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Translating associations between common kidney diseases and genetic variation in to the clinic

Paul E Drawz, MD, MHS, MS¹ and John R Sedor, MD²

¹ Division of Nephrology and Hypertension, Case Western Reserve University, Cleveland, OH, USA

² Department of Medicine, MetroHealth System Campus; CWRU Center for the Study of Kidney Disease and Biology; Department of Physiology and Biophysics, School of Medicine, Case Western Reserve University, Cleveland, OH, USA

Abstract

Studies of the genetics of common diseases have revealed multiple risk alleles associated with end-stage renal disease, albuminuria, serum creatinine, diabetes, coronary heart disease, and elevated triglycerides. These associations have prompted further basic science research, which has led to the discovery of novel pathways and a better understanding of the pathophysiology of common diseases. Currently, the ability to translate these discoveries into clinical practice is limited by the small effect size of these risk alleles and a lack of studies demonstrating meaningful impact of genetic variation on risk assessment and clinical outcomes. Advances in genetic testing will continue to yield highly significant associations but translation into clinical practice will require effective collaboration between physicians and basic and social scientists. Rigorous clinical trials will eventually reveal which combination of genetic tests improves risk stratification and identifies individuals most likely to benefit from specific prevention strategies and therapies.

Keywords

risk assessment; genetics; nephrology; prediction; clinical utility

Introduction

Reports of genetic variants associated with common disease traits have exploded of the last 36 months. Multiple risk alleles, which are common single nucleotide polymorphisms (SNPs) within the studied population samples, have been associated with diabetes (1), coronary heart disease (2), obesity (3), elevated triglycerides (4), and renal function and chronic kidney disease (CKD) (5–10). Additionally, rare heterozygous SNPs within genes, known to cause Bartter's and Gitelman's syndromes, produce clinically significant blood pressure reduction and protect from development of hypertension in a community-based population sample (11). Other types of genetic variation, deletions and copy number variants, have also been associated with diseases that commonly afflict our patients.

Corresponding author: John R Sedor, MD, Center for the Study of Kidney Biology and Disease, 2500 MetroHealth Drive R415, Cleveland, OH 44109-1998, john.sedor@case.edu, Phone: 216-778-4993, Fax: 216-778-8248.

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The impact of these discoveries on individual or public health has yet to be demonstrated. For some diseases, these associations have identified novel pathways of disease pathogenesis, such as complement activation in age-related macular degeneration and defects in autophagy and the interleukin-23/interleukin-17 effector pathways in Crohn's disease (12). However, translating these discoveries into clinically useful tests has proven difficult (13). When evaluated as "stand-alone" predictors of disease, risk alleles typically perform poorly with an area under the receiver operating characteristics curve (AUC) often ≤ 0.60 , a level too low to have any clinical utility (14–17). Even addition of genetic markers to clinical prediction models has led to little or no improvement in the models' ability to discriminate between patients who do and do not develop disease (16–19). Despite the fact that hundreds, if not thousands, of genetic risk markers may be required to fully explain genetic variation, it is likely that genetic testing will eventually play an important role in the prevention and treatment of common diseases (13,20).

Genetic architecture of Mendelian and common disease traits differ: challenges for clinical utility

For decades, genetics focused mainly on relatively rare Mendelian disorders. This line of investigation led to important discoveries, such as the gene for cystic fibrosis (21), which caused disease. These early investigations were limited by the available technologies and primarily focused on families with multiple individuals affected by the disease of interest. With the advent of high-throughput and rapid sequencing genotyping technologies, the ability to evaluate multiple genetic variants in large cohorts at significantly reduced cost has provided geneticists the power to identify common genetic variants associated with diseases frequently seen in the clinic. Common variants are typically considered to be present in greater than 1 to 5% of the population (22,23). These advances have shifted the focus from rare Mendelian disorders to common diseases such as diabetes, coronary heart disease, and chronic kidney disease. The two most common methods for evaluating the association between genetic variants and common disease phenotypes are genome-wide association scans (GWAS) (23) and mapping by admixture linkage disequilibrium (MALD) (24,25) (see articles by Adler *et al*, Winkler *et al* and Freedman *et al* in this issue for a description of these analytic designs). Using the map of genetic variation developed by the HapMap investigators and capitalizing on allele frequency differences between individuals of with African, Asian, and European ancestry, investigators can effectively evaluate for associations between specific diseases and genetic variants throughout the genome.

Both GWAS and MALD involve the identification of loci within the genome where variation is common. The variation at these loci, referred to as single nucleotide polymorphisms or SNPs, is rarely directly associated with change in a gene's expression, structure, or function, and most often, SNPs are not located within a coding region. That is, these types of genetic variation have not provided a mechanism for the disease. However, investigators have hypothesized that variations in nearby alleles, inherited with the associated sentinel SNP, regulate disease risk, severity or progression (22), a premise that remains speculative. Almost all genetic variants demonstrated to be associated with common disease phenotypes are small effect, that is, these alleles only explain a small amount of the phenotypic variation in patients with disease.

GWAS and MALD association studies have resulted in the discovery of multiple common, low effect traits for conditions such as diabetes (1), coronary heart disease (2), obesity (3), elevated triglycerides (4), and CKD (detailed below) (5–10). In diabetes for instance, a GWAS of 14,586 cases and 17,968 controls revealed associations between development of type 2 diabetes and 10 susceptibility loci with odds ratios between 1.12 and 1.37 (1). Another illustration of the discovery of multiple common, small effect traits comes from a GWAS which identified 20 polymorphisms associated with height (26). Despite a large number of highly

significant associations, these alleles in aggregate explain only 3% of the variation in stature, a small fraction of the estimated 90% heritability (26). Two possible explanations for the “missing” heritability include rare variants with large effect size and/or multiple variants with smaller effects. Current studies are underpowered to detect either possibility (27).

Given the low effect size of most genetic variants identified by GWAS, it is not surprising that addition of genetic markers to prediction models has led to little or no improvement in clinical prediction models as measured by changes in AUC, also known as the C-statistic (16–19). The AUC is a measure of how well a risk stratification model discriminates between those who do and do not develop a disease. A perfect model will have an AUC of 1 while a model that is no better than chance will have an AUC of 0.50. An AUC greater than 0.80, 0.70 to 0.79, 0.60 to 0.69, and 0.50 to 0.59 indicate excellent, good, fair, and poor predictive ability, respectively. Prediction model evaluation has traditionally involved an evaluation of the AUC (28).

However, while many investigators measure the change in AUC with the addition of new markers, evaluation of change in AUC is insensitive to small changes in model improvement for risk stratification models that already have moderate to high levels of discrimination, even with the addition of highly significant biomarkers (29,30). Other methods for assessing improvement in risk stratification have been developed and include net reclassification improvement (NRI), a measure of how accurately two models classify subjects into clinically meaningful categories (29). Future studies evaluating the impact of genetic markers on clinical prediction should take these considerations into account. Once a genetic marker or set of markers have been shown to improve risk stratification, clinical trials will be needed to evaluate whether prevention strategies and treatments are effective for high and low risk patients.

Genetic variation and common renal phenotypes: current status

This topic has been addressed by the other contributions in the *Seminars in Nephrology* issue. Briefly, multiple investigators have attempted to identify genetic markers associated with renal function, quantified by serum creatinine, creatinine clearance, estimated glomerular filtration rate (GFR), and albumin to creatinine ratios. Many of these studies have been conducted in populations where the majority of subjects have normal renal function. In the Framingham population, broad sense heritability, a measure of the contribution of genetic variation to a phenotypic trait, was estimated to be 0.33 for GFR, and linkage analysis identified regions for GFR regulation on chromosomes 3, 4, and 11 (peak LOD score 2.28 with > 3.3 considered significant) (7). A study in West Africans with diabetes estimated heritability of GFR to be 0.57 and found one marker on chromosome 16 that achieved a significant LOD score of 3.56 (6). Among three isolated European populations, significant linkage to serum creatinine was shown on chromosome 22q13 (LOD score 3.43) (5).

The most significant break through in CKD genetics occurred with the discovery that variants within the gene encoding the non-muscle myosin heavy chain type II isoform A, *MYH9*, are associated with non-diabetic renal diseases in African American patients (see articles by Freedman *et al* and Winkler *et al* in this issue). In contrast to genetic variants associated with other common diseases, much of the excess risk associated with non-diabetic ESRD in African Americans may be explained by an increased prevalence of *MYH9* risk alleles (31). The mechanism by which *MYH9* variants cause kidney disease remains unclear. *MYH9* is expressed not only in the kidney but also in the liver and platelets (31). In the kidney, *MYH9* is localized to the glomerulus, specifically the podocyte, but is also found in arteriolar and peritubular capillary endothelial cells (32). *MYH9* is associated with non-diabetic end-stage renal disease (ESRD), hypertensive ESRD, albuminuria in hypertensive African American patients, and focal segmental glomerulosclerosis (31,33–35). A subsequent study of African American kidney disease patients found *MYH9* to be significantly associated with hypertensive

ESRD and the addition of three *MYH9* SNPs to a prediction model including age, gender and admixture significantly improved the AUC, although only to 0.70 (33).

MYH9 is one of a few “successes” from early genome wide association analyses with kidney disease phenotypes. The initial findings are robust. The association with renal disease has been replicated in multiple cohorts and for different definitions of disease; its contribution to disease pathogenesis in African American CKD patients appears to be significant. The gene product localizes to the glomerulus and its function is known and can plausibly be implicated in renal dysfunction. Further research is required to more specifically define the protein function, biologic significance, and determine if the marker improves clinical risk assessment. Finally, clinical trials need to be undertaken to assess whether certain treatments benefit patients with and without the risk allele. Given that *MYH9* variation explains much of excess risk for end stage renal disease, investigators are optimistic that genetic testing may be useful in clinical nephrology practice.

Clinical prediction in nephrology – current status

The development of prediction models for kidney diseases is in its infancy compared to other fields such as cardiology where the Framingham equation has been refined, evaluated in multiple cohorts, and is used to guide therapy for dyslipidemia (36–38). In nephrology, two prediction models have been recently developed, one for prevalent CKD, one for incident CKD (39,40). Using data from the National Health and Nutrition Examination Surveys, a prediction model for prevalent CKD was developed that included demographic information and past medical history (39). The model had excellent discrimination on internal validation (AUC 0.88) but only good performance when validated in a population from the Atherosclerosis Risk in Communities Study (ARIC; AUC 0.71) (39). For the incident CKD prediction model, investigators pooled subjects from ARIC and the Cardiovascular Health Study (40). The prediction model, again using demographic information and past medical history, displayed moderate discrimination in a 1/3 validation sample (AUC 0.68–0.70) (40). Whether the addition of risk alleles such as *MYH9* will improve the predictive ability of these models is unknown and awaits clear understanding of the genetic architecture of chronic kidney diseases.

Genetic variation in common diseases: pointing to new pathogenetic pathways and explaining variation in treatment response

While the current clinical utility of genetic risk alleles identified from genome-wide association studies is minimal, these studies have advanced our understanding of the pathophysiology of common diseases and shown potential for translating into clinical practice in the near future (12). For example, *MYH9* is associated with non-diabetic ESRD, hypertensive ESRD, FSGS, and albuminuria in hypertensive African Americans but not diabetic ESRD (31,33–35). These results suggest that the mechanisms underlying the pathogenesis and progression of renal disease differ depending on the etiology. These results have important implications for the study of new prevention and treatment strategies for CKD as results may differ based on *MYH9* status.

Another example of a genome-wide association study revealing underlying pathophysiology comes from a study of patients with type 2 diabetes. SNPs associated with transcription factor 7-like-2 (*TCF7L2*) were found to be associated with risk for type 2 diabetes (41). *TCF7L2* is linked to the Wnt signaling pathway and is expressed in pancreatic β -cells; subjects with two risk alleles had decreased insulin secretion (41). These findings underscore the importance of β -cell function in the pathogenesis of type 2 diabetes. In a post-hoc analysis, investigators stratified diabetic patients, entered into a clinical trial comparing the efficacy of a sulfonylurea with metformin, by *TCF7L2* risk allele status. The hypothesis predicted that sulfonylureas would be less effective in patients with the *TCF7L2* risk allele due to β -cell dysfunction. Among

patients taking sulfonylureas, carriers of the *TCF7L2* risk allele were less likely to achieve an $A1c < 7\%$ whereas there was no difference in response rate by risk status among patients taking metformin (41), a drug that does not target the β -cell. These studies raise the possibility of customizing diabetes treatments on the basis of *TCF7L2* status but again, further studies are needed.

Sustained virological response (SVR) after treatment for hepatitis C is another example of genetic variation predicting response to therapy and elucidating underlying pathophysiology. Clinical wisdom states African American patients with hepatitis C respond poorly to antiviral therapy. Interferon- λ proteins had previously been shown to have antiviral activity (42). A genome-wide association study found that SVR was strongly associated with a SNP 3 kilobases upstream of the *IL28B* gene, which encodes interferon- λ -3 (43). As with *MYH9*, a significant proportion of the difference in SVR observed between African Americans and European Americans could be explained by the *IL28B* polymorphisms (43). This study is instructive in defining potential use of genotyping for common variants in clinical practice. The effect of the *IL28B* variant is similar across the different population groups, but the treatment-responsive variant is found at a lower frequency among African-American groups. However, African-American hepatitis C patients with the treatment-responsive variant do respond to therapy and are more treatment-responsive than are European-American subjects with the less responsive genotypes. Therefore a genetic variant associated with a clinically important trait, not simply race, explains treatment response. Given this observation, development of controlled clinical trials to prospectively evaluate the utility of *IL28B* variants in management of antiviral therapy for hepatitis C would be indicated.

Both *TCF7L2* and *IL28B* are examples of variants that may have low effects on risk for disease but are clinically significant because genetic variation in these may be useful to define therapy. It is likely that one of the major impacts of current genome-wide association studies in the area of common diseases will be through increasing our understanding of the pathophysiology of common diseases and identification of targets and pathways for drug development. These studies model approaches to test utility of *MYH9* genotyping in clinical nephrology practice.

Future directions: prospects for “personalized” medicine in nephrology

Despite the fact that the goal of “personalized” medicine has not yet been realized, numerous discoveries and advances have already come out of the genetic association studies that have been reported. Using refined and more efficient techniques, including deep sequencing, ongoing studies will likely continue and even accelerate the discovery of risk alleles associated with common diseases. These discoveries are the first step in a process that branches to include basic research into the underlying biologic mechanisms and clinical research translating these discoveries into prediction models for clinical use (see Figure 1). Additionally, work is underway on the next phase of genetic studies which involve whole genome sequencing. A multinational effort is ongoing to sequence the entire genome of over 1000 individuals (www.1000genome.org). The results will be publicly available and serve as a reference for investigators interested in regions of the genome that have previously been linked to diseases. Furthermore, a number of kidney disease cohorts with detailed phenotype data and ample samples for current and future genetic studies have been developed including Family Investigation of Nephropathy and Diabetes (FIND) (44), the Epidemiology of Diabetes Interventions and Complications Study (EDIC) (45), and Genetics of Kidneys in Diabetes Study (GoKinD) (46) and the Chronic Renal Insufficiency Cohort (CRIC). Additionally, the recently funded Nephrotic Syndrome Study Network, or NEPTUNE, will focus on focal segmental glomerulosclerosis, minimal change disease, and membranous nephropathy. These and other studies will invariably accelerate the discovery of risk alleles for numerous common kidney diseases.

The discovery of an association between a genetic marker and risk for a disease or risk for progression or complication of a disease should initiate basic and clinical research with the goal of translating these discoveries into results that are clinically applicable. Basic research including more refined association studies and sequencing is required to identify the gene or mechanism specifically responsible for the association. Once the gene or mechanism has been identified, studies of protein structure and function and associated biologic pathways may reveal potential drug targets which will be yet another impetus for clinical research.

The identification of significant risk alleles should initiate trials to assess the impact of these genes on clinical risk assessment, not just their isolated sensitivity and specificity. Studies are necessary to evaluate the impact of these new variables when added to prediction models that include available demographic and clinical variables. Most importantly, do the new genetic markers *improve* our ability to discriminate between those who do and do not develop diseases or progress to clinically meaningful outcomes? Simply because an allele is found to have a large odds ratio does not mean it will improve risk classification (30,47). Without an assessment of the accuracy of risk stratification, future studies targeting “high” risk groups will be difficult to interpret because of uncertainty regarding possible misclassification of subjects as “high” risk as well as difficulty in practically translating the results of genetic tests into an accurate risk assessment that can then be communicated to patients.

Once accurate prediction models are developed, studies will be required to evaluate whether risk can be modified by targeted interventions such as intense lifestyle modifications, medications, or procedures. For instance, patients identified as high risk for breast cancer may benefit from tamoxifen (48) or even bilateral prophylactic mastectomy (49) as is considered for women with BRCA1/2 mutations. However, randomized-controlled clinical trials evaluating the impact of these interventions on important outcomes are required before such an approach can be advocated. Without rigorous clinical research, it will be difficult and even controversial for clinicians to translate genetic risk into therapeutic recommendations (50). Another issue with possible recommendations, especially for prevention, is most current prevention strategies, such as diet, exercise, and smoking cessation, benefit all patients. Unless new prevention strategies are identified that specifically benefit patients with certain risk alleles, the cost of genetic testing will likely outweigh any benefit given current non-specific prevention strategies.

Two additional approaches will likely lead to the discovery of important associations in the field of common diseases. First, combining data from multiple cohorts will allow for studies that are powered to detect common variants with small effects and rare variants with large effects that are associated with common diseases. Second, as sequencing technology continues to become more efficient and less expensive, deep sequencing in regions that are known to be associated with common diseases will reveal more specific information about the alleles that confer risk for disease. Knowledge of the exact risk allele will provide for more accurate assessment of associations with disease and facilitate basic research into the underlying pathophysiology. Eventually, as the number of known risk alleles increases, the cost of genetic testing decreases, and interventions targeting specific risk profiles are developed, physicians will be able to provide patients with preventive and treatment strategies tailored to their disease as defined by their clinical and genetic profiles.

Conclusion

Genetic studies are revealing numerous associations between polymorphisms and common diseases. These initial discoveries are hypothesis generating. Only through vigorous basic and clinical research will these findings from genetic studies be translated into the evidence needed to practice “personalized” medicine.

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Figure 1.

Basic and clinical research initiated as a result of identification of a risk allele associated with a common disease