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REVIEW ARTICLE

Molecular genetics of inherited kidney disease in Saudi Arabia

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ABSTRACT

Human kidneys serve important physiological functions in the body. There is an increasing evidence suggesting that the majority of renal diseases have an underlying genetic component. At least 40 genes have been shown to be involved in kidney development and many more genes are expressed within the kidney and regulate renal physiology. It is observed that genetic and congenital disorders are more common in Arab countries than in industrialized countries. Saudi Arabia is the largest Arab country and estimation of patients with end-stage kidney failure is 136 for each million yearly. Preliminary observations indicate that children in Saudi Arabia probably have a higher incidence of polycystic kidney disease, familial juvenile nephronophthisis, congenital urological anomalies, and familial nephrotic syndrome. Molecular diagnosis would help enormously in prevention and introduce early management which could ensure a better outcome. This is a review article of molecular studies conducted in the Kingdom of Saudi Arabia from 1990 till present time to elucidate disease-causing genes of inherited kidney disease.

Keywords: Inherited kidney disease, mutations, molecular genetics, consanguinity, Saudi Arabia.

Genetics of Kidney

The human kidneys serve important physiological functions of excreting waste products from the body and maintaining fluid h omeostasis. T he k idneys a lso h ave endocrine roles and are a key regulator of blood pressure and mineral metabolism.

There is increasing evidence suggesting that the majority of renal diseases have underlying genetic component. Familial aggregation studies the comparisons of incidence rates between different racial or ethnic populations and segregation analysis support the role of genetics in various renal diseases (1). This is particularly true in children as around 70% of cases of kidney disease in childhood are congenital with a likely genetic basis with the possibility of even higher percentage in countries with a high consanguinity rate (2).

At least 40 genes have been shown to be involved in kidney development and many more genes are expressed within the kidney and regulate renal physiology (3).

The development of the kidney in mammals progresses through three spatially and temporally distinct stages: pronephros, mesonephros, and metanephros. The first two stages are transient structures in mammalians and do not contribute to the formation of the mature kidney, but they play major roles in the development of the gonads, adrenal gland, and hematopoietic precursors. In the third stage, the metanephros persists and gives rise to the functional kidneys. The metanephric or adult kidney is derived from the reciprocal interactions of two primordial mesodermal derivatives, the ureteric bud and the metanephric mesenchyme (4). Mesenchymal cells near the bud become induced and convert to an epithelium which goes on to generate the functional filtering unit of the kidney, the nephron.

Genetic studies in mice have allowed researchers to begin to unravel the molecular basis of kidney development in human. Transcription factors such as Lim-1, Foxc-1, Wilms' Tumor gene 1 (WT1), Eya1, and Pax2, all act in the metanephrogenic mesenchyme (MM) to induce the expression of Glial cell-derived neurotrophic factor (GDNF) and Six2 (5). GDNF signaling is the main regulator of ureteric budding and branching morphogenesis, whereas Six2 is required for MM cell renewal (6). Proteins of the bone morphogenetic proteins family modulate ureteric bud branching and keep bud development. As nephrons form, they express critical transcription factors such as WT-1, Pax-2, and Hoxa11 and d11, condense, and secrete Wnt-4. Wnt-4

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acts in an autocrine loop to stimulate its own synthesis and is required for cells to differentiate into epithelia. As nephrons mature, regions of them differentiate to perform specific physiological functions, a process that requires the proteins WT-1, Lmx-1b, Notch-2, Jagged-1, and Hnf-1 (7).

In human, congenital abnormalities of the kidney are frequently observed in children and represent a significant cause of morbidity and mortality. These conditions are phenotypically variable, leading to a spectrum of renal diseases. Many inherited renal disorders are quite rare, with an incidence of 1:10,000–1:100,000 (8). The following universal principles concerning inherited renal disease can be identified:

1) More than one child in a family may be affected.
2) The child with hereditary renal disease frequently presents with growth failure.
3) The inherited pattern is usually autosomal recessive, but it may also be autosomal dominant or X-linked.

Diseases caused by recessive genes usually manifest prenatally, or in childhood or adolescence [e.g., nephrotic syndrome (NS)]. Those caused by dominant genes typically manifest in adulthood [e.g., autosomal dominant polycystic kidney disease (PKD)] (9). Genotype–phenotype correlation is strong in recessive single-gene renal disorders, this correlation is reduced in those caused by dominant genes because of incomplete penetrance and variable expression in different organs (9). Figure 1 illustrated classification of genetic renal diseases.

The globally increasing number of patients with end-stage kidney disease (ESKD) urges the identification of molecular pathways involved in renal pathophysiology, to serve as targets for intervention. The study of the most common genetic cause of renal failure may lead to a reduction in the number of kidney diseases progressing to ESKD. Moreover, kidney disease is a growing financial problem. For example, from 1993 to 2005, the total costs of medical care for patients with ESKD increased from the US $8–$20 billion in the US (10). Here in the Kingdom of Saudi Arabia, the estimated cost per annum incurred toward maintenance hemodialysis is the US $19,400 with more than 7,200 patients receiving regular dialysis (11). After obesity and breast cancer, kidney disease is the most prevalent ailment in Saudi Arabia, with thousands of patients diagnosed each year. According to the latest WHO data published in April 2011, deaths related to

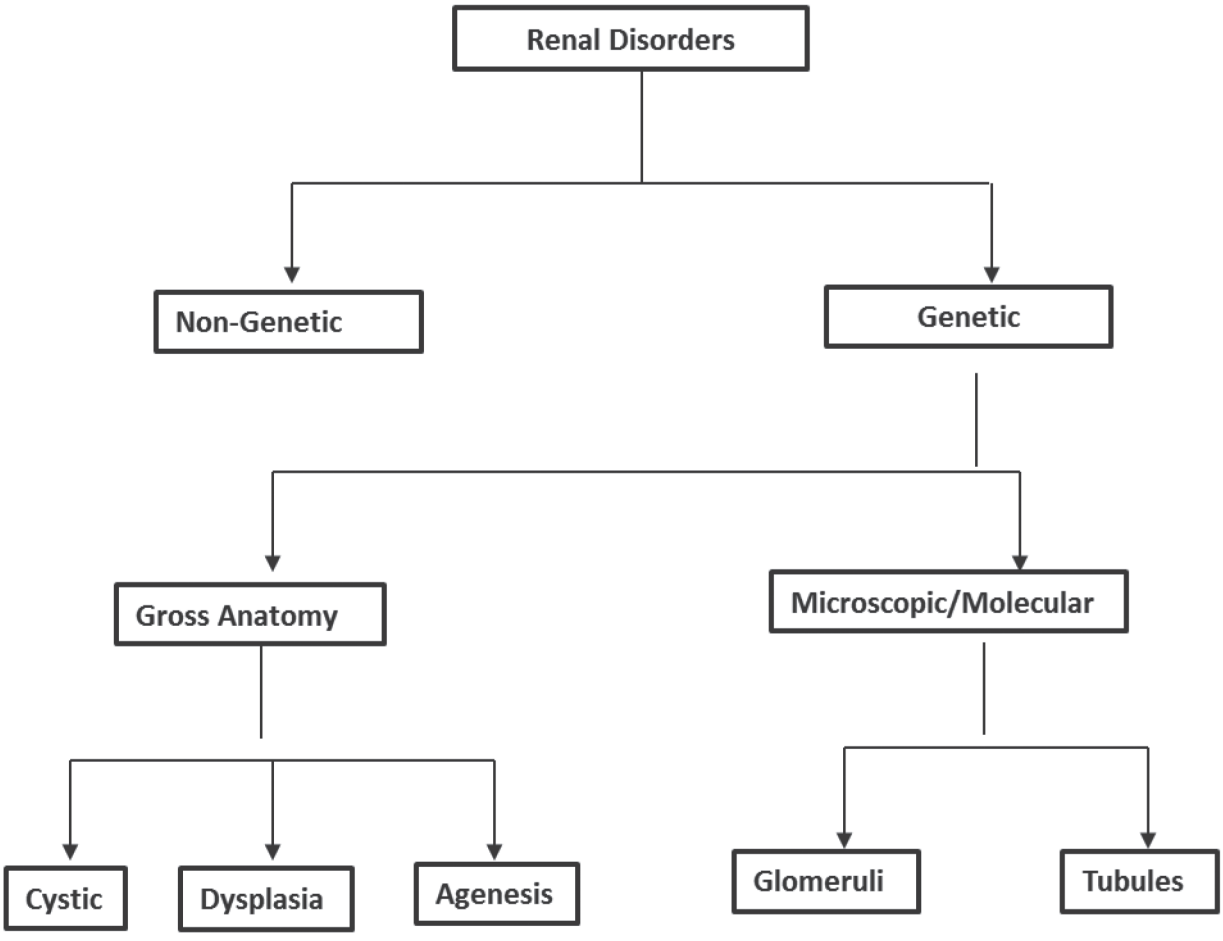

Figure 1. *Classification of the pathological effect of genetics renal disease.*

kidney disease in Saudi Arabia reached 2,540 or 2.92% of total deaths. The age-adjusted death rate is 25.45 per 100,000 of population ranks Saudi Arabia number 48 in the world.

Genetics of Saudi Population

Saudi Arabia is the largest Arab country occupying most of the Arabian Peninsula. It is bounded on the north by Jordan and Iraq and on the south by Yemen and Oman. It is bounded by the Red Sea on the west and Arabian Gulf (Persian Gulf) on the east. The country's total area (2,250,000 km²) is barren desert. The population is cosmopolitan and comprised of large and small minorities. According to the 2017 census, the Saudi population is estimated to be 32 million, 70% Saudi native and 30% expatriates, the majority of whom were Arabs. Those considered to be Saudi natives are the early settlers of the urban centers or those originating mostly from neighboring Arab countries in addition to Bedouins (the nomadic Arabs of the desert). Saudi Arabia has one of the highest growth rates in the world (approximately 400,000 live births per year). Typically, family size is large, with six children being an average number of offspring per family. Tribal communities are rather isolated and mainly include Bedouins population. It is estimated that eight tribes account for around 10% of the country's population. Islam is the predominant religion among Saudis. Despite the westernization affecting a considerable sector of the society, many still maintain their cultural ties and religious principles. Uncle-niece/aunt-nephew marriages are virtually non-existent as it is not permitted in Islam. Prenatal diagnosis and pre-implantation genetic diagnosis are acceptable for purposes of reassurance or of therapy. Many religious Muslim scholars discourage consanguineous marriages, but such marriages have been traditionally practiced over many generations because of social, economic, and geographical factors. In Saudi Arabia, the overall rate of consanguineous marriage is reported to be 57.7% with regional variation from a low of 34.0% to a surprisingly high of 80.6% (12–14). The most frequent pattern is first cousin marriages (28.4%) followed by distant relative marriages (15.2%) and second cousin marriages (14.6%) (12).

Molecular Studies of Inherited Kidney Disease in the Saudi Population

It is observed that genetic and congenital disorders are more common in Arab countries than in industrialized countries; recessively inherited disorders account for a substantial proportion of physical and mental handicap (15). The consanguinity rate together with a cultural preference for endogamous unions resulted in a high incidence of recessive disorders such as sickle-cell anemia, beta-thalassemia, inborn errors of metabolism, hereditary hearing impairments, and a multitude of novel Mendelian diseases (16,17). Many novel primarily recessive Mendelian diseases are also very evident in the Saudi population and characterization of new gene loci is facilitated in the population where the average family size is such that pedigrees with multiple affected individuals are readily available (18).

In 2014, Saudi Centre for Organ Transplantation Data reported the number of Saudi patients with end-stage kidney failure (ESKF) as 15,782 patients; 14,366 patients were treated by hemodialysis; and 1,416 patients were treated with peritoneal dialysis. Causes of renal failure among hemodialysis patients are presented in Table 1. The estimation of new affected cases is 136 for each million yearly (19).

In the Kingdom of Saudi Arabia (KSA), very limited epidemiologic data exist. Most of the studies conducted were describing clinical observation and statistics of inherited kidney diseases. Almost all of the studies published are from referral centers in regions. Preliminary observations indicate that children in Saudi Arabia probably have a higher incidence of PKD, familial juvenile nephronophthisis (NPHP), congenital urological anomalies, and familial NS (20–23).

NS is characterized by heavy proteinuria, hypoproteinemia, and edema. It is mainly steroid sensitive with the good outcome but it could be congenital or steroid-resistant (SRNS) with guarded prognosis progressing to ESKD in the majority of cases. SRNS is the second most likely cause of childhood ESKD. The incidence of familial cases is from 3% to 5% (24). Several genes have been implicated in inherited forms of NS occurring in children. Proteins encoded by these genes influence the function of the podocytes. Mutations in the *NPHS2* gene, encoding protein podocin, are a common cause of childhood SRNS. Patients with NS with homozygous or compound heterozygous mutations in the *NPHS2* gene have a reduced risk for recurrence after transplantation (25), indicating the clinical importance of a molecular genetic diagnosis. A molecular genetic diagnosis in families with SRNS is

Table 1. *causes of renal failure.*

Cause of renal failur`e	No.	%
Diabetic nephropathy	5,991	41.7
Hypertensive nephropathy	5,100	35.5
Unknown etiology	1,016	7.1
Primary glomerular disease	689	4.8
Obstructive uropathy	320	2.2
Hereditary renal disease	279	1.9
Congenital malformation	215	1.5
Primary tubulo-interstial disease	161	1.1
Vasculitis	183	1.3
Pregnancy related	110	0.8
Others	302	2.1
Total	14,366	100

useful for the clinician to decide further management as most of those with genetic mutations do not respond to immunosuppression. A molecular genetic diagnosis in such families should be requested to avoid subjecting children to unnecessary immunosuppression. Studying histological biopsies of patients with the glomerular disease was much abundant in many centers in the country. These studies concluded that minimal change disease and focal segmental glomerulosclerosis are the most common primary glomerular disorder encountered in children in Saudi Arabia (26–31).

Recently, the first molecular study of NS in KSA was published (32). The study detected likely causative mutations in 51% of families studied and found that the most common genetic cause of NS was a homozygous mutation in the *NPHS2* gene (22%). Mutations in the *NPHS1*, *PLCE1*, and *MYO1E* genes allowed a molecular genetic diagnosis in 12%, 8%, and 6% of families, respectively. Interestingly, another study from the western province involved a heterogeneous group of 44 children with SRNS (above 1 year of age; excluding congenital and infantile nephrotic) who were tested for *NPHS2*, *NPHS1*, and *WT1*. Presumably, disease-causing mutations were detected in five children (11.4%) of which three (6.8%) had *NPHS2* mutation and two (4.5%) had *NPHS1* mutation. The explanation was that other un-tested genes could be the underlying genetic cause (33). The international study by Hildebrandt group at Harvard medical school revealed that 45.2% of Saudi children with SRNS had underlying genetic cause compared to 25.6% of children from Germany and 21.3% of those Switzerland with the majority caused by other genes (not *NPHS2*, *NPHS1*, or *WT1*) (34). Using the whole exome sequencing, Hildebrandt group detected a causative mutation in a known SRNS gene in 38% of consanguineous families and in 13% of nonconsanguineous families, and 48% of children with congenital NS with the majority of other genes (35).

Progress over the last decade has led to an understanding of the role of primary cilia in normal mammalian development. The class of inherited disorders that involve aberrant ciliary function are known as ciliopathies, and although their range of severity can vary, they share some common and unexpected clinical phenotypes. The common feature for most ciliopathies is cystic change and dysplasia of the kidneys with a spectrum of clinical phenotypes. Ciliopathy diseases include PKD, Meckel Gruber syndrome (MKS), NPHP, Bardet–Biedl syndrome (BBS), and Joubert syndrome (JBT). Molecular studies of Saudi population were conducted lately for some of these disorders such as BBS (36), JBT (37), NPHP (38), MKS (39), Alport Syndrome (40), and cystic kidney in fetuses and neonate (41). These studies highlighted common genes and the frequency of mutations cause these syndromes in our population.

Other molecular studies were conducted as well and covered rare syndromes that have kidney phenotypes such as nephrogenic diabetes insipidus (NDI) and cystinosis.

NDI is a disorder of water balance. Individuals with NDI produce too much urine (polyuria), which causes them to be excessively thirsty (polydipsia). Ninety percent of inherited cases can be caused by mutations in the *AVPR2* gene in an X-linked recessive pattern of inheritance while remaining 10% can be caused by *AQP2* mutations in an autosomal recessive inheritance. This rare condition was diagnosed in Saudi families, and novel mutations were identified in both genes *AVPR2* and *AQP2* (42).

Cystinosis is an autosomal recessive disease characterized by the accumulation of the amino acid cysteine within cells. The kidneys and eyes are more vulnerable to damage than other organs. Mutations in CTNS, encoding cystinosin, are the only known cause of the disorder. Twenty-one patients from 13 Arab families were screened for mutations in the *CTNS* gene that revealed eight mutations, four of which are novel (43). The authors concluded that these mutations would provide the basis for the routine molecular diagnosis of cystinosis in the region.

The molecular genetic diagnosis has a role in families where stillbirth and early neonatal death have occurred; such cases are not uncommon in the Arabian Peninsula. Such devastating phenotypes need further understanding and investigation to allow insights into disease pathogenesis and to allow screening, if appropriate, of future pregnancies.

Bilateral renal agenesis is an example of neonatally fatal kidney disease. The failure of both kidneys to develop in utero results in oligohydramnios. The lack of amniotic fluid may cause compression of the fetus, further fetal malformations, and lethal pulmonary hypoplasia. Bilateral renal agenesis is more common in infants with a parent who has a renal anomaly, particularly unilateral renal agenesis. Studies have shown that unilateral and bilateral renal agenesis may be genetically related (44). For the isolated non-syndromic renal agenesis, only segregation studies have been performed and no loci and/or genes have been mapped so far. Physicians should try to get samples from those cases, and challenges arise when the pregnancy results in fetal death. Postmortem samples can be done in case of failure of getting amniocentesis or cordocentesis antenatally, which is the usual story due to oligohydramnios.

Congenital abnormalities of kidney and urinary tract (CAKUT) is another example of neonatal kidney disease and the underlying cause 50% of childhood (9). Here in KSA, it is estimated that CAKUT is the etiology of 45%–64.5% chronic kidney disease (CKD) and ESKD in children (41). Despite such a high number of cases with CAKUT, no molecular studies have yet started.

Collaborative research with researchers from developed countries led to KSA contribution to a better understanding of the genetic bases of some of rare renal syndromes and diseases, such as Schimke immuno osseous dysplasia (45), familial hypomagnesemia with hypercalciuria and nephrocalcinosis (46), NS (47), and renal tubular acidosis (48).

Future Approaches

The human genome has around 20,000 genes and around 180,000 coding exons. There are at present 3,500 known simple disease-causing genes. There are 1,800 genes with an unknown molecular basis, and 1,900 further genes suspected to be Mendelian inheritance genes. This points to the fact that there are more genes yet to be discovered and mechanisms of genes function yet to be investigated.

Molecular studies of renal disease are now widely available in KSA, therefore efforts should be concentrated on studying the frequency of mutations of known genes that cause specific renal phenotype; In addition, many renal diseases still offer research opportunity to discover the underlying causative gene(s).

There are many techniques to identify disease-causing genes. These include homozygosity mapping, LOD score analysis, association studies, candidate gene screening, Genome-wide knockdown studies, and whole exome sequencing. Here, we are not in a position to describe advantages and disadvantages of each technique, rather we suggest what we think is better for our population to prevent inherited kidney disease and advance our knowledge of molecular causes of unknown renal disease.

Because autosomal recessive (AR) diseases have strong genotype–phenotype correlations, the diagnostic approach of AR disease is a very powerful tool to manage and detect monogenic kidney disease. Therefore, mutational screening of known genes causing renal disease by sequencing would be an appropriate approach. Also applying customized gene panel for the renal disease would help enormously in solving many cases.

At the research level, we cannot suggest a single technique due to various different studies, resources and techniques available. At present, we think applying exome sequencing guided by linkage analysis (homozygosity and autozygosity mapping) would be the most appropriate approach considering many potentials and pitfalls in the genetic diagnosis of kidney diseases (40).

The estimated prevalence of ESKD in KSA is 1,100 per million population. This scary figure urges every healthcare providers to do his best to prevent ESKD in our population. Molecular diagnosis would help enormously in prevention and introduce early management which could ensure a better outcome.

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List of abbreviations

KSA:	Kingdom of Saudi Arabia
SRNS:	steroid resistant nephrotic syndrome
LOD:	logarithm of the odds (to the base 10)
SSNS:	steroid sensitive nephrotic syndrome

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