tions that may occur globally or locally, if a subset of sodium pumps are a part of specialized microdomains in such cells, or they may involve the postulated actions of the sodium pump as part of a signaling complex that responds to ouabain occupancy by activating intracellular signaling cascades. It is likely that all three mechanisms occur in a variety of physiologic situations.

It is clear today that the sodium pump, the first protein discovered as an ATP-dependent active ion transporter, whose ion pumping is central to renal function plays a more complex role in the regulation of salt and electrolyte homeostasis than previously recognized. The modulation of its actions by endogenous inhibitors has profound effects on cardiovascular and renal function. Identification of these endogenous modulators will be an exciting next step in better understanding their role in renal physiology.

DISCLOSURES
None.

REFERENCES


Appraising the Value of Genomic Association Studies

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Approaches to identify genetic determinants of disease susceptibility have evolved considerably in the past two decades. Pedigree-based linkage analysis and positional cloning strategies for finding genes responsible for Mendelian disorders caused by defects in single genes (monogenic) have now given way to a new era of genome-wide association studies (GWAS). These latter studies are designed to map loci conferring risk for more common, genetically complex diseases. Each of these approaches is fundamentally distinct, operate with contrasting assumptions, and generate results with different implications for clinical medicine.

In Mendelian disorders, rare genetic variants, usually referred to as mutations, confer a major portion of disease risk. Monogenic disorders make it feasible to construct a precise genotype–phenotype relationship and enable genetic testing to assess the probability of disease occurring in individuals and the first-degree relatives of an affected proband. Effective genetic counseling is plausible in this setting; however, monogenic mutations causing Mendelian disorders have limited value in predicting risk for disease in general populations because of the rarity of such alleles. For analysis of risk in populations, genome-wide associations are used as a probative tool based on a “common disease–common variant” hypothesis.

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This hypothesis assumes a major portion of population risk for a common disease is conferred by a limited number of common genetic variants with minor allele frequencies $>5\%$, but the value of knowing specific genotypes for predicting risk in individuals on the basis of information extracted from population-based genomic association studies is also uncertain. A competing theory, the “common disease–rare variant” hypothesis, posits multiple rare variants confer risk for common diseases. This latter hypothesis has gained little traction so far but may catch on with widespread use of rapidly evolving, next-generation DNA sequencing technology.

Just in the past 2 yr, there have been >100 published findings from GWAS in diabetes, inflammatory bowel disease, various cancers, and ischemic heart disease, along with many other disorders and traits. The most robust results have been replicated in independent populations, providing assurance these are not spurious associations; however, a frequent observation is common variants account for only a small proportion of population-attributable risk, or the reduction in disease incidence that would occur in the absence of the variants.

In most published studies of this type, risk among carriers of common variants is estimated by an odds or hazard ratio with typical reported values being $<1.5$, suggesting that no single common risk genotype or haplotype has much predictive power by itself. In other words, statistical significance in these studies does not easily translate into results that are meaningful clinically. This conundrum is crucial to understanding the limitations in using results from any single GWAS for predicting individual disease susceptibility, although the financial success of several direct-to-consumer genetic testing companies depends on ignorance of this principle.

Despite the relatively weak predictive value of common variants identified in association with common diseases using genome-wide association, there remains high hope that identification of new disease susceptibility loci will provide additional insights into the biologic basis of common disorders and illuminate new therapeutic targets. Take, for example, the identification of common alleles in the transcription factor $\mathbf{7}$–like 2 gene (TCF7L2) that is associated with risk for type 2 diabetes. Originated in an Icelandic population, the association of TCF7L2 with diabetes has been replicated in many other geographically and ethnically diverse groups. Variants in this gene may also exert other effects, such as in the response to certain classes of hypoglycemic agents. There have also been separate associations with colon cancer, demonstrating the potential for pleiotropic effects of this genetic susceptibility gene. Perhaps this is not too surprising given that TCF7L2 encodes a ubiquitous transcription factor participating in the Wnt signaling pathway.

Could this gene be associated with renal function traits or susceptibility to developing chronic kidney disease in the setting of diabetes or other conditions? In this issue of JASN, Kötten et al. address these questions by testing TCF7L2 variants for associations with renal function in three large populations ascertained originally for epidemiologic studies of heart disease. Their study reveals significant associations with reduced renal function or progression of chronic kidney disease among all participants but also among a subset of individuals without diabetes, raising the intriguing notion that genetic variation in TCF7L2 predisposes to renal dysfunction independent of its effect to increase risk for overt diabetes. Even though the level of risk conferred by TCF7L2 variants (hazard ratios ranged from 1.17 to 1.27 per copy of the risk allele) will probably not be useful in making clinical predictions regarding the risk for developing kidney failure in individuals, this finding does open our eyes to the possibility that there may be fundamental disease susceptibility pathways that underlie risk for both diabetes and renal dysfunction occurring either separately or together.

What is beyond GWAS? The current growth in identified disease susceptibility loci will eventually slow down, but the work needed to decipher the meaning of these findings in biologic and clinical contexts will likely go on for decades. It remains unclear whether knowledge of individual genomic profiles will affect clinical decision making more so than currently available information, such as a detailed family history. For perspective, consider that the odds for having type 2 diabetes is approximately 1.5 times greater among heterozygous carriers of the most informative TCF7L2 variant, whereas simply knowing that one parent has the disease offers 3.5 times greater odds.

Predictive medicine has often been cited as a likely benefit of the genomics revolution, but the GWAS avalanche may not fulfill this promise. Indeed, some are now pointing away from the predictive value of GWAS results and focusing attention more on the elucidation of new “druggable” pathways in common diseases. In the case of TCF7L2, further progress in unraveling its underlying biology and physiology may eventually reveal novel drug targets.

Understanding the basis for genetic susceptibility to common diseases requires much more than knowing the findings reported out of numerous, high-profile GWAS. More extensive consideration of gene–gene interactions (epistasis), gene–environment interactions, and the role of epigenetic influences on gene expression all will be critical. Clinical decision analysis incorporating the latest findings from GWAS may eventually help in appraisal of the value of these data in what might be a new era of evidence-based genomics.

DISCLOSURES

None.

REFERENCES


Multitarget Therapy of Lupus Nephritis: Base Hit or Home Run?

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In the Fall of each year, the attention of many Americans is diverted to their national pastime—baseball—and to base hits and home runs. The former often lack any definitive impact on the outcome of the game, but the latter usually have a decided effect, noted immediately. This analogy has its parallel in therapeutic trials: Some must await more conclusive observations, whereas others have an immediate and lasting effect on the treatment approaches to a disease. The article describing the benefits of multitarget therapy (mycophenolate mofetil and tacrolimus) on class V + IV lupus nephritis by Bao et al.1 from the Research Institute of Nephrology in Nanjing, China, that appears in this issue of JASN falls into the base hit category, at least in my opinion.

Lupus nephritis is an extremely heterogeneous disorder, in terms of pathogenesis, morphology, clinical features, prognosis, and responsiveness to therapy.2,3 This heterogeneity, coupled with unpredictable clinical behavior, makes the execution of definitive clinical trials in lupus nephritis difficult and problematic.

Variations in the morphology of lupus nephritis are central to the understanding of the trial by Bao et al. The morphologic pattern of class V + IV lupus nephritis, according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification schema,4 is the subject of interest in this trial. This pattern is widely known to have a much worse prognosis than either class V (membranous lupus nephritis) or class IV (diffuse lupus nephritis) alone. A new safe and effective therapy for class V + IV lupus nephritis would be most welcome. The results of this trial should be compared with the results of previous studies in roughly comparable conditions. Using a regimen consisting of short-term oral cyclophosphamide and steroids and a World Health Organization (WHO) classification schema, Najafi et al.5 found a remission rate (serum creatinine ≤1.4 mg/dl and proteinuria ≤0.33 g/d) of only 0.33 g/d) of only 27% after 6 yr of follow-up in the WHO class Vc/Vd lupus nephritis category. Heterogeneity in outcome (remissions or renal survival) in the WHO class Vc/Vd group was found de-


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