# Genetics, Genomics, and Precision Medicine in End-Stage Kidney Disease

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**Summary:** Recent advances in genetics of renal disease have deepened our understanding of progressive kidney disease. Here, we review genetic variants that are of particular importance to progressive glomerular disease that result in end-stage kidney disease (ESKD). Some of the most striking findings relate to *APOL1* genetic variants, seen exclusively in individuals of sub-Saharan African descent, that create a predisposition to particular renal disorders, including focal segmental glomerulosclerosis and arterionephrosclerosis. We also review the genetics of cardiovascular disease in ESKD and note that little work has been published on the genetics of other ESKD complications, including anemia, bone disease, and infections. Deeper understanding of the genetics of ESKD and its complications may lead to new therapies that are tailored to an individual patient's genetic profile or are discovered based on genetic approaches that identify novel pathways of renal cell injury and repair.
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End-stage kidney disease (ESKD) is the end result of diverse renal diseases and is attended by much morbidity and mortality. Mortality rates among dialysis patients are very high, as tracked by the United States Renal Data System. Table 1 shows the mortality rates among the general Medicare population, for individuals 65 to 74 years of age, with various conditions; the ESKD population has by far the highest mortality rate. Mortality rates are similar between hemodialysis and peritoneal dialysis patients, with death rates being 220 per 1,000 patient-years and 210 per 1,000 patient-years, respectively. Age-adjusted mortality rates, given here for 2015 and for individuals 65 to 74 years of age and on dialysis, are higher among European Americans (253) compared with African Americans (189; 25% lower) and others (166; 34% lower) (Table 2).

The lion's share of ESKD mortality is owing to cardiovascular disease (CVD). Several recent reviews have summarized the current state of knowledge in this area, including articles by Bansal[1] and Regunathan-Shenk et al,[2] with a focus on disadvantaged minorities, by Tuegel and Bansal,[3] Subbiah et al,[4] and a review of inflammation and premature aging in chronic kidney disease (CKD) by Kooman et al.[5]

Many genetic loci and variants have been associated with glomerular disease, tubular disease, and kidney function. Several excellent recent reviews are available; these include a review of the genetics of diabetic complications by Dahlstrom and Sandholm.[6] The focus of this article is to review what is known about the genetics of ESKD itself (as distinct from the genetics of nephrotic syndrome and systemic kidney diseases, all of which may progress to ESKD) and the genetics of three principal complications of ESKD (CVD, infection, and bone disease), and mortality among ESKD patients. Because much of the data were acquired via genomic studies (ie, genome-wide association studies), this review also draws from these studies. At this time, this body of work offers insights into possible mechanism of kidney disease and its complications, but as yet the field has not matured sufficiently that it can make recommendations that will affect the practice of medicine. This may change in the near future.

## GENETIC STUDY DESIGNS

As a brief review of genetic methodology, there are three principal approaches to finding genetic variants that are associated with disease.[7] First, family studies involve comparing the genomes of affected and unaffected family members. At present, this typically is performed by whole-exome sequencing, which will identify variants that affect the portion of the genome that codes for proteins. If the whole-exome sequencing approach does not provide an answer, then a whole-genome scan may be required to find variants in regulatory regions that might

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**Table 1.** Mortality Rates Among the Medicare Population: 2014 to 2015

| Morbidity | Mortality, deaths/1,000 patient-years | |
|---|---|---|
| | Males | Females |
| All Medicare | 27 | 18 |
| Dialysis | **223** | **211** |
| Transplant | 66 | 60 |
| Congestive heart failure | 112 | 101 |
| Acute myocardial infarction | 87 | 94 |
| Stroke | 72 | 57 |
| Cancer | 73 | 64 |
| Diabetes | 40 | 31 |

Death rates are shown for the general Medicare population (age, 65−74 y) from 2014 to 2015, adjusted for race. Dialysis patients (indicated in boldface) included both hemodialysis and peritoneal dialysis patients; these patients have the highest mortality rates among any large disease population receiving Medicare.
Reprinted from US Renal Data Systems Report, 2017, Table 5.5.[51]

explain the disorder, although given the length and complexity of the human genome, this can be challenging. Second, for common diseases for which hundreds or ideally thousands of cases can be assembled, a genome-wide association study (GWAS) may identify common variants present on the array that are in linkage dysequilibrium with the as-yet-unknown disease variant, and these common variants suggest the genomic location of the disease variant.[8] Third, a particularly powerful version of GWAS, termed *mapping by admixture linkage disequilibrium* (MALD), can identify disease-associated variants in an admixed population.[7] MALD can be used only for diseases showing disparities in prevalence between the two ancestral populations contributing to the admixture (eg, ESKD in African Americans). The underlying hypothesis is that the causal variant will be more frequent on a chromosomal segment derived from the population with the higher disease prevalence. An admixed population carries ancestry from at least two distinct population groups that have been genetically isolated from each other for sufficient time for the processes of selection pressure or genetic drift to have led to genome-wide differences between the two study populations, in both coding and noncoding regions of the genome. The study design involves comparing cases and controls, all drawn from the same admixed population, genotyping for single-nucleotide polymorphisms (SNPs) differing in frequencies between the two population groups, and looking for substantial differences in local ancestry between the two study groups to localize a genomic region harboring the ancestry-specific causal variant.

## GENETICS OF END-STAGE KIDNEY DISEASE

There is strong evidence for a genetic contribution to ESKD risk. A Swedish study identified 971 ESKD cases among adoptees, and studied the probands, their biologic parents, and their adoptive parents.[9] For adoptees of biologic parents with ESKD, the odds ratio (OR) for ESKD was 6.1 (95% confidence interval [CI], 3-14), whereas the OR for ESKD was not significant for adoptees whose adoptive parents had ESKD. These findings suggest a strong genetic contribution to ESKD. Furthermore, African Americans, and indeed individuals with sub-Saharan African heritage and particularly those with West African heritage, living around the world, have a substantially higher risk for ESKD; the responsible locus was identified using the MALD approach and the mechanism for much of this risk involves *APOL1* genetic variants, as will be discussed later.

It should be noted that genetic studies that recruit ESKD patients and compare them with non−kidney disease controls generally are unable to distinguish between genetic variants that increase the rate of progression to ESKD (thus, reducing the number of such subjects who die before reaching ESKD, all other things being equal) and those that increase the propensity to have any degree of progressive glomerular injury, resulting in ESKD. Although it may not matter practically from an epidemiologic perspective, the underlying biology may differ.

### Diabetic Nephropathy

Many studies have sought genetic variants that are associated with diabetic nephropathy but fewer studies have

**Table 2.** Racial/Ethnic Differences in Death Rates Among Dialysis Patients

| Age group, y | White | Black | Black/White death rate ratio | Other |
|---|---|---|---|---|
| 0-21 | 10 | 18 | 1.8 | 8 |
| 22-44 | 33 | 44 | 1.3 | 18 |
| 45-64 | 100 | 100 | 1 | 74 |
| 65-74 | 221 | 175 | 0.79 | 142 |
| ≥75 | 358 | 272 | 0.76 | 235 |

The all-cause mortality rates shown are from dialysis patients during 2015, expressed as deaths per 1,000 patient-years. Note that the black/white mortality rate ratio among dialysis patients was numerically higher among individuals <45 years of age, whereas the rate was numerically lower among those ≥65 years of age. The reasons for these disparities, and their shifts over time, are not well understood.
Reprinted from US Renal Data Systems Report 2017, Table 5.2.[51]