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GENETICS

MAPPING PATHWAYS OF CKD

Although genome-wide association studies (GWAS) have identified genetic loci that are significantly associated with chronic kidney disease (CKD), molecular understanding of the mechanisms by which single nucleotide polymorphisms might affect renal function is often lacking. Now, researchers have combined GWAS data, renal transcription profiles and biological knowledge to produce a molecular map of CKD that places candidate genes into functional context.

Matthias Kretzler and colleagues analysed the expression levels of 40 GWAS-derived, CKD-candidate genes in kidney biopsy samples from 157 Europeans with nine forms of CKD and 10 living kidney donors. Of the 29 genes that were differentially expressed in these groups, the renal transcript levels of 18 genes correlated significantly with estimated glomerular filtration rate. These genes were tested for their functional context by identifying their associated pathways. Then, a network of 97 pathways linked by shared genes was constructed.

"The network formed two main clusters comprising inflammation-related and metabolism-related pathways, with the *NRF2*-mediated oxidative-stress-reponse pathway serving as a 'hub' between the clusters," comments Kretzler. The activation of inflammatory signalling cascades and the loss of metabolic functions provide a platform from which to explore causal relationships in CKD. "Targeting key regulatory hubs of the interlinked pathways will be a rational therapeutic approach to affect the CKD network at multiple levels." The various forms of CKD showed substantial overlap in gene-expression changes, irrespective of the initiating disease mechanism. Kretzler notes that this observation is "consistent with longstanding knowledge of nephropathology."

In the future, the researchers plan to investigate the molecular relationships between genotypic alterations, transcriptional changes and clinical markers in CKD in more detail. They will focus on defining the value of these factors for predicting CKD progression and remission as well as developing approaches to identify therapeutic targets that affect a substantial proportion of the pathways that they have identified.

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