# Polycystic Kidney Disease 2 (PKD2 / PKD2-type ADPKD): Comprehensive Disease Characterization Report

**Target disease:** Polycystic Kidney Disease 2 **MONDO ID:** MONDO:0013131 · **OMIM:** #613095 (PKD2 phenotype); *173910 (PKD2 gene) · HGNC: 9009 · UniProt: Q13563 (polycystin-2/TRPP2) Category:** Mendelian (autosomal dominant)

## Summary

Polycystic Kidney Disease 2 (PKD2) is the genetically defined, clinically milder form of **autosomal dominant polycystic kidney disease (ADPKD)**, caused by heterozygous, predominantly loss-of-function variants in **PKD2**, the gene encoding **polycystin-2 (PC2 / TRPP2)**. It accounts for approximately **15% of genetically resolved ADPKD**, with the remaining ~85% attributable to *PKD1* (polycystin-1) (PMID: 27259053). Polycystin-2 is a ~110 kDa, six-transmembrane, non-selective cation channel of the transient receptor potential (TRP) family that localizes to the primary cilium and co-assembles with polycystin-1 to form a mechano-/chemosensory complex governing intracellular $Ca^{2+}$ and cyclic AMP (cAMP) signaling (PMID: 17217069; PMID: 32251715).

Cystogenesis follows a **cellular-recessive "two-hit" mechanism**: on a germline-heterozygous background, individual tubular epithelial cells acquire a somatic "second hit" inactivating the wild-type allele, then clonally expand into fluid-filled cysts. Downstream, dysregulated **cAMP/vasopressin-V2-receptor, MAPK, mTOR and Rho/planar-cell-polarity (PCP)** signaling drives epithelial proliferation and transepithelial chloride/fluid secretion, so that hundreds-to-thousands of cysts accumulate over decades and progressively destroy renal architecture (PMID: 11286938; PMID: 26113401; PMID: 41946363).

Compared with PKD1, PKD2 produces fewer, later-developing cysts and substantially delayed kidney failure — **median age at death or end-stage renal disease (ESRD) ~69 years for PKD2 versus ~53 years for PKD1** — with less hypertension, urinary-tract infection and hematuria, and a distinctive female survival advantage. Nonetheless, PKD2 measurably

shortens life expectancy and "cannot be regarded as a benign disorder" (PMID: 10023895). It is diagnosed by unified age-dependent ultrasound criteria supplemented by gene-panel/genome sequencing, and the vasopressin-V2-receptor antagonist **tolvaptan** is the approved disease-modifying therapy, slowing both eGFR decline and total-kidney-volume (TKV) growth (PMID: 18945943; PMID: 37250503). This report consolidates 12 confirmed findings across 56 reviewed papers into a knowledge-base-ready characterization spanning etiology, phenotypes, molecular mechanism, anatomy, natural history, epidemiology, diagnostics, prognosis, treatment, prevention, and comparative/model-organism biology. Evidence types are indicated throughout as **[human clinical]**, **[model organism]**, **[in vitro/structural]**, **[organoid/single-cell]**, **[computational]**, or **[veterinary]**.

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## 1. Disease Information

**Overview.** PKD2 is a subtype of ADPKD — the most common life-threatening monogenic kidney disease — characterized by progressive, bilateral development of fluid-filled renal cysts that enlarge over decades, distort renal parenchyma, and cause chronic kidney disease that may progress to ESRD. It is a systemic ciliopathy, with extrarenal cyst formation (liver, pancreas) and vascular manifestations (intracranial aneurysms, cardiovascular disease). PKD2 specifically denotes ADPKD caused by variants in the *PKD2* gene, which is clinically milder and later-onset than *PKD1*-associated disease (PMID: 20807608).

**Key identifiers.**

| Resource | Identifier |
|---|---|
| MONDO | MONDO:0013131 |
| OMIM (phenotype) | #613095 (Polycystic kidney disease 2) |
| OMIM (gene) | *173910 (PKD2) |
| HGNC (gene) | 9009 (PKD2) |
| UniProt | Q13563 (polycystin-2 / TRPP2) |
| Orphanet | ORPHA:730 (ADPKD; PKD2 as molecular subtype) |
| ICD-10 | Q61.2 (Polycystic kidney, autosomal dominant) |
| ICD-11 | GB61 / LB33 (polycystic kidney disease, autosomal dominant) |
| MeSH | D016891 (Polycystic Kidney, Autosomal Dominant) |

**Synonyms / alternative names:** ADPKD type 2; PKD2-type autosomal dominant polycystic kidney disease; polycystic kidney disease 2 (adult); PC2/TRPP2-related polycystic kidney disease.

**Data provenance:** The information in this report is derived predominantly from **aggregated disease-level resources** — OMIM, Orphanet, cohort/registry studies (e.g., the European PKD1-PKD2 Study Group, the Genkyst cohort), and mechanistic literature — rather than from individual-patient EHR data.

## 2. Etiology

**Primary cause (genetic).** PKD2 is a **monogenic autosomal dominant** disorder caused by germline heterozygous variants in *PKD2*. Mutations in *PKD1* or *PKD2* are the known causes of ADPKD, accounting for ~85% and ~15% of genetically resolved cases respectively: *"Mutations in PKD1 or PKD2 (~85% and ~15% of resolved cases, respectively) are the known causes of ADPKD"* (PMID: 27259053) **[human clinical]**. Cyst formation, however, is **cellular-recessive**: a germline first hit alone is insufficient, and a somatic second-hit inactivation of the wild-type allele within an individual epithelial cell is required to initiate a clonal cyst (PMID: 11286938).

**Genetic risk factors.** - *Causal gene:* **PKD2** (germline heterozygous variant) — the necessary and defining risk factor. - *Genotype as modifier of severity:* In the validated **PROPKD score**, a PKD2 mutation contributes **0 points** (lowest risk): *"being male: 1 point; hypertension before 35 years of age: 2 points; first urologic event before 35 years of age: 2 points; PKD2 mutation: 0 points; nontruncating PKD1 mutation: 2 points; and truncating PKD1 mutation: 4 points"* (PMID: 26150605) **[human clinical]**. Median age at ESRD by PROPKD risk stratum: 70.6 (low), 56.9 (intermediate), 49 years (high). - *Somatic second hit:* A stochastic, acquired inactivation of the remaining wild-type allele triggers each cyst (PMID: 11286938; PMID: 42436404).

**Environmental / demographic risk factors.** - **Sex:** Male sex confers 1 PROPKD point and worse outcomes; in PKD2 specifically, women survive longer than men (71.0 vs 67.3 years), a sex effect not seen in PKD1 (PMID: 26150605; PMID: 10023895). - **Hypertension before age 35 and early urologic events** are prognostic risk factors (2 points each in PROPKD) (PMID: 26150605). - **Family history of intracranial aneurysm / subarachnoid hemorrhage** raises neurovascular risk. - Age is the principal cumulative driver — cyst burden accumulates over decades and penetrance is age-dependent.

**Protective factors.** No validated genetic protective variant is established for PKD2. The strongest relative "protective" determinant is simply carrying a *PKD2* rather than *PKD1* mutation (later onset, milder course). Female sex is associated with a survival advantage in PKD2 (PMID: 10023895). Therapeutically, hydration/vasopressin suppression and V2R antagonism slow (not prevent) progression.

**Gene–environment interactions.** A conceptual framework proposes that intrinsic sequence-dependent mutational susceptibility (guanine-rich tracts at the *PKD1* locus) interacts with a local **inflammatory microenvironment of oxidative stress and epithelial proliferation** to promote recurrent somatic second hits (PMID: 42436404) **[computational]**. Renal injury accelerates cyst formation in animal models, indicating environmental "third-hit" stressors modulate penetrance (PMID: 25137562) **[model organism]**.

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## 3. Phenotypes

PKD2 shares the full clinical spectrum of ADPKD but with reduced severity and later onset. Key phenotypes, characteristics, and suggested HPO terms:

| Phenotype | HPO term | Type | Onset / severity / frequency | QoL impact |
|---|---|---|---|---|
| Multiple bilateral renal cysts | HP:0000803 / HP:0000113 | Physical/ imaging | Adult-onset; progressive; near-universal in penetrant carriers | Core disease driver |
| Progressive renal insufficiency → ESRD | HP:0000083 / HP:0003774 | Lab/ clinical | Late; progressive; ~50% of ADPKD reach ESRD by ~60 (later in PKD2, median ~69–74 y) | High (dialysis/ transplant) |
| Hypertension | HP:0000822 | Clinical sign | Adult; less frequent in PKD2 (OR 0.25 vs PKD1) | Moderate–high |
| Hematuria | HP:0000790 | Sign/lab | Episodic; less frequent in PKD2 (OR 0.59) | Moderate |
| Urinary tract infections | HP:0000010 | Clinical | Recurrent; less frequent in PKD2 (OR 0.50) | Moderate |
| Flank/abdominal pain | HP:0030157 / HP:0011340 | Symptom | Chronic/episodic | Moderate–high |
| Nephrolithiasis | HP:0000787 | Clinical | Adult | Moderate |
| Polycystic liver disease | HP:0006557 | Physical | Adult; progressive | Variable |
| Intracranial (berry) aneurysm | HP:0004944 | Vascular | Adult; ~4–11.5% general ADPKD | Potentially catastrophic |
| Cardiac valvular abnormality / LVH | HP:0001654 / HP:0001712 | Clinical | Adult | Variable |

**Frequency data.** PKD2 patients are markedly **less likely** than PKD1 patients to have hypertension (OR 0.25), UTI history (OR 0.50), or hematuria (OR 0.59) (PMID: 10023895) **[human clinical]**. Cardiovascular manifestations — *"hypertension, left ventricular hypertrophy, cardiac valvular abnormalities, and intracranial aneurysms"* — occur in a high percentage of ADPKD patients (PMID: 28682033). Intracranial aneurysm prevalence in general ADPKD populations is **4%–11.5%** (PMID: 39973757).

**Age of onset / progression:** adult-onset, insidious, chronic and progressive over decades. **Severity:** mild-to-moderate relative to PKD1, but variable within and between families.

**Quality-of-life impact:** dominated by chronic pain, hypertension management, progression to dialysis/transplantation, and anxiety related to aneurysm risk. Per-phenotype standardized QoL (EQ-5D/SF-36) data specific to PKD2 were not identified and represent a knowledge gap.

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## 4. Genetic / Molecular Information

**Causal gene. PKD2** (HGNC:9009; chromosome 4q22.1), encoding **polycystin-2 (PC2 / TRPP2)**, OMIM gene *173910; phenotype OMIM #613095. PKD2 accounts for ~15% of resolved ADPKD (PMID: 27259053).

**Protein product.** *"Polycystin-2 has a calculated molecular mass of 110 kDa, and according to structural predictions it contains six membrane-spanning domains and a pore-forming region between the 5th and 6th membrane-spanning domain"* (PMID: 17217069) **[in vitro/structural]**. It functions as a TRPP2 non-selective cation channel in primary cilia (PMID: 17204494).

**Variant classification and type.** Most pathogenic PKD2 variants are **truncating (loss-of-function)** — nonsense, frameshift, splice-site — but numerous **missense/point mutations** also cause disease with dramatic functional consequences (PMID: 37028763). Comprehensive Sanger + MLPA screening of a large Italian ADPKD cohort found diagnostic variants on PKD2 in 17 of 173 mutation-positive families, including novel variants and large rearrangements (PMID: 37231942) **[human clinical]**. Variants are classified per ACMG/AMP (pathogenic / likely pathogenic / VUS) in ClinVar.

**Functional consequences — structure-resolved.** Cryo-EM (2.7–3.2 Å) of ADPKD pore-helix variants reveals **distinct mechanisms**: *"Variant C632R reduces protein thermal stability, resulting in impaired channel assembly and abolishes primary cilia trafficking. In contrast, variants F629S and R638C retain native cilia trafficking, but exhibit gating defects"* (PMID: 39314384) **[in vitro/structural]**. Systematic testing of 31 point mutations (in a gain-of-function PC2_F604P background) shows mutations in transmembrane, pore, and much of the extracellular "tetragonal opening for polycystins" domain are critical for channel function, whereas many C-terminal-tail mutations are mild (PMID: 37028763). The dominant molecular mechanism is **loss of function** (channel/trafficking defect); the germline heterozygous state plus somatic second hit produces cellular loss of function.

**Origin.** Germline (inherited or de novo). Cyst-initiating second hits are **somatic** (PMID: 11286938). Deep-intronic/pseudoexon and complex rearrangements can underlie otherwise unsolved cases (PMID: 42502691; PMID: 37231942).

**Modifier genes / loci.** Marked within-family disease variability implies strong modifier effects: *"marked within-family renal disease variability is well documented in ADPKD and suggests a strong modifier effect from as yet unknown genetic and environmental factors"* (PMID: 21071968). Atypical/phenocopy genes include **GANAB** (glucosidase IIα; PC1 maturation) and **DNAJB11** (ER co-chaperone), which impair polycystin-1 processing/cleavage (PMID: 27259053; PMID: 39530576). Sex acts as a major non-genic modifier (§5, §15).

**Epigenetic / chromosomal.** No recurrent large chromosomal abnormality defines PKD2; disease arises at the single-gene level. Metabolic reprogramming secondary to polycystin loss can alter acetyl-CoA and histone acetylation, an indirect epigenetic consequence (PMID: 31488901). Complex genomic rearrangements at PKD loci are occasionally causal (PMID: 37231942).

**Suggested annotations:** HGNC:9009 (PKD2); GO:0005262 (calcium channel activity); GO:0005929 (cilium); GO:0072659 (protein localization to membrane). CHEBI: cAMP (CHEBI:17489), calcium(2+) (CHEBI:29108).

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## 5. Environmental Information

**Environmental factors.** No classical exogenous toxin, radiation, or occupational exposure is established as causal — PKD2 is fundamentally genetic. The relevant "environmental" contributor is the **local renal microenvironment**: oxidative stress and epithelial proliferation within an inflammatory milieu are proposed to promote somatic second-hit mutations, and renal injury accelerates cyst formation in models (PMID: 42436404; PMID: 25137562).

**Lifestyle factors.** High vasopressin tone (dehydration, high salt/protein intake) drives cAMP-mediated cystogenesis; conversely, hydration and V2R suppression are protective in principle. Hypertension control modifies renal and cardiovascular outcomes. Metformin, tested as an AMPK activator, did **not** significantly slow kidney-function decline in non-diabetic ADPKD (PMID: 41254555).

**Infectious agents.** Not applicable as a cause. Secondary complications include cyst and urinary-tract infections, but no pathogen initiates PKD2.

## 6. Mechanism / Pathophysiology

### Causal chain

```
Germline heterozygous PKD2 LOF variant (all cells)
        |
        ▼
Somatic "second hit" inactivating wild-type PKD2 allele in a tubular epithelial cell
   (favored by oxidative/inflammatory renal microenvironment)
        |
        ▼
Loss of functional polycystin-2 (TRPP2) channel / PC1–PC2 complex in that cell
        |
        ▼
Disrupted ciliary Ca²⁺ signaling → ↑ intracellular cAMP (vasopressin-V2R driven)
   + dysregulated mTOR, MAPK/ERK, Rho GTPase/PCP, metabolic reprogramming
        |
        ▼
Clonal epithelial proliferation + transepithelial Cl⁻/fluid secretion
        |
        ▼
Focal cyst formation → progressive enlargement (hundreds–thousands of cysts)
        |
        ▼
Distortion of parenchyma, interstitial fibrosis, inflammation
        |
        ▼
Declining GFR → chronic kidney disease → ESRD (median ~69 y in PKD2)
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**Upstream events** are the genetic two-hit inactivation and loss of ciliary polycystin channel signaling; **downstream events** are cAMP/mTOR/MAPK/Rho-driven proliferation, fluid secretion, fibrosis and GFR loss.

**Molecular pathways.** Dysregulated **cAMP** (via vasopressin V2R), **mTOR**, **MAPK/ERK**, **Hedgehog**, and **Rho GTPase / planar-cell-polarity (PCP)** signaling (PMID: 26113401; PMID: 33308138; PMID: 41946363). *"Alteration of these multiple signal transduction pathways leads to cystogenesis accompanied by dysregulated planar cell polarity, excessive cell proliferation and fluid secretion"* (PMID: 26113401).

**Cellular processes.** Excess proliferation, apoptosis dysregulation, impaired autophagy, altered planar cell polarity, and abnormal fluid secretion; primary-cilium dysfunction is central (PMID: 34009558). Patient-derived organoids show **elongated primary cilia, polarity disruption, and elevated Rho/PCP signaling** (PMID: 41946363).

**Protein dysfunction.** Loss-of-function of the PC2 channel via defective assembly/trafficking (C632R) or defective gating (F629S, R638C) (PMID: 39314384). PC1–PC2 co-assembly is required for a functional ciliary channel: *"Polycystin-1 has both ion channel and adhesion G-protein coupled receptor (GPCR) features-but its role in forming a channel complex or as a channel subunit chaperone is undetermined"* (PMID: 32251715) **[in vitro/structural]**.

**Metabolic changes.** ADPKD cells undergo **metabolic reprogramming**; polycystins may affect metabolism through direct effects on **mitochondrial function**, altering redox state and acetyl-CoA, thereby influencing histone acetylation and gene expression (PMID: 31488901). AMPK/mTOR is a therapeutically relevant node.

**Immune involvement / tissue damage.** A renal inflammatory microenvironment with oxidative stress promotes somatic mutation and cyst progression; interstitial **fibrosis** and inflammation are downstream tissue-damage mechanisms (PMID: 42436404; PMID: 39530576).

**Molecular profiling.** RNA-seq of Pkd2 conditional mice shows differential expression of metabolism, cell-proliferation and immune-response genes, and sex-dependent transcriptional differences (PMID: 41077129) **[model organism]**. *"Single-cell transcriptomics of PKD1/PKD2-mutant organoids revealed genotype-specific alterations. Genetic ablation of IFT88 disrupted cilia and selectively attenuated Rho/PCP activity in mutant backgrounds, supporting a cilia-dependent cyst-activating (CDCA) mechanism in cystogenesis"* (PMID: 41946363) **[organoid/single-cell]**. Single-cell multiomic methods have detected rare pathological glomerular subgroups in PKD organoids (PMID: 42469013).

**Suggested annotations:** GO:0060271 (cilium assembly), GO:0003351 (epithelial cilium movement), GO:0007204 (positive regulation of cytosolic $Ca^{2+}$), GO:0030036 (actin cytoskeleton organization), GO:0006874 (cellular $Ca^{2+}$ homeostasis); CL:0002518 (kidney epithelial cell), CL:1000454 (kidney collecting duct epithelial cell), CL:1000838 (kidney proximal convoluted tubule epithelial cell).

## 7. Anatomical Structures Affected

- **Primary organ:** Kidneys (UBERON:0002113) — bilateral cystic transformation of tubular epithelium. Lateralization: **bilateral**, generally symmetric.
- **Secondary organs:** Liver (UBERON:0002107) — polycystic liver disease; pancreas; occasionally spleen, ovaries, arachnoid, seminal vesicles.
- **Vascular / cardiac:** Cerebral arteries (intracranial/berry aneurysms), heart (LVH, valvular abnormalities) (PMID: 28682033).
- **Body systems:** Renal/urinary, hepatobiliary, cardiovascular, cerebrovascular.

**Tissue / cell level. Renal tubular epithelial cells** are the cyst-lining cells of origin; classical ADPKD cysts arise throughout the nephron, whereas some atypical forms (DNAJB11) originate predominantly from the **proximal tubule** (PMID: 39530576). Collecting-duct epithelium is a key site of vasopressin-V2R/cAMP-driven fluid secretion.

**Subcellular level.** The **primary cilium** (GO:0005929) is the central organelle; the **ciliary membrane**, **endoplasmic reticulum** (PC2 also resides in the ER; GO:0005783), **apical plasma membrane**, and **mitochondria** (GO:0005739) are involved.

**Suggested annotations:** UBERON:0002113 (kidney), UBERON:0001232 (collecting duct), UBERON:0004134 (proximal tubule), UBERON:0002107 (liver); CL:0002518 (renal epithelial cell).

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## 8. Temporal Development

**Onset.** Adult-onset, **insidious and chronic**. Cysts are typically detectable in adulthood; PKD2 presents later than PKD1. Age at presentation with kidney failure is **74.0 years for PKD2 vs 54.3 years for PKD1** (PMID: 10023895).

**Progression.** Slow, **progressive**, lifelong. Cyst number and total kidney volume increase roughly exponentially with age; age-adjusted HtTKV growth rate is significantly higher in PKD1 than PKD2 carriers (PMID: 30097754). Stages parallel CKD staging (G1→G5). Course is progressive rather than relapsing-remitting; duration is chronic/lifelong.

**Developmental switch.** *"There is a similar developmental switch in Pkd2 conditional mice with delayed cyst formation after Pkd2 inactivation at or beyond postnatal day 14"* (PMID: 41077129) **[model organism]**. Inactivation before ~P14 causes rapid cystogenesis — implying a critical early-life window of maximal cystogenicity.

**Critical periods for intervention.** Earlier therapeutic intervention (tolvaptan in early-stage CKD) yields greater lifetime benefit (PMID: 31014270).

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## 9. Inheritance and Population

**Epidemiology.** ADPKD overall affects an estimated **~1 in 1,000 people** (prevalence 1:1,000–1:2,500); PKD2 constitutes ~15% of resolved cases (PMID: 31488901; PMID: 27259053). ADPKD accounts for ~5% of ESRD in developed countries (PMID: 20807608).

**Inheritance & genetics.** - **Pattern:** Autosomal dominant (germline heterozygous PKD2 variant); cyst formation requires a somatic second hit (cellular-recessive) (PMID: 11286938). - **Penetrance:** Age-dependent, approaching complete by later adulthood. - **Expressivity:** Highly variable inter- and intra-familially, implying strong modifier effects (PMID: 21071968). - **Anticipation:** Not a feature (PKD2 is not a repeat-expansion disorder). - **De novo / mosaicism / cryptic variants:** De novo variants occur; complex/cryptic variants can be missed by standard testing (PMID: 42502691).

**Population demographics.** - **Sex ratio:** Both sexes affected (AD). In PKD2, women survive longer than men (71.0 vs 67.3 y); no such sex effect in PKD1 (PMID: 10023895). - **Geographic/ethnic distribution:** ADPKD is pan-ethnic and worldwide; no strong PKD2-specific founder effect is emphasized in the reviewed literature, though novel and population-specific variants are continually catalogued (PMID: 37231942; PMID: 36186434).

**Natural history — PKD2 vs PKD1 (European PKD1-PKD2 Study Group; 333 PKD1, 291 PKD2, 398 controls):**

| Metric | PKD1 | PKD2 | Controls |
|---|---|---|---|
| Median age at death or ESRD (y) | 53.0 (95% CI 51.2–54.8) | **69.1 (66.9–71.3)** | 78.0 (73.8–82.2) |
| Age at presentation with kidney failure (y) | 54.3 | **74.0** | — |
| Hypertension (PKD2 vs PKD1) | ref | OR 0.25 | — |
| UTI history | ref | OR 0.50 | — |
| Hematuria | ref | OR 0.59 | — |

*"Median age at death or onset of end-stage renal disease was 53.0 years (95% CI 51.2-54.8) in individuals with PKD1, 69.1 years (66.9-71.3) in those with PKD2, and 78.0 years (73.8-82.2) in controls"* and *"Although PKD2 is clinically milder than PKD1, it has a deleterious impact on overall life expectancy and cannot be regarded as a benign disorder"* (PMID: 10023895) **[human clinical]**. PKD2 reaches ESRD roughly **16 years later** than PKD1 but still shortens life expectancy.

## 10. Diagnostics

**Imaging (first-line).** Renal ultrasonography is the mainstay. **Unified age-dependent ultrasound criteria** (derived to accommodate the milder PKD2) for individuals of unknown genotype: *"the presence of three or more (unilateral or bilateral) renal cysts is sufficient for establishing the diagnosis in individuals aged 15 to 39 y, two or more cysts in each kidney is sufficient for individuals aged 40 to 59 y, and four or more cysts in each kidney is required for individuals > or = 60 yr"* (PMID: 18945943) **[human clinical]**.

| Age (y) | Diagnostic threshold | Exclusion |
|---|---|---|
| 15–39 | ≥3 renal cysts (unilateral or bilateral) | — |
| 40–59 | ≥2 cysts in **each** kidney | — |
| ≥60 | ≥4 cysts in **each** kidney | <2 cysts excludes disease at ≥40 |

Standard PKD1 criteria under-perform in PKD2 due to reduced sensitivity (PMID: 18945943; PMID: 20219617). CT and **MRI** provide total-kidney-volume measurement (Mayo Imaging Classification; prognostic HtTKV growth rate) (PMID: 30097754).

**Genetic testing.** Molecular testing resolves equivocal imaging, negative/indeterminate family history, and evaluation of young at-risk potential living kidney donors (PMID: 20807608). Approaches: - **Gene panels / targeted NGS** covering PKD1, PKD2 (and GANAB, DNAJB11, PKHD1, etc.), with **MLPA** for large rearrangements (PMID: 37231942; PMID: 36186434). - **Whole genome sequencing paired with transcriptome (RNA) sequencing** resolves cryptic deep-intronic/pseudoexon variants missed by exome testing: *"Genome sequencing was paired with transcriptome sequencing to evaluate the dinucleotide variant"* — a de novo deep-intronic SNV forming a dinucleotide variant with an adjacent common variant created a novel splice donor activating a 114-bp pseudoexon with an in-frame PTC (PMID: 42502691) **[computational]**.

**Biomarkers.** Height-adjusted TKV and eGFR trajectory are the principal prognostic biomarkers; serum **endothelin-1** independently predicts hypertension and associates with renal/overall survival in ADPKD (PMID: 30022320).

**Clinical criteria & differential diagnosis.** Diagnosis integrates family history + imaging ± genetics. Differentials: autosomal recessive PKD (PKHD1), atypical ADPKD (GANAB, DNAJB11), nephronophthisis, tuberous sclerosis, von Hippel–Lindau, acquired cystic disease, simple cysts.

**Screening.** Cascade imaging/genetic screening of at-risk relatives; presymptomatic testing and living-donor evaluation. Intracranial aneurysm screening (MRA) is targeted to those with family history of aneurysm/SAH; patients without aneurysms on initial imaging are at relatively low risk of de novo aneurysm (PMID: 40934139).

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## 11. Outcome / Prognosis

**Survival / mortality.** Median age at death or ESRD is **~69 years in PKD2** vs ~53 in PKD1 and ~78 in controls (PMID: 10023895). About **half of ADPKD patients reach ESRD by ~60**, later in PKD2. PKD2 shortens overall life expectancy despite its milder course.

**Morbidity.** Hypertension, chronic pain, nephrolithiasis, cyst/urinary infections, polycystic liver disease, and cardiovascular/cerebrovascular complications. Intracranial aneurysm rupture is a low-frequency but high-severity outcome.

**Prognostic factors.** Genotype (PKD2 = lowest PROPKD risk, 0 points), sex (male worse; female advantage specific to PKD2), early hypertension, early urologic events, and TKV/HtTKV growth rate (PMID: 26150605; PMID: 30097754). Endothelin-1 is a prognostic vascular biomarker (PMID: 30022320).

**Recovery.** No cure; ESRD is managed by dialysis and kidney transplantation (excellent post-transplant outcomes). Disease-modifying therapy slows but does not halt progression.

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## 12. Treatment

**Disease-modifying pharmacotherapy — tolvaptan (vasopressin V2-receptor antagonist).** Tolvaptan slows both **TKV growth and renal-function decline** over 3 years (TEMPO 3:4, NCT00428948), confirmed in the TEMPO extension and REPRISE (NCT02160145) trials (PMID: 33471240; PMID: 30689194). A pooled analysis in older patients (>55 y, CKD G3/G4; 95 matched pairs) showed *"The eGFR annual decline rate was significantly reduced by 1.66 mL/min/1.73"* vs standard of care (PMID: 37250503) **[human clinical]**. Benefit on eGFR occurs **regardless of TKV response** (PMID: 33471240). Modeling predicts ESRD delay of ~5 years (up to 6.6 y in early CKD) (PMID: 31014270). *"Tolvaptan has demonstrated efficacy in slowing kidney enlargement and preserving eGFR in high-risk patients. Its use requires careful monitoring of liver enzymes and management of aquaretic side-effects"* (PMID: 41815030). It is safe in combination with statins (PMID: 32241780). *Mechanism:* V2R blockade lowers collecting-duct cAMP, reducing proliferation and fluid secretion. **NCIT:** C61895 (Tolvaptan).

**Other pharmacotherapy.** - **Octreotide-LAR** (somatostatin analog) — approved in some settings; reduces cyst growth (PMID: 34009558). - **Antihypertensives:** ACE inhibitors / ARBs are agents of choice (PMID: 28682033). NCIT: C61627 (ACE inhibitor). - **Metformin (AMPK activator):** meta-analysis of 4 RCTs (213 non-diabetic ADPKD patients) found **no significant effect** on eGFR decline (SMD 0.19; 95% CI −0.08 to 0.46; p=0.17) or htTKV (p=0.53), with more GI adverse events (RR 2.93) (PMID: 41254555). - **Pioglitazone (PPARγ agonist):** preclinical promise, under clinical evaluation (PMID: 33308138). - **Probenecid (adjunct):** ABCG2 inhibition attenuated tolvaptan-induced polyuria while preserving efficacy in a preclinical ADPKD model and reduced urine volume/nocturia in a phase II trial (PMID: 42298327).

**Experimental / emerging targets.** EGFR, AMPK, KEAP1-Nrf2, sphingolipids, MAPK, and cell therapy are under investigation (PMID: 34009558). Patient-derived organoid HTS nominates **Rho GTPase inhibitors (e.g., ML141)** as cyst-reducing across PKD1/PKD2 genotypes (PMID: 41946363); **valosin-containing protein (VCP)** is a novel ciliary-morphology target (PMID: 40662578).

**Surgical / interventional.** Cyst aspiration/fenestration for pain, nephrectomy (space/infection/pre-transplant), and — for ESRD — **dialysis and kidney transplantation** (NCIT: C15366). Aneurysm clipping/coiling where indicated.

**Supportive care.** Pain control, hydration, blood-pressure control, treatment of infections and stones, statins for cardiovascular risk.

**Personalized medicine.** Genotype (PKD2 vs PKD1, truncating vs non-truncating) and TKV-based Mayo class guide risk stratification and tolvaptan candidacy (PMID: 26150605; PMID: 30097754).

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## 13. Prevention

- **Primary prevention:** Not possible for a monogenic germline disease. Risk-factor modification (blood-pressure control, hydration/vasopressin suppression, avoidance of nephrotoxins) mitigates progression.
- **Secondary prevention:** Early diagnosis via cascade imaging/genetic screening; early tolvaptan in rapid progressors; targeted MRA aneurysm screening for those with family history (PMID: 40934139).
- **Tertiary prevention:** Manage hypertension, CKD, infections, aneurysms; timely transplant planning.
- **Reproductive / genetic prevention:** *"preimplantation genetic testing (PGT) for polycystic kidney disease"* is validated and applied clinically, including for PKD2 couples (PMID: 30927425) **[human clinical]**. Prenatal testing and genetic counseling (risk assessment, family planning) are standard.
- **Immunization / public health:** Not applicable (non-infectious, non-environmental etiology).

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## 14. Other Species / Natural Disease

**Key finding:** Naturally occurring ADPKD in companion animals is **PKD1-orthologous, not PKD2**. *"Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disease in cats"* (PMID: 37489504) **[veterinary]**, and it is *"associated with a mutation from C to A at position 10063 in exon 29 of the feline PKD1 gene"* (PMID: 31155548) **[veterinary]** — i.e., the polycystin-1 ortholog. Feline ADPKD is common in Persian/Persian-related and Scottish Fold cats; in a University of Tokyo referral cohort (n=1,281), 1.8% carried the conventional PKD1 variant; concurrent renal+hepatic cysts occur (~12.6%, up to 31% in Persians), and Budd-Chiari-like complications are described (PMID: 32687010; PMID: 41669239).

**Implication:** No established naturally occurring **PKD2-orthologous** polycystic kidney disease exists in companion animals; PKD2 disease biology depends on **engineered rodent models**.

**Taxonomy / orthologs (suggested):** NCBI Taxon 9606 (human), 10090 (mouse), 10116 (rat), 9685 (cat), 7955 (zebrafish). Orthologous gene: mouse Pkd2 (NCBI Gene 18764); human PKD2 (NCBI Gene 5311). The cilia-polycystin axis is broadly conserved across vertebrates.

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## 15. Model Organisms

**Requirement for conditional models.** Germline **Pkd2 (and Pkd1) knockout is embryonic-lethal**, so conditional/inducible models are required (PMID: 41077129; PMID: 25137562).

**Mouse (primary model).** Kidney-specific conditional *Pkd2* knockouts recapitulate cystogenesis and reveal: - A **developmental switch** — *"delayed cyst formation after Pkd2 inactivation at or beyond postnatal day 14"* (PMID: 41077129) **[model organism]**. - **Sex as a major disease modifier:** *"We confirm that sex is a key modifier of ADPKD progression with differences in disease severity occurring in the context of significant transcriptional differences between males and females that are independent of the Pkd2 genotype"* (PMID: 41077129) **[model organism]**. - Genetic-interaction studies: ablating ciliary adenylyl-cyclase trafficking (**ANKMY2**) or adenylyl-cyclase-to-cilia targeting suppresses cystogenesis in Pkd1 models, and IFT88 ablation confirms cilia-dependent cystogenesis (PMID: 41474822; PMID: 40501923).

**Non-mammalian / in vitro.** *Xenopus* oocytes for PC2 channel electrophysiology (PMID: 37028763); cryo-EM structural biology of PC2 variants (PMID: 39314384); **patient-derived multi-lineage adult renal organoids (MAROs)** that recapitulate elongated cilia, polarity disruption, elevated Rho/PCP signaling, and enable single-cell transcriptomics and HTS drug screening across PKD1/PKD2 genotypes (PMID: 41946363; PMID: 42469013).

**Model types available:** knockout, conditional/inducible knockout, gain-of-function point-mutant channels (e.g., PC2_F604P). **Phenotype recapitulation:** strong for renal cystogenesis, cilia biology, and signaling. **Limitations:** embryonic lethality of full knockouts; rodent Pkd2/Pkd1 escape the recurrent somatic mutagenesis seen at the human locus (guanine-rich architecture), limiting spontaneous two-hit modeling (PMID: 42436404); standardized QoL/extrarenal features incompletely captured.

**Resources:** MGI (mouse), RGD (rat), ZFIN (zebrafish), IMPC/KOMP, Cellosaurus (organoid/cell lines).

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## Mechanistic Model / Interpretation

PKD2 is best understood as a **ciliary channelopathy operating through a two-hit, dosage-sensitive mechanism**. The germline PKD2 loss-of-function variant sets a permissive background; a stochastic somatic second hit — favored by an oxidative, proliferative, inflammatory renal microenvironment — extinguishes functional polycystin-2 in a single tubular cell. Because PC2 (with PC1) tunes ciliary $Ca^{2+}$ and restrains cAMP, its loss unleashes a proliferative-secretory program (cAMP↑, mTOR, MAPK, Rho/PCP), converting the affected clone into an expanding cyst. Multiplied across a lifetime and across thousands of nephrons, this produces the macroscopic bilateral cystic kidneys and progressive GFR loss.

The comparatively mild PKD2 phenotype — 0 PROPKD points, ~16-year-later ESRD, less hypertension/hematuria/UTI — reflects **residual/less-disruptive polycystin complex function and slower cyst kinetics** relative to PKD1, not a different mechanism. This unifies the clinical, structural, and model-organism data: cryo-EM shows variant-specific trafficking-vs-gating defects; conditional mice show a postnatal developmental switch and sex modification; organoids show genotype-specific but mechanistically convergent Rho/PCP-driven, cilia-dependent cystogenesis. Therapeutically, everything downstream of cAMP is the tractable target — hence tolvaptan's efficacy, probenecid's aquaretic-sparing adjunct role, and the emerging Rho-inhibitor and adenylyl-cyclase-trafficking strategies.

# Evidence Base

| PMID | Contribution | Evidence type |
|---|---|---|
| 10023895 | Definitive PKD2 vs PKD1 natural history (median ESRD/death 69.1 vs 53.0 y); milder but not benign; female survival advantage | Human clinical |
| 27259053 | PKD2 ≈15% of resolved ADPKD; GANAB as atypical gene | Human clinical |
| 26150605 | PROPKD score — PKD2 = 0 points (lowest risk) | Human clinical |
| 17217069 | PC2/TRPP2 = 110 kDa, 6-TM, pore between TM5–TM6 | In vitro/structural |
| 39314384 | Cryo-EM: C632R trafficking defect; F629S/R638C gating defects | In vitro/structural |
| 11286938 | Two-hit cellular-recessive clonal cystogenesis model | Model/conceptual |
| 26113401 | Multi-pathway cystogenesis: PCP, proliferation, fluid secretion | Review |
| 41077129 | Conditional Pkd2 developmental switch; sex as major modifier | Model organism |
| 28682033 | Cardiovascular/neurovascular extrarenal manifestations | Review |
| 39973757 | ICA prevalence 4–11.5% in general ADPKD | Human clinical |
| 37250503 | Tolvaptan reduces annual eGFR decline by ~1.66 mL/min/1.73 $m^2$ | Human clinical |
| 41815030 | Tolvaptan efficacy + monitoring requirements | Review |
| 18945943 | Unified age-dependent ultrasound diagnostic criteria | Human clinical |
| 32251715 | PC1 co-assembly/chaperone role with PC2 channel in cilia | In vitro/structural |
| 21071968 | Variable expressivity / modifier effects | Review |
| 30927425 | PGT applied clinically for PKD | Human clinical |
| 41946363 | Patient organoids: genotype-specific cystogenesis; Rho/PCP inhibitors (CDCA) | Organoid/single-cell |
| 42502691 | Genome+RNA-seq resolves cryptic pseudoexon variants | Computational |
| 31155548 / 37489504 | Natural feline ADPKD is PKD1-orthologous, not PKD2 | Veterinary |

| PMID | Contribution | Evidence type |
|---|---|---|
| 41254555 | Metformin: no significant benefit in non-diabetic ADPKD | Human clinical (meta-analysis) |
| 42298327 | Probenecid mitigates tolvaptan aquaresis while preserving efficacy | Model + phase II |

## Limitations and Knowledge Gaps

1. **No primary experimental dataset** was analyzed; conclusions rest on literature synthesis of aggregated disease-level resources, not de novo statistical analysis of patient-level data.
2. **PKD2-specific QoL** (EQ-5D/SF-36/PROMIS) data are sparse; most QoL and cardiovascular figures derive from mixed ADPKD (PKD1+PKD2) cohorts.
3. **Modifier genes** driving PKD2's marked intra-familial variability remain largely unidentified (PMID: 21071968).
4. **Founder effects / geographic variant distribution** specific to PKD2 were not well characterized in the reviewed literature.
5. **No natural PKD2 animal model** exists; mechanistic inferences transfer from PKD1 models and engineered Pkd2 mice, which may not capture human-specific somatic-mutation dynamics (PMID: 42436404).
6. **Therapeutic evidence** is dominated by mixed-genotype ADPKD trials; PKD2-subgroup-specific efficacy of tolvaptan and emerging agents is under-reported.

## Proposed Follow-up Experiments / Actions

1. **PKD2-stratified re-analysis** of tolvaptan trial data (TEMPO/REPRISE) to quantify genotype-specific eGFR/TKV effect sizes and number-needed-to-treat.
2. **Modifier-locus GWAS/burden analysis** within PKD2 families to explain the female survival advantage and intra-familial variability.

3. **Prospective PKD2 organoid biobank** with single-cell multi-omics to map genotype-specific cystogenic trajectories and validate Rho/PCP and adenylyl-cyclase-trafficking (ANKMY2) targets as PKD2-effective (PMID: 41946363; PMID: 41474822).
4. **Structure-guided variant functional classification** — extend cryo-EM/electrophysiology to reclassify PKD2 VUS as trafficking- vs gating-defective, informing ACMG calls (PMID: 39314384).
5. **Clinical trial of probenecid–tolvaptan co-therapy** in PKD2 to improve tolerability/adherence (PMID: 42298327).
6. **Routine genome+RNA-seq** for ultrasound-positive but molecularly unsolved ADPKD to capture cryptic PKD2 pseudoexon/deep-intronic variants (PMID: 42502691).
7. **PKD2-specific QoL cohort study** using EQ-5D/PROMIS to fill the quality-of-life evidence gap.

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*Report compiled from 12 confirmed findings across 56 reviewed papers over 5 investigative iterations. Evidence source types are distinguished throughout (human clinical, model organism, in vitro/structural, organoid/single-cell, computational, veterinary). All mechanistic and clinical claims are cited to primary literature by PMID.*

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