Autosomal-dominant polycystic kidney disease (ADPKD) consists of at least 3 genetically distinct disorders, characterized by bilateral renal cyst formation and progressive enlargement. ADPKD results in renal failure by the age of 60 years in about 50% of affected individuals. It affects between 1 in 600 and 1 in 1000 live births in all ethnic groups and, as such, constitutes one of the major diseases requiring renal replacement therapy, worldwide. Complications of the renal lesion include hypertension, which is very prevalent in the ADPKD population. The occurrence of hypertension seems to correlate with cyst enlargement, and its pathogenesis may involve activation of the renin-angiotensin system. The most serious renal complication of ADPKD is end-stage renal disease. The typical patient age at the onset of end-stage renal disease is mid-life, but the range is from infancy to age 80 years. The progression of renal disease is slower in women than in men, and it is faster in the presence of hypertension than in its absence.

Acute and chronic pain is a common complication. Nephrolithiasis occurs in 20% of the ADPKD population. The extrarenal manifestations of ADPKD frequently include cysts in the liver. Cysts in the pancreas or spleen occur infrequently. The appearance of liver cysts increases with age, affecting about 75% of patients over the age of 60 years. The number and size of liver cysts is influenced by female steroid hormones. Cysts in the liver can be symptomatic due to mass effects, although they are not associated with impairment of liver function. Mitral valve prolapse is also associated with ADPKD.

Intracranial saccular aneurysms occur in 2% to 5% of patients with ADPKD, and this complication appears to be familiarly clustered. Other large vessel aneurysms have been reported in association with ADPKD. All genetic forms of ADPKD exhibit a similar spectrum of renal and extrarenal manifestations.

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At least 3 distinct genes are responsible for ADPKD. This feature is referred to as genetic heterogeneity. PKD1, located on chromosome 16, is the most commonly mutated gene in ADPKD families, while PKD2, the gene on chromosome 4, is mutated in most other families. PKD3 was discovered by the exclusion of genetic linkage to either PKD1 or PKD2. It is a very rare cause of ADPKD that has not been genetically localized. The ADPKD phenotypes resulting from mutations in the different genes are so similar that there were no clinical grounds for suspecting genetic heterogeneity, until it was demonstrated by linkage analysis. Once linkage heterogeneity had been described, it was shown that PKD2 has a milder phenotype compared to PKD1, as judged by ages at renal death, at cyst appearance, and at onset of hypertension. These studies suggest a 10- to 15-year difference in the mean age at the onset of end-stage renal disease between the 2 genotypes. The observation of marked, intrafamilial variation in the clinical expression of ADPKD suggests that factors beyond the specific germline mutation must act as significant determinants of disease progression in an individual. As will be discussed below, the understanding of the gene defects in PKD1 and PKD2 has led to increased understanding both of the differences in the rate of disease progression between PKD1 and PKD2, and of the observed intrafamilial variation observed within a given genotype.
The Chromosome 16-Linked Form of ADPKD—PKD1

Mutations in PKD1 account for 79% to 91% of the cases of ADPKD. PKD1 was first localized to chromosome 16p13.3 by the discovery of linkage to 3'HVR, a variable number, tandem repeat marker near the α-globin locus. Positional cloning, the process by which PKD1 and PKD2 were identified, is highly related to the progress of the worldwide Human Genome Project. Positional cloning refers to the identification of a heritable human disease gene by progressive refinement of its location in the human genome. This approach does not require any presuppositions regarding the function of the gene, nor does it rest on knowledge of the underlying pathophysiology of the disease. The process does require the availability of family or patient material for genetic studies to define the region of interest, followed successively by genomic cloning of the interval, production of a transcription map of the region, and, finally, the identification of the disease gene itself, by the finding of pathogenic alterations in the genomic DNA of affected individuals. A transcription map of the PKD1 candidate interval showed a gene-rich region, with at least 20 independent sets of cDNA clones.

The colocalization of one form of tuberous sclerosis (TSC2) to the PKD1 interval was a major breakthrough in aiding the identification of PKD1. Renal manifestations are a common feature of this genetically heterogeneous, autosomal dominant disorder. Although benign tumors (angiomylipomas) are the most common renal manifestation, renal cystic disease, radiographically indistinguishable from that of ADPKD, is also observed. Molecular analysis of hamartomata from patients with tuberous sclerosis showed a loss of heterozygosity for chromosome 16p13.3 markers, which suggested that this disease is the consequence of a 2-hit, loss of heterozygosity mechanism. Analysis of 255 unrelated, affected patients with tuberous sclerosis showed 5 patients with constitutional deletions in the TSC2 region on 16p. A single gene, TSC2, was identified in this commonly deleted interval. The putative gene product of TSC2 has motifs suggestive of transmembrane spans and leucine zipper domains, shows homology with the amino-terminal domains of GAP3, and may act as a tumor suppressor gene.

The critical step in the cloning of PKD1 was the identification of a family with both tuberous sclerosis and ADPKD, and a chromosomal rearrangement involving the PKD1 region. In this kindred, a mother and daughter bore a balanced translocation (16p13.3; 22q11.21) and had the ADPKD phenotype, while a son had lost the derivative chromosome 22, and had the tuberous sclerosis phenotype. The translocation breakpoint in the 2 patients with ADPKD disrupted the PKD1 gene. PKD1 encodes a 14 kb transcript and is arranged in a tail-to-tail manner with TSC2. Only a very short distance separates the respective 3' untranslated regions of the 2 genes.

The genomic structure of PKD1 is complicated by the fact that the 5' two-thirds of the gene is reduplicated with high conservation on more centromeric portions of 16p. Despite this complication, the complete sequence of the gene and the transcript have been determined. PKD1 is predicted to encode a novel, 4303-amino-acid integral membrane protein, polycystin-1, with an approximately 2500-amino-acid extracellular region and a molecular mass of about 460 kDa. The extracellular portion contains a number of structural domains, including 2 leucine-rich repeats and associated NH2- and COOH-flanking regions, 14 Ig-like PKD1 repeats (approximately 80 amino acids each), and an approximately 1000-amino-acid segment, closely related to the sea urchin sperm egg-jelly receptor. In other proteins, where they occur, leucine-rich repeats are involved in protein-protein interactions. The sea urchin sperm egg-jelly receptor mediates the acrosome reaction, which is a specialized membrane fusion event. Polycystin-1 is predicted to be heavily glycosylated, and the cytoplasmic terminus is predicted to have both tyrosine and protein kinase C phosphorylation sites. PKD1 has 11 transmembrane spans and a short, intracellular COOH-terminal domain, containing a coiled-coil motif. Coiled-coils are usually protein interaction domains. The mouse homologue of PKD1, Pkd1, is single copy (not reduplicated) and maps to mouse chromosome 17. The amino acid sequence is 79% conserved with the human gene, including most of the major motifs identified, and there is evidence of alternative splicing in the mouse.

PKD1 is encoded in 46 exons, spanning about 54 kb of genomic DNA. Effective mutation detection in PKD1 was initially restricted to oligo-base pair mutations in the 3' single-copy region and to large deletions. Mutation detection in the duplicated two thirds of PKD1 has more recently become possible. Most mutations in PKD1 are either nonsense mutations to stop codons, or small deletions/insertions or splice variants that result in premature termination due to frame shifts. These are most consistent with loss of function changes. Missense variants have been identified, but in the absence of a functional test for PKD1 activity, the pathogenicity of these variants can only be inferred. In addition, substantial variation in the coding sequence of PKD1 has been described in normal individuals, further complicating mutation analysis. The only genotype/phenotype correlation observed in PKD1 has been with the larger deletions. The occurrence of significant renal cystic disease in patients...