Genetic Complexity of Autosomal Dominant Polycystic Kidney and Liver Diseases

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ABSTRACT
Data indicate significant phenotypic and genotypic overlap, plus a common pathogenesis, between two groups of inherited disorders, autosomal dominant polycystic kidney diseases (ADPKD), a significant cause of ESRD, and autosomal dominant polycystic liver diseases (ADPLD), which result in significant PLD with minimal PKD. Eight genes have been associated with ADPKD (PKD1 and PKD2), ADPLD (PRKCSH, SEC63, LRPS, ALG8, and SEC61B), or both (GANAB). Although genetics is only infrequently used for diagnosing these diseases and prognosing the associated outcomes, its value is beginning to be appreciated, and the genomics revolution promises more reliable and less expensive molecular diagnostic tools for these diseases. We therefore propose categorization of patients with a phenotypic and genotypic descriptor that will clarify etiology, provide prognostic information, and better describe atypical cases. In genetically defined cases, the designation would include the disease and gene names, with allelic (truncating/nontruncating) information included for PKD1. Recent data have shown that biallelic disease including at least one weak ADPKD allele is a significant cause of symptomatic, very early onset ADPKD. Including a genic (and allelic) descriptor with the disease name will provide outcome clues, guide treatment, and aid prevalence estimates.


CLINICAL AND GENETIC CHARACTERISTICS OF ADPKD AND ADPLD
Disease severity in autosomal dominant polycystic kidney disease (ADPKD) is highly variable.1 Whereas half of affected individuals reach ESRD by approximately 60 years,2,3 <1% of patients exhibit very early onset (VEO) disease, with a diagnosis made in utero or during infancy.4–6 At the other end of the spectrum, patients can live a normal lifespan without requiring RRT. Most patients with ADPKD develop liver cysts as they age, with severe Polycystic liver disease (PLD) requiring surgical intervention occurring in a small minority of patients.2,3 Autosomal dominant polycystic liver disease (ADPLD) is characterized as PLD, including severe, symptomatic disease that is indistinguishable from that found in ADPKD, but without (or only occasional) renal cysts.9 ADPKD is genetically heterogeneous, with two major genes, PKD1 (Chr. 16p13.3; approximately 78% families) and PKD2 (4p21; approximately 15%), and a rare third locus, GANAB (11q12.3; approximately 0.3%), discovered last year.3,10–15 For ADPLD, PRKCSH (19p13.2; approximately 20%) and SEC63 (6q21; approximately 15%) are the major genes, but LRPS (11q13.2), GANAB (approximately 2%), ALG8 (11q14.1; approximately 3%), and SEC61B (9q22.33; approximately 1%) have more recently been associated with ADPLD (Table 1).15–20 The difference in renal survival between PKD1 and PKD2 patients has been highlighted in multiple studies (Table 2).3,21 In addition, PKD1 patients have a larger height-adjusted total kidney volume (HTKV); an early measure of the severity of renal disease in ADPKD) and lower eGFR than PKD2 patients.14,22 A further difference is the number of kidney cysts, with fewer in PKD2 than PKD1 (Figure 1, A and C), although the rate of growth of the kidney cysts does not differ between the groups.23 Occasionally, severe PLD can be the major clinical phenotype in ADPKD (Figure 1B and G). PRKCSH and SEC63 have not been clinically differentiated and majorly consist of PLD without renal cysts, although a few kidney cysts have been described in 28%–35% of cases, and renal involvement may have been underestimated (Figure 1H).9 Missense mutations to LRPS have been identified in four families, two with moderate-to-severe PLD without renal cysts, one with moderate PLD and three kidney cysts, and one with mild PLD but severe PKD in one family member.19 The renal prognosis in GANAB is consistently mild with progression to ESRD unlikely.

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Table 1. Classification of ADPKD and ADPLD including gene descriptor

<table>
<thead>
<tr>
<th>Designationa,b</th>
<th>Description</th>
<th>Phenotype</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPKD-T</td>
<td>ADPKD due to PKD1 truncating mutationc</td>
<td>Severe Very high (55 yr) Absent to severe Figure 1A, Table 2</td>
<td></td>
</tr>
<tr>
<td>ADPKD-PKD1NT</td>
<td>ADPKD due to PKD1 nontruncating mutationd</td>
<td>Mild to severe High (67 yr) Absent to severe Figure 1, B and G, Table 2</td>
<td></td>
</tr>
<tr>
<td>ADPKD-PKD1 ULP</td>
<td>ADPKD due to PKD1 ultra low penetrance allele</td>
<td>Extremely mild None Absent to severe Figure 1D, Table 4</td>
<td></td>
</tr>
<tr>
<td>ADPKD-PKD2</td>
<td>ADPKD due to PKD2 mutation</td>
<td>Mild Low (79 yr) Absent to severe Figure 1C, Table 2</td>
<td></td>
</tr>
<tr>
<td>ADPKD-GANAB</td>
<td>ADPKD due to GANAB mutation</td>
<td>Very mild None Absent to severe Figure 1E, Table 4</td>
<td></td>
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<tr>
<td>ADPKD-PRKCSH</td>
<td>ADPKD due to PRKCSH mutation</td>
<td>Absent to very mild None Mild to severe Figure 1H</td>
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<tr>
<td>ADPKD-SEC63</td>
<td>ADPKD due to SEC63 mutation</td>
<td>Absent to very mild None Mild to severe 18</td>
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<tr>
<td>ADPKD-LRPS</td>
<td>ADPKD due to LRPS mutation</td>
<td>Absent to very mild None Mild to severe 19</td>
<td></td>
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<tr>
<td>ADPKD-GANAB</td>
<td>ADPKD due to GANAB mutation</td>
<td>Very mild None Mild to severe Table 2</td>
<td></td>
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<tr>
<td>ADPLD-ALG8</td>
<td>ADPLD due to ALG8 mutation</td>
<td>Absent to very mild None Absent to severe 20</td>
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<tr>
<td>ADPLD-SEC61B</td>
<td>ADPLD due to SEC61B mutation</td>
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<td></td>
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<tr>
<td>Biallelic</td>
<td>Typical ADPKD due to two PKD1 alleles</td>
<td>Severe High to very high Absent to severe Table 4</td>
<td></td>
</tr>
<tr>
<td>ADPKD-PKD1 b</td>
<td>Symptomatic infantile ADPKD due two PKD1 alleles</td>
<td>Severe infantile Extremely high Absent to mild Table 4</td>
<td></td>
</tr>
<tr>
<td>ADPKD-PKD2 b</td>
<td>Symptomatic infantile ADPKD due two PKD2 alleles</td>
<td>Severe infantile Extremely high Absent to mild Table 4</td>
<td></td>
</tr>
</tbody>
</table>

1, truncating; NT, nontruncating.

*Examples are shown to illustrate the disease plus gene terminology but other combinations are possible.

*ADPKD is defined as dominantly inherited disease with significant PKD,31,32 with or without significant PLD, and without phenotypes suggesting an alternative disease. Subjects with a proven pathogenic ADPKD allele, even if the renal disease does reach the imaging criteria, would be considered ADPKD.

*Frameshifting deletion, duplication or insertion, nonsense, typical splicing mutation (disrupting the canonic intronic dinucleotides), or inframe deletion, duplication or insertion of ≤4 amino acids.

*Misense, atypical splicing mutation (not disrupting the canonic intronic dinucleotides), or inframe deletion, duplication, or insertion of ≤5 amino acids.

*ADPLD is defined as dominantly inherited disease with significant PLD without significant PKD.

*PKD due to two mutations to the same ADPKD gene found on opposite alleles (in trans).

(Figure 1E), although all patients had some kidney cysts; predominant liver involvement was described in 4 of 11 families.15,20 Inactivating mutations to ALG8 were recently shown to cause ADPLD in five pedigrees, four with severe PLD and some kidney cysts, but one patient only had renal cysts.20 Mutations to SEC61B were identified in two families with mild PLD and no apparent renal phenotype.20

A loss-of-function genetic mechanism (due to a dosage/threshold or somatic second hit mechanism) has been established for these diseases.24 Studies of pathogenesis of ADPKD and ADPLD also show a commonality with all ADPLD proteins (except LRPS) involved in the glycosylation, quality control assessment, or translocation across the ER membrane of membrane/secreted proteins.15,20,25 A renal cystic phenotype is induced by inactivation of Prkcs or Sec63 in the kidney, which can largely be rescued by Pkd1 overexpression.26 The action of these genes, and of GANAB, ALG8, and SEC61B, seems to be through inefficient maturation and trafficking of membrane/secrated proteins, with the PKD1 protein, polycystin-1 (PC1), particularly susceptible to dosage reduction of any of these proteins.15,20,26,27

**AN INCREASING ROLE FOR ROUTINE GENETIC ANALYSIS IN ADPKD AND ADPLD?**

Molecular genetics has been performed routinely for several years in the management of a number of monogenic disorders, such as cystic fibrosis, where it is used for diagnostics and also recently to guide allelic-specific therapeutics.28,29 Genetic testing is part of either the diagnosis workup or the therapeutic decision-making algorithms of several kidney diseases, including steroid-resistant FSGS, atypical hemolytic uremic syndrome, and Alport syndrome.30 The introduction of next-generation sequencing (NGS) has allowed the development of cost- and time-efficient strategies, often including screening panels of candidate genes or whole-exome sequencing, improving diagnostics, providing prognostic value, and broadening the phenotypic spectrum of many kidney diseases.30

Genetics is presently rarely used for routine diagnostics and prognostics in ADPKD and ADPLD, with imaging much more commonly employed for these purposes.22,31–34 However, because new methods are revolutionizing molecular diagnostics, increasing availability, and reducing costs35—and the prognostic value is starting to be realized36—we
propose that genetic information can play a more central role in the management of patients with ADPKD and ADPLD.

THE DIAGNOSIS VALUE OF MOLECULAR GENETICS IN ADPKD

Simple renal cysts (not considered to be of germline genetic origin) are commonly observed in the general population and increase in frequency with age. Consequently, age-related cyst number criteria have been determined for ultrasound (U/S), or the more sensitive MRI, to diagnose ADPKD, or to exclude a diagnosis in the setting of a positive family history. As an example, >10 total cysts detected by MRI are considered sufficient for a positive diagnosis in subjects <40 years. These criteria work well in the setting of a positive family history if multiple bilateral cysts (>10 per kidney) are detected, or if no cysts are detected in an older individual. However, if the family history is negative (10%–25% of ADPKD families) and/or when few cysts are detected, the imaging-based diagnosis is less clear. This uncertainty is exemplified by GANAB, or patients with ADPKD due to an ultra-low penetrant (ULP) PKD1 allele (Figure 1, D and E), where only a small number (or even no) cysts might be detected, although genetically they are proven affected. It might be considered unimportant to diagnose these individuals because they are unlikely to develop renal insufficiency. However, the consequences of employing such a patient as a kidney donor in terms of their long-term renal function is unknown; these patients can have clinically significant extrarenal complications or the offspring, such as PLD in GANAB, and evidence that biallelic disease, the coincidence of a ULP PKD1 allele in trans with a fully inactivating PKD1 allele, can result in early onset PKD (see later section), suggests that obtaining a firm diagnosis is important.

GENETIC DIAGNOSTICS IN ADPKD AND ADPLD: PROGNOSTICS, COMPLICATIONS, AND PROSPECTS

Genetic testing in the clinical management of these diseases has been overlooked for several reasons. First, analysis of PKD1 has been complicated due to its location in a segmentally duplicated region of the genome; three-quarters of the gene, 5' to exon 1 to exon 33, is duplicated six times more proximally on chromosome 16, where they encode pseudogenes with high sequence similarity to PKD1. Hence, long-range PCR methods have been employed to specifically amplify PKD1 for molecular diagnostics by Sanger and NGS, with doubts that this gene is adequately covered by whole-exome sequencing methods, limiting the availability and increasing the costs of testing. However, the development of specific NGS protocols to screen PKD1 by hybridization capture methods and diversity in the groups offering clinical ADPKD molecular diagnostics is likely to increase its availability and reduce costs, even if specificity and sensitivity data are not yet widely available. Second, although both diseases are genetically heterogeneous (Table 1), because the majority of clinically significant renal patients are PKD1 the value of testing is perceived as limited. However, evidence of the incomplete penetrance of many nontruncating PKD1 alleles (not fully inactivating the protein and so associated with milder kidney disease, also termed hypomorphic) has shown potential prognostic value, and is changing this perception. Third, there is extreme allelic heterogeneity, with >1500 different PKD1 alleles, >700000 different PRKCSH, and >450000 SEC63 pathogenic mutations described (with fewer for the other genes), necessitating analysis of the coding regions of all genes for comprehensive analysis. Sanger-based single gene approaches were hence costly and cumbersome, but with NGS panel approaches simultaneous screening of all genes is possible. Fourth, because 30%–35% of PKD1 pathogenic alleles are nontruncating (with significant levels at the other loci), it has proved a challenge to differentiate pathogenic from neutral changes, and their degree of penetrance. The development of better algorithms for predicting the pathogenicity and penetrance of nontruncating gene variants, collation of information on these variants (pathogenic to neutral), and more

### Table 2. Age at ESRD in the different ADPKD subgroups

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of Patients (Number of Pedigrees)</th>
<th>Median Age at ESRD, yr</th>
<th>Reference, Year of Publication</th>
</tr>
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<tbody>
<tr>
<td>ADPKD-PKD1T</td>
<td>219 (54)</td>
<td>54</td>
<td>59, 2002</td>
</tr>
<tr>
<td></td>
<td>701 (450)</td>
<td>55.1</td>
<td>36, 2016</td>
</tr>
<tr>
<td></td>
<td>249 (72)</td>
<td>52.5</td>
<td>55, 2016</td>
</tr>
<tr>
<td>ADPKD-PKD1NT</td>
<td>323 (228)</td>
<td>65.8</td>
<td>36, 2016</td>
</tr>
<tr>
<td></td>
<td>152 (51)</td>
<td>70.8*</td>
<td>55, 2016</td>
</tr>
<tr>
<td>ADPKD-PKD2</td>
<td>291 (31)</td>
<td>74</td>
<td>21, 1999</td>
</tr>
<tr>
<td></td>
<td>395 (71)</td>
<td>72</td>
<td>85, 2003</td>
</tr>
<tr>
<td></td>
<td>117 (23)</td>
<td>70</td>
<td>101, 2009</td>
</tr>
<tr>
<td></td>
<td>248 (112)</td>
<td>77.8</td>
<td>10, 2016</td>
</tr>
<tr>
<td></td>
<td>213 (57)</td>
<td>80</td>
<td>55, 2016</td>
</tr>
<tr>
<td></td>
<td>293 (203)</td>
<td>77.8</td>
<td>97, 2017</td>
</tr>
<tr>
<td>ADPKD-GANAB</td>
<td>22 (11)</td>
<td>No cases of ESRD described</td>
<td>15, 2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20, 2017</td>
</tr>
</tbody>
</table>

*TGESP* PKD1NT group included nonsynonymous missense mutations but excluded patients with inframe short deletion or insertion.
informative diagnostic reports will increase the value of molecular diagnostics in these disorders.14,56,57

INTRODUCING A DISEASE, PLUS GENE AND ALLELIC TERMINOLOGY FOR ADPKD AND ADPLD

In autosomal dominant tubulointerstitial kidney disease (ADTKD), where there is also genetic and phenotypic heterogeneity, a terminology describing the disease and the genetic etiology has been adopted (i.e., ADTKD-MUC1, ADTKD-UMOD, ADTKD-HNF1B, and ADTKD-REN).58 We propose to introduce a similar nosology for ADPKD/ADPLD (see Table 1 for that a few large cysts in the right kidney largely explain the enlarged HtTKV. (D) ADPKD-PKD1 ULP: Contrast-enhanced CT-scan of a 48-year-old woman, with a ULP PKD1 nontruncating mutation (c.9829C>T, p.Arg3277Cys), who has a total of five cysts in the right kidney and one cyst in the left kidney, a normal eGFR, and nonenlarged kidneys. (E) ADPKD-GANAB: CT-scan of 45-year-old woman with a GANAB mutation (c.1914_1915delAG; p.Asp640fs) who has bilateral kidney cysts, a normal eGFR (104 ml/min) and HtTKV (318 ml/m), and without significant PLD. (F) A common differential diagnosis: ADTKD-HNF1B. MRI of 30-year-old woman with a large deletion of the entire HNF1B gene, who has preserved kidney function (75.5 ml/min per 1.73 m²) and approximately ten cysts per kidney (HtTKV=196.9 ml/m). (G) ADPKD-PKD1NT MRI of 54-year-old woman with severe PLD (HtTLV=4695 ml/m; liver resection performed after this MRI) and normal-sized kidneys, with a total of 12 bilateral small cysts. A PKD1NT allele was identified (c.3284A>G, p.Tyr1095Cys), with no mutation identified in other ADPLD genes. (H) ADPLD-PRKCSH MRI of a 49-year-old man with predominant PLD (HtTLV=7271 ml/m; liver resection was performed after this MRI) and mild PKD (eight cysts in the left kidney). A right nephrectomy was performed at 42 years (atrophic cystic kidney with suspected malignancy). The PRKCSH (c.1386T>G, p.Tyr462*) mutation was identified. MRI, magnetic resonance imaging; CT, computed tomography.

Figure 1. These eight kidney and liver images illustrate the different genic and allelic forms of ADPKD and ADPLD, and the most frequent differential diagnosis. (A) ADPKD-PKD1NT: MRI of a 45-year-old male patient with a truncating PKD mutation (c.4880_4883delATGT; p.Tyr1627fs), who has an eGFRCKDEPI=15.1 ml/min per 1.73 m² and HtTKV=3853 ml/m. (B) ADPKD-PKD1NT: MRI of a 55-year-old woman with a PKD1 nontruncating mutation (c.2180T>C, p.Leu727Pro) with well preserved kidney function (eGFR=63.4 ml/min per 1.73 m²) and HtTKV=439 ml/m. Significant PLD is present. (C) ADPKD-PKD2: MRI of a 53-year-old man, with a PKD2 mutation (c.1057G>A, p.Glu353Lys), who has well preserved kidney function (eGFR=68.6 ml/min per 1.73 m²) and HtTKV=1245 ml/m. Note
Brief Review

The nosology: ADPKD—We propose to include this grouping in ESRD.62 Conversely, early diagnosis can serve to identify children diagnosed in utero or during childhood at risk of early hypertension, urologic events, reduced eGFR, and ESRD.4–6,63,64 We propose to use the term ADPKD_{VEO} when the diagnosis is made in utero or before 18 months, and ADPKD_{EO} when the diagnosis is made before 15 years, in both cases excluding asymptomatic individuals diagnosed by systematic familial screening or incidentally (see Table 3 for proposed diagnosis criteria).

In a proportion of these cases a specific cause of biallelic disease has been demonstrated; for instance, coinheritance of the familial PKD1 mutation in trans with a second ULP PKD1 allele (Tables 1 and 4).4,41,43–45,48 Monoallelic ULP patients are unlikely to develop renal insufficiency but may develop a small number of cysts in adulthood (Figure 1D). The best characterized such allele is PKD1: p.Arg3277Cys (Table 4).4,41,42,45,54 The combination of two ULP PKD1 alleles can also result in ADPKD_{VEO} with an apparent negative family history (cysts undetected in the monogenic parents—often with lower resolution U/S analysis), or adult onset ADPKD (Tables 1 and 4).4,41,42,45 This mechanism can involve PKD2, described as homozygosity of a PKD2 hypomorphic allele arising through uniparental disomy.65 Inference from mouse studies, and lack of described human patients, indicates that biallelism of fully inactivating PKD1 or PKD2 mutations is not compatible with life,66,67 showing that these ULP alleles have residual function and indicating that a dosage/threshold mechanism best explains ADPKD.24,45,66,69 Rarely, digenic disease, involving PKD1 and PKD2, has been described, resulting in more severe disease than for either variant monogenically, but not VEO.61,70,71 Pathogenic alleles in other cystogenes may cause VEO PKD in combination with a PKD1 or PKD2 mutation, such as digenic disease involving a PKD1 and HNF1B allele,43 emphasizing the importance of comprehensive analysis of not only PKD1 and PKD2 in these cases. Occasionally, a contiguous gene syndrome (CGS) due to deletion of PKD1 and the tuberous sclerosis complex (TSC) gene TSC2 is associated with a more severe renal phenotype than TSC or ADPKD alone, often leading to renal insufficiency in childhood.72–74 CGS individuals with mosaicism can have milder, more typical ADPKD with TSC.74

Differential diagnosis from other inherited renal cystic diseases

A number of other diseases can appear similar to ADPKD or ADPLD, although they are usually differentiated on clinical grounds. Autosomal recessive polycystic kidney disease (ARPKD), associated with biallelic PKHD1 mutations, although typically an infantile disease can manifest later in life with an ADPKD-like renal phenotype, but congenital hepatic fibrosis rather than PLD usually differentiates the two.75 Monoallelic mutations to PKHD1 have been described to cause increased kidney echogenicity and/or multiple small liver cysts (mimicking ADPLD) in approximately 15% of carriers.20,76 However, with a carrier rate of approximately 1 in 70 it seems that other genetic/environmental factors must be necessary to reveal the monoallelic cystic phenotype. The association of PKD with hyperinsulinic hypoglycemia was recently described in 11 pedigrees and linked to biallelic mutations (including a specific promoter mutation) of PMM2, encoding the N-linked glycosylation enzyme, phosphomannomutase 2, again linking glycosylation defects and PKD.77 ADTKD because of MUC1 or UMOD mutations can result in the development of small renal cysts late in the disease, but the lack of renal enlargement, and the parallel decline of kidney size and kidney function with advancing disease, usually differentiate them from ADPKD.78 ADTKD–HNF1B is associated with a highly heterogeneous phenotypic spectrum, including maturity onset diabetes of the young, a personal or familial history of urogenital malformations, early onset gout, and/or the presence of elevated liver enzymes or hypomagnesaemia, but dominant HNF1B mutations can sometimes phenocopy ADPKD (Figure 1F).58,79 Mutations to SEC61A1 have recently been identified in two families with ADTKD; glomerular cysts on renal

Very early onset (VEO) ADPKD

When screening children at risk for ADPKD, renal cysts are detected in a majority of affected individuals, even in early childhood, but they do not necessarily implicate a more severe prognosis.62 Conversely, early diagnosis can serve to identify asymptomatic individuals with “symptomatic”
biopsy and multiple bilateral renal cysts without renal enlargement were present in some family members.\textsuperscript{80} HANAC due to \textit{COL4A1} mutations can also result in renal cysts, although the additional features, such as hematuria, muscles cramps or elevated creatinine phosphokinase, tortuosity of the retinal artery, and brain small-vessel disease, usually allow for a differential diagnosis.\textsuperscript{81} Syndromic forms of PKD can sometimes prove challenging as a differential diagnosis from ADPKD. Oro-facial-digital syndrome type 1 is a rare X-linked dominant disorder with male prenatal lethality, where the monoallelic female renal presentation can occasionally present with kidney cysts with only discreet dermatologic features.\textsuperscript{84} In each of these cases, genetic analysis of a panel of PKD genes can better reveal the full etiology and aid diagnostics.

### OTHER INFLUENCES ON PHENOTYPE, AND GENETICALLY UNRESOLVED CASES

Accumulating data in ADPKD indicates that males tend to have more severe renal disease.\textsuperscript{3,14,21,36,59,85} Severe PLD associated with \textit{PKD1}, \textit{PKD2}, \textit{PRKCSH}, and \textit{SEC63} mutation is predominantly a female disease, where growth moderates after menopause, suggesting a strong hormonal influence on the phenotype.\textsuperscript{89} It is unclear if there is a similar female bias associated with severe PLD and the rarer ADPLD genes.

The ADPKD-\textit{PKD1}\textsuperscript{NT} population encompasses a large spectrum, from fully inactivating mutations (similar to ADPKD-\textit{PKD1}\textsuperscript{NT}) to ULP alleles associated with mild PKD (Figure 1D).\textsuperscript{86} The Canadian cohort suggested that \textit{PKD1} patients with inframe indels had renal severity intermediate between missense and \textit{PKD1}\textsuperscript{NT}.\textsuperscript{55} In HALT PKD, ADPKD-\textit{PKD1}\textsuperscript{NT} patients were further classified into strongly or weakly predicted mutation strength groups (MSG2 or MSG3, respectively) using an \textit{in silico} algorithm. MSG3, but not MSG2 patients, had significantly higher eGFR and lower HtTKV than ADPKD-\textit{PKD1}\textsuperscript{NT}.\textsuperscript{14} However, no automated schema to assign MSG scores to \textit{PKD1} variants is yet available and so at this stage we have not included these groups into the classification. However, as mutation screening becomes more widespread, variants are better collated, \textit{in silico} tools are improved, and \textit{in vitro} assays of \textit{PKD1} variants are developed, better classification of \textit{PKD1}\textsuperscript{NT} variants should be possible.\textsuperscript{14,56,87}

### ESTIMATING THE PREVALENCE OF ADPKD AND ADPLD

Prevalence estimates can have important implications for drug development, with orphan diseases defined by a prevalence of \textless{}1 per 2000.\textsuperscript{91} Older population-based studies have estimated a lifetime risk of ADPKD at 1 per 1000, or even higher if autopsies—that likely included patients with few kidney and liver cysts and excellent renal prognoses plus other phenocopying disorders—are taken into consideration.\textsuperscript{92,93} More recent population-based minimum point prevalence estimates of 2.9 and 3.3 per 10,000, reflecting individuals with clinically significant disease, fall below the orphan threshold.\textsuperscript{94–96} ADPKD-\textit{PKD2} genetic prevalence in European individuals from the ExAC database was calculated at 1.64 per 10,000, suggesting a higher prevalence of the total ADPKD population.\textsuperscript{97} ADPLD prevalence, estimated in a single study at 1 per 158,000, is likely underestimated, because many affected individuals probably remain asymptomatic and undiagnosed.\textsuperscript{98} Conducting a combined analysis of clinical records, imaging, and genetic data in a geographically circumscribed area would be invaluable to refine prevalence estimates for the total population and genic/allelic groups.
Table 4. Ultra low penetrant (ULP) alleles of PKD1 and PKD2 involved in biallelic ADPKD

<table>
<thead>
<tr>
<th>ULP Allele*</th>
<th>Other Mutant Allele</th>
<th>Phenotype Description, Age at Phenotype</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>PKD1 c.9829C&gt;T (p.Arg3277Cys)</td>
<td>None</td>
<td>Pedigree M34-6 relatives, 0–7 kidney cysts, 28–79 yr</td>
<td>41</td>
</tr>
<tr>
<td>PKD1 c.9829C&gt;T (p.Arg3277Cys)</td>
<td>PKD1 1.9829C&gt;T (p.Arg3277Cys)</td>
<td>Pedigree M34-ESRD in two siblings, 62 and 75 yr</td>
<td>41</td>
</tr>
<tr>
<td>Pedigree PK10362-ESRD 76 yr</td>
<td>Pedigree PK11509-ESRD 48 yr</td>
<td>EHK, 22 pw (TOP)</td>
<td>36</td>
</tr>
<tr>
<td>PKD1 ex1–5del</td>
<td>PKD1 c.6472C&gt;T (p.Gln2158*)</td>
<td>EHK (&gt;10 SD), at birth; HTN, 5 m; eGFR=56, 17 yr</td>
<td>41</td>
</tr>
<tr>
<td>PKD1 c.6658C&gt;T (p.Arg2220Trp)</td>
<td>PKD1 c.7483T&gt;C (p.Cys2495Arg)</td>
<td>Two siblings EHK, RD; HTN 0 m, eGFR=70 or 65 at 1 or 8 yr</td>
<td>42</td>
</tr>
<tr>
<td>PKD1 c.9563A&gt;G (p.Asn3188Ser)</td>
<td>PKD1 c.9563A&gt;G (p.Asn3188Ser)</td>
<td>Father, BCK, Sibling 1, EHK, 22 pw, eGFR 67, 15.5 yr</td>
<td>41</td>
</tr>
<tr>
<td>PKD1 c.5848G&gt;A (p.Val1950Met)</td>
<td>PKD1 1.8362_8363ins34 (p.Ser2788fs)</td>
<td>EHK, OH; double nephrectomy, RD, neonatal demise</td>
<td>44</td>
</tr>
<tr>
<td>PKD1 c.[3133C&gt;G;4709C&gt;T] (p.Val1045Met;Thr1570Met)</td>
<td>EHK (approximately 18 SD), at birth, HTN, 2 m; eGFR=52, 18 yr</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>PKD1 c.5305C&gt;T (p.His1769Tyr)</td>
<td>PKD1 c.6727C&gt;T (p.Gln2243*)</td>
<td>Sibling 1- SIE, age?; Sibling 2- SIE, few cysts, age?</td>
<td>34</td>
</tr>
<tr>
<td>PKD1 c.6763C&gt;T (p.Arg2255Cys)</td>
<td>PKD1 1.8259C&gt;G (p.Tyr2753*)</td>
<td>EK, CRI, age?</td>
<td>43</td>
</tr>
<tr>
<td>PKD1 c.12413G&gt;A (p.Asp4138His)</td>
<td>PKD1 c.4199del (p.Leu1400fs)</td>
<td>Sibling 1- MEK, ESRD 29 yr</td>
<td>43</td>
</tr>
<tr>
<td>PKD1 c.3828G&gt;A (p.Val1274Met)</td>
<td>PKD1 c.5830G&gt;A (p.Glu4025Gly)</td>
<td>Sibling 2- MEK, eGFR 91, 25 yr</td>
<td>43</td>
</tr>
<tr>
<td>PKD1 c.8984A&gt;G (p.Asn3295Ser)</td>
<td>PKD1 c.10232G&gt;A (p.Trp3411*)</td>
<td>EHK, 22 pw</td>
<td>4</td>
</tr>
<tr>
<td>PKD1 c.9548G&gt;A (p.Asn3183Gln)</td>
<td>PKD1 c.11614G&gt;T (p.Glu3872*)</td>
<td>EHK (6 SD), 22 pw</td>
<td>4</td>
</tr>
<tr>
<td>PKD1 c.12161C&gt;T (p.Ser4045Phe)</td>
<td>PKD1 c.7978G&gt;T (p.Asp2660Tyr)</td>
<td>EHK (4 SD), 26 pw</td>
<td>4</td>
</tr>
<tr>
<td>PKD1 c.11834C&gt;T (p.Trp3945Met)</td>
<td>PKD1 c.2180T&gt;C (p.Leu727Pro)</td>
<td>EHK (14 SD), 15 pw (TOP)</td>
<td>4</td>
</tr>
<tr>
<td>PKD1 c.8129C&gt;A (p.Try2710Asn)</td>
<td>PKD1 1.1010_1013dup (p.Leu3384Glyfs*33)</td>
<td>EHK (3 SD), 17 pw</td>
<td>4</td>
</tr>
<tr>
<td>PKD1 c.5830G&gt;A (p.Gly1944Arg)</td>
<td>PKD1 1.5515G&gt;T (p.Trp1839Cys)</td>
<td>EHK (2 SD), 25 pw</td>
<td>4</td>
</tr>
<tr>
<td>PKD1 c.6173G&gt;A (p.Gln2058Arg)</td>
<td>PKD1 c.9562A&gt;G (p.Asn3188Asp)</td>
<td>EHK (14 SD), at birth; eGFR=56, 20 yr</td>
<td>4</td>
</tr>
<tr>
<td>PKD1 c.12074A&gt;G (p.Glu4025Gly)</td>
<td>PKD1 c.2582G&gt;A (p.Trp861*)</td>
<td>EHK (10 SD), 22 pw; CKD3a, 4 yr</td>
<td>4</td>
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<tr>
<td>PKD1 c.4831G&gt;A (p.Val1611Ile)</td>
<td>PKD1 c.12503dup (p.Ser4169Leufs*41)</td>
<td>EHK (3 SD), 22 pw</td>
<td>4</td>
</tr>
<tr>
<td>PKD2 c.1967T&gt;G (p.Leu656Trp)</td>
<td>PKD2 c.1967T&gt;G (p.Leu656Trp)</td>
<td>EHK (approximately 18 SD), at birth, HTN, 2 m; eGFR=52, 18 yr</td>
<td>4</td>
</tr>
<tr>
<td>PKD2 c.1967T&gt;G (p.Leu656Trp)</td>
<td>PKD2 c.12413G&gt;A (p.Asp4138His)</td>
<td>Sibling 1- EHK, neonatal cyst, 8 yr, HTN</td>
<td>4</td>
</tr>
<tr>
<td>PKD2 c.12413G&gt;A (p.Asp4138His)</td>
<td>PKD2 c.3828G&gt;A (p.Val1274Met)</td>
<td>Sibling 2- EHK, multiple cysts, 7 yr, Sibling 3- EHK, multiple cysts, 17 m</td>
<td>4</td>
</tr>
</tbody>
</table>

*Other described examples where the high frequency of the ULP allele in normal individuals or in silico analysis makes the ULP allele an unlikely cause of the VEO

**Pedigree PK11509- ESRD 48 yr

†Detected by computed tomography or magnetic resonance imaging.

‡Identified alone in one parent, no cysts detected on ultrasound.

§Homozygosity due to maternal isodisomy.

¶Likely ADPKD VEO but no details about presence or not of oligohydramnios and evolution after diagnosis (hypertension/kidney function/overt proteinuria).

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CLINICAL IMPLICATIONS

Stratifying the ADPKD population is a prerequisite to the personalization of patient care. Combining genic and allelic information with the sex and clinical information (early hypertension and urinary tract infections), the PROPKD score, has shown strong renal prognostic value. Age-adjusted TKV is also a valuable prognostic marker. Multidisciplinary approaches involving clinical, imaging, and genetic data should now be favored as they help diagnostics, including the characterization of atypical clinical presentations,
while predicting the evolution of patients with ADPKD, which is key to targeting therapies. Genic and allele information may also be important in the future as specific treatments proximal to the basic defect are developed, as is occurring in other common genetic diseases.100

ACKNOWLEDGMENTS

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DISCLOSURES

None.

REFERENCES


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