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Studying the genetic makeup of a population is a powerful tool for healthcare systems. For rare Mendelian diseases it offers the opportunity to identify underlying mutations, providing future opportunities for diagnosis, carrier screening, pre-natal testing and disease prevention. The Saudi Human Genome Program (SHGP) is a national project that has and will continue to contribute strongly, to the understanding of both health and disease, firstly in the Saudi population, but also in the general understanding of both rare and common diseases. It will enhance current approaches to both the diagnosis and treatment of disease, and establish a foundation for “Precision Medicine” in the Arab world and beyond.

Consanguineous marriage, defined as a union in which a couple are related as second cousins or closer, is practiced in societies around the world collectively representing over 1 billion people. As with India, Pakistan, Turkey, Iran and most countries in the Middle East and North Africa, consanguineous marriage is customary in Saudi Arabia (Fig. 1). In Saudi Arabia the overall incidence of consanguineous marriages is 57.7% with regional differences accounting for a low of 34.0% and a high of 80.6%. In Northern European and other populations where parental consanguinity is rare, births are associated with an overall 2-3% risk of a congenital disorder. Of these, 4-5% (a relatively small 0.17% overall) may be attributed to autosomal recessive disorders. However, in consanguineous communities there is a higher risk of congenital disorders, with clustering of disease causing recessive variants in extended families, clans or tribes, with a corresponding increase in these communities, of births with recessive diseases. Indeed within a Pakistani cohort, the incidence of congenital disorders was almost doubled, as a consequence of consanguinity-related birth defects.

In Saudi Arabia, the parental consanguinity rate and a cultural preference for endogamous unions (intra-tribal marriage is preferred), results in a high incidence of recessive disorders due to homoallelic mutations inherited by descent. In addition to well-characterized recessive diseases such as sickle-cell anemia, cystic fibrosis, congenital myopathies, retinopathies and others are a multitude of novel, again recessively segregating syndromic and non-syndromic Mendelian diseases. The identification and characterization of novel Mendelian diseases is facilitated in the Saudi population, where large families (nuclear and extended) with multiple affected individuals are often available for study. Microarrays that facilitate SNP genotyping on a genome wide basis, positional cloning/candidate gene sequencing, and most recently whole exome sequencing, coupled with consanguineous pedigrees permitting autozygozity mapping, provide a powerful tool for discovery of genes underlying novel recessive disorders in this population.

Whilst significant efforts were present in the literature from the mid-90’s describing characterization of Mendelian diseases in the Saudi population, the Arab world is poorly represented in genome databases that resulted from the HapMap project, 1,000 genomes project and other international efforts of the early 2000’s to the current time. The unique and unstudied nature of the Saudi population was evident from early studies identifying novel alleles, for instance of CFTR in patients with cystic fibrosis. In more recent times allele frequencies associated with pharmacogenetically relevant loci have been “inverted” in an Arab cohort relative to that for Caucasians. Similarly, a multitude of novel genes underlying recessive Mendelian disorders have been identified using families from Saudi Arabia over the last two decades. Indeed searching the Online Mendelian Inheritance in Man (OMIM) database for “Saudi Arabia” will bring up 442 entries (http://omim.org/).
It is with this background that the SHGP was launched late in December 2013, with a mission to identify genetic variation in the population and a build a foundation for the development and practice of “precision medicine”. The aim was to encompass rare diseases, oncology and common polygenic diseases including type 2 diabetes, cardiovascular disease and others. In addressing these goals, and in contrast to other similar programs, the SHGP chose to initially focus on rare diseases, consistent with the higher incidence of these within the Saudi population and the opportunity for a more immediate impact. Given the size of the population and high incidence of consanguineous marriage, it was reasonable to speculate that most rare recessive diseases would be encountered in Saudi Arabia. At the beginning of this millennium, only 200 or so Mendelian disorders had been described. Sequencing of the human genome and rapid technological developments from that time to launch of the SHGP in 2013, resulted in listing of over 3,000 disease-causing genes in the OMIM database (http://omim.org/). Coverage of these genes and undoubtedly those associated with novel disorders expected in the Saudi population could have been addressed through whole genome sequencing, or more practically by whole exome sequencing (WES). However, the cost of clinical grade WES, interpretative challenges and ethical issues relating to incidental findings needed consideration. The SHGP sought to circumvent these issues by adopting a targeted approach, initially encompassing all disease-causing genes listed as of August 2013 by OMIM (the “Mendeliome”), These were divided into 13 panels each addressing a subset of clinical phenotypes (e.g. neurological, renal, vision impairment, hearing impairment etc.). By doing so, limited clinical judgement in terms of phenotype or knowledge in terms of genotype, was required, to request the panel most likely to identify the genetic basis of a Mendelian disorder. The SHGP has since screened well over 5,000 Saudi patients covering the full spectrum of Mendelian diseases with results of the first 2,357 cases having been recently reported. Findings are described in brief in the paragraph below.

Analytical sensitivity of the 13 panels combined (the “Mendeliome”), based upon a set of 642 Sanger sequenced positive controls, accumulated from approved research projects and diagnostic testing, was 80%. Analytical specificity based upon Sanger confirmation, was 93% for single nucleotide variants (SNVs) and 78% for indels. Based upon the 2,357 cases, a diagnostic yield of 43% on average was achieved across the 13 panels of the “Mendeliome”. Both inter and intra-panel variation based upon phenotypes and sub-phenotypes respectively was observed. A notable outcome of adopting the “Mendeliome” approach to identify causative genes and mutations associated with disease was expansion of the clinical spectrum (phenotypic and genotypic heterogeneity) of known genetic disorders. Among the most significant contributions of the SHGP to date is improved annotation of the human variome. Variants were identified in several genes (e.g. AR114EP, ZNF526, WDR45B and WDR81) where candidacy listed in OMIM could now be considered confirmed consequent to identification of additional alleles by the SHGP. The SHGP reported 788 disease related variants (433 of which were novel) representing the largest set of such variants reported to date from a single study and confirming the relatively unstudied nature of the Arab population. Even at this early stage the SHGP contribution to documenting genetic variation in the Arab world is very significant and invaluable to the precise interpretation of molecular genetic tests for Mendelian diseases. The SHGP study also reported hundreds of variants reported in HGMD that have minor allele frequencies >1% in the Arab population, in some instances 5%. Clearly they can no longer be regarded as pathogenic. Homozygous loss of function alleles, identified at relatively high frequency by the SHGP, in the absence of a clinical phenotype, also bring into question the listing of some disease genes (e.g. CACNA1F, MYH8 and PRX1).

Since publication of the first cohort of rare disease variants by the SHGP, the overall number of such variants has expanded to over 1,800 (unpublished data). This highlights the value of this program to diagnosis of rare diseases in the Arab world and in the delivery of “precision medicine” for Mendelian disorders. The benefits for diagnosis of “familial” or “individual” single gene disorders are clear, and in some instances, may guide treatment to reduce morbidity. However, unlike oncology or pharmacogenetics where therapies may be targeted or tailored respectively, for rare diseases, beyond diagnosis, the major benefit in Arab countries lies in screening and prevention. Arguably one may consider this as precision medicine applied at the level of a population.

Saudi Arabia like many countries has an active newborn screening (NBS) programme addressing inherited metabolic diseases (IMD). The program is selective in that participation is by individual clinical centres or through referral of symptomatic patients, thus not reaching all 500,000 plus newborn babies. Approximately 50% of diseases identified by newborn screening are manageable. However, in many cases the phenotype cannot be prevented and even if treated, may result in significant morbidity. Economic cost is a factor in that early detection and treatment with drugs or supplements is rewarding, but over the lifetime of a patient this may become prohibitively expensive. Ultimately, identification of the genetic lesion underlying many of these disorders, and the provision of screening and counseling to reduce the incidence of live births with IMD or other recessive disorders, would be the preferred option.

Addressing this subject, premarital screening for sickle-cell anemia and thalassemia has been compulsory in Saudi Arabia for over 10 years. As these, like other recessive diseases, have an increased prevalence in populations where consanguineous marriages are common; the
first solution offered is prevention through discouragement of consanguineous unions. While logical, this approach often meets with resistance as it ignores cultural norms that are strongly embedded, valued and justified in many populations. Pre-marital screening offered to couples, enabling informed decisions on marriage, with full knowledge of risks and prenatal options, has been readily adopted in Saudi Arabia. The Ministry of Health’s (MOH) mandatory pre-marital screening has been applied to approximately 150,000 couples for each of the past 6 years. Importantly, over a 10-year period the percentage of couples found to be at risk, who choose not to go ahead with marriage, has increased from 10% to 60% (MOH – unpublished data) and justifies screening for a wider array, if not all rare inherited diseases in the Saudi population. For those couples at risk, that nevertheless choose to proceed with their marriage, preventative options including pre-implantation genetic diagnosis (PGD) or prenatal testing are accepted in the community. PGD, by its nature cannot be made available to a large number of couples and will have little impact on reducing inherited diseases on a national scale. Prenatal testing at King Faisal Specialist Hospital and Research Centre alone, has increased from 5 to over 500 cases per year, over a 10-year period. Prenatal testing can be more widely applied, particularly if analysis of Cell Free Fetal DNA is developed further, facilitating application across a large geographical region, with a challenging climatic environment and a still developing healthcare system.

Source: Adapted from Bittles, 2009

Figure 1. The value of the Precision Medicine approach may be modeled according to the two largest critical inputs: (1) the increase in efficacy, measured in QALYs, in the biomarker-positive population, and (2) the percent of the overall disease population identified by the diagnostic marker. Markers which identify larger populations and which add significantly to efficacy favor the development of a drug-diagnostic pair. This is true from both the pharmaceutical company and the physician/payer perspectives.
Over 400 of the rare disease causing variants identified by the SHGP, have been observed in patients from more than 1 nuclear family and may be considered as founder mutations. Whilst these would have priority in a pre-marital screening program for prevention of rare diseases, current technologies such as microarrays would permit screening of several hundred thousand individuals for all mutations identified in the population. Given the lifetime cost of caring for individuals with rare diseases, a strong economic case can be made for such screening and prevention in Saudi Arabia.

Indeed, this has been approved and is to be implemented in the near future as an expansion of the SHGP.

The initial focus of the SHGP on rare diseases is invaluable to the expansion of molecular diagnostics and for carrier screening and prevention of disease in the “Circle of Life” (Figure 2). In addition many lessons may be learned from deciphering the basis of rare diseases that mimic common disorders worldwide.

References

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Prevention of Disease in the “Circle of Life”