KIDNEY HEALTH AUSTRALIA | CARI GUIDELINES

Autosomal Dominant Polycystic Kidney Disease: A Path Forward

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Summary: Autosomal dominant polycystic kidney disease (ADPKD) is the commonest inherited cause of renal failure in adults, and is due to loss-of-function mutations in either the *PKD1* or *PKD2* genes, which encode polycystin-1 and polycystin-2, respectively. These proteins have an essential role in maintaining the geometric structure of the distal collecting duct in the kidney in adult life, and their dysfunction predisposes to renal cyst formation. The typical renal phenotype of ADPKD is the insidious development of hundreds of renal cysts, which form in childhood and grow progressively through life, causing end-stage kidney failure in the fifth decade in about half affected by the mutation. Over the past 2 decades, major advances in genetics and disease pathogenesis have led to well-conducted randomized controlled trials, and observational studies that have resulted in an accumulation of evidence-based data, and raise hope that the lifetime risk of kidney failure due to ADPKD will be progressively curtailed during this century. This review will provide a contemporary summary of the current state of the field in disease pathogenesis and therapeutics, and also briefly highlights the importance of clinical practice guidelines, patient perspectives, patient-reported outcomes, uniform trial reporting, and health-economics in ADPKD.

Keywords: Autosomal dominant polycystic kidney disease, clinical trials, clinical trials, therapy

For most of the 20th century, autosomal dominant polycystic kidney disease (ADPKD) has been an enigmatic disorder, shrouded in mystery, neglected by researchers, and considered the "Rodney Dangerfield" disorder in nephrology.[1] Nephrologists watched their high-risk patients and their families develop kidney failure, feeling helpless at times and uncertain about the efficacy of treatments. However, since the seminal discovery of the causative gene locus 30 years ago,[2] rapid progress in the field has been made, and there is optimism that the incidence of end-stage kidney failure (ESKF; or chronic kidney disease [CKD] stage 5) will decline in the coming decades, as earlier detection and treatment of individuals at high-risk for kidney failure is implemented. Underpinning this successful journey to solve ADPKD has been a vital partnership between affected families, patient-support organizations, and the medical community, as exemplified at a recent meeting.[3] The culmination of this intense effort to find "a cure," are the growing number of large-scale clinical trials of interventional treatments and observational cohorts as well as multi-center and global research networks,[4] which leaves no doubt that the era of effective therapeutics and evidence-based medicine in ADPKD is in full swing. While heartening, a number of "holes" in our understanding of ADPKD exist,[5] and emphasize the importance for continuous and objective appraisal of published studies using consensus meetings[6] and evidence-based tools, to decipher the accumulation of knowledge as well as assist in the planning of future work. This review will provide a contemporary summary of the current state of the field in disease pathogenesis and therapeutics, and also briefly highlight the importance of clinical practice guidelines,

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GENETIC BLUEPRINT OF ADPKD AND ITS APPLICATION TO DIAGNOSTICS AND THERAPEUTICS

ADPKD (OMIM ID: 173900) belongs to a family of disorders that are characterized by mutations in proteins localized to the primary cilia (ciliopathies).[7,8] The *PKD1* gene is located on the short arm of chromosome 16 (16p13.3) and is adjacent to the tuberous sclerosis (*TSC2*) gene. It has a large (46 exons, 52-kb), complex, and unusual genomic structure, making genetic testing complicated[9,10] and predisposing to a high spontaneous mutation rate.[11] More than 70% of the 5' region of the *PKD1* gene (exons 1-33) is duplicated (six times with 98%-99% homology; called pseudogenes, *PKD1 P1-P6*) in regions proximal to the master gene.[12] This intrachromosomal duplication together with the high GC ratio (>85%)[13] and a long polypyrimidine tract in intron 21, predispose the *PKD1* genome to unequal recombination and gene conversion events, that give rise to a high spontaneous mutation rate. The *PKD1* gene transcribes a 14-kb messenger RNA containing a 12,909 coding sequence that generates a protein product of 4,304 amino acids in length (~600 kDa), called polycystin-1. By comparison, the *PKD2* gene is far less complex and more straightforward to perform DNA sequencing than the *PKD1* gene. It is located on the long arm of chromosome 4 (4q21; 68-kb 15 exons) and encodes a protein product of 968 amino acids (~110 kDa), denoted polycystin-2.[14]

Features of Pathogenic PKD Gene Mutations

The genetic complexity of ADPKD is further highlighted by the tremendous allelic heterogeneity of the causative mutations, which challenges the development of personalized mutation-specific therapy[15] as a treatment approach. The Mayo Clinic ADPKD Mutation Database (www.pkdb.mayo.edu; accessed January 20, 2015) lists 1,272 pathogenic mutations for *PKD1* and 202 pathogenic mutations for *PKD2*. Similarly, a large French cohort study reported 735 distinct *PKD1* pathogenic mutations in 1,065 mutation positive pedigrees, indicating >70% of mutations are unique.[10] The causative mutations in these and other studies are dispersed throughout the *PKD* genome without any regional "hotspots."[10] In cohort studies, definite pathogenic mutations (defined as mutations predicted to truncate protein, such as frameshift, nonsense, typical splicing variants, and large rearrangements) account for at least two thirds of the detected mutations, whereas the remainder are due to nondefinite mutations (ie, mutations that do not affect the reading frame) and their pathogenicity (unless previously reported) may be more difficult to prove without functional assays.[14]

Genetic Factors Influencing Variability in Expressivity

Identifying ADPKD patients at high risk of developing ESKF during life, is important for patient counselling and guiding therapeutic choices. There is significant interfamilial and intrafamilial variability in disease phenotype and risk for developing end-stage kidney disease, and this may be mediated by a number of genetic mechanisms. (1) *Category of the mutation-causing gene*: *PKD1* mutation carriers have a worse renal prognosis than *PKD2*. In one study, the median age of ESKF was 58 years for *PKD1* mutation carriers compared with 79 years for *PKD2* carriers.[16] *PKD1* carriers also have larger kidneys and a greater number of cysts.[17] (2) *Type of the allelic mutation*: ESKF occurs at 55 years for patients with truncating mutations compared with 67 years in those with non-truncating lesions.[16] In contrast, heterozygous hypomorphic mutations (ie, partial loss of a gene) cause mild cystic renal disease.[18] (3) *Presence of mutations in multiple genes or alleles*: Mutation of the *PKD* gene in combination with a non-PKD cystogenic gene may cause severe-infantile-onset ADPKD. The classic example is mutation of the *PKD1* along with that of the contiguous gene *TSC2*[19] but another example is mutations in both *PKD1* and *HNF-1β* genes.[20] Bilineal inheritance of mutations in both *PKD1* and *PKD2* may exacerbate[21] or attenuate[22] risk for ESKF. Along these lines, hypomorphic *PKD* allelic variants in combination with a completely inactive allele are also associated with more severe renal disease than carriage of the hypomorphic allele alone.[18,23] (4) *Role of modifier genes and epigenetic factors*: Twin and sibling studies have identified that modifier genes and epigenetic factors are likely to influence disease severity,[24,25] and may explain at least half of the phenotypic variability in ADPKD.[25] Several modifier genes have been investigated, and microRNAs[26] and transcription factor networks[27,28] have been suggested as potential candidates.

Genetic Mechanisms Underlying the Latency of Disease Onset and Focal Nature of Cyst Formation

The puzzle of disease latency as well as the focal and non-synchronized manner of renal cyst formation has already been highlighted as an area requiring further understanding,[29] as it bears critical importance on the approach to future treatments. In mice, homozygous deletion of *PKD1* is embryonic lethal[30] whereas postnatal heterozygous inactivation leads to slowly progressive age-dependent development of renal cysts.[31] On the other hand, in humans it has been hypothesized