Though it has been known for decades that calorie restriction is an effective way to combat obesity-related insulin resistance (and also aging), the present study reveals a mechanism for these effects.

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Chronic Kidney Disease and GWAS: "The Proper Study of Mankind Is Man"

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DOI 10.1016/j.cmet.2010.05.009

Genome-wide association studies (GWAS) have been applied to complex diseases such as diabetes and hypertension, successfully uncovering strong gene associations of potential pathophysiologic significance. Recently, two studies (Köttgen et al., 2010; Chambers et al., 2010) have been applied to uncover genes relevant to the pathophysiology of chronic kidney disease (CKD).

Chronic kidney disease (CKD) is defined as an irreversible reduction in glomerular filtration rate (GFR), the first process of urine production that often progresses to end stage renal disease (ESRD), whereby the level of GFR falls below the minimal level to sustain life. The final common pathway to ESRD, achieved regardless of the initiating event, is characterized by glomerular sclerosis, interstitial fibrosis, and inflammation and loss of kidney function. The burden of ESRD worldwide is growing, and as much as 13% of the United States population is at risk (Coresh et al., 2007). Animal studies have focused on the profibrotic and inflammatory roles of the renin-angiotensin system (RAS) (Chevalier et al., 2009), and inhibition of this system is the focus of current therapy. This approach has proven only partially successful, as such treatment delays rather than prevents ESRD. Thus, the need to identify better targets to prevent ESRD is urgently needed. Genome-wide association studies (GWAS) have been widely used since 2005 (Klein et al., 2005) to understand the underlying genetic component(s) of complex phenotypes, i.e., phenotypes that do not exhibit classical Mendelian inheritance resulting from a single gene alteration (Lander and Schork, 1994). More than any other approach, these studies have reproducibly associated closely linked genetic loci, identified by single nucleotide polymorphisms (SNPs), to these traits. At best, they have led to the delineation in many parts of the human genome of sequences showing association with common disease traits, e.g., diabetes, obesity, hypertension, etc. and have also been used to find association with normal physical traits such as height, hair, and eye color (Hindorff et al., 2010). GWAS require the study of the DNA from several thousands of individuals with and without a demonstrable and measurable phenotype. SNPs associated with these characteristics are identified by hybridization with known SNP arrays. An international project has developed a haplotype map (HapMap; http://hapmap.ncbi.nlm.nih.gov/) of the genome, which identifies variable regions of the human genome and associated genetic variation. Once the associated areas of DNA have been located, there follows a search in the region to find candidate genes potentially involved in the pathologic physiology responsible for susceptibility to the trait or disease under investigation. In most GWAS, each discovered DNA variant usually has only a small impact on the increased risk of the disease, as was predicted 50 years ago by D.S. Falconer (1960), and that is also the case in two

recent papers by Köttgen et al. (2010) and Chambers et al. (2010).

Köttgen et al. (2010) and Chambers et al. (2010) apply GWAS to large numbers of CKD patients. In these studies, GFR is not assessed directly but instead is derived from values of serum creatinine and cystatin C, two generally accepted but flawed indirect markers of glomerular filtration. This weakness is fully recognized by both groups. In a search for common genetic variants associated with CKD and using a now standard approach, each study identified four variable genomic regions that had strong association with the estimated glomerular filtration rates (eGFR) calculated by either serum creatinine (eGFRcreat) or serum cystatin C concentrations (eGFRcyst). Of the 20 genes close to these four regions, several genes were highlighted based on the strength of the association to CKD, higher renal expression relative to other organs, the presence of nonsynonymous mutations, and/or their suspected function or relationship to kidney disease. These genes had metabolic and transport functions. *NAT8*, which was almost exclusively expressed in renal epithelial cells, codes for an enzyme that catalyzes transfer of acetyl groups and may participate in detoxifying xenobiotics. This gene has no known relationship with CKD. Two solute and drug transport proteins found in proximal tubule epithelial cells, which mediate endogenous and xenobiotic transport, were also highlighted for these properties. Another gene of interest, *UMOD*, whose product is uromodulin, is restricted to the distal tubule epithelium. Mutations in this gene are associated with rare causes of renal disease, and knockout animals show a reduced GFR. A meta-analysis of the highlighted *UMOD* mutant suggests that the gene has a protective role in CKD.

Several interesting observations can be drawn from these studies. The genetic markers were not associated with many of the more common causes of chronic renal disease, such as diabetes and hypertension, nor did they identify associations with mutants among the genes in the RAS pathway. The localization of these genes to the tubule compartment suggests that the stresses represented by hypertension, diabetes, and possibly xenobiotics may impinge on a common pathway centered in the renal epithelium. These genes have not been previously identified as contributing to acute or chronic renal failure and highlight the potential of this new technology to identify novel pathways and targets of treatment to halt progression to end stage renal disease.

Some obvious weaknesses in these studies should be pointed out. Köttgen et al. calculate the effect of each locus on the measured variability of eGFR in the population. The effect, not unexpectedly, is small, accounting for less than 2% of the observed variation in GFR and suggests that rare variants are yet to be discovered that will have greater effect on CKD. The major obstacle to discovery of such loci is the feasibility of performing whole-genome sequencing, and newer technologies are rapidly being developed, such as by the 1000 Genomes project. Perhaps the loci may only represent one gene in a pathway that, when explored, may have a greater effect in CKD. The absence of patients of African ancestry in the study, in which a significant association between nondiabetic ESRD with common variants in the *MYH9* gene coding for nonmuscle myosin heavy-chain type II has been observed (Kopp et al., 2008), was not seen in these studies, raising the question of just how relevant these studies are to CKD in humans of non-European ancestry.

Nonetheless, it will be exciting to witness the exploration of these potential pathways to understand mechanisms of renal failure, to develop biomarkers of renal injury, and to exploit these newly discovered pathways to develop strategies to halt the progression to end stage renal disease. And it all begins with humankind.

ACKNOWLEDGMENTS

This work was supported, in part, by research grants from the National Institute of Diabetes and Digestive and Kidney Diseases (R01-DK-54471) and a VA Merit Review and with resources and the use of facilities at the John L. McClellan Memorial Veterans Hospital (Little Rock, AR, USA). The subtitle of this preview, "The Proper Study of Mankind is Man," is taken from Alexander Pope's poem "The Proper Study of Mankind" (1870).

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