AJKD

Core Curriculum 2016

Autosomal Dominant Polycystic Kidney Disease: Core Curriculum 2016

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease. It is characterized by relentless development of kidney cysts, hypertension, and eventually end-stage renal disease (ESRD). ADPKD is associated with abdominal fullness and pain, cyst hemorrhage, nephrolithiasis, cyst infection, hematuria, and reduced quality of life, among other symptoms. The disease is a consequence of mutations in *PKD1* or *PKD2*, encoding polycystin 1 (PC-1) and polycystin 2 (PC-2), respectively. Many recent advances have been made in understanding and managing ADPKD. This Core Curriculum outlines the different aspects of molecular genetics, pathophysiology, diagnosis, and management of kidney and extrarenal complications in ADPKD.

Additional Readings

» Chapman AB, Devuyst O, Eckardt K, et al. Autosomal dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2015;88(1):17-27.

» Ong AC, Devuyst O, Knebelmann B, et al. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *Lancet.* 2015;385(9981):1993-2002.

EPIDEMIOLOGY

ADPKD was first described more than 300 years ago. Population-based epidemiologic studies with ascertainment of autopsies have estimated that ADPKD affects 1 in 400 to 1,000 live births, or 12.5 million people worldwide. Other studies based on clinical registry data suggest lower prevalence rates, ranging from 1 in 543 to 1 in 4,000. ADPKD affects both sexes equally and occurs in all ethnicities. It accounts for 5% to 10% of ESRD cases, making it the fourth leading global cause for kidney failure. In the United States, incidence rates of ESRD due to ADPKD are higher in men than in women (8.2 compared to 6.8 per million, respectively). In recent years, some studies have reported later onset of ESRD; this may be due to reduced cardiovascular mortality of older patients before reaching ESRD or increased access of older patients to kidney replacement therapy.

Additional Readings

» Reule S, Sexton DJ, Solid CA, Chen SC, Collins AJ, Foley RN. ESRD from autosomal dominant polycystic kidney disease in the United States, 2001-2010. *Am J Kidney Dis.* 2014;64:592-599.

» Spithoven EM, Kramer A, Meijer E, et al; ERA-EDTA Registry; EuroCYST Consortium; WGIKD. Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival–an analysis of data from the ERA-EDTA Registry. *Nephrol Dial Transplant.* 2014;29(suppl 4):iv15-iv25.

GENETICS

ADPKD is a Mendelian autosomal dominant disorder. Therefore, individuals at risk have a 50% chance of inheriting the disease. It is genetically heterogeneous, with 2 causative genes identified: *PKD1*, which encodes PC-1 and accounts for 85% of cases; and *PKD2*, which encodes PC-2 and accounts for 15% of cases (Fig 1). Population-based studies from Canada and the United States have suggested a higher prevalence of *PKD2*-associated disease, such that mutations in this gene may account for up to one-fourth to one-third of all ADPKD cases. Although some have postulated that there is a third PKD gene, convincing evidence to support this putative gene is lacking.

ADPKD has strikingly high phenotypic variability. Mutations in *PKD2* versus *PKD1* lead to much milder disease, with average ages at ESRD of 79.7 and 58.1 years, respectively (Table 1). Milder disease is also noted in ADPKD cases associated with nontruncating versus truncating mutations of *PKD1* (the latter account for 65% of *PKD1* mutations). The genotype-phenotype relationship in ADPKD is not completely understood. The disease is associated with a variety of phenotypes, from newborn infants with massive cystic kidneys to patients whose kidney function persists at adequate levels well into old age. Key influences determining this variability are the identity of the affected locus (*PKD1* vs *PKD2* mutation), the allelic variant (truncating, nontruncating, or hypomorphic), timing of gene inactivation, mosaicism, and genetic background. Men may have a slightly more severe phenotype. Affected family members

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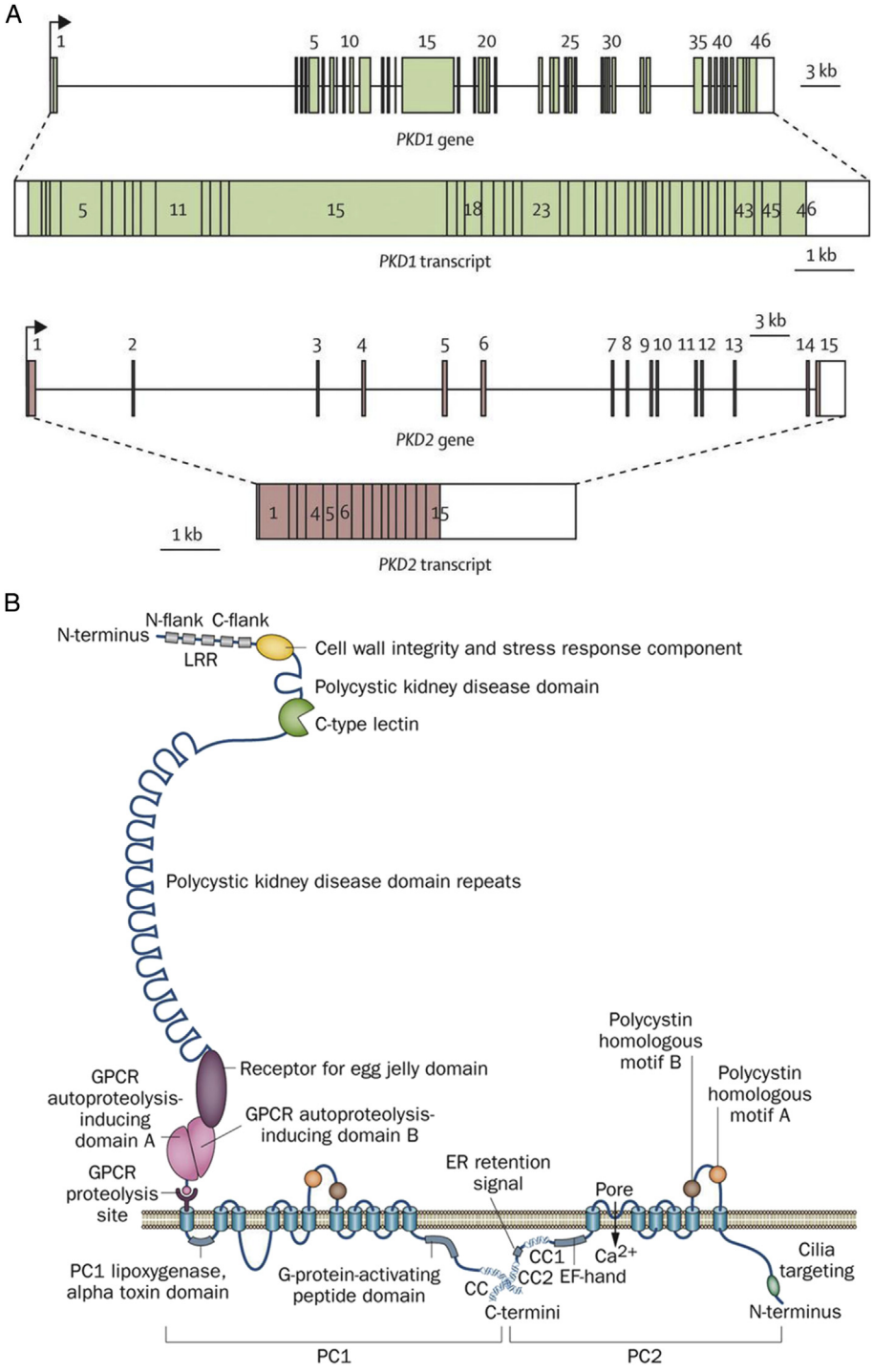

Figure 1. (A) *PKD1* and *PKD2* genes and transcripts. Numbered boxes indicate exons; in total, there are (top) 46 for *PKD1* and (bottom) 15 for *PKD2*. The coding regions are shaded; 5′ and 3′ untranslated regions are not shaded. Reproduced from Torres et al ("Autosomal dominant polycystic kidney disease." *Lancet*. 2007;369(9569):1287-1301) with permission of Elsevier. (B) Predicted structures of polycystin 1 (PC1) and polycystin 2 (PC2): PC1 is a receptor-like protein with a large ectodomain, 11 transmembrane domains, and a cytoplasmic tail consisting of ~200 amino acids. The last 6 transmembrane domains of PC1 are homologous to the transmembrane region of PC2. PC2 is a transient receptor potential–like calcium channel that has an EF-hand motif and an endoplasmic reticulum (ER) retention signal in the carboxy (C) terminus and a proposed cilia targeting sequence in the amino (N) terminus. PC1 and PC2 physically interact through coiled-coil domains in the cytoplasmic tail of PC1 and in the carboxy-terminal tail of PC2. Reproduced from Chebib et al ("Vasopressin and disruption of calcium signaling in polycystic kidney disease" *Nat. Rev. Nephrol.* 2015;11:451–464) with permission of Nature Publishing Group. Abbreviations: GPCR, G protein–coupled receptor; LLR, leucine rich repeat.