

# Genotype–Phenotype Correlations in Autosomal Dominant and Autosomal Recessive Polycystic Kidney Disease

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The phenotypes that are associated with the common forms of polycystic kidney disease (PKD)—autosomal dominant (ADPKD) and autosomal recessive (ARPKD)—are highly variable in penetrance. This is in terms of severity of renal disease, which can range from neonatal death to adequate function into old age, characteristics of the liver disease, and other extrarenal manifestations in ADPKD. Influences of the germline mutation are at the genic and allelic levels, but intrafamilial variability indicates that genetic background and environmental factors are also key. In ADPKD, the gene involved, *PKD1* or *PKD2*, is a major factor, with ESRD occurring 20 yr later in *PKD2*. Mutation position may also be significant, especially in terms of the likelihood of vascular events, with 5' mutations most detrimental. Variance component analysis in ADPKD populations indicates that genetic modifiers are important, but few such factors (beyond co-inheritance of a *TSC2* mutation) have been identified. Hormonal influences, especially associated with more severe liver disease in female individuals, indicate a role for nongenetic factors. In ARPKD, the combination of mutations is critical to the phenotypic outcome. Patients with two truncating mutations have a lethal phenotype, whereas the presence of at least one missense change can be compatible with life, indicating that many missense changes are hypomorphic alleles that generate partially functional protein. Clues from animal models and other forms of PKD highlight potential modifiers. The information that is now available on both genes is of considerable prognostic value with the prospects from the ongoing genetic revolution that additional risk factors will be revealed.

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Positional cloning approaches have successfully identified the cause in most common Mendelian diseases in the past 20 yr or so. However, it is clear that this is only the first step to understanding how the disease manifests in an individual patient. The rule, rather than the exception, even in “simple” genetic diseases is of wide phenotypic variability, in terms of both the array of clinical phenotypes and the severity of disease (1,2). Better understanding of the factors that underlie this variability are clearly of prognostic value but may also shed light on pathogenesis. This phenotypic variability is due to heterogeneity at the gene (genic) and mutation (allelic) levels, but considerable intrafamilial variance indicates that genetic background (modifying factors) and the environment also impinge in a major way on how diseases present and progress. In reality, the clinical manifestations of Mendelian diseases are analogous to a complex trait (1). In recent years, molecular analysis of disease populations and detailed studies of families have revealed the relative contribution of the factors described in a variety of monogenic diseases. Breakthroughs in understanding the molecular basis of the common forms of polycystic kidney disease (PKD) in humans—autosomal dominant (AD-

PKD) and autosomal recessive (ARPKD)—mean that genotype–phenotype correlations are now possible in these disorders (Figure 1). These findings are already of prognostic value and are providing clues to pathogenesis.

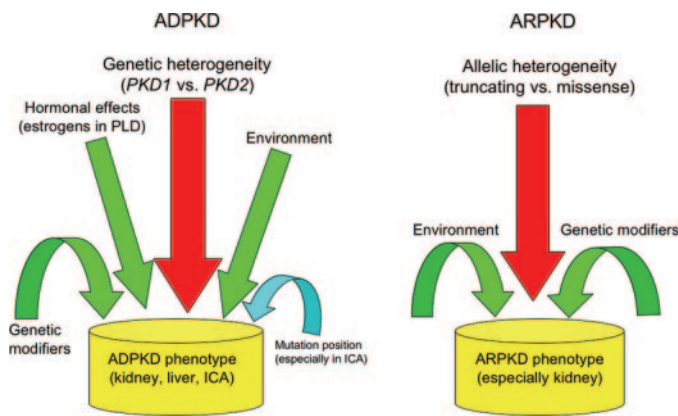
## Phenotypic Variability

The severity of the renal disease in ADPKD is highly variable, ranging from rare *in utero* cases with massively enlarged cystic kidneys (3,4), through more typical presentations with ESRD in the sixth decade, to cases with adequate kidney function into old age (5,6). Extrarenal cystic manifestations are common, with hepatic cysts the most clinically relevant. Approximately 75% of patients develop liver cysts by the seventh decade, but a small minority of mainly women develop massive polycystic liver disease (PLD) that requires surgical resection (7). The most important noncystic disease association is intracranial aneurysms that occur in approximately 8% of patients with ADPKD with evidence of familial clustering (8).

The presentation of ARPKD also shows a wide clinical spectrum, with the majority having significant renal disease, ranging from massively enlarged and cystic kidneys *in utero*, causing neonatal death in approximately 30% of cases, to neonatal survivors with a significant renal phenotype that may result in ESRD (9–11). At the other extreme are cases with minimal kidney involvement in which complications of congenital hepatic fibrosis, Caroli disease, and extrahepatic biliary disease

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**Figure 1.** Diagram showing the relative contributions of various factors to the resulting phenotypes in autosomal dominant (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). Strong factors are shown in red, moderate in green, and lesser effects in blue.

are the major clinical phenotype (12,13). The biliary disease seems to be a relatively constant feature that manifests as patients age, whereas the kidney disease is an early and highly variable symptom, with kidney size often decreasing over time in the patient (14,15).

## Molecular Diagnostics

ADPKD is genetically heterogeneous, with two genes identified: *PKD1* (16p13.3) and *PKD2* (4q21) (16–18). *PKD1* is the major locus, accounting for approximately 85% of families (19,20). Further genetic heterogeneity has been suggested by unlinked families (21,22), but no further genes have been identified, and, indeed, there is doubt about the existence of a *PKD3* (23–25). *PKD1* has 46 exons and encodes a large protein, polycystin-1 (4303 amino acids) (16). Exons 1 to 33 lie in a complex genomic region that is reiterated approximately six times further proximally on chromosome 16 (26,27). Similarity between *PKD1* and these pseudogenes means that locus-specific amplification methods are required to analyze *PKD1* (28). *PKD2* has 15 exons and encodes polycystin-2 (968 amino acids) (18,29).

A high level of allelic heterogeneity is found for both genes, with a total of 270 different mutations reported for *PKD1* and 73 for *PKD2* (up to 2003; Human Gene Mutation Database [http://www.hgmd.org]). More complete information in the ADPKD Mutation Database (http://pkdb.mayo.edu) describes 298 *PKD1* and 106 *PKD2* mutations. The vast majority of mutations are unique to a single family. For *PKD1*, 200 (67%) mutations are definitely pathogenic (nonsense, frameshifting, or splicing), and 98 (33%) are missense or other in-frame events. For *PKD2*, a larger proportion of mutations are truncating, 97 (91.5%), and only nine (8.5%) are in-frame. In a recent screen of 202 well-characterized probands with ADPKD (the Consortium of Radiologic Imaging Study of PKD [CRISP] population), comprehensive mutation analysis of both genes identified a probable mutation in almost 90% of cases (Rosetti *et al.*, submitted). This study involved a systematic algorithm for scoring the likely pathogenicity of missense and other atyp-

ical changes. Although these methods are far from perfect for mutation prediction, they do show the prospects for molecular diagnostics in ADPKD. Although gene-based diagnostics are not necessary in every patient with ADPKD (renal imaging is a reliable diagnostic tool in most), it can be helpful in childhood cases with unknown etiology and critical for young living-related donors for whom imaging data are less reliable. It is likely to become more important as therapies are developed.

There is little evidence of genetic heterogeneity in typical ARPKD cases. The disease gene, *PKHD1* (6p21), has 67 exons and encodes the large protein fibrocystin (4074 amino acids) (30,31). As in ADPKD, many different *PKHD1* mutations cause ARPKD. To date, 305 different mutations are listed in the ARPKD/*PKHD1* Mutation Database (http://www.humgen.rwth-aachen.de), accounting for more than 700 mutant alleles. In this case, only approximately 40% are predicted to truncate the protein, with approximately 60% missense. Several studies have used detailing algorithms to assess the pathogenicity of these changes to aid their use for diagnostics (12,32,33). Approximately one third of *PKHD1* mutations are unique to a single family. Some ancestral mutations are common in particular populations, and one mutation, T36M, of Northern European origin, accounts for approximately 17% of mutant alleles (34,35). Molecular diagnostics for ARPKD is important for prenatal testing, including preimplantation genetic diagnostics, and for establishing a firm diagnosis (36).

## Genic Influences on Phenotype in ADPKD

*PKD1* is a more severe disease than *PKD2*, with earlier diagnosis, a higher incidence of hypertension and hematuria, and ESRD occurring on average 20 yr earlier (54.3 *versus* 74 yr) (37,38). All published, early-onset ADPKD cases for which the gene is known are *PKD1* linked (39,40). Severe PLD is associated with *PKD2* as well as *PKD1*, and the relative frequency of intracranial aneurysms (ICA) is approximately equal in the two gene types (41,42). *PKD2* is a more severe disease in men (average age at ESRD 68.1 in men; 76.0 in women), but no gender difference at time to ESRD was found in recently studied *PKD1* populations (37,43,44). However, analysis of magnetic resonance–derived kidney and cyst volumes in the CRISP population indicated that the relative and absolute rates of cystic growth were faster in men than in women (20). These data are consistent with an older study that suggested that male gender is associated with a poorer outcome in *PKD1*-linked families (6).

One family with bilineal inheritance of *PKD1* and *PKD2* showed that co-inheritance of a mutation in both genes is not lethal, but it did seem to be associated with more severe disease than that found with either disease alone in the family (24). Recent analysis of the CRISP population found that age-corrected *PKD1* kidneys were two thirds larger than in *PKD2*, consistent with larger renal volume being associated with more severe disease (20,45). Analysis of the reason for the difference showed that the rate of cystic expansion was not significantly different by gene type but that *PKD1* kidneys had more cysts compared with age-matched *PKD2* organs. These data suggest that the rate of cyst development, especially early in the dis-

ease, is important in dictating disease severity. More early cysts in PKD1 is consistent with a two-hit model of cystogenesis (46), because *PKD1* is a larger mutational target. The process of cystogenesis, therefore, consists of a gene-related cyst initiation step and a gene-independent cyst expansion phase (20).

### Allelic Influences on Phenotype

In ARPKD, the specific combination of mutations seems to dictate significantly the phenotypic outcome. When patients are defined as severe (died by the neonatal period) or moderate (survived the neonatal period), a striking finding, first proposed by Bergmann (47) and now confirmed in other studies (32,48,49), is that all patients with two mutations that are predicted to truncate fibrocystin have the lethal phenotype. As a result, missense changes are more common in those with the moderate phenotype, which have either two missense or a missense and a truncating change (49). These data indicate that a proportion of missense mutations are hypomorphic alleles that generate some partially functional fibrocystin. Alternatively spliced products, which have been suggested to be common in *PKHD1* (31), may also be a factor in the significance of some missense changes, although it is striking that regardless of the position of truncating mutations, they are associated with lethality when found with a second truncating event. The population with predominant liver disease does not show a unique mutation profile but a combination of truncating and missense or two missense, as seen in the moderate group (12). These data suggest that the minimal kidney disease that is seen in these cases is due to the presence of one or two hypomorphic missense alleles that effect the renal phenotype in a major way. Preliminary analysis of the significance of specific missense alleles has been made by analysis of the phenotype in cases which they occur with a truncating mutation or are homozygous (11). Variability between cases with the same mutation combination also emphasizes that other genetic and environmental factors influence the phenotype.

Allelic effects seem to be less evident in ADPKD. In a large study of 461 affected patients with PKD2 from 71 families, there was no clear correlation between mutation type or mutation position and the severity of kidney disease (43). Intrafamilial variability was, however, highlighted with rare cases with ESRD before 50 yr in families with otherwise more typical PKD2. In PKD1, no correlation between mutation type and disease has been found, indicating that missense changes likely inactivate the allele, similar to truncating changes. One correlation that has been described was between the position of the mutation, 5' or 3' to the median mutation position, whereby patients with 5' changes reached ESRD 3 yr earlier (53 *versus* 56 yr) (44). Patients with 5' mutations also seem to be more prone to ICA, and this was especially clear in ones with rupture before 40 yr and in families with multiple cases with ICA or other vascular events (42). The reason for this effect is not known but could be associated with cleavage of the protein at the GPS domain (3048 amino acids) into N and C terminal products or possible dominant negative effects (50).

### Genetic Modifying Effect

Considerable intrafamilial phenotypic variability has been described in ADPKD. Geberth *et al.* (51) showed in parent-offspring pairs that ESRD could occur up to 26.3 yr earlier or 27.2 yr later in the offspring, illustrating considerable variability that is not accounted for by genic or allelic effects. A comparison of monozygotic twins and siblings showed greater variance in time to ESRD in siblings, supporting a role for genetic background (52). Extreme divergent phenotypes were seen in one pair of dizygotic twins, one with early-onset disease and the other with a more typical presentation (53). Two studies have analyzed intrafamilial variability in large populations (315 patients in 83 pedigrees or 406 patients in 66 pedigrees) of families with ADPKD by variance component analysis (54,55). One found that inherited differences in genetic background were estimated to account for 18 to 59% of the phenotypic variance in PKD1 disease markers in patients before ESRD when phenotypes such as renal volume, proteinuria, and serum creatinine were analyzed and 43% in the subsequent progression to ESRD (55). In the other study, analysis of patients without ESRD ( $n = 247$ ) or with ESRD ( $n = 159$ ) produced estimates of heritability of 42 or 78%, respectively (54). On the basis of these figures, the authors indicated that genetic modifiers account for a significant part of the variability that is seen in PKD1 and PKD2 populations and, given a large enough population, that it may be possible to identify such factors (54,56).

Several candidate gene association studies have been carried out in ADPKD to identify genetic modifiers, but consistent with studies in many other diseases, positive results have usually not been reproducible (57). Thirteen studies tested the I/D polymorphism of the angiotensin-1-converting enzyme gene (*ACE*) and, although initial studies found the DD phenotype associated with more severe disease (58), a recent meta-analysis found no significant association (59). Mixed or negative results have also been obtained with the *ENOS* gene and other components of the renin-angiotensin system (58,60,61).

A number of patients who had ADPKD and cystic fibrosis were analyzed. Three patients had milder disease compared with siblings with ADPKD alone, suggestive of a role for cystic fibrosis transmembrane conductance regulator (CFTR) in cyst fluid secretion in ADPKD (62,63), a role that is supported by other experimental data (64). However, one other study found little difference, and the total number of cases is small (65). One example in which co-inheritance of a mutant gene does influence the severity of PKD is in cases with contiguous deletions that disrupt the *PKD1* and adjacent tuberous sclerosis gene, *TSC2* (66). These patients typically have severe, early-onset PKD, plus TSC phenotypes. The *TSC2* protein, tuberin, may act in similar downstream pathways to polycystin-1, suggesting synergistic effects (67), but recently a more direct mode of action was suggested with the two proteins interacting in a complex (68).

Whereas the majority of families with ARPKD show a relatively concordant phenotype, in approximately 20%, a striking intrafamilial phenotypic variability is observed (11). This can manifest as neonatal death and survival in the same family or



as a striking difference in the severity of kidney or liver disease. No association studies have been described in human ARPKD (the population is small), but other studies have highlighted potential modifiers. Genetic modifiers have been mapped in mouse models of recessive PKD, and in one case, the *Kif12* gene was identified as a possible modifier in the *cpk* mouse (69). Another possible modifying factor is the maturity onset diabetes of the young-5 (MODY5)-associated protein HNF1 $\beta$  that regulates *PKHD1* expression by binding to its proximal promoter (70).

## Environmental Influences

It seems certain that nongenetic factors, including environmental exposures, significantly influence the severity of renal disease and other extrarenal manifestations in PKD. There is good evidence from the preponderance of PLD in women and that the disease is exacerbated by multiple pregnancies and other estrogen exposure that hormonal factors are important in the development of this disease (71). The faster growth of kidney cysts in male individuals with ADPKD and also earlier ESRD in male individuals with PKD2 suggest that male hormonal factors may be important in renal cystic disease (20,43). Caffeine exposure has been considered a risk factor in PKD, and evidence that caffeine can increase the production of cAMP in cyst-derived cells, which stimulate proliferation and fluid secretion (72), provides some justification for avoiding caffeine-containing beverages. Smoking has been shown to be a risk factor for more rapid progression in patients with renal disease, including ADPKD, with increased risk for chronic renal failure and ESRD, especially in men (73). This risk may be due to the known vascular effects and higher BP that are associated with smoking. Proteinuria and risk for chronic kidney disease and ESRD are associated with obesity, especially in men. Dietary changes, such as low-protein intake or flax seed oil, some of which have shown promise in animal studies, have been negative or not tested in human ADPKD (74).

## Conclusions

It is now possible to start dissecting the relative importance of various genetic and environment factors to the presentation and progression of PKD. In ADPKD, the gene involved is a major predictor of severity, with genetic background and environmental factors moderately involved and allelic effects probably less important (Figure 1). In ARPKD, the combination of alleles is a major factor in disease severity. While candidate association studies have been disappointing for finding genetic modifiers in human PKD, recent development of high-resolution single-nucleotide polymorphism arrays and mapping the haplotype block structure of the human genome make genome-wide association studies to find modifiers now a reality. Equally important are the larger populations that now are being assembled for observational and clinical trials of ADPKD that will provide the clinically well-characterized groups that are required for these studies.

## Disclosures

None.

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