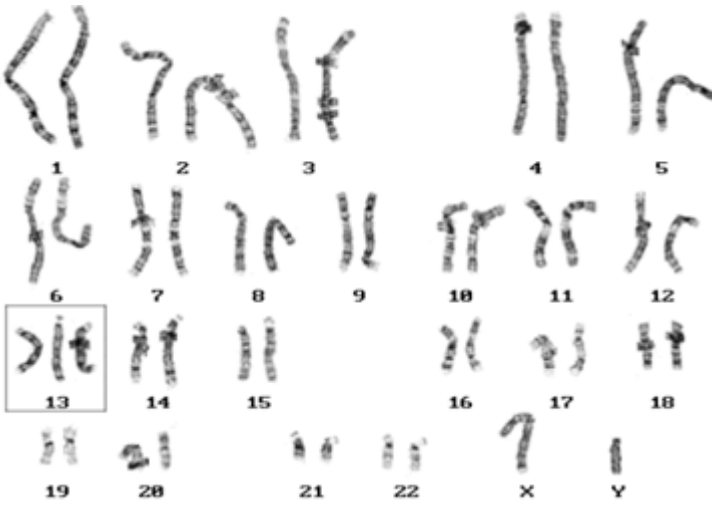

Figure 2. Patau syndrome

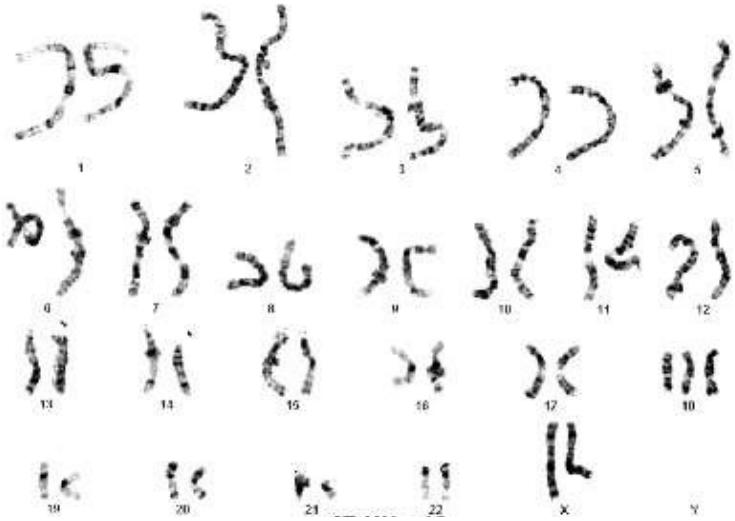

Figure 3: Edward syndrome

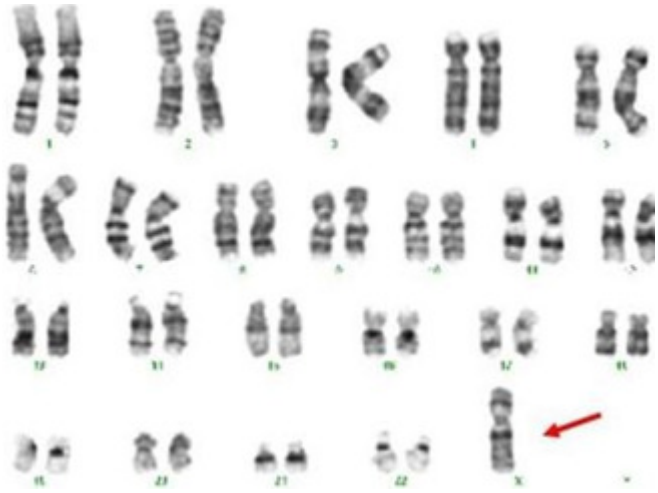

Figure 4. Turner syndrome

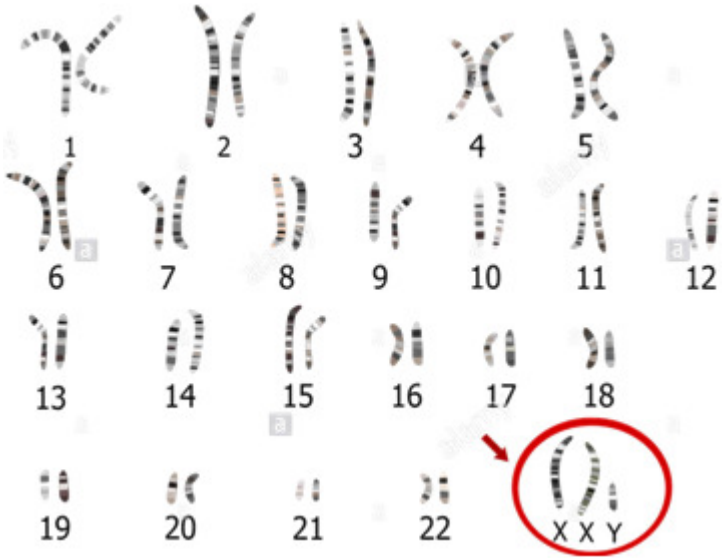

Figure 5. Klinefelter syndrome

DISCUSSION

Cytogenetic testing is widely available, usually in the form of traditional karyotyping and FISH analysis. Molecular karyotyping is only available in a few centers. The first Saudi national newborn screening program was for congenital hypothyroidism and was established in November 1989 (Al-Jurayyan *et al.,* 1996). The pioneering work of the Tandem Spectrometry Lab at KFSHRC on the use of electrospray in the implementation of tandem spectrometry in the analysis of various metabolites in body fluids is noteworthy. It has set the stage for the first implementation of computer-assisted algorithm in the simultaneous estimation of many metabolites and flagging of abnormal results, the basis of today's newborn screening around the world (Rashed *et al.,* 1994, 1995, 1997, 1999). Owing to this history, KFSHRC has a long tradition in performing newborn screening for 16 different inborn errors of metabolism, which evolved into a pilot program starting in 2004 to screen newborns from participating hospitals around the country. More recently, the MOH has assumed full responsibility of newborn screening, which is now performed as a national program. There are no national guidelines on newborn screening for deafness, which is left to the discretion of the individual hospitals.

While the newborn screening program was widely accepted, the premarital screening program was more

controversial. After considerable deliberation, a law was passed in 2002 that mandates screening for hemoglobinopathies, thalassemias, and G6PDH deficiency prior to issuing a marriage contract. Aside from the controversy surrounding the issue of autonomy, the program delivered sobering results after its establishment with nearly 90% of "incompatible" couples moving ahead with their marriage plans (the law explicitly allows couples to exercise freedom of choice upon learning their results) (AlHamdan *et al.,* 2007). This was clearly the result of inadequate pre- and posttest counseling. Indeed, major developments in the program to address these deficiencies have significantly reduced the percentage of "incompatible" marriages to a national average of 40%, with marked regional variations (large cities such as Riyadh are nearing 20% whereas rural areas with strong tribal traditions continue to see a majority of "incompatible" couples moving ahead with marriage) (Memish and Saeedi, 2011) (Ayman Alsulaimani, pers. comm.). There is strong interest in expanding the premarital screening program to include all Mendelian disorders by utilizing the newly available and affordable next-generation sequencing tools, and local research is ongoing in order to provide empirical data on the practicality of this approach.

Prenatal genetics is largely practiced by maternal-fetal medicine specialists due to severe deficiency in the number of qualified clinical geneticists. Recent years have witnessed a tremendous growth in the demand for chorionic villous sampling and amniocentesis for the diagnosis of single gene disorders. At KFSHRC alone, the number of prenatal samples that are tested for single gene disorders has increased from 5 in 2004 to 250 in 2013. Therapeutic abortion is permitted by law if performed within 120 days from the time of fertilization in order to comply with the Islamic view of the timing of ensoulment (Alkuraya and Kilani, 2001). However, the approved indication for the procedure, which is "severe malformation", must be authorized by three attending-level physicians. The definition of "severe" is left to the discretion of the medical team after consulting with the family. For example, intellectual disability is a common indication for many therapeutic abortion procedures. Contrary to commonly held views, we have shown that early prenatal diagnosis is the method of choice for couples who had one or more children with single gene disorders, as long as they are provided with a culturally sensitive genetic counseling that addresses their religious and cultural concerns (Alkuraya and Kilani, 2001). Nearly 45% of these couples opt for early prenatal diagnosis compared to 35% who choose preimplantation genetic diagnosis (PGD) (Alkuraya *et al.,* 2013). PGD is available freely at KFSHRC but is also provided by the private sector. Noninvasive prenatal screening using cell-free fetal DNA in maternal blood is quickly becoming integrated in prenatal care. KFSHRC offers this test routinely to all pregnant women regardless of their perceived risk and the MOH is considering making this test available throughout its vast network of hospitals and medical centers.

Not surprisingly, the high rate of consanguinity has greatly impacted the landscape of genetic disorders in Saudi Arabia and a quick search for published genetic diagnoses from Saudi Arabia readily reveals the clear bias toward autosomal recessive disorders. There are important practical implications of the role consanguinity plays in shaping the genetics of Mendelian diseases in Saudi Arabia. For recessive disorders, consanguinity favors homozygosity over compound heterozygosity, especially for less common conditions, and this is reflected in the finding that the overwhelming majority of recessive mutations identified in Saudi diagnostic laboratories are homozygous, a pattern that is echoed by published studies from Saudi Arabia (Alkuraya, 2010a). This phenomenon can easily be leveraged in the area of diagnostics such that an inexpensive genome-wide homozygosity scan can greatly aid in the diagnostic work up as shown in detail elsewhere (Alkuraya, 2010b). For example, examining the genes within the homozygous intervals can easily help the clinician to either confirm or reconsider an uncertain clinical diagnosis. This can also help guide the sequencing effort when a disorder is genetically heterogeneous, especially when the mutation is not readily detectable, for example, deep intronic, where prioritizing a particular gene can make more involved tests, for example, RTPCR, more justifiable. One could argue that this is less relevant now with the availability of whole-exome sequencing. However, a homozygosity scan can greatly reduce the number of candidate variants as we have shown in many instances (Alkuraya, 2013b). That consanguinity can render homozygous DNA variants that arose as recently as two generations ago (in the case of first cousin union) makes it possible for private mutations to be over represented and for allelic heterogeneity to be common as we have shown previously (Aldahmesh *et al.,* 2009). This has important implications, in that screening approaches that rely on common mutations are unlikely to be effective in Saudi Arabia, hence the push for sequencing-based approaches (Kaya *et al.,* 2011). Interestingly, this level of homozygosity has the potential to reveal unusual patterns of inheritance. In addition to pseudodominance inheritance, which is seen not infrequently, classical dominant disorders may assume a recessive pattern of inheritance, for example, we have a case of Treacher-Collins syndrome caused by a homozygous truncating mutation in *TCOF1* while the heterozygous parents were completely unaffected (unpublished). Alternatively, the same gene that is known to cause a particular phenotype in the heterozygous state may result in a novel phenotype in the homozygous state as we have shown for *ELOVL4* (Aldahmesh *et al.,* 2011a).

Similar to the practice of clinical genetics elsewhere, syndromic and nonsyndromic forms of intellectual

disability and developmental delay account for the majority of referrals to pediatric genetic services in Saudi Arabia. Our unpublished data clearly show that the majority of these cases have an underlying recessive cause of their disability, which is in clear contrast to outbred populations where recent studies on the utility of whole-exome sequencing revealed little or no contribution of recessive mutations (de Ligt *et al.,* 2012; Rauch *et al.,* 2012).

Many disorders have been first described/mapped in Saudi patients (Table (Table1).1). Other disorders are known to exist elsewhere but are particularly common in Saudi Arabia (Table (Table2).2). For some, this can easily be explained by the disease's high degree of genetic heterogeneity such that consanguinity can be an important catalyst in unmasking the recessiveness of numerous potential mutations across many loci, for example, ciliopathies, retinal dystrophies, and deafness. For others, a strong founder effect can be invoked as in many inborn errors of metabolism (1.5 in 1000 newborns are diagnosed with a metabolic disease in the Saudi newborn program) and congenital glaucoma. Geographic variation in the incidence of diseases has been suggested by some but the mobility of the population lessens the practical utility of this map especially when one considers that the geographic variation falls largely along tribal lines, which suggests that knowledge about the tribal origin can be more helpful clinically (Al-Owain *et al.,* 2012).

The high rate of consanguinity in Saudi Arabia has long been exploited to accelerate the annotation of recessive Mendelian genes and the recent years have witnessed a marked shift towards building infrastructure that permits this line of research to be performed locally. This trend has made a positive impact on the attitude of young Saudis to pursue careers in human genetics. But the study of rare recessive Mendelian disorders is only one of many opportunities that genomic research in Saudi Arabia has to offer. For example, identification of Mendelian forms of common diseases can provide novel insights into pathogenic mechanisms that could prove relevant to the common forms of these diseases (Al-Mayouf *et al.,* 2011; Alangari *et al.,* 2012; Aldahmesh *et al.,* 2013a). Beyond Mendelian disorders, genomic analysis of Saudis has proved to be a valuable resource to track nullizygous DNA segments and biallelically inactivated genes in nondiseased individuals (Khalak *et al.* 2012). Not only does this line of research have the potential to improve the annotation of the human genome in terms of its clinical relevance, but it can also identify novel druggable targets by identifying genes whose loss of function brings about desirable phenotypic traits as recently shown with *PCSK9* and *CCR5* (Lederman *et al.* 2006; Rader and Daugherty 2008). In addition, the lack of representation of Saudi genomes in international GWAS consortia presents an opportunity to identify potentially novel risk alleles for common diseases as shown recently with the identification of a novel risk allele for complications of HBV infection (Al-Qahtani *et al.,* 2013). A very recent study has shown the potential of genetically isolated societies to reveal novel risk alleles using a fraction of the usual study cohort size for a typical GWAS (Moltke *et al.,* 2014), and this should provide an additional impetus to explore the genetics of common diseases among Saudis.

In recognition of these opportunities, the Saudi Government has recently announced its plan to fund the sequencing of 100,000 Saudis as part of the newly launched Saudi Human Genome Project. The above lines of research and others will form the basis of selecting the 100,000 Saudis to be sequenced. For example, 10,000 healthy Saudis will have their genomes sequenced specifically in search of biallelically inactivated genes (Kaiser, 2014).

It is clear that Saudi Arabia has been and will continue to be an important resource in the study of Mendelian genes, and recent technological advances are diversifying the relevance of this resource to the various fields of genomic medicine. The time has never been more opportune for conducting genomic research in Saudi Arabia to empower Saudis to reap its promise of better health.

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