FOCUS ON AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary cause of renal failure, and emerging findings from clinical and basic research are expanding our understanding of the disorder. This issue includes three original articles that provide new information about aspects of ADPKD: an analysis of population-based sequencing data of ADPKD-associated genes that provides a more complete picture of disease prevalence and two studies that explore genetic and pathogenic factors that underlie the condition.

ADPKD Prevalence by Sequencing

Estimating prevalence of ADPKD and autosomal dominant polycystic liver disease (ADPLD) is challenging because of incomplete clinical ascertainment due to many patients remaining asymptomatic while the disease progresses. In an analysis of population-based sequencing data of genes involved in these disorders, the authors found that protein-truncating and clinically confirmed mutations provide a lifetime risk of ADPKD of at least 9 cases per 10,000 people; protein-truncating mutations in genes that cause ADPLD are as common as 20 cases per 10,000. Individually rare variants in genes of potential relevance as ADPKD modifiers are cumulatively common, but most have uncertain clinical significance. Further research using exome or targeted gene resequencing in patients with ADPKD will help evaluate these rare variants. See Lanktree et al., pages 2593–2600.

Mcp1 Promotes ADPKD Cyst Expansion

In patients with ADPKD, most of whom have a mutation in PKD1 or PKD2, abnormally large numbers of macrophages accumulate around kidney cysts and promote cyst growth, leading to a progressive decline in GFR and often to ESRD. Previous research by the authors and others had suggested that the macrophage-homing monocyte chemoattractant protein-1 (Mcp1) may be a signal for macrophage-mediated cyst growth. Using a mouse model that involves Pkd1 knock-out in tubular cells, the authors show that loss of Pkd1 results in marked upregulation of Mcp1. Tubule-specific double knock-out of both Mcp1 and Pkd1 suppresses macrophage accumulation in the polycystic kidney and slows cyst growth and decline in GFR, as does administering an inhibitor of the Mcp1 receptor in Pkd1 knockout mice. These findings provide insight into Mcp1’s role in cyst growth and suggest a potential therapeutic strategy to explore. See Cassini et al., pages 2471–2481.

Abnormal alternative splicing of PKD1

ADPKD’s major form caused by heterozygous mutations in PKD1, the gene that encodes polycystin-1 (PC1). The human PKD1 gene is unusual in that it contains two long cytosine- and thymine-rich polypyrimidine tracts in introns 21 and 22. The authors found that abnormal splicing across these PKD1 introns often occurs, leading to premature translational termination and a smaller-than-expected protein product, which they named Trunc_P1. They suggest that in heterozygous individuals with a null PKD1 allele, decreased levels of full-length PKD1 mRNA caused by abnormal splicing at the normal PKD1 allele may reduce PKC1 signaling to cross a critical “cystogenic” threshold. See Lea et al., pages 2482–2492.

OTHER RESEARCH

Assessing Renal Perfusion and Oxygenation

Tubulointerstitial or renal medullary hypoxia may be initiating factors in some forms of CKD, and disturbances in regulation of medullary perfusion is involved in the pathogenesis of hypertension. In this study, normotensive volunteers performed a handgrip exercise to induce renal sympathetic nerve activation. Magnetic resonance imaging revealed that this induced an expected decrease in perfusion and oxygenation in the renal cortex, but in the renal medulla, oxygenation increased despite reduced perfusion. Individuals with high-normal resting systolic pressure experienced larger handgrip exercise–induced reductions in renal blood flow than did those with lower pressure. This approach to measuring both perfusion and oxygenation may provide a useful way to investigate the sensitivity of the renal response to sympathetic stimulation. See Haddock et al., pages 2510–2517.

Gene Variants Linked with Fibroblast Growth Factor 23

Fibroblast growth factor 23 (FGF23), a bone-derived hormone that regulates phosphorus and vitamin D metabolism, contributes to the pathogenesis of mineral and bone disorders in CKD and is an emerging cardiovascular risk factor. In a meta-analysis of genome-wide association studies of circulating FGF23 concentrations among 16,624 individuals of European ancestry from seven cohort studies, the authors found (after adjusting for age, sex, study site, and principal components of ancestry) that common genetic variants are associated with differences in circulating FGF23 concentration. Several are closely linked with enzymes, transporters, and receptors known to be critical to vitamin D metabolism and regulation of phosphate levels. Future study of such variants may help illuminate the mechanism and clinical implications of FGF23’s role in vitamin D and phosphate homeostasis. See Robinson-Cohen et al., pages 2583–2592.