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Genetics and the Kidney: Promise, Potential and Challenges

INTRODUCTION

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Our interest in the genetics of chronic kidney disease was driven by a question that repeatedly arises in the clinic, “Which of my patients with a systemic disease that can involve the kidneys will develop progressive nephropathy?” For example, we can focus on two patients with longstanding diabetes mellitus, a condition all too familiar to the practicing nephrologist. Despite equally poor glycemic and blood pressure control, they exhibit markedly different patterns of complications (phenotypes). One patient has a lower extremity amputation with stage 5 chronic kidney disease; while the second has normal kidney function and normoalbuminuria with mild diabetes-associated retinopathy. This scenario is all the more striking when the patients are close relatives, concordant for diabetes but discordant for its serious micro- and macrovascular complications. These two patients with the same disease process had vastly different outcomes. Presented with this scenario, a number of clinician-scientists hypothesized that an individual’s genes could prove to be the Rosetta stone, solving the puzzle and leading to cost-effective and patient-specific care

Is chronic kidney disease genetically mediated? Familial clustering of chronic kidney disease was first reported approximately 20 years ago ¹. A series of seminal studies built on this observation demonstrated that familial clustering was a characteristic of virtually all common forms of kidney disease and could not be explained by clustering of diabetes, hypertension or environmental exposures ^{2,3}. Formal analyses of broad sense heritability and family segregation demonstrated that chronic kidney disease pathogenesis, similar to other common diseases ⁴, was partly regulated by inherited factors. Gene mapping studies rapidly ensued. Single center studies and large consortia used a variety of gene mapping methodologies and reported a long list of linked and associated genetic loci and variants. The original studies were plagued by lack of reproducibility ⁵. In retrospect, these efforts were often hampered by poor understanding of the genetic architecture of common complex genetic traits, inadequately powered sample sizes and genotyping platforms which were insufficiently robust to identify variants responsible for common disease.

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The last decade has seen rapid discoveries and technological innovations in human disease genetics⁶. Breathtaking advances have better defined the genetic architecture of many chronic diseases affecting our patients⁷. Concomitantly, the challenges of translating these discoveries into the clinical arena have become evident⁸. The euphoria that initially accompanies significant medical discoveries can dissipate as investigators and practitioners recognize that understanding the function of a genetic variant in disease pathogenesis or predicting the disease course of a given patient requires additional investigation⁹.

This issue of *Seminars in Nephrology* reviews key recent discoveries in the genetics of chronic kidney disease. The discovery that variants in the *MYH9*, which encodes the myosin 2A motor protein, associated with non-diabetic kidney disease in African American patients has led to new insights in the pathogenesis and treatment of the disease historically known as hypertensive nephrosclerosis^{10–12}. The interested reader should be aware that the field of chronic kidney disease genetics is rapidly evolving and major investigative consortia from around the world are now reporting their findings, which are replicated and highly significant even after adjustment for multiple comparisons on a genome-wide scale. For example, since this issue was planned, the CHARGE consortium reported robust association of variants in the gene encoding Tamm-Horsfall protein (*UMOD*) with reduced kidney function in four population-based cohorts comprising nearly 20,000 subjects¹³. We also asked distinguished investigators outside of the field of nephrology to highlight the issues confronting translation of genomic data into clinical practice, including the use of genetic data for prediction and patient responses to information concerning their genetic risk.

So the genome is now out of the bottle. The notion of personalized medicine and use of genetic variants to diagnose, manage and treat disease is inculcated into the popular culture. The *New York Times* reported cocktail parties attended by Wall Street elite promoting DNA testing direct-to-consumers¹⁴ and public radio broadcasts programs on the social and medical implications of genetics and race¹⁵. As physicians, our goal for the two hypothetical patients described above is to empower the individual at greatest risk for nephropathy to modify all remediable risk factors prior to the onset of clinical disease, while sparing the individual genetically programmed not to develop kidney disease the toxicities of unnecessary intervention. However, a great deal of thoughtful, multidisciplinary basic and patient-oriented research remains to be performed in order for us to declare success. Hopefully these papers will spark the innovation and creativity needed to help move these discoveries into the mainstream of medical care for patients.

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