II An Overview of Medical Genetic Services in Saudi Arabia

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نبذة مختصرة

المملكة العربية السعودية هي أكبر دولة في الشرق الأوسط ويبلغ عدد سكانها أكثر من ٣٢ مليون نسمة. شهدت المملكة تطوراً ملحوظاً في نظام الرعاية الصحية على مدى العقود الفائتة، حيث أنها أصبحت تعد اليوم من بين أفضل الأنظمة الصحية حول العالم، وفقاً لمعايير منظمة الصحة العالمية. تعتبر جامعات المملكة العربية السعودية، كجامعة الملك سعود وجامعة الملك عبد العزيز على سبيل المثال، من بين أفضل الجامعات في آسيا والعالم العربي. وقد مكن استثمار المملكة في التعليم العالي والرعاية الصحية والبحث العلمي من إحراز تقدم كبير في جميع هذه المجالات. يلعب مجال علم الوراثة الطبية دوراً مركزياً في نظام الرعاية الصحية السعودي، حيث أن ارتفاع حجم الأسرة ونسبة زواج الأقارب تؤدي إلى وجود نسب مرتفعة من الاضطرابات الوراثية، مما يشكل عبئًا كبيرًا على المملكة. يلعب أخصائيو علم الوراثة في المملكة ذوو الكفاءة العالية، دوراً مهماً في إنشاء واستمرارية الخدمات الوراثية بما في ذلك التشخيص والبحوث والتدريب. حالياً، هناك حوالي ٤٠ طبيبا وراثيا و١٤ مستشاراً وراثياً ينشطون الآن، كما لا يزال آخرون طور التدريب حالياً في المملكة وخارجها. بالإضافة إلى ذلك، هناك العديد من علماء الوراثة الجزيئية والباحثين. في هذا الفصل، نستعرض بإيجاز الخدمات الوراثية المتاحة حاليًا المملكة العربية السعودية كالمرافق التشخيصية والعلاجية وبرامج الوقاية مثل فحص الأطفال حديثي الولادة، وفحص ما قبل الزواج. يتناول هذا الفصل أيضاً موضوع المشاركة السعودية في الأبحاث الدولية، وتحديد الجينات والطفرات الجينية الجديدة، وتوليد قواعد البيانات.

Abstract

The Kingdom of Saudi Arabia (KSA) is the largest country in the Middle East with a population of over 32 million. There has been a remarkable development of the healthcare system over the past decades bringing KSA to among the top 15% of health systems worldwide, according to the World Health Organization (1). KSA universities such as King Saud University and King Abdulaziz University rank among the top in Asia and the Arab World (2, 3). Investment in higher education, healthcare and scientific research enabled KSA to take large strides in all these areas. The field of medical genetics plays a central role in each of these since the large family sizes and high rates of consanguinity have caused genetic diseases to be a huge burden to the Kingdom. Highly trained Saudi geneticists have been crucial to the establishment and continuity of genetic services including diagnostics, research, training and advocacy. Currently, there are about 40 certified Saudi clinical geneticists and 14 genetic counselors in practice, with several more in training locally and abroad. In addition, there are many molecular geneticists and scientists. Within the limits of this chapter, we briefly review the currently available genetic services. These include clinical diagnostic, therapeutic facilities, prevention programs such as neonatal screening, premarital screening, and preimplantation genetic diagnosis. In addition, we consider the contribution to international research through impactful publications, identification of new genes and gene mutations and generation of variant polymorphism databases and variant screening panels.

Introduction

The Kingdom of Saudi Arabia (KSA) lies at the furthermost part of southwestern Asia. It is bordered by the Arabian Gulf, United Arab Emirates and Qatar in the east; Red Sea in the west; Kuwait, Iraq and Jordan in the north; Yemen and Oman in the south. It occupies about four-fifths of the Arab Peninsula, with a total area exceeding 2,000,000 square kilometers. The population at the time of writing is 32,552,336 individuals, two-thirds of whom are Saudi Nationals (4, 5). The Kingdom is divided into 13 administrative regions, namely: Riyadh, Makkah, Madinah, Al-Qaseem,

Eastern, Aseer, Tabouk, Hail, Northern Borders, Jizan, Najran, Al-Jouf, and Al-Baha (4). Riyadh is the capital city of Saudi Arabia. The Riyadh region has a population of over 7 million (4).

The 2030 vision was adopted as a methodology and roadmap for economic and developmental action in the KSA. It sought to identify the general directions, policies, goals, and objectives of the Kingdom. Genetic services will be affected positively through several of the Vision 2030 objectives such as offering a fulfilling healthy life by improving healthcare services, increasing employment by developing human capital in line with the labor market needs, improving university rankings, as well as enhancing governmental effectiveness via improvement of the quality of services provided to citizens (5).

Healthcare System Across the Kingdom

According to the World Health Organization's (WHO) ranking of the world's health systems for 2018, KSA ranks number 26 among 190 countries (1). The Ministry of Health (MOH) provides approximately 60% of healthcare services in KSA, free of charge. The private sector provides approximately 20% of services. The remainder is provided by various other entities such as university hospitals, tertiary referral centers and organizations that provide healthcare for staff and their families, including The National Guard, Armed forces, the Ministry of Interior, and Saudi Aramco (6-8).

Clinical genetic services in KSA consist of those provided by clinical and metabolic specialists, genetic counselors, and diagnostic laboratories, in addition to preventive and training programs. Several centers provide clinical, molecular and cytogenetic services as well as biochemical genetics. Clinical services also include preimplantation genetic diagnosis (PGD), genetic counseling, and human leukocyte antigen (HLA) and tissue typing. These services are mainly provided by government hospitals and research centers, as well as some private outpatient clinics (Figure 1).

In 1978, King Faisal Specialist Hospital and Research Center (KFSHRC) in Riyadh hired Dr. Nadia Sakati, the first clinical geneticist in KSA, and in 1985, recruited the late Prof. Pinar Ozand as a consultant in inborn errors of metabolism. Together, they established genetic services in KSA. Among their achievements was initiating a fellowship training program in clinical genetics. Early fellows graduating from this program received further training in the USA and became board certified. During Prof. Pinar's chairmanship of the research center genetic department, many top notch genetic services were initiated for the first time in KSA and the Gulf region. These included tandem mass spectrometry (TMS), PGD, microarray-based medical genomics, as well as transcriptomic and molecular cytogenetics approaches (9). The genetic services at KFSHRC continued to grow over time. The Medical Genetics Program, established in 2011, is the main tertiary referral center for genetic diseases in the Kingdom. Its many services include the Medical Genetics Support Center, Outreach Health Programs and the Enzyme Replacement Therapy (ERT) Relocation Program. The latter was designed to allow patients to be treated at their own home. The Medical Diagnostic lab provides advanced genetic testing including whole exome and whole genome sequencing (WES, WGS). Special areas of interest include immunogenetics and cancer genetics. In addition, KFSHRC has many other services that serve patients including bone marrow transplant and stem cell transplant. The research center has state of the art technology and highly trained personnel. It has received funding for many research projects that have led to the discovery of many novel genes with several quality publications (10-15).

King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, SA | King Abdulaziz University Hospital (KAUH), Jeddah,SA | Saudi Aramco Medical Services Hospital, Damam,SA

Figure 1: Examples of tertiary hospitals in different Saudi cities that offer genetic services.

Other hospitals in Riyadh providing genetic services include King Fahad National Guard Hospital (NGH) and its associated institutes: King Saud bin Abdulaziz University, King Abdulaziz Medical City and King Abdallah International Medical Research Center known (KAIMRC), Prince Sultan Military Medical City (PSMMC), King Fahad Medical City (KFMC), King Saud Medical City (KSMC), King Khalid University Hospital and the Princess Noura affiliated King Abdallah University hospital. These hospitals have medical genetic sections that serve under the respective pediatric departments. They are staffed by clinical geneticists and biochemical consultants. Some also have genetic counselors and qualified dieticians. They care for both inpatients and outpatients, including ERT patients. The KSMC is the regional premarital screening (PMS) clinic. The PSMMC has established a birth defect registry and provides some genetic laboratory testing locally including single nucleotide polymorphism (SNP) array comparative genomic hybridization (CGH), initiated in 2018. The NGH/KAIMRC have established a genetic database program called Majeen (see below) and have started to provide WES as a clinical diagnostic test.

Jeddah is the second largest city in Saudi Arabia after Riyadh and the biggest seaport in the Red Sea. It has a population of just over 4 million (4). King Abdulaziz University (KAU) serves the largest number of students in the Kingdom in a single institute (16). Genetic services at KAU include the Department of Genetic Medicine (GM) at the University Hospital of the Faculty of Medicine (Figure 1), the Center of Excellence in Genomic Medicine Research (CEGMR), the Princess Al-Jawhara Center of Excellence in Research of Hereditary Disorders (PACER-HD), the King Fahad Medical Research Center (KFMRC) and the Center of Innovation in Personalized Medicine (CIPM), in addition to several research groups of specific interests. The Department of GM carries out clinical and academic duties including daily general and specialized genetic clinics, undergraduate genetic curriculum for medical students, postgraduate clinical and laboratory training and master programs. The metabolic service at KAU is very active and provides neonatal screening (NNS), diagnostic and therapeutic care, as well as dietary services, and is among the ERT outreach centers in KSA. It receives referrals for protein dialysis and hemofiltration provided by the nephrology service. The CEGMR provides diagnostic genetic laboratory services for the KAU hospital and other centers in the region, and does research mainly on genomics of cancers, neurodegenerative disorders, deafness and thrombophilia (17-19). The PACER-HD identifies novel mutations and utilizes structural bioinformatics and induced pluripotent stem cells for the study of various disorders, mainly cardiac, complex gastrointestinal diseases, pediatric syndromes and certain common gynecological conditions (20-24). The CIPM works to provide PGD as well as personalized medicine treatments. Collectively, the centers at KAU have hundreds of personnel, state-of-the art infrastructure, a strong skill base in cutting edge technologies and effective collaborations both within the Kingdom and with leading scientists and centers across the world.

MOH services in Jeddah include genetic clinics at the Maternity and Children Hospitals, the national NNS and PMS programs and general services for affected patients. The NGH in Jeddah has two clinical geneticists who run the clinical and metabolic services (including NNS) and have access to diagnostic laboratory services. The Jeddah Armed Forces Hospital (AFH) has a well-established genetic service run by certified clinical geneticists, with access to advanced laboratory testing. It screens for 16 metabolic disorders. In addition, there are several private labs in Jeddah that provide genetic diagnostic services of all types.

In the Eastern Province, the Dammam Specialist Hospital established a clinical genetic department staffed by clinicians and genetic counselors. It specializes in cancer genetics, especially colon cancer and breast cancer. They have a special interest in epilepsy genetics and developing screen panels. They perform basic genetic testing locally and have access to specialized testing. The MOH in the Eastern Province has clinical geneticists working in the pediatric departments in Dammam, Al-Ihsa and Al-Qateef Central Hospital. The University Hospital clinicians have access to clinical genetic testing in Riyadh.

The Dhahran Aramco Facility (Figure 1) focuses on the diagnosis of pediatric syndromes and chromosomal disorders. It has access to advanced clinical and laboratory diagnostic and treatment services. The facility is affiliated with Johns Hopkins Hospitals and has ongoing research collaborations.

Genetic research in the Eastern region focuses mainly on single gene and rare diseases affecting the local population. The high consanguinity rates in this region, especially in the rural areas, resulted

in the identification of many new rare diseases. Geneticists in this region collaborate with other research teams in KSA and elsewhere to identify causal gene mutations for prevalent disorders.

In Makkah, the medical genetics department at Umm Al-Qura University was established in 2006. There are several molecular genetic scientists. Researchers affiliated to Umm Al-Qura University work on various disorders including familial unknown rare syndromes, Familial Hypercholesterolemia (FH), polycystic kidney disease, and others (25-28). The department has provided scholarships for overseas training for several of their residents, some of whom have now returned as certified clinical geneticists. They work closely with other hospitals and have training in various subspecialties including metabolic genetics and oncogenetics. The MOH geneticists in Makkah work under the pediatric department and have strong collaborations with several research centers across the country. The Western region NNS program is led by the Maternity and Children's Hospital (MCH) of Makkah.

In Madinah, Taibah University established a center for genetics and inherited diseases and has also provided scholarship training in clinical and molecular genetics for several staff. Currently, in the MOH, one clinical geneticist looks after genetic syndromes and another is specialized in metabolic disorders. Two more are in training and are expected to join soon.

In the Southern region, the MOH, National Guard and Armed Forces hospitals collaborate together to provide clinical assessment of the patients in the region. There are several clinical geneticists and some have access to diagnostic services in the Kingdom. Other cities are starting to develop services. In most places, this starts by hiring a clinical geneticist in the pediatric department, as was done in the city of Taif.

Preventive Services

Disease prevention takes a very high priority in KSA and several programs are in place. The first Saudi NNS program was established in November 1989 for the screening of congenital hypothyroidism (29). By 1991, cord blood screening for congenital hypothyroidism was effective in 20 different centers. TMS was introduced in KFSHRC in 1994. The first MS/MS pilot study was published in 1999 (30). This was funded by the King Salman Center for Disability Research (KSCDR). Over the next few years newborn screening expanded on a small scale. In August 2005, the national NNS started phase I and included 24 birth centers and 120,000 newborns. By 2008, it covered over 400,000 newborns. A period of transition followed until the MOH assumed full responsibility for newborn screening in 2012. Nowadays, NNS is performed as a national program with three central laboratories distributed in Eastern, Central and Western regions. The program is linked to an online database that connects labs and physicians all over the Kingdom, in hundreds of hospitals (31, 32).

Another important preventive program is the national PMS program. A royal decree mandating PMS was passed on 8/3/2002 (corresponds to the Hijri date of 4/1/1423). By this decree, marriage licenses could not be issued unless the bride and groom had undergone testing for the two most common autosomal recessive disorders in the country, thalassaemia and sickle cell disease in addition to some infectious diseases. In consideration of autonomy, although the test is mandatory, the ultimate decision to marry is left to personal choice. The MOH is the body responsible for the organizational arrangements of the PMS program. Initially met with some resistance from some members of the general public, the program is slowly gaining popularity in the community. Nevertheless, many couples decide to marry despite their risk of having affected children (33, 34). The program is under continuous surveillance and is likely to include additional tests in the future. This will be even more beneficial when the results of the Saudi Genome Project (see below) are available and validated.

As for prenatal diagnosis, most tertiary centers offer it in the form of chorionic villus sampling and amniocentesis for the diagnosis of single gene disorders. KFSHRC and a few other private and public centers in the large cities offer PGD (35, 36). Moreover, noninvasive prenatal screening using cell-free fetal DNA in maternal blood is practiced in several centers, but it is not offered routinely on a national scale yet.

Prevention of genetic disorders also relies heavily on defining local issues, public education, quality research and career training. All these facets have been heavily addressed in KSA. In this regard, several centers have provided overseas scholarship training in clinical genetics, genetic counseling and medical genetic research for

members of their staff, who bring back knowledge and expertise. In addition, local postgraduate education exists in the form of clinical fellowship training and master's programs (Figure 2). The genetic fellowship program initiated by KFSHRC has been accredited by the Saudi Commission for Health Specialties (SCHS) in 2009. Candidates are usually locally or regionally trained pediatricians. More than 20 doctors have graduated from this program and have become certified geneticists serving in the region. More centers are becoming involved. Currently, SCHS-accredited master's programs for training in genetic counseling are offered by KFSHRC in Riyadh, as a joint program with Al-Faisal University, and by the department of genetic medicine at KAU in Jeddah. The latter also offers a Master degree in Molecular Genetics. This too is accredited by SCFHS. The molecular genetics students' thesis work is to identify mutations in familial cases and risk loci for common polygenic diseases of national importance. They are trained in advanced bioinformatics to handle large scale genome data analysis. New graduates from this program are expected to make a large impact on the challenges faced by the national healthcare infrastructure and specialist manpower across the Kingdom. Overall, these various training programs have proven popular and the number of applicants for all these genetic career paths is outstripping the number of students that can currently be admitted (Figure 2).

Medical Genetics Research Across the Kingdom

Scientists and clinicians in KSA are heavily involved in genetic research and continually produce high quality publications. Funding opportunities are many and sources include the King Abdullah City for Science and Technology (KACST), local universities and research centers, the Ministry of Education (MOE), privately funded research chairs/centers, and others. Several high-tech research labs exist, such as those of KFSHRC, KAIMRC, KAU, King Abdallah City of Science and Technology (KAUST). Computational facilities such as the Computational Bioscience Research Center (CBRC) at KAUST provide computational biology and bioinformatics with applications in life sciences. Researchers at CBRC develop computationally driven methodologies, tools and resources to speed up the process of biological discovery. Overall, many genetic researchers across KSA quickly adopted the new technologies and advanced bioinformatics analysis methods to identify defective genes in rare diseases seen in Saudi families. Most KSA research groups have access to high throughput technologies such as SNP microarray and WES to identify the potential candidate regions of defective genes and specific genetic mutations, respectively.

A simple Pubmed search for publications in genetics between 2005-2018 reveals that the focus of this field in KSA is on single gene disorders,

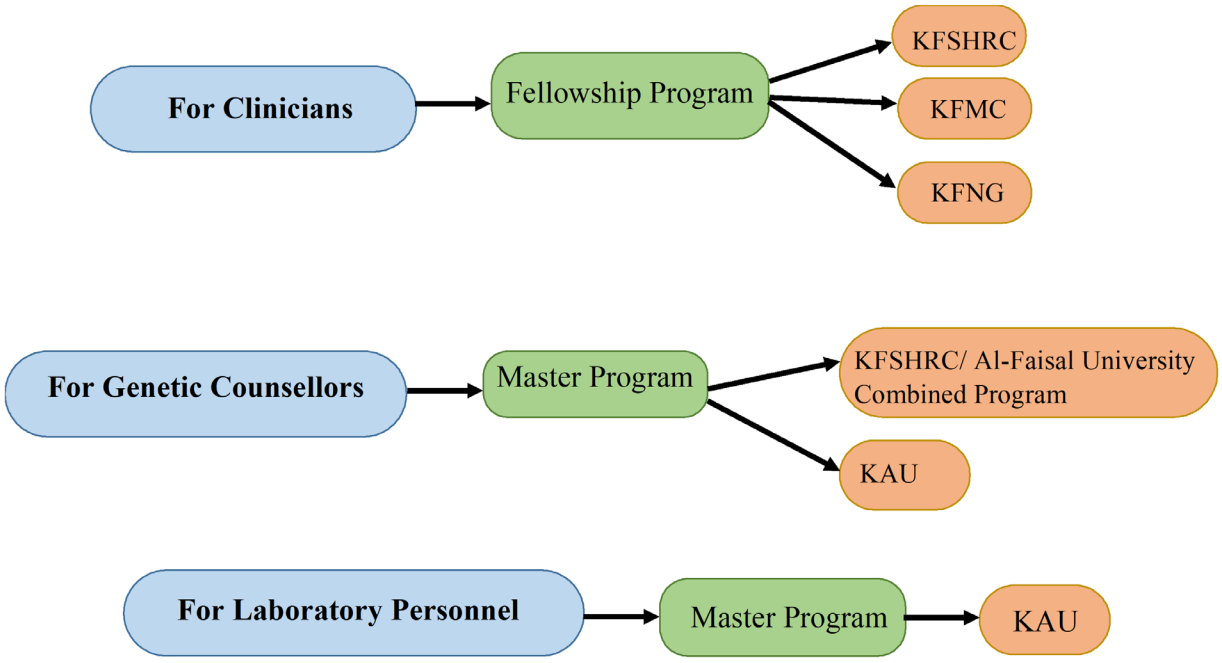

Figure 2: Genetic career paths options in KSA. KFSHRC: King Faisal Specialist Hospital and Research Center, KFMC: King Fahad Medical City, KAU: King Abdulaziz University

Table 1: Genetic syndromes first described by Saudi clinicians.

	Syndrome	Omim	Alternative Titles	Physician
1	Woodhouse-Sakati	# 241080		Nadia Sakati
2	Sanjad-Sakati	# 241410		Nadia Sakati
3	Acrocephalo Polysyndactyly Type III	# 101120	Sakati-Nyhan Syndrome	Nadia Sakati
4	Multicentric Osteolysis, Nodulosis, and Arthropathy	# 259600	Al-Aqeel Sewairi Syndrome	Aida Al-Aqeel - Wafa Alsewairi
5	Transaldolase Deficiency	# 606003	Eyaid Syndrome	Wafa Ai-Eyaid
6	Alkuraya-Kucinskas Syndrome	# 617822	ALKKUCS	Fowzan Alkuraya
7	Congenital Disorder of Glycosylation, Type IIa, CDG2a	#212066	Alkuraya Syndrome	Fowzan Alkuraya
8	Neurodevelopmental Disorder with Spastic Quadriplegia and Brain Abnormalities with or without Seizures; NEDSBAS	# 617977	Elhattab-Alkuraya Syndrome	Fowzan Alkuraya
9	Spondyloepimetaphyseal Dysplasia	# 616723	Faden-Alkuraya Type	Maha Faden Fowzan Alkuraya

with much fewer genetic association studies of polygenic disorders. Among the latter, cancer was the most studied, followed by diabetes, obesity, and cardiovascular disease. Several advances have been made in the realm of breast and colon cancer genetics, hematological cancers and others (37, 38). The last decade (2010-now) has witnessed a big spurt in the detection of novel mutations for many genetic diseases specific to KSA (39-44). Several syndromes have been described for the first time by Saudi physicians (Table 1).

Genomics and Data Sharing in the Kingdom

The Saudi Human Genome Project (SGP) was established across several centers in KSA over the years 2015-2016. The project is supported and coordinated by KACST and is implemented in collaboration with industry leaders. Research is led by international and national research partners such as KFSHRC, KAIMRC and others. The project aims to identify the genetic basis of disease in the Saudi population through advanced genome sequencing and bioinformatics techniques and data analysis, leading to the identification of Saudi-specific gene variants (45). An outcome of this project has been the generation of a database of variant polymorphisms among Saudi nationals. In addition, this project has led to the development of screening panels of gene variants for 13 broad disease areas such as cardiology, neurology, pulmonology, obesity/diabetes, etc. More than 2000 genes in total were covered by these screening panels in Ion Torrent next generation sequencing platform. A unique gene panel for common single gene diseases seen in KSA was also developed. The utilization of this panel is expected to help prioritize certain genes over hundreds of candidate genes contributing to common polygenic diseases. It will also play a role in unique biomarker development and in pharmacogenetics specific to the local population (14, 46, 47).

Another database termed “Majeen” has also been established in the National Guard Hospital. Several centers have initiated hospital-based birth defect registries, notably the Prince Sultan Military Medical City. There is also a plan for a national birth defect registry.

The Saudi Society of Medical Genetics (SSMG) was set up in 2009 as a non-profit scientific organization under the registry and supervision of the Saudi Council of Health Specialization. It is an active society, especially in terms of educational activities. The SSMG launched its journal of biochemical and clinical genetics in 2018. https://www.ssmg.org.sa/en/

Epilogue

Overall KSA has taken large leaps in this rapidly expanding field. Starting with only two geneticists in 1985, there are now tens of geneticists serving around this vast country. Alongside them are an ever-growing team of genetic counselors, dieticians, molecular scientists, bioinformaticians

and others. This teamwork can keep this field booming in the following years. This is a very exciting time to be involved in genetics, even more so in a country racing against time to achieve progress in all aspects of life. Personally, the authors note that things have changed drastically over the past 10 years: patients and families are more knowledgeable and cooperative, society is more open to new challenges, laboratory investigations are more widely available and other specialties are much more aware of the role of genetics in their respective practices. Continuous growth is expected to be seen as tens of graduates from local programs begin working in various centers across the country. In addition, those returning from their scholarships in North America and Europe will bring with them new experiences to be shared.

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