

# Autosomal dominant polycystic kidney disease: genetics, epidemiology, and treatment

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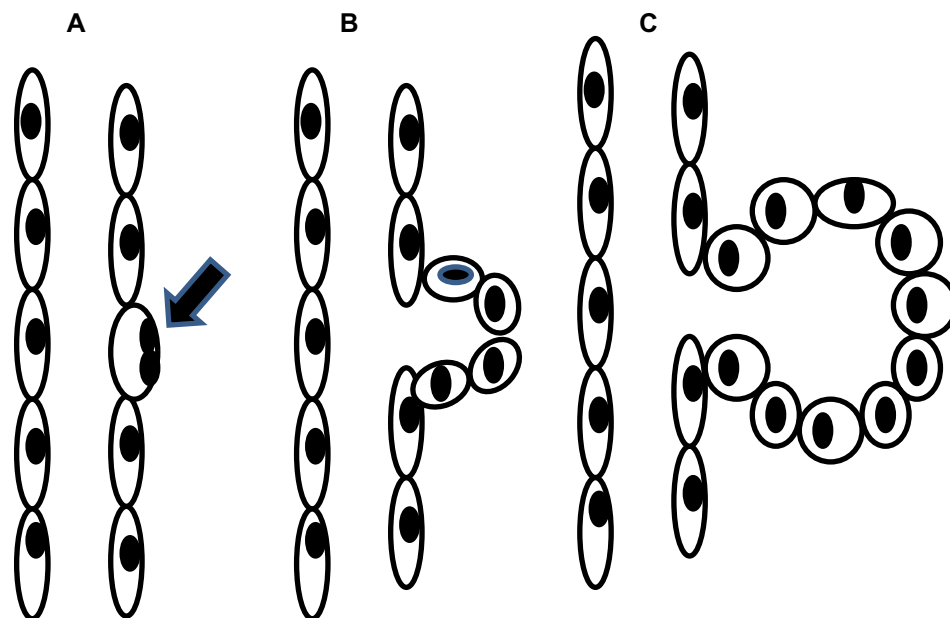
**Abstract:** Autosomal dominant polycystic kidney disease (ADPKD) is the most common potentially lethal genetic disorder, accounting for 2%–8% of end-stage renal disease worldwide. While development of renal cysts is the major characteristic of ADPKD, several disease-related complications contribute significantly to morbidity and mortality. Since introduction of renal replacement therapies, cardiovascular disease is the leading cause of death among ADPKD patients. Loss of renal function requiring renal replacement therapy occurs in 50% of patients by the age of 60 years. The results of recent large epidemiological studies in ADPKD have shown little progress in delaying onset of renal failure despite an improvement in patient mortality. Significant progress has been made over the past decade in elucidating the genetics of the disorder. Genetic testing is now available in most countries, and development of more reliable methods for prenatal diagnosis of ADPKD has increased the sensitivity of testing. While there are no approved drugs for treatment of ADPKD within the USA, the first agent targeting renal disease progression in this disorder was recently approved for clinical use in Japan. Furthermore, several additional drugs for treatment of ADPKD are currently under clinical investigation. Overall, this presents an optimistic future for new therapeutic interventions in this disease. This paper reviews the current knowledge related to the epidemiology, genetics, and treatment of ADPKD.

**Keywords:** autosomal dominant polycystic kidney disease, hereditary renal disease, renal cyst, genetics

## Introduction

Autosomal dominant polycystic kidney disease (ADPKD) results from a mutation in either of two genes, ie, *PKD1* encoding the protein polycystin 1 (PC1) or *PKD2* encoding polycystin 2 (PC2).<sup>1–3</sup> The key feature of the disease, namely, development of multiple fluid-filled cysts within the kidneys, results from focal proliferation of single tubular epithelial cells, as shown in the sequential steps depicted in Figure 1A–C.<sup>4,5</sup> Continued cell proliferation and fluid secretion results in cyst growth throughout the lifetime, causing displacement and loss of the normal renal parenchyma, with increasing impairment of renal function (Figure 2). Polycystin proteins are expressed in several tissues, including the biliary ducts of the liver, pancreas, endothelial cells, and myocardial smooth muscle cells.<sup>6,7</sup> Polycystins interact through their carboxyl-terminal tails to form a complex with both receptor and ion channel functions.<sup>8</sup> At a cellular level, PC1 is expressed in the plasma lateral membrane of renal tubular cells, at apical junctions, and in the primary cilium.<sup>9–11</sup> Within these locations, PC1 forms a complex with PC2 and other intracellular adhesion molecules. In addition, both of the polycystin proteins in their cleaved forms have been found in urinary exosome-like

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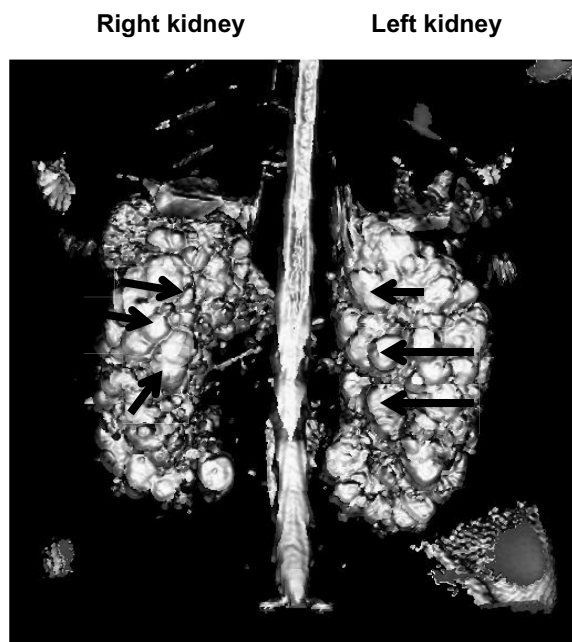


**Figure 1** Schematic of cyst growth progression.

**Notes:** (A) Arrow indicates renal tubular cell that undergoes abnormal proliferation. (B) Tubule becomes distended. (C) Cyst pinches off from tubule.

vehicles that interact with the primary cilium.<sup>12</sup> This has been suggested as a mechanism to explain the localization of PC1 at disparate cellular locations. However, despite significant progress toward understanding the pathophysiology of ADPKD, the precise function of the polycystins, and their role in cystogenesis is incompletely understood.

Consistent with the broad cellular and tissue expression of the polycystins, ADPKD is a systemic disorder. Cysts occur in multiple organs, most commonly the liver and pancreas. Liver cysts, which develop from cholangiocytes lining the biliary ducts, are more common in women, suggesting a role for estrogen in liver cyst growth.<sup>13</sup> It is significant that the leading cause of death among affected patients is cardiovascular complications.<sup>14,15</sup> Hypertension occurs early in ADPKD, and is an important risk factor associated with rapid decline in kidney function and development of left ventricular hypertrophy and consequent cardiovascular morbidity.<sup>16–18</sup> Renal cyst growth results in compression of the renal vasculature, and the resulting intrarenal ischemia has been implicated in activation of the renin–angiotensin–aldosterone system (RAAS).<sup>19</sup> RAAS stimulation occurs early in ADPKD before decline in renal function, even prior to development of hypertension, and contributes to left ventricular hypertrophy and atherosclerosis.<sup>19,20</sup> Moreover, consistent with the vascular expression of the polycystins, endothelial dysfunction also occurs early in ADPKD, and has been detected in normotensive patients with preserved kidney function.<sup>21</sup> A key mechanism contributing to endothelial dysfunction in the earlier stages of ADPKD is increased oxidative stress.<sup>22,23</sup> Further extrarenal manifestations of ADPKD include intracranial aneurysms, cardiac valvular defects, abdominal wall hernias, and nephrolithiasis. Pain and hematuria are common complications and frequent reasons leading to diagnosis.



**Figure 2** Magnetic resonance image of ADPKD kidneys in a 14-year-old male. The left and right kidneys are indicated. The arrows indicate a few of the multiple cysts of varying size that completely fill both kidneys. The parenchyma is completely displaced by cysts.

**Abbreviations:** ADPKD, autosomal dominant polycystic kidney disease.

## Epidemiology

ADPKD affects an estimated 600,000 individuals in the USA, with an incidence rate of approximately 1/500 to 1/1,000 individuals. The disease affects both sexes equally and all races and ethnicities. In population-based studies, male sex has been associated with both earlier age at diagnosis of hypertension and earlier age at onset of end-stage renal disease.<sup>24–26</sup> Up to 50% of patients with ADPKD require renal replacement therapy by the age of 60 years. Based on the 2013 US Renal Data System report, cystic kidney disease was the fourth most common cause for patients initiating renal replacement therapy in the USA between 2009–2011.<sup>27</sup> A recent study based on the UK Renal Registry reported an incidence rate of 6.8% for adult ADPKD patients commencing renal replacement therapy between 2000 and 2011.<sup>28</sup> A report from the European Renal Association European Dialyses and Transplant Registry based on data collected between 1991 and 2010 demonstrated little apparent improvement in postponing age at onset of end-stage renal disease over the past two decades.<sup>29</sup> However, a slight improvement in ADPKD patient mortality was indicated by a UK General Practice Research Database study that showed a trend toward decreased mortality associated with increasing coverage and intensity of antihypertensive therapy.<sup>30</sup>

## Genetics of ADPKD

### Genes

ADPKD results from a mutation in either of two genes, ie, *PKD1* located on chromosome 16p13.3<sup>1</sup> or *PKD2* located on chromosome 4q21.<sup>2,31</sup> While there have been reports of a potential third PKD locus,<sup>32,33</sup> these have not been substantiated by reanalysis of PKD3 families.<sup>34</sup> However, in animals, mutation in several other genes, including *Anks6* in the Han Sprague Dawley rat and *Bicc1* in the Jcpk mouse, has been associated with slowly progressive disease that has similar characteristics to ADPKD.<sup>35,36</sup> A comprehensive overview of genetic models of polycystic kidney disease has previously been presented by Torres and Harris.<sup>37</sup> The *PKD1* gene is large, comprising 46 exons that encode a 12,909 base pair transcript.<sup>3</sup> Sequence analysis of *PKD1* is complicated by duplication of exons 1–33 in six pseudo genes which share approximately 98% identity with the gene.<sup>38</sup> *PKD2* is a smaller gene, with 15 exons coding a 2,904 base pair transcript.<sup>2</sup> Mutation of *PKD1* accounts for approximately 85% of all disease cases, with *PKD2* mutation accounting for the remaining 15%. More recently, a higher incidence of *PKD2* mutations has been reported in the Canadian and US populations (26% and 36%, respectively).<sup>39,40</sup> There is significant

heterogeneity in disease phenotype between affected individuals. *PKD1* mutation is associated with more severe and rapidly progressive disease, with onset of end-stage renal disease occurring by the mid to late 50s. Disease associated with *PKD2* mutation is milder, with the onset of end-stage renal disease typically delayed by 10–20 years compared with *PKD1*. Results from the Consortium of Radiologic Imaging Study of PKD indicated that kidneys of *PKD1*-affected individuals were significantly larger than those with *PKD2*, with more cysts developing at an earlier age, while renal growth rate was similar for *PKD1* and *PKD2*.<sup>41</sup>

Sequence analysis of *PKD1* is complex due to the similarities between *PKD1* and the pseudo genes (*PKD1P1*–*PKD1P6*). However, strategies have been developed that exploit the slight sequence differences between *PKD1* and the pseudogenes, allowing unique amplification of the target.<sup>42</sup> In contrast, as *PKD2* is a nonduplicated gene sequence, analysis by conventional sequencing strategies is possible for mutation identification. More recently, next-generation sequencing has been successfully applied to sequence analysis of both *PKD1* and *PKD2*.<sup>43</sup>

### Allelic heterogeneity

To date, the Mayo Clinic PKD mutation database (<http://pkdb.mayo.edu/>) lists 1,272 potentially pathogenic mutations in *PKD1* and 202 in *PKD2*. Several studies have reported an association between mutation position or mutation type with severity of ADPKD phenotype. A more 5' mutation location in *PKD1* has been associated with earlier age at onset of end-stage renal disease and a vascular phenotype.<sup>44,45</sup> Similarly, in a European study, *PKD1* mutation type was shown to influence renal disease severity.<sup>46</sup> In *PKD2*, while mutation position and type have been suggested to influence disease severity, the association is less well delineated over normal disease variability.<sup>47</sup>

### Hypomorphic alleles and mosaicism

Presentation of unusual cases of severe ADPKD that manifest as onset of symptomatic disease in early childhood have been associated with coinheritance of an incompletely penetrant (hypomorphic) allele in trans with either a *PKD1* truncating mutation or a second *PKD1* missense mutation.<sup>48,49</sup> When occurring alone, hypomorphic alleles are usually associated with mild disease; however, when homozygous or presenting as a compound heterozygote, they may manifest as a severe phenotype. Several hypomorphic alleles have been described for *PKD1*, including p.R3227C, p.Y528C,<sup>48,50</sup> and T2250M.<sup>51</sup>

Genetic mosaicism, where cells carrying a mutation and nonmutated cells are present in the same individual, has been described in ADPKD.<sup>52</sup> Mosaicism may result from either a germline or a somatic mutation, and may complicate genetic diagnosis. In the case of a somatic mutation, different levels of the mutated allele may be present in different tissues.

## Genetic testing

Mapping of *PKD1* and *PKD2* and flanking microsatellite markers has allowed genetic diagnosis by linkage analysis.<sup>53,54</sup> Determination of the disease-associated haplotype allows ascertainment of at-risk family members and also identification of the disease-associated causative gene. Linkage analysis requires a definitive diagnosis in at least one family member, and several other family members must be available and willing to participate in testing.<sup>55</sup> Existence of mosaicism may also complicate diagnosis. Since development of reliable methods for sequencing *PKD1*,<sup>42</sup> diagnosis by mutation identification is possible and available in several countries, including the USA. However, the pathogenicity of certain missense variants may be difficult to establish even with available predictive tools. Preimplantation diagnosis (PGD) with in vitro fertilization presently has limited availability for ADPKD diagnosis. While PGD has been successfully applied in cases of other severe hereditary diseases, testing is more complex in ADPKD due to the presence of the large duplicated region in *PKD1*.<sup>56</sup> Introduction of a single cell duplex-polymerase chain reaction method for PGD that includes an intragenic and extragenic marker for *PKD1*,<sup>57</sup> coupled with more reliable cell sampling techniques for PGD, has increased the reliability of testing in ADPKD.<sup>58</sup>

## Second hit and potential third hit?

The fact that cyst formation is focal, with only a small number of tubular epithelial cells forming cysts within the nephron, has led to the hypothesis that a “second hit” resulting in loss of heterozygosity is necessary for cyst formation.<sup>59,60</sup> Thus, the disease could be viewed as recessive at the tissue level, requiring a second somatic mutation in addition to the germline mutation for initiation of cystogenesis. The continued development of cysts throughout life supports this hypothesis. Several studies have identified second somatic mutations in addition to the germline mutation in individual cysts from the kidney or liver in patients where the primary mutation affected *PKD1* or *PKD2*.<sup>59,61,62</sup> Studies in animal models of PKD further support a second-hit mechanism.<sup>63</sup> In human disease, the mechanism leading to loss of heterozygosity

is unknown. Whether the presence of a germline mutation directly conveys a degree of instability to the normal gene copy or whether a potential third hit is necessary remains to be tested. However, there are similarities between growth of a benign tumor and cyst growth, such that clues may be obtained from the cancer paradigm. Chromosomal instability is a hallmark of cancer cells. Interestingly, multiple cytogenetic aberrations have been found in individual ADPKD cyst cells by comparative genomic hybridization and loss of heterozygosity analyses.<sup>64</sup> Moreover, a recent study indicated potential genomic instability in peripheral blood lymphocyte DNA isolated from ADPKD patients.<sup>65</sup> Chronic inflammation and oxidative stress occur in ADPKD, and both processes have been linked to molecular mechanisms associated with DNA damage and chromosomal instability leading to cancer initiation.<sup>66</sup>

There is also strong evidence suggesting that gene dosage alone, whether associated with increased or decreased expression of *Pkd1* or *Pkd2*, is sufficient for cyst development.<sup>67–69</sup> Likewise, analyses of families with hypomorphic alleles similarly support an effect of gene dosage on phenotype development.<sup>48</sup>

## Modifier genes

Significant phenotypic variability is apparent even among members of the same family, all of whom carry the same germline mutation. This has been partly attributed to the expressed effects of genes that modify disease severity (modifier genes). Based on study of PKD1 families, heritability analyses confirmed that one or more modifier genes in the genetic background accounted for a significant fraction of the phenotypic variability seen in patients with a *PKD1* mutation.<sup>70</sup> While several individual genes have been examined as candidate modifiers of ADPKD severity, the results of these studies have been varied and confounded by small study populations and lack of patient stratification. A larger study that included 794 PKD1 patients examined 173 candidate genes and found suggestive evidence for an association between the Dickkopf 3 gene and estimated glomerular filtration rate.<sup>71</sup> In a few pedigrees with cases of severe very early-onset disease, in addition to the germline *PKD* mutation, *HNF-1 $\beta$*  or *PKDH1* mutations have been described in the severely affected patients.<sup>72</sup> This suggests that these genes may modify disease expression. The results from a large ongoing genome-wide association study funded by the National Institutes of Health (U01 DK079856) will provide further insight into the identity of genes that modify ADPKD severity.

## Extracellular matrix gene expression

Abnormal expression of extracellular matrix proteins has been described in ADPKD, and is thought to contribute to proliferation of cyst epithelial cells and cyst growth. Overproduction of extracellular matrix proteins has been reported in both ADPKD cell and animal studies.<sup>73,74</sup> Moreover, upregulated gene expression of several matrix protein-related messenger RNAs (mRNAs) has been described in human cystic tissue.<sup>75</sup> Mutations in several cell adhesion and matrix protein-related genes, including laminin-5, have been shown to result in a cystic phenotype.<sup>76</sup> In a more recent study, increased type 1 collagen and matrix metalloproteinase expression has been suggested to induce cyst formation and expansion in both in vivo and in vitro models.<sup>77</sup> The role of polycystins, focal adhesions, and extracellular matrix adhesions in progression of cystic disease has recently been reviewed by Drummond.<sup>78</sup>

## Epigenetics

Epigenetic modulation including histone modification, DNA methylation, or noncoding RNA expression is an important mechanism of cellular regulation. Several recent studies have examined potential epigenome changes in ADPKD. Histone deacetylation is controlled by histone deacetylases (HDACs). Loss of function mutations in HDAC5 have been shown to decrease cyst formation in a *Pkd2*<sup>-/-</sup> mouse model, suggesting a role for HDACs in cystogenesis.<sup>79</sup> Administration of a HDAC inhibitor to pregnant *Pkd2*<sup>+/-</sup> female mice resulted in significant cyst reduction in kidneys of *Pkd2*<sup>-/-</sup> embryos.<sup>79</sup> Similar results have been reported in *Pkd1* mice following HDAC inhibition.<sup>80</sup> Significantly, in renal epithelial cells, *HDAC5* expression is regulated by flow-mediated shear stress in a polycystin-dependent manner.<sup>79</sup>

Hypermethylation of *PKD1* and other genes related to ion transport and cell adhesion has been identified in ADPKD renal tissue.<sup>81</sup> Oxidative stress and inflammatory cytokines have both been implicated in epigenetic instability.<sup>82</sup> Both oxidative stress and inflammation play significant roles in the pathophysiology of ADPKD, and it is therefore intriguing to postulate a role for epigenetic modulation in ADPKD.

## Micro RNA

Micro RNAs (miRNAs) are short noncoding nucleotides approximately 20 nucleotides in length that play a significant role in post-transcriptional regulation of gene expression. Several differentially expressed miRNAs have been described in animal models of ADPKD.<sup>83,84</sup> In particular, the oncogenic cluster miRNA17–92 is upregulated in mouse models of PKD while inactivation of miRNA17–92 retards cyst growth.<sup>85</sup>

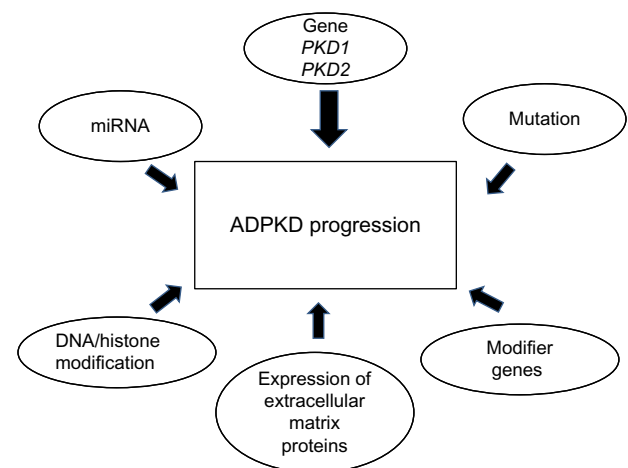
Furthermore, members of the miRNA-17 family have been shown to post-transcriptionally regulate *PKD2*.<sup>86</sup> The RNA binding protein, bicaudal 1, regulates PC2 by interfering with miR-17 family binding, enhancing PKD2 translation.<sup>87</sup> In contrast, in non-PKD disease models, loss of bicaudal 1 expression results in a PKD-like phenotype.<sup>88</sup> Dysregulated expression of several miRNAs has been found in the urine of human ADPKD patients when compared with urine from patients with chronic kidney disease, including miRNA-1 and miRNA-133, previously implicated as tumor suppressors, and miRNA-223/miRNA-199.<sup>89</sup> Thus, a role for miRNAs in the pathogenesis of ADPKD is suggested, and modulation of miRNA levels may have future therapeutic benefits. A summary of the various genetic influences on ADPKD progression is shown in Figure 3.

## Treatment

There is currently no approved therapy to slow progression of ADPKD. Treatment of hypertension or disease-related symptoms are the mainstays of management for ADPKD patients. However, over the past 5 years, significant advances have been made regarding potential new interventions in ADPKD. ClinicalTrials.gov (<https://clinicaltrials.gov>) currently lists 20 active and five additional trials with unknown status in ADPKD.

## Blood pressure management

Early activation of the RAAS in ADPKD is an important factor contributing to the development of hypertension. Studies in adults and children have indicated that hypertension is associated with larger kidney volumes, increased left ventricular mass index, and a risk for left ventricular



**Figure 3** Genetic and epigenetic factors that affect progression of ADPKD. **Abbreviation:** ADPKD, autosomal dominant polycystic kidney disease; miRNA, microRNA.

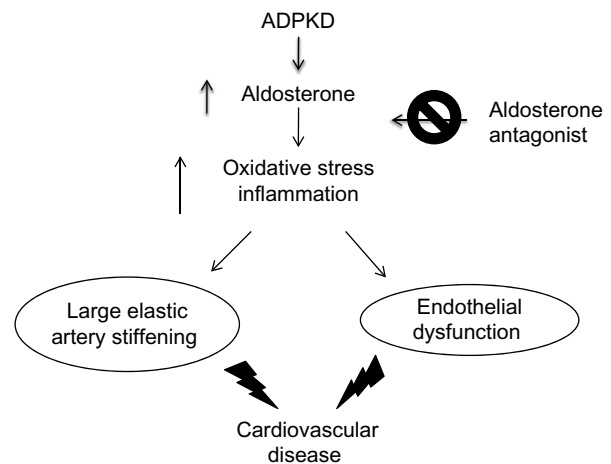
hypertrophy.<sup>17,19</sup> Rigorous blood pressure control has been shown to reduce left ventricular mass index in hypertensive patients with ADPKD.<sup>90</sup> Also, some studies have reported an improvement in kidney survival in more recent years, associated with increased use of drugs targeting the RAAS.<sup>26,91</sup> Similarly, data from the UK General Practice Database demonstrated a significant trend toward decreased mortality among ADPKD patients, associated with increased use of antihypertensive agents and number of agents prescribed.<sup>30</sup> However, a recent large study of 3,598 ADPKD patients from the UK Renal Registry between 2000 and 2011 failed to show any improvement in age at onset of renal replacement therapy.<sup>28</sup> The multicenter HALT-Progression of Polycystic Kidney Disease clinical trial is testing the effect of blood pressure control and the effect of angiotensin-converting enzyme inhibitor (ACEI) monotherapy compared with a combination of an ACEI and an angiotensin receptor blocker on renal outcomes.<sup>92</sup> The results of this study will provide guidance regarding optimum blood pressure targets and RAAS intervention in ADPKD.

## Bosutinib

Bosutinib (SKI-606) is a tyrosine kinase inhibitor with action on Bcr-Abl and Src kinase family members. Activation of protooncogene c-Src occurs by autophosphorylation at tyrosine (Y)<sup>418</sup> and is associated with increased proliferation and matrix adhesion in tumors.<sup>93</sup> In ADPKD, pY(418)-Src is increased in cyst-lining cells, while inhibition of protooncogene c-Src with SKI-606 attenuates hyperproliferation and reduces renal epithelial cell-matrix adhesion.<sup>94</sup> Similarly, SKI-606 retarded renal cyst formation in animal models.<sup>95</sup> Preclinical results indicate that bosutinib may be beneficial in ADPKD, and the results of an ongoing clinical trial will provide further information on these benefits. However, significant side effects have been noted in cancer studies, which may affect the long-term use of the drug.

## Mineralocorticoid inhibition

Patients with ADPKD demonstrate impaired endothelium-dependent dilation,<sup>21,96,97</sup> as well as large elastic artery stiffening indicated by increased aortic pulse wave velocity.<sup>98</sup> Activation of the RAAS occurs early in ADPKD and in several other pathological conditions, and aldosterone excess has been implicated in the development of endothelial dysfunction even in the general population (Figure 4).<sup>19,99,100</sup> In contrast, aldosterone antagonists have been shown to improve arterial dysfunction and decrease mortality in patients with heart failure receiving ACEI.<sup>101,102</sup> Similarly, spironolactone reduced



**Figure 4** Relationship between aldosterone and vascular disease in ADPKD.

**Notes:** Elevated aldosterone levels in ADPKD may promote oxidative stress and inflammation leading to endothelial dysfunction, arterial stiffening, and cardiovascular disease. Use of an aldosterone receptor antagonist such as spironolactone may block these effects.

**Abbreviation:** ADPKD, autosomal dominant polycystic kidney disease.

inflammation and preserved endothelial function in elderly hypertensive patients treated with calcium antagonists and angiotensin blockers.<sup>103</sup> This indicates that spironolactone may be an effective adjunctive therapy in ADPKD patients taking an ACEI for prevention of endothelial dysfunction and reduction of inflammation. The benefits of spironolactone therapy in ADPKD will be revealed by the outcome of an ongoing clinical trial (ClinicalTrials.gov identifier NCT01853553).

## Inhibition of mTOR

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that regulates cell growth, proliferation, and survival.<sup>104</sup> The mTOR pathway is regulated by PC1, and thus plays a significant role in ADPKD.<sup>105</sup> Rapamycin effectively decreases cyst growth in animal models of ADPKD.<sup>106,107</sup> However, results from human studies using either sirolimus (rapamycin) or everolimus have not been as impressive. To date, the results of six clinical trials, five using sirolimus and one using everolimus, have been published.<sup>108–113</sup> The trial durations were short, with the longest trial being 24 months. Only one small study showed an improvement in renal function in patients treated with sirolimus.<sup>112</sup> The effects on kidney volume were modest. However, the short trial duration and low patient number in some trials may have influenced the ability to detect a change in total kidney volume. There were significant side effects associated with therapy in all trials. A meta-analysis that included four of the above studies indicated that short-duration mTOR inhibitor therapy is relatively safe when used to slow down the increase in kidney volume

in patients with early-stage disease, but had limited impact on slowing the decrease in renal function.<sup>114</sup>

## Niacinamide

The nicotinamide adenine dinucleotide-dependent protein deacetylase sirtuin 1 (SIRT1) is upregulated in renal epithelial cells of a *Pkd*-mutant mouse.<sup>115</sup> In a *Pkd1* and *Sirt1* double knockout mouse model cyst formation is exacerbated over that found in the *Pkd* mutant mouse indicating a potential role for SIRT1 in cystogenesis.<sup>115</sup> Treatment of the *Pkd1* knockout mouse with nicotinamide (niacinamide), a pan-sirtuin inhibitor, delayed cyst growth. Thus, a potential therapeutic role of niacinamide in ADPKD is suggested. An ongoing Phase II pilot study (ClinicalTrials.gov identifier NCT02140814) is currently evaluating niacinamide in ADPKD.

## Somatostatin

Disruption of intracellular calcium homeostasis occurs in ADPKD and is linked with increased tissue levels of cyclic adenosine monophosphate (cAMP).<sup>116</sup> Enhanced cAMP and protein kinase A signaling may impact tubulogenesis and epithelial cell proliferation, thereby facilitating cystogenesis. Somatostatin has been shown to decrease cAMP production and fluid secretion in both renal tubular cells and liver cholangiocytes.<sup>117</sup> This observation has led to clinical trials testing the effectiveness of the somatostatin analogs, octreotide and lanreotide, in human ADPKD.<sup>118–123</sup> To date, results from four trials have been published. Three of these trials tested octreotide LAR, a long-acting formulation of octreotide, and one lanreotide. While the primary endpoint in three of the studies assessed structural changes in the liver, a small effect on total kidney volume was observed.<sup>118,120,122</sup> However, no study has demonstrated a significant sustained beneficial effect on kidney growth with longer treatment duration.<sup>119,121,123</sup> The effect of slowing the increase in liver volume has been more promising insofar as sustained beneficial effects on liver growth have been observed. Somatostatin analogs hold promise for the treatment of polycystic liver disease, but larger trials of longer duration are needed to fully assess the benefits of this therapy.

## Statins

Statins are hydroxyl-methyl glutaryl coenzyme A inhibitors that reduce cholesterol levels. Statins also have pleiotropic effects, including an ability to reduce inflammation.<sup>124</sup> Several studies have shown that statins improve hemodynamic parameters in chronic kidney disease.<sup>125,126</sup> This suggests a potential beneficial action in ADPKD. A reduction in cyst

burden and improvement of renal function has been observed with statin treatment in animal models of ADPKD.<sup>127,128</sup> To date, three clinical studies have assessed the benefit of statins in ADPKD. In a small study, simvastatin improved glomerular filtration rate and increased effective renal plasma flow when compared with placebo treatment.<sup>126</sup> However, a study in 49 patients did not show any improvement in renal function parameters with pravastatin treatment.<sup>129</sup> Both of these studies were relatively small, and therefore possibly underpowered to show an effect. The results of a recent larger, placebo-controlled study of pravastatin in children and young adults with ADPKD were more promising.<sup>130</sup> Over a 3-year duration, treatment with pravastatin lowered the incremental increase in height-corrected total kidney volume when compared with placebo treatment. In this study, all subjects were also treated with an ACEI. Future large studies of adequate duration are needed to assess the benefits of statin therapy in the adult ADPKD population.

## Tolvaptan

Vasopressin is an adenylyl cyclase antagonist and its activity is mediated by binding to the V2 receptor. In cell and animal studies, V2 receptor antagonists, including tolvaptan, have been shown to lower cAMP levels, blocking vasopressin-mediated fluid secretion into cysts, thereby ameliorating the cyst burden in animal models of PKD.<sup>117</sup> The results of a 3-year, randomized, double-blind, placebo-controlled clinical trial with tolvaptan that included 1,445 participants have shown promise for ADPKD.<sup>131</sup> A significantly smaller increase in total kidney volume over 3 years (2.8% versus 5.5% per year) and a slower decline in renal function was observed in the tolvaptan-treated patients when compared with controls. This effect was greatest during the first year of treatment. Fewer patients in the tolvaptan-treated group reported PKD-related complications, including pain and hematuria. Elevated liver enzyme levels experienced by some patients mean that monitoring of liver function is necessary during treatment. Tolvaptan has recently been approved in Japan for the treatment of ADPKD, while additional clinical studies are ongoing in the USA (Otsuka Pharmaceutical Development and Commercialization, Inc).

## Triptolide

Triptolide, a diterpene derived from the herb *Tripterygium wilfordii*, induces apoptosis and has anti-inflammatory benefits.<sup>132</sup> In animal models of ADPKD, triptolide restores calcium signaling, attenuates cyst formation, and improves renal function.<sup>133–135</sup> In a small uncontrolled clinical study of

nine proteinuric ADPKD patients treated with triptolide for 6 months, a decrease in proteinuria, inhibition of increase in total kidney volume, and stabilization of renal function were observed.<sup>136</sup> A larger randomized, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov identifier NCT02115659) of triptolide is currently ongoing and will provide insight into the benefits of triptolide in ADPKD.

## Conclusion

In conclusion, studies of the natural history of ADPKD have improved our understanding of the course of disease and identified several factors that impact disease progression. Significant strides have been made in elucidating the genetics of the disorder, thereby furthering our understanding of the etiology of phenotypic variability. Genetic testing by mutation identification for both *PKD1* and *PKD2* is now feasible, and preimplantation genetic diagnosis is available in some countries.

While an improvement in mortality for patients with ADPKD has been reported over the past two decades, progress in prolonging renal function has been disappointing. However, based on the outcomes of recent and ongoing clinical trials, the first drugs to slow progression of renal disease in ADPKD should become available within the next few years. Cardiovascular disease remains the leading cause of mortality in affected patients, so there is an urgent need to establish the efficacy of interventions to decrease cardiovascular risk. The anticipated results of the HALT-PKD trial should better inform regarding optimal blood pressure management and therapy in ADPKD patients with regard to both renal and cardiac outcomes. An ongoing mineralocorticoid antagonism study may identify an intervention to ameliorate endothelial dysfunction in this at-risk population. New therapies to treat cystic disease in the liver may soon become available. Thus, the next decade should herald significant improvement for patient outcomes in ADPKD.

## Disclosure

The author has served on an advisory panel for Otsuka Pharmaceutical Co, USA.

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