

Summary: Hereditary kidney disease comprises approximately 10% of adults and nearly all children who require renal replacement therapy. Technologic advances have improved our ability to perform genetic diagnosis and enhanced our understanding of renal and syndromic diseases. In this article, we review the genetics of renal diseases, including common monogenic diseases such as polycystic kidney disease, Alport syndrome, and Fabry disease, as well as complex disorders such as congenital anomalies of the kidney and urinary tract. We provide the nephrologist with a general strategy to approach hereditary disorders, which includes a discussion of commonly used genetic tests, a guide to genetic counseling, and reproductive options such as prenatal diagnosis or pre-implantation genetic diagnosis for at-risk couples. Finally, we review pregnancy outcomes in certain renal diseases.

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Approximately 10% of adults and nearly all children who undergo renal replacement therapy have an inherited kidney disease. Because of advances in technology, the diagnosis of genetic disorders has improved, enabling better understanding of the genetic causes of renal and other syndromic diseases. Renal disorders are unique in that patients are likely to reproduce, and therefore, it is important that they are aware of the potential to avoid or prevent transmission of genetic disorders to their children by using genetic testing. Despite recent advances in genetic testing, studies have shown that use of genetic testing is not as high as it can be, suggesting that awareness is lower than in other fields of medicine. This may be the result of several factors, including the perception that establishing the genetic cause will not affect management of the disorder.¹⁻³ To make options available to patients, accurate diagnosis of the precise genetic cause of the disorder is essential. Genetic disorders involving the kidneys are diverse and include chromosomal, monogenic, and multifactorial or polygenic causes. Patterns of inheritance are detailed in [Table 1](#). In this article, we review common genetic etiologies and commonly used genetic tests, and provide a guide to genetic counseling and reproductive options

for couples at risk to have a child with a genetic renal disorder. We also describe pregnancy outcomes of the best-studied inherited renal diseases.

CHROMOSOMAL DISORDERS AND COPY NUMBER VARIANTS

Chromosomal abnormalities or aneuploidy refer to abnormal dosage of genes, either in the form of whole-chromosome monosomies or trisomies, or partial monosomies/trisomies in the form of deletions and duplications. Such abnormalities generally present with syndromic or dysmorphic features, growth problems, birth defects, and developmental disabilities. Genome-wide scans for such imbalance, through the use of chromosomal microarrays, are used routinely for diagnosis to detect subtle microdeletions or duplications, termed *copy number variants* (CNVs), providing an additional yield of 10% to 15% if routine karyotype is normal. Renal structural anomalies are common in chromosome abnormalities. It is routine to screen individuals for renal anomalies by ultrasound in the setting of a chromosome abnormality. Examples of common chromosome abnormalities and recurrent microdeletions with renal involvement are provided in [Table 2](#). For example, microdeletion of chromosome 17q12 along with deletion of the *HNF1B* gene, as well as mutations in this gene, are a cause of structural renal abnormalities.⁴ Furthermore, the detection of several recurrent CNVs by microarrays, with variable expression and reduced penetrance for features such as birth defects, has led to the theory that these variants may represent susceptibility alleles that require other genetic hits or triggers before they are expressed.

MONOGENIC DISORDERS

Monogenic disorders, or genetic disorders caused by mutations in a single gene, typically follow an

*Division of Medical Genetics, Department of Genetics and Genomic Sciences/Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY.

†Division of Nephrology, Department of Medicine, Albert Einstein College of Medicine, Jacobi Medical Center, Bronx, NY.

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Address reprint requests to Lakshmi Mehta, MD, Division of Medical Genetics, Department of Genetics and Genomic Sciences/Pediatrics, Icahn School of Medicine, Mount Sinai Medical Center, Box 1497, New York, NY 10029.
E-mail: lakshmi.mehta@mssm.edu

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Table 1. Patterns of Inheritance

Type of Disorder	Chance of Inheritance in Each Pregnancy
Autosomal dominant	50%
Autosomal recessive	25%
X-linked in a woman	25% for affected son 25% for carrier daughter 25% for healthy son 25% for noncarrier healthy daughter
X-linked in a man	100% for daughters who are obligate carriers; sons will not be affected
De novo dominant	50%

autosomal-dominant, recessive, or X-linked inheritance pattern. In such disorders, genetic testing to establish the causative mutation can be complicated owing to allelic heterogeneity (many mutations in the same gene) or locus heterogeneity (many genes may be implicated for a phenotype). Molecular diagnostics for establishing a monogenic cause has evolved from the sequencing of an individual gene suspected to be the cause based on clinical suspicion, to sequencing many genes simultaneously using next-generation sequencing technology to accommodate a broad differential diagnosis. In recent years, whole-exome sequencing has led to the identification of novel genes for renal disease and expansion of the phenotypes and natural history of rare disorders. [Table 3](#) illustrates the use of sequencing technologies. Multiple additional technologies are available to enhance gene identification, such as homozygosity mapping using microarray technology. Identification of the precise genetic cause enables accurate genetic counseling and prediction of risks for affected children; furthermore, it allows for reproductive options such as prenatal diagnosis or pre-implantation genetic diagnosis (PGD). Several common monogenic renal disorders are reviewed briefly later, with regard to their genetics and inheritance patterns, as well as pregnancy outcomes.

Autosomal dominant polycystic kidney disease

Autosomal-dominant polycystic kidney disease (ADPKD) is one of the most common genetic diseases in human beings and may be caused by mutations either in the *PKD1* or *PKD2* gene, which encodes the polycystin-1 and polycystin-2 proteins, respectively. In approximately 90% of patients, the condition is inherited with a positive family history, whereas in 10% the disorder appears to be owing to a de novo mutation. ADPKD occurs with an incidence ranging from 1 in 400 to 1 in 1,000 persons.⁵ The average age of onset of ESRD for *PKD1* mutation is earlier than for *PKD2* mutation, with an average age of 54.3 versus 74 years.⁶ In patients with ADPKD, 85% are caused by mutations in *PKD1* whereas 15% are caused by mutations in *PKD2*. A rare contiguous deletion of the *PKD1* gene together with the tuberous sclerosis gene *TSC2* causes a combination of features of both diseases. The current testing strategy would be to sequence both genes simultaneously. Mutations are detectable in approximately 90% of patients who are tested, making it a viable diagnostic option when imaging studies and family histories are equivocal.

Pregnancy outcomes in women with ADPKD are varied. One study showed a higher incidence of hypertensive disorders of pregnancy in women with

Table 2. Renal Involvement in Chromosomal Abnormalities and Copy Number Variants

Disease	Chromosomal Anomaly	Renal Findings
Down syndrome	Trisomy 21	Hydronephrosis, multicystic kidneys, obstructive lesions, renal agenesis
Turner syndrome	Monosomy X	Structural: horseshoe kidney, duplication Vascular: hypertension, hypoplastic vessels, or aortic arch
Williams syndrome	Deletion 7q11	Asymmetric kidneys, solitary kidney, reflux, bladder diverticulae, nephrocalcinosis
DiGeorge/velocardiofacial Syndrome	22q11.2 microdeletion	Absent, dysplastic, multicystic kidneys, obstructive uropathy, reflux
CAKUT	17q12 deletion (<i>HNF1B</i>)	Multicystic, dysplastic, hypoplastic kidneys, renal agenesis, ectopic kidney, reflux, hydronephrosis

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