AJKD
World Kidney Forum

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

Jameela A. Kari, MD, FRCP,[1] Detlef Bockenhauer, MD, PhD,[2] Horia Stanescu, MD, PhD,[2] Mamdooh Gari, PhD,[3] Robert Kleta, MD, PhD,[2] and Ajay K. Singh, MBBS[4]

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.
Am J Kidney Dis. 63(2):304-310.

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

From the [1]Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia; [2]Institute of Child Health, University College London, London, United Kingdom; [3]Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia; and [4]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Received April 16, 2013. Accepted in revised form August 2, 2013. Originally published online November 18, 2013.

Address correspondence to Jameela A. Kari, MD, FRCP, King Abdulaziz University, PO Box 80215, Jeddah 21589, Kingdom of Saudi Arabia. E-mail: jkari@doctors.org.uk

0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2013.08.033

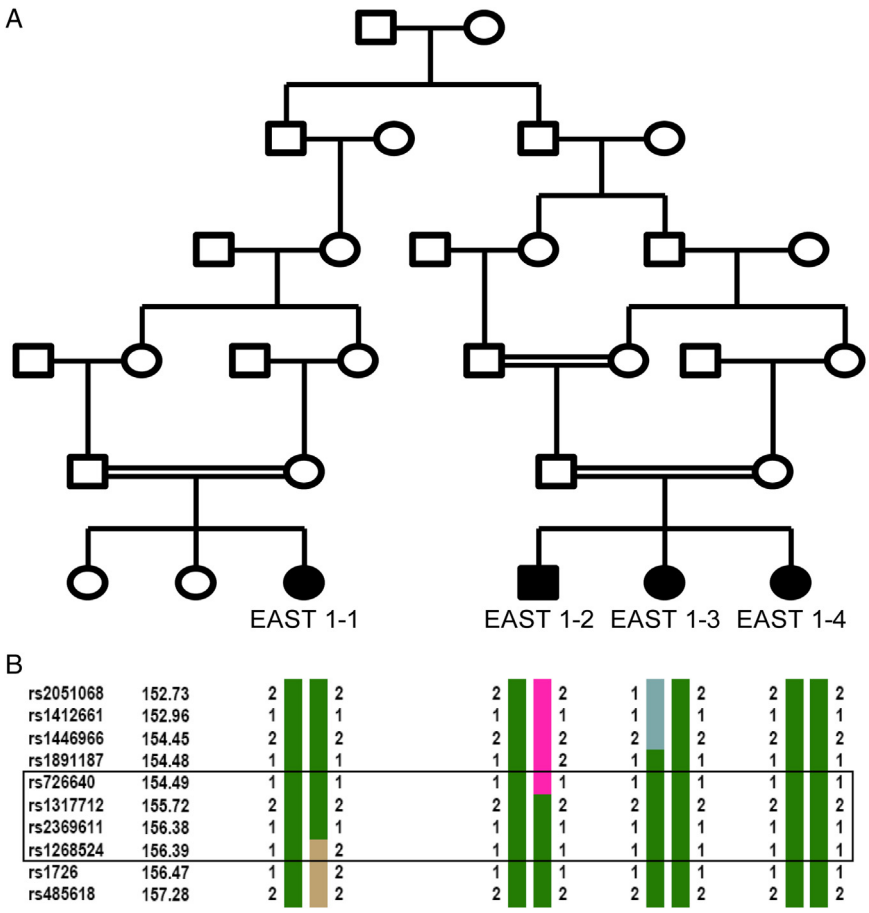

Figure 1. Genetic mapping in a consanguineous pedigree. (A) Pedigree of a family affected with EAST (the presence of epilepsy, ataxia, sensorineural deafness, and tubulopathy) syndrome. The disease allele was present in one of the ancestors in the first generation of the family and transmitted through 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