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Consanguinity in Saudi Arabia: A Unique Opportunity for Pediatric Kidney Research

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Identification of disease-related genes is a critical step in understanding the molecular basis of disease and developing targeted therapies. The genetic study of diseases occurring in the offspring of consanguineous unions is a powerful way to discover new disease genes. Pediatric nephrology provides an excellent example because ~70% of cases of kidney disease in childhood are congenital with a likely genetic basis. This percentage is likely to be even higher in countries with a high consanguinity rate, such as the Kingdom of Saudi Arabia. However, there are a number of challenges, such as cultural, legal, and religious restrictions, that should be appreciated before carrying out genetic research in a tradition-bound country. In this article, we discuss the background, opportunities, and challenges involved with this unique opportunity to conduct studies of such genetic disorders. Keys to success include collaboration and an understanding of local traditions and laws.
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INDEX WORDS: Consanguinity; genetic disease; linkage analysis; gene discovery; identical by descent (IBD); homozygosity mapping; kidney research; pediatrics; population differences; Saudi Arabia.

The past decade has seen an explosion in the elucidation of Mendelian disorders. This has been made possible by the deciphering of the human genome and the development of new next-generation sequencing technologies.[1] Nevertheless, to date, only about 2,000-3,000 of the estimated 25,000 protein-coding genes have been linked to disease, with several thousands more expected to be disease related.[2] Identification of these genes is hampered because many of these disorders are very rare and cases therefore appear to be sporadic and thus may not be recognized as having a genetic cause. Even when the disorder is believed to be genetic, identification of the underlying mutations is difficult because we all carry many thousands of such variants in our genome and, in most cases, sorting the causative ones from all the other variants is extremely difficult, if not impossible. This is where genetic studies of consanguineous populations present a unique opportunity for disease gene discovery.

CONSANGUINITY, LINKAGE ANALYSIS, AND GENE DISCOVERY

For many of the disease genes that have been identified to date, the studies have been performed in families from geographically or culturally isolated populations. The success of mapping disease-causing genes in isolated populations is related mainly to chromosomal stretches being inherited identical by descent (IBD), that is, when a part of the chromosome inherited from the father has the same sequence as the corresponding part of the homologous chromosome inherited from the mother.[3] When parents are related, there is a greater likelihood of the offspring inheriting autosomal recessive conditions, but this relatedness also makes it more probable that disease-causing mutations occur in blocks of homozygosity. Thus, looking at blocks of homozygosity in such populations can help researchers hone in on the region of the causative mutation.

An example is given in Fig 1, which shows a pedigree of a rare autosomal recessive disease (Fig 1A) and a schematic of the mutation-mapping process (Fig 1B). For a

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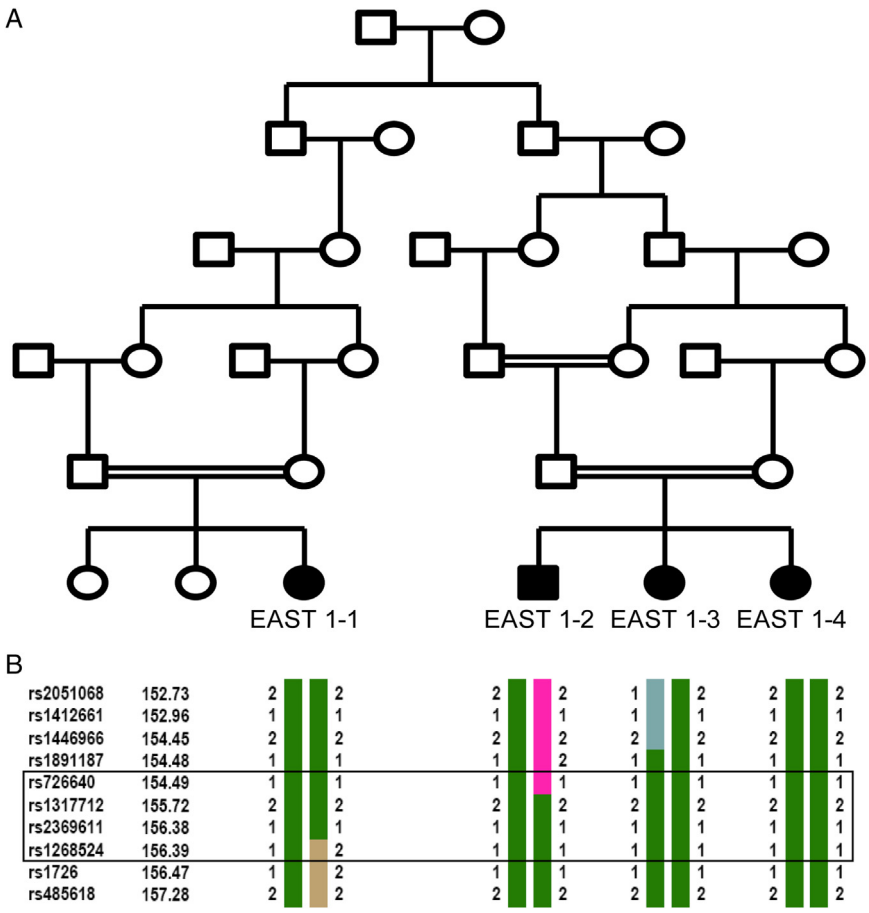

Figure 1. Genetic mapping in a consanguineous pedigree. (A) Pedigree of a family affected with EAST (the presence of epilepsy, ataxia, sensorineural deafness, and tubulopathy) syndrome. The disease allele was present in one of the ancestors in the first generation of the family and transmitted through the generations. The affected children in the youngest generation then inherited the disease allele from both parents, resulting in homozygosity for the allele. While the statistical risk for each child to inherit the disease allele from both unaffected parents is 25% (1 in 4), in one branch of this family, all 3 children happened to be affected. (B) Identity by descent is demonstrated by haplotype analysis. In this case, chromosomes were mapped by determining single-nucleotide polymorphisms (SNP) along the chromosomes. Individuals can be either type 1 or type 2 for the individual SNP. All affected members are homozygous for the disease allele (boxed region). The region in which the disease allele must occur has been limited by recombination events in EAST 1-1 and EAST 1-2. Adapted from Bockenhauer et al[4] with permission of the Massachusetts Medical Society.

simple Mendelian disease transmitted in an autosomal recessive manner, the affected patient inherits the causative IBD allele from both parents. It originates in a common ancestor and is transmitted through different branches of the pedigree and united through the consanguineous bond (indicated by double lines in the pedigree). In any child born from such a consanguineous union, there will be several homozygous chromosomal regions of IBD, but one region (that harboring the variant that is causal for the trait) will be shared between individuals expressing the trait, while not being homozygous in individuals who do not express the trait. With each recombination of the chromosomes during meiosis, the borders limiting the IBD alleles may be narrowed, leading to a situation as shown in Fig 1B, in which the recombination events have limited the stretch of IBD to a very short region.

The possibility of detecting stretches of homozygosity by assessing genetic markers on the DNA of individuals in inbred/consanguineous pedigrees established the practical foundations of the homozygosity mapping approach to positional cloning.[5] Although the probable cause of a rare autosomal recessive trait in a consanguineous family is IBD homozygosity, there also is the same risk as in the offspring of nonconsanguineous unions of compound heterozygote mutations, which will be missed by strict homozygosity mapping.[6] Therefore, the analysis is better performed in such a way as to also identify linkage in regions of compound heterozygosity.[7] New sequencing technologies, such as whole exome or genome sequencing, are dramatically speeding up the pace of gene discovery.[1] However, the more DNA being sequenced, the more variants identified, and the challenge remains to identify the disease-causing mutation amid the noise of the many other changes. For this reason, it remains important to combine these new technologies with mapping strategies, such as linkage analysis, to narrow the focus in the search for the disease allele.

GENETIC CONSEQUENCES OF CONSANGUINITY

The exact risk of consanguineous unions to the health of the progeny is difficult to determine because of confounding factors, such as living standards and available levels of health care. One large study reported an excess risk of 4.4% of prereproductive death in offspring of first-cousin marriages.[8] Other studies have reported an excess risk of birth defects of 0.7%-3.8%.[9] However, these numbers have to be

Table 1. Summary of Published Descriptive Studies From Saudi Arabia

Type of Kidney Disease	Main Findings	Study
Polycystic kidney disease	15 children, diagnosed at a median age of 10 mo, with a better prognosis for those diagnosed after 6 mo of age	Matto et al[16] (1994)
Primary hyperoxaluria type 1 (PH1)	16 children presented with nephrocalcinosis and chronic kidney failure	Snajad et al[17] (1999)
Distal renal tubular acidosis (dRTA)	7 patients with the autosomal recessive inherited syndrome of dRTA and sensorineural hearing loss	Zakzouk et al[18] (1995)
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)	7 children with similar clinical and biochemical data to previous reports; however, they tend to show a slower rate of progression to end-stage renal disease	Kari et al[19] (2003)
Fanconi-Bickel syndrome	10 patients with impaired glucose tolerance/diabetes range hyperglycemia after oral glucose tolerance test	Taha et al[20] (2008)

interpreted with caution because they may be influenced by social, economic, or demographic factors; differences in reproductive behavior; and early- and late-onset morbidity and mortality.[8-10]

PATTERNS OF CONSANGUINITY

Consanguinity is present in ~10% of the global population.[11] Although consanguinity now tends to be frowned upon in the West, this has not always been the case. In both Europe and the United States, marriages among first cousins were common and widely encouraged through the mid-19th century. A famous example is that of Charles Darwin, who married his first cousin Emma Wedgwood and remarked: "the widely different habits of life of men and women in civilized nations, especially among the upper classes, would tend to counterbalance any evil from marriages between healthy and somewhat closely related persons."[12] Consanguinity in Western countries now is limited mostly to immigrant communities. For example, 55% of marriages between Mirpuri (Kashmiri) Pakistani Muslim immigrants in the United Kingdom are between first cousins.[11,13,14]

Although consanguineous unions of first cousins are permissible in most religions (some, eg, the Roman Catholic and Eastern Orthodox Churches, require special dispensation), nowadays consanguinity is most common in Muslim-majority countries. The Koran does not contain any specific encouragement of the practice,[9] and one of the hadith (recorded instructions from the Prophet Mohammed) actually discourages marriage within the family. Yet the Prophet Mohammed married his daughter Fatimah to his cousin Ali, so consanguineous marriage can be interpreted as following the example of the Prophet. The origins of consanguineous marriage in the Arab world date back to pre-Islamic Arab traditions in which first-cousin marriages of the paternal subtype (parallel cousin marriages between a man and his father's brother's daughter) were encouraged. The origins of this tradition likely are social and economic: in communities in which the woman is married off to the husband's family, treatment of the woman is expected to be more congenial if she already is part of the family. And in communities in which dowry payments are custom, intrafamilial marriages minimize these costs or at least keep them within the family.

In present-day Saudi Arabia, >50% of all marriages are consanguineous (marriages between cousins).[15] The actual degree of inbreeding is compounded further by the high frequency of marriages occurring within a clan, tribe, or caste.

CONSANGUINITY AND THE STUDY OF GENETIC DISEASES OF THE KIDNEY IN THE KINGDOM OF SAUDI ARABIA

Overview

More than 70% of kidney diseases in children have a genetic cause.[1] In the Kingdom of Saudi Arabia, although very limited epidemiologic data exist, it is likely that because of consanguinity, genetic causes account for the vast majority of kidney disorders (Table 1).[16-20] Consanguinity is the most obvious explanation for the high rate of autosomal recessive diseases observed in Saudi Arabia.[21] Preliminary observations indicate that children in Saudi Arabia, compared with children in other parts of the world, appear to have a higher incidence of familial juvenile nephronophthisis; polycystic kidney disease; tubular diseases such as familial hypomagnesemia, hypercalciuria, nephrocalcinosis syndrome, and renal tubular acidosis; congenital urologic anomalies; and familial nephrotic syndrome.[21] This pattern is similar to that observed in Lebanon,[22] Turkey,[23] and Kuwait,[24] where consanguinity also is common.

Box 1. Centers for Genetics in Saudi Arabia and Representative Publications

- King Faisal Specialist Hospital and Research Centre (Riyadh)
  - ◇ Department of Genetics, Research Centre: A molecular genetic analysis of childhood nephrotic syndrome in a cohort of Saudi Arabian families[32]
  - ◇ Stem Cell Therapy and Tissue ReEngineering Program: Genetic diagnosis in consanguineous families with kidney disease by homozygosity mapping coupled with whole-exome sequencing[31]
- Saudi Diagnostic Laboratory (Riyadh)
- King Abdulaziz University (Jeddah)
  - ◇ Center of Excellence in Genomic Medicine Research: Mutational screening of RET, HRAS, KRAS, NRAS, BRAF, AKT1, and CTNNB1 in medullary thyroid carcinoma[33]
  - ◇ Princess Al-Jawhara Center of Excellence in Research of Hereditary Disorders: Knowledge regarding the national premarital screening program among university students in western Saudi Arabia[34]
- King Abdulaziz Medical City at National Guard Hospital (Riyadh)

The rate of consanguinity means that some genetic kidney diseases have been detected for the first time in Saudi Arabia. For example, Ohlsson et al[25] published the first report of a syndrome of "marble brain disease" comprising osteopetrosis, renal tubular acidosis, and cerebral calcification. Marble bone disease is associated with intellectual disability and stunted growth and has been linked to carbonic anhydrase II enzyme deficiency.[26] Long-term follow-up of children with this disease also has been reported from Saudi Arabia.[27]

Other new associations also have been discovered in Saudi Arabia and reported as a basis for new syndromes.[28-30] In recent years, new high-throughput genotyping and sequencing technologies have become available, which assist in mutation detection in known disease genes in individuals with inherited kidney disease.[31] In this workflow, whole-genome single-nucleotide polymorphism analysis coupled with exome sequencing on genomic DNA samples from affected members of families with inherited kidney disease facilitates the detection of culprit genes in kidney diseases with overlapping histopathologic features.

Resources

There is substantial opportunity for research in genetically transmitted diseases in Saudi Arabia, with increasing recognition of the need for multiple genetic centers. A number of genetic research centers have been established (Box 1) in 2 larger cities (Riyadh and Jeddah). Although other cities in Saudi Arabia lack such centers, developing experience in researching genetic diseases has been strongly supported by the government of Saudi Arabia.

King Abdulaziz University's Center of Excellence in Genomic Medicine Research and the division of Pediatric Nephrology recently established a formal collaboration with University College London in the United Kingdom. In addition, there is ongoing collaboration with the University of Michigan and Harvard Medical School in the United States. Through these collaborations, all children with congenital nephrotic syndrome and steroid-resistant nephrotic syndrome are screened for mutations in *NPHS1* (nephrin), *NPHS2* (podocin), and *WT1* (Wilms tumor protein).[35] Patients for whom mutations in known disease genes are not detected then will be included in projects for the identification of new disease genes. The collaborations aim to transfer knowledge between the centers to improve understanding of genetic kidney disease in general and in Saudi Arabia specifically.

The Importance of Understanding Tradition

Pursuing studies in consanguineous populations in Saudi Arabia or elsewhere in the world requires an appreciation of the challenges that tradition and customs pose for screening and treating genetic disease. Although the opportunities for investigating the genetics of kidney disease in consanguineous populations are exceptional, there are a number of challenges. Chief among these are the cultural, legal, and religious limitations posed by a tradition-bound country. Screening for genetic diseases is very important for clinical care, as well as the starting point to the genetic discovery process, but families may fear being stigmatized by their community. Although there is no explicit religious restriction regarding genetic research, the diagnosis of a genetic disease can result in feelings of inferiority and shame and in reduced chance of marriage for other members of the family, in a culture in which most marriages are arranged. In addition, there are legal issues around international genetic studies because the movement of DNA material outside Saudi Arabia is restricted.[36]

Screening for Genetic Disease

In Saudi Arabia, screening for genetic disease is endorsed by the government through royal decrees and fatwas; however, the practice and enforcement of these rulings can be variable. Some of the rules also are conflicting, adding confusion to the situation. In addition, genetic screening is not offered for all genetic diseases. For example, a royal decree passed in 2003 mandates a premarital screening test followed by nondirective genetic counseling for hemoglobinopathies, but not for any of the genetically transmitted kidney diseases. Termination of pregnancy in the first 120 days after

conception is permitted though a 1990 ruling (Fatwa) if there is a severe untreatable malformation in the fetus,[37] but prenatal diagnosis and termination of pregnancy are not offered to carrier couples. In Saudi Arabia, pregnant woman receive routine ultrasound scanning during their first antenatal visit. Pretest information is usually provided to the couple regarding possible abnormalities that could be found and an explanation of possible consequences.[38] If the results indicate an abnormality, the woman will be referred for a detailed anomaly scan, and further invasive techniques, such as amniocentesis, might be offered.

In routine prenatal ultrasound screening in Saudi Arabia, renal anomalies are reported to be detected in 0.7% of screened fetuses, which is similar to other countries.[38,39] However, the availability and accuracy of ultrasound screening often are limited in rural areas and small cities. In larger cities, the situation is better, but still not always ideal. A study from Riyadh found that the antenatal detection rate of posterior urethral valve was only 27%, which is substantially lower than the international rate of 70%.[40] If a severe genetic or congenital disorder is detected, the couple has to face the major decision of whether to terminate the pregnancy. This is performed in a few centers, but often leads to ethical dilemmas. However, social attitudes are changing and becoming more accepting of termination of pregnancy in some conditions.[41]

Biochemical neonatal screening programs for congenital hypothyroidism were first begun in Saudi Arabia in 1985,[37] and by 1991, such screening was available at 20 centers. In 2005, a national screening program started, and by 2008, it covered 400,000 newborns overall. Electrospray tandem mass spectrometry was first used for neonatal screening of 16 inherited metabolic diseases in 1995 and in 2005 was established on a national scale, now reaching almost 90% of all newborns in Saudi Arabia.[41] However, there are geographic limitations in the availability of physicians who have the specific expertise needed for many of the rare conditions. Also, there is a large need for additional training and education about the disorders that may be detected through newborn screening programs. Unfortunately, while many programs provide for screening and diagnosis, most have limited resources for long-term management, including the provision of necessary treatment and services, which may defeat the purpose of these vital screening programs.[42]

Storage and Use of Samples

A national biobank has been established only recently in the Kingdom and to date, DNA, RNA, and plasma samples are stored mainly at local genetic centers. Deposited material includes tumor tissue, as well as selected DNA and RNA samples, which are not collected systematically, but by interested clinicians, as well as by disease-specific investigators. Consent for sample collection is obtained through individual research protocols.

A bylaw to the regulations governing research ethics with respect to living creatures was produced by the National Committee for Bioethics in Saudi Arabia, which regulates all matters of scientific research, including dealing with and researching genetics materials.[36] It states that genetic research should be in line with Islamic values, local culture, and environmental safety standards. The bylaw further stipulates that the analysis should be performed in accordance with the practices of internationally recognized research on genetic material. It regulates saving the genetic data in the local genetics banks, which feed it to a central repository at King Abdullah City for Science and Technology.

An important aspect of the bylaw is that genetic material should be analyzed within Saudi Arabia if possible. However, such material can be sent across the borders[43] provided that a number of conditions are met. First, the destination must be a known research center with a good reputation; there should be a signed contract to protect the national rights (including involvement in decisions and recognition of all procedures done with samples, as well as rights in publications) and rights of all parties. Second, the contract should be agreed to by the local administration (if it is possible to do the same research through national collaborations, this is preferred). Third, samples should be coded so that studied individuals will not be identifiable. In addition, approval of a local ethics committee can be overridden by the national committee, which retains the right (which should be made clear in the contract) to stop the research if they find that it is not useful or is harmful to the Saudi society. It is permissible to send samples for diagnostics tests provided that the tests are not available in Saudi Arabia.[43]

Genetic Counseling

Genetic counseling by a geneticist or genetic counselor is available only in select centers. For genetic kidney diseases, counseling usually is done by the nephrologist involved in requesting the analysis.

SUMMARY

The next frontier in genetic discovery for kidney disease in children arguably lies in exploring rare and complex genetic

disorders. A highly consanguineous population such as in Saudi Arabia presents a unique opportunity to conduct such studies. Examples from other disciplines, such as genetic discovery in autism,[44] provide a model for how this can be done successfully. Keys to success include collaboration and an understanding of local traditions and laws.

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