Precision Medicine in Autosomal Dominant Polycystic Kidney Disease

Kuwait's National ADPKD Clinic Experience

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Outline

- Brief introduction for ADPKD
- Genetic basis
- Phenotypic variability
- ADPKD National Clinic and Precision medicine experience.
- The Future.

History of Polycystic Kidney Disease

- First detailed reporting of Polycystic Kidney Disease dates back to 16th Century.
- It was a period defined by co-existence of a longing to emulate ancient cultures & the yearning to develop a new science based on observation.

History of Polycystic Kidney Disease

- Stefan Bathory, King of Poland. (1533-1585)
- King's kidneys were examined and described ;

"large like those of a bull, with an uneven and bumpy surface, nothing like Buccella or I had ever seen"

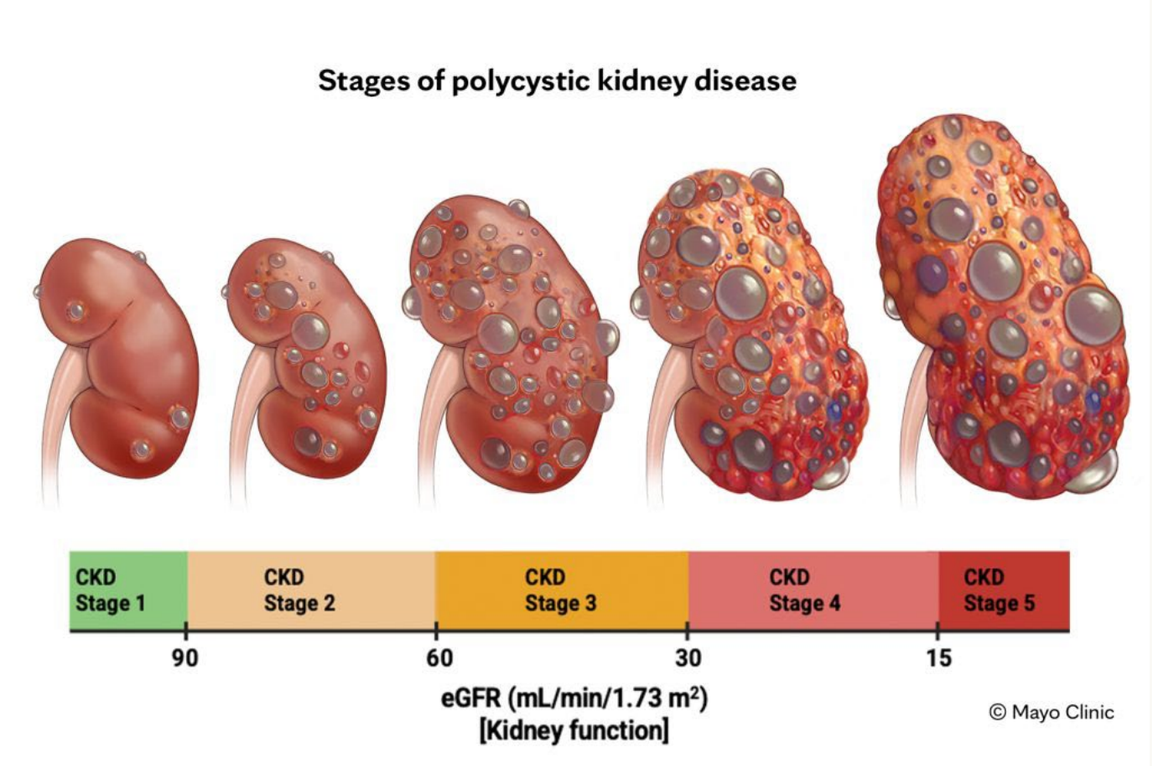
Jan Zigulitz, the surgeon

ADPKD: Disease Fundamentals

What is ADPKD?

Progressive genetic disorder characterized by bilateral renal cyst development

- Fluid-filled cysts replace normal kidney tissue
- Gradual loss of renal function over decades
- Most common inherited kidney disease



Prevalence

1 in 800 - 1,000

Major Cause of Renal Failure

5-10%

It accounts for a significant portion of all End-Stage Renal Disease (ESRD) cases worldwide.

Hajji et al. (2019)

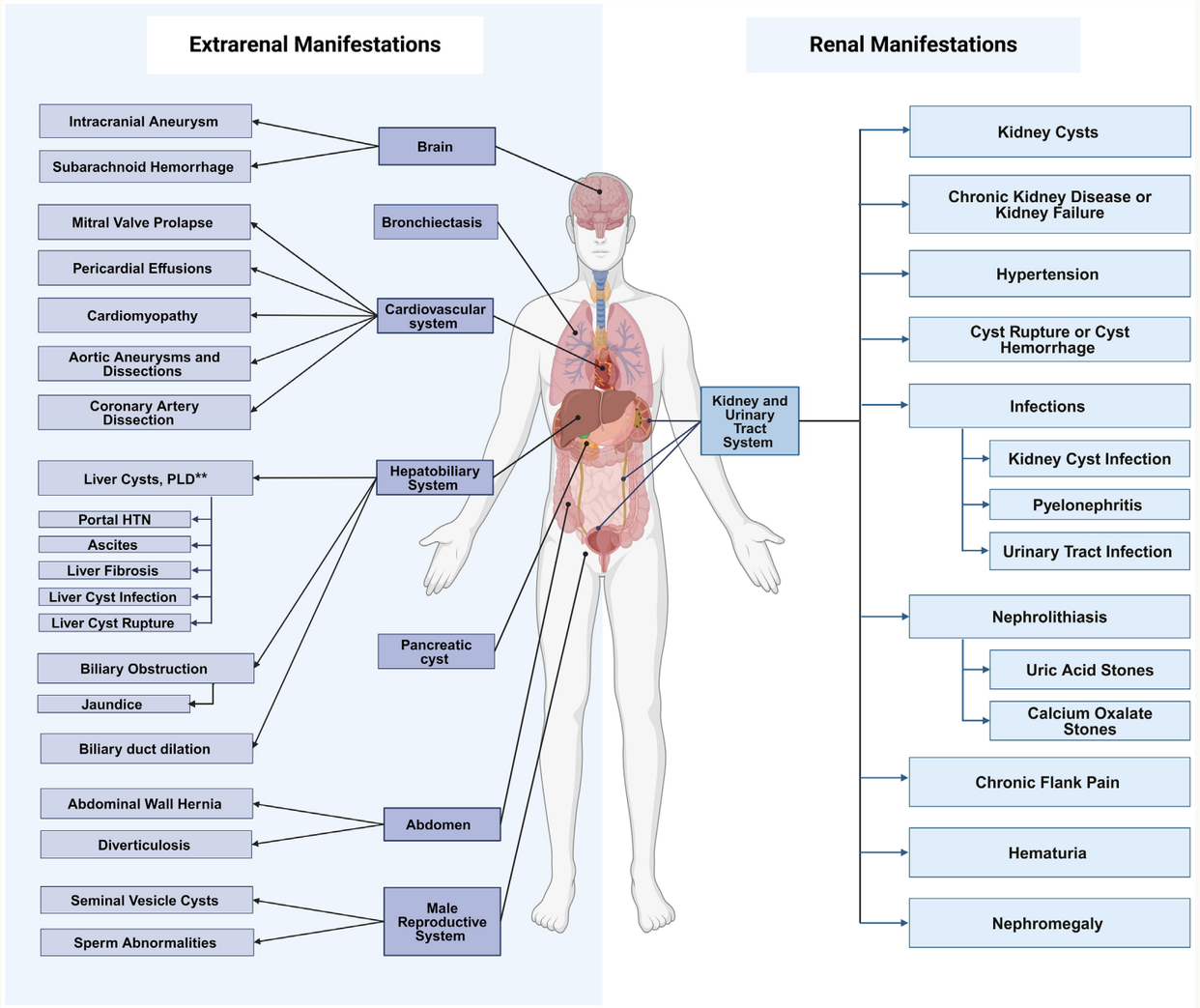
ADPKD Clinical Manifestations

Renal Manifestations

- Renal Cysts
- Flank/abdominal pain (60%)
- Hypertension (early finding)
- Hematuria from cyst rupture

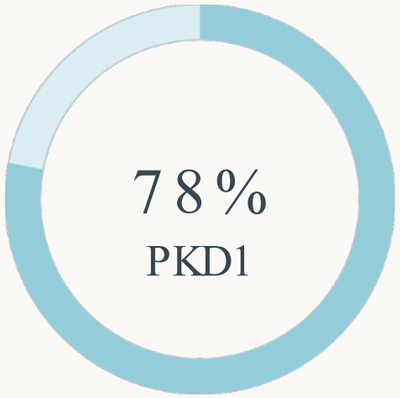
Extra-Renal Manifestations

- Intracranial aneurysms (8–10%)
- Hepatic cysts (common, usually asymptomatic)
- Cardiac valvular disease (MVP, AR)



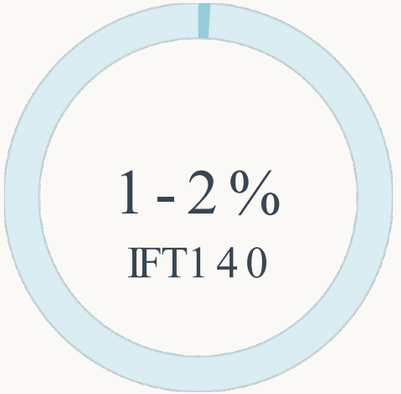
Borghol et al. (2025)

GENETIC CAUSES OF ADPKD

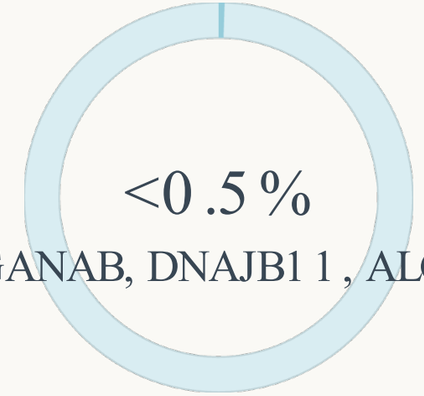


Most common, severe phenotype

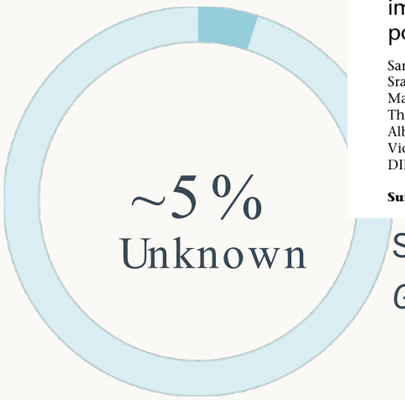
Second most common, milder disease



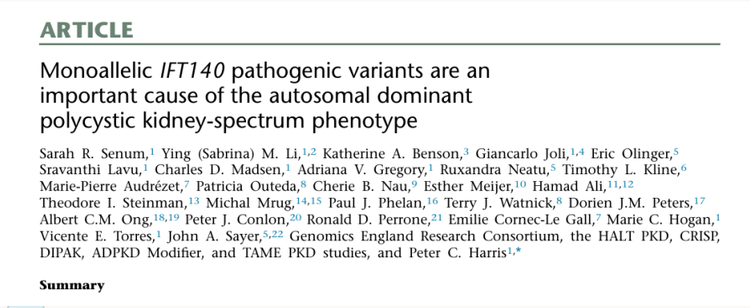
Mild PKD phenotype



Rare causes with variable presentations



Genetic cause unidentified



ARTICLE

Monoallelic *IFT140* pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype

Sarah R. Senum,[1] Ying (Sabrina) M. Li,[1,2] Katherine A. Benson,[3] Giancarlo Joli,[1,4] Eric Olinger,[5] Sravanthi Lavu,[1] Charles D. Madsen,[1] Adriana V. Gregory,[1] Ruxandra Neatu,[5] Timothy L. Kline,[6] Marie-Pierre Audrézet,[7] Patricia Outeda,[8] Cherie B. Nau,[9] Esther Meijer,[10] Hamad Ali,[11,12] Theodore I. Steinman,[13] Michal Mrug,[14,15] Paul J. Phelan,[16] Terry J. Watnick,[8] Dorien J.M. Peters,[17] Albert C.M. Ong,[18,19] Peter J. Conlon,[20] Ronald D. Perrone,[21] Emilie Cornec-Le Gall,[7] Marie C. Hogan,[1] Vicente E. Torres,[1] John A. Sayer,[5,22] Genomics England Research Consortium, the HALT PKD, CRISP, DIPAK, ADPKD Modifier, and TAME PKD studies, and Peter C. Harris[1,*]

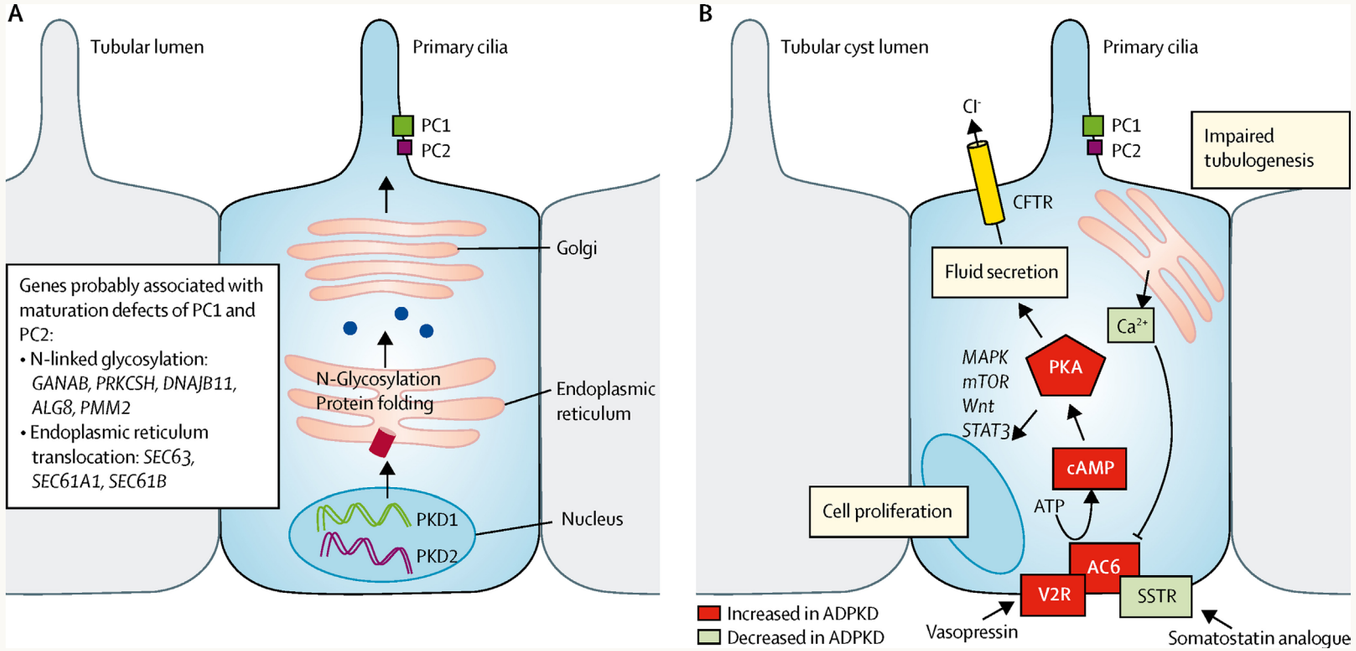
Summary

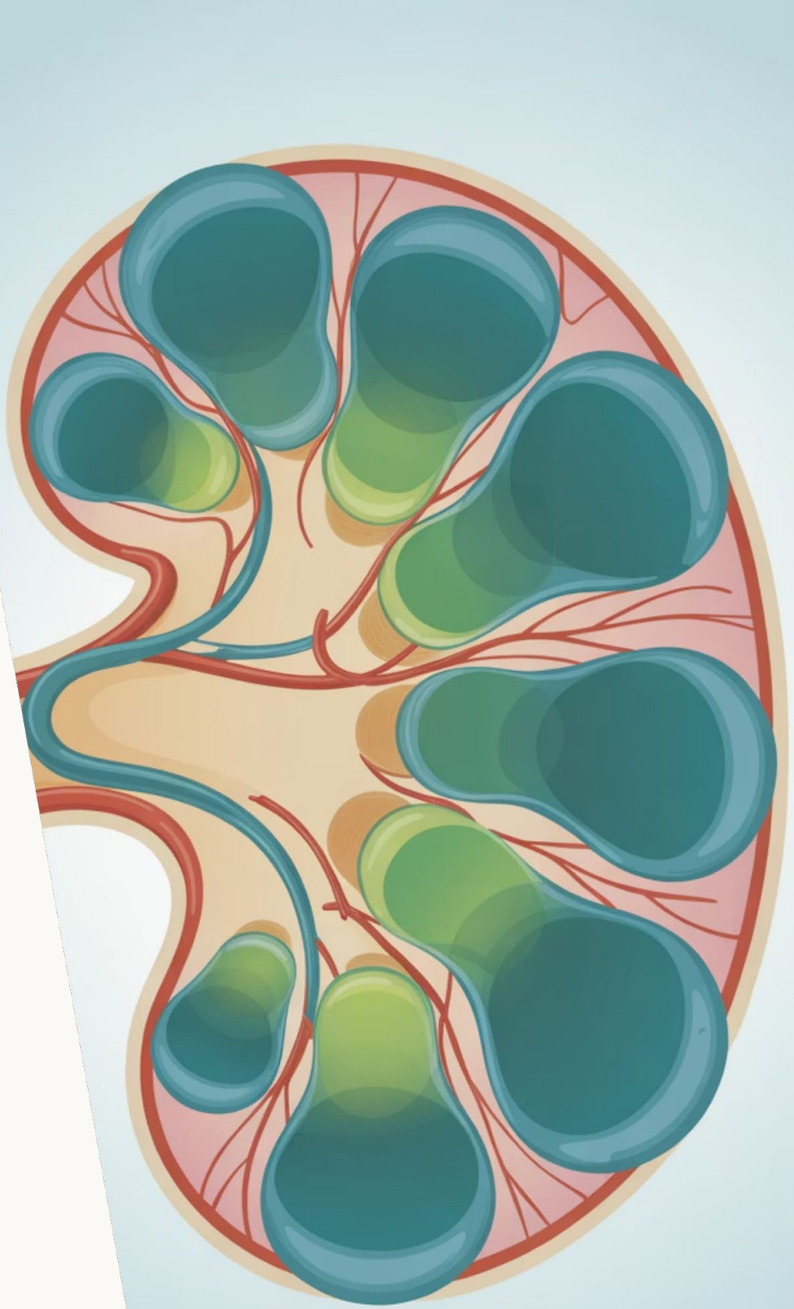
Senum et al. (2022) *American Journal of Human Genetics*

ADPKD Pathophysiology

Core Pathogenesis

Defective polycystin-1/2 → disturbed Ca^{2+} signaling → ↑ cAMP → cyst proliferation & fluid secretion





Cornec-Le Gall et al. (2019)

Cystogenesis

Core Pathogenesis

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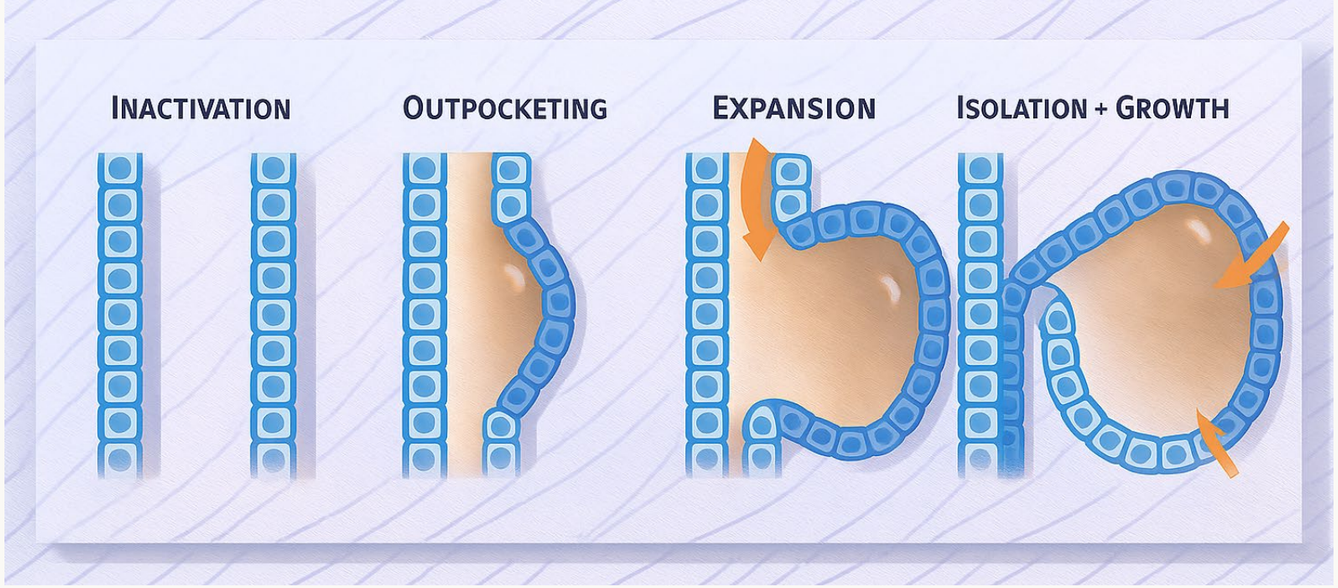
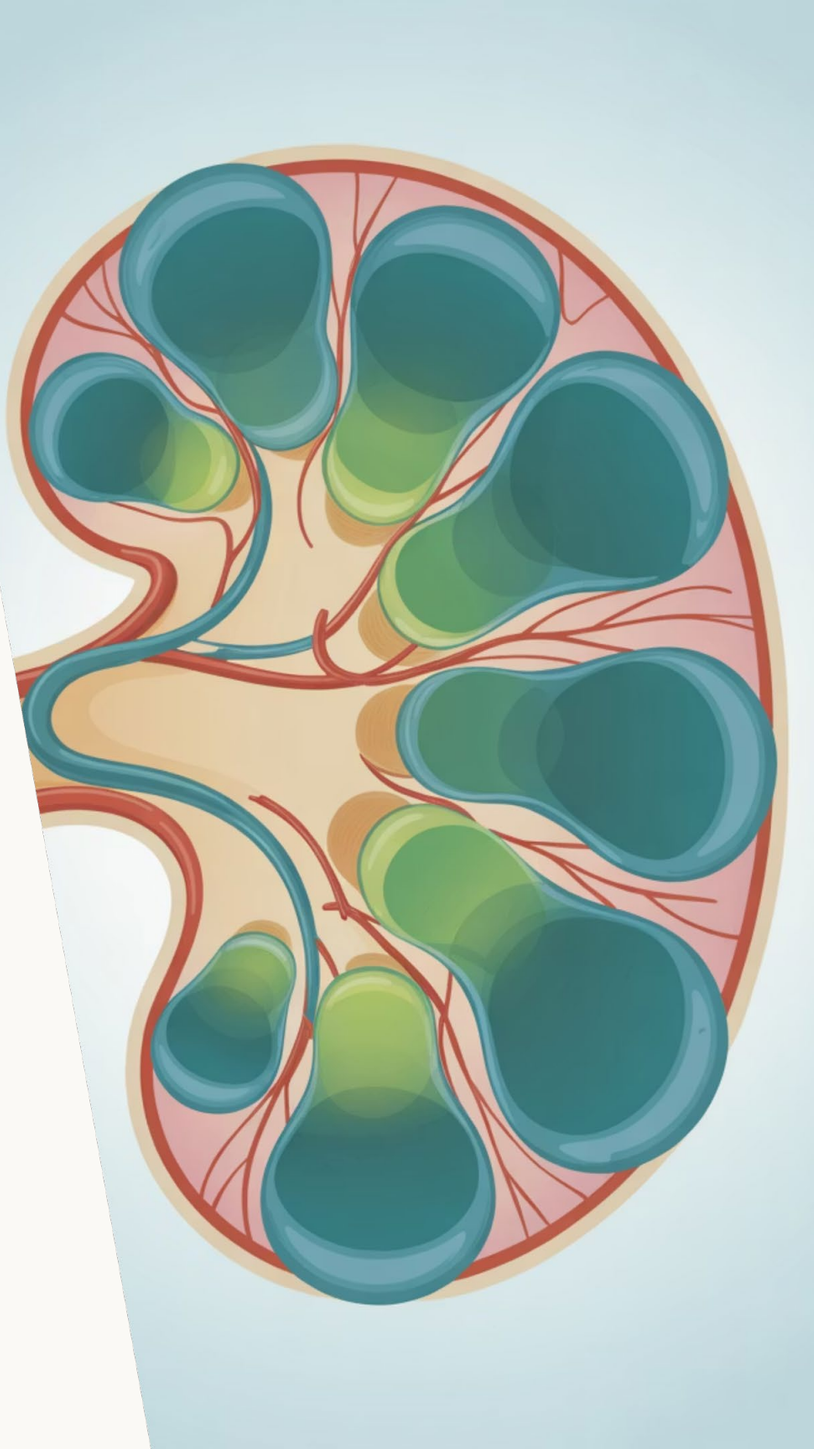


Few kidney tubular cells lose normal function and start to proliferate abnormally. They create small fluid-filled pouches.

Ongoing fluid secretion and cell growth cause cysts to enlarge and multiply, gradually replacing normal kidney tissue.



The Spectrum of Disease Severity

Mild Phenotype

Few cysts, preserved kidney function into late adulthood, minimal symptoms

Moderate Phenotype

Progressive cyst growth, hypertension by age 35, ESKD by age 60-70

Severe Phenotype

Early-onset disease, massive kidney enlargement, ESKD before age 55

Genic Heterogeneity

Allelic Heterogeneity

Phenotypic Variability

Modifier Genes

Environmental influences

Phenotypic variability in ADPKD results from genic and allelic heterogeneity, modifier genes, and environmental influences, all contributing to the diverse severity and progression seen among patients.

Genotype-Phenotype Correlations

1

PKD1 Truncating Mutations

Aggressive disease course leading to median ESRD at 51–55 years.Patients experience rapid eGFR decline: **−4.7 mL/min/yr**

2

PKD1 Non-Truncating Mutations

Intermediate severity, delaying median ESRD onset to 60–65 years.Moderate eGFR decline rate: **−3.5 mL/min/yr**

3

PKD2 Mutations

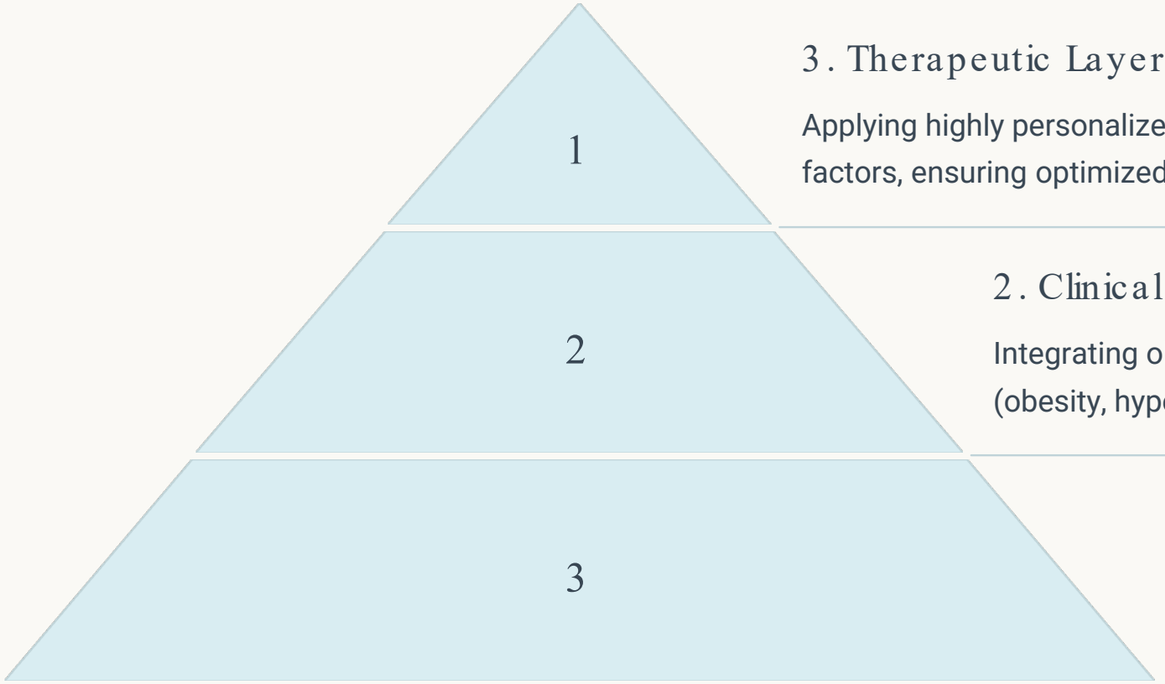
The mildest major subtype, pushing median ESRD onset to 75–80 years.Slowest progression characterized by eGFR loss of only **−2 mL/min/yr**

4

Atypical Genes (IFT140/GANAB/DNAJB11)

Typically present with a substantially milder phenotype.Key features include small kidneys and preserved renal function (eGFR).

Precision Medicine Framework for ADPKD



3. Therapeutic Layer: Personalized Intervention

Applying highly personalized treatment decisions based on the combined genetic risk and clinical progression factors, ensuring optimized and targeted intervention.

2. Clinical Layer: Risk Stratification

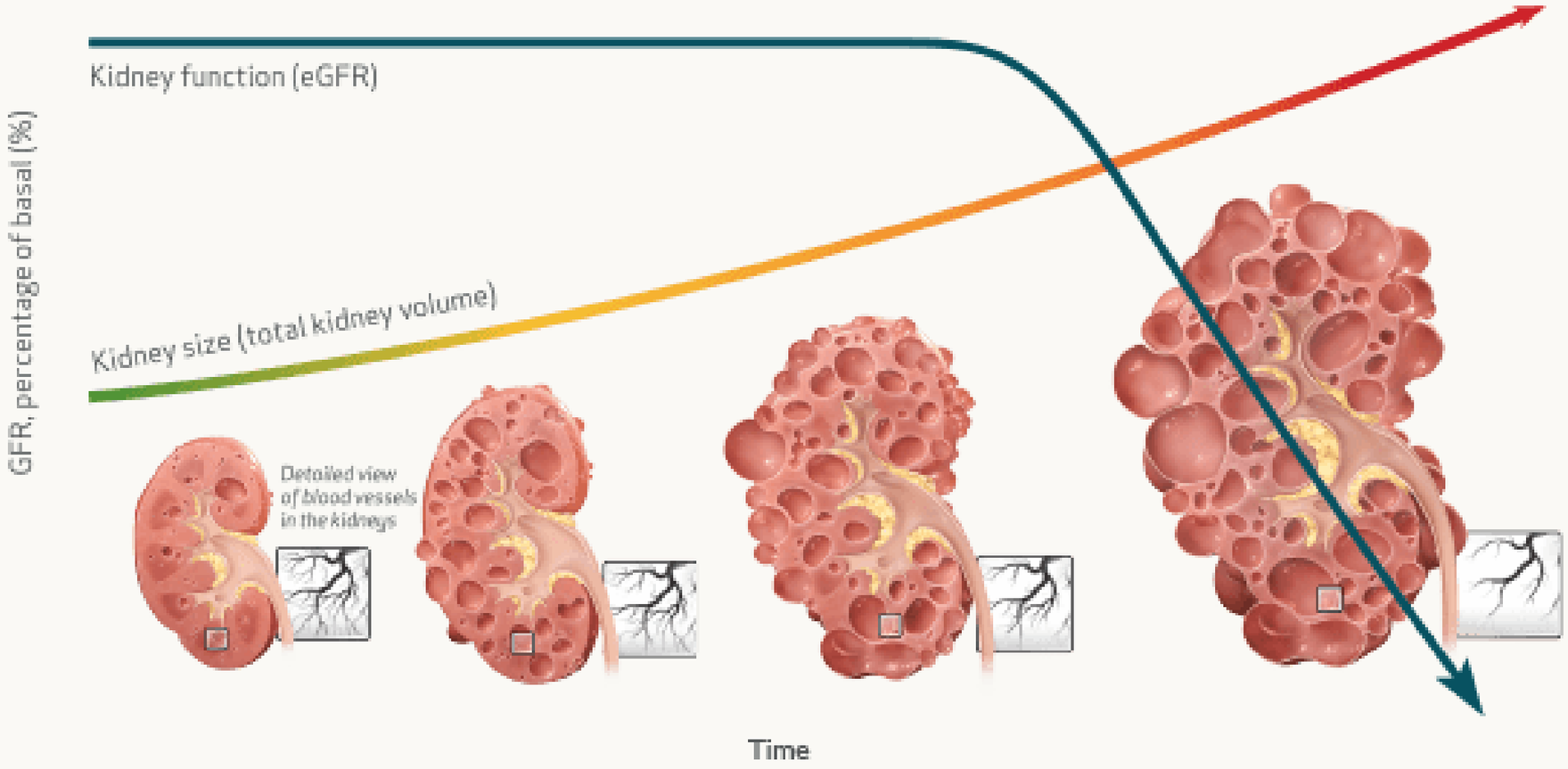
Integrating objective measurements (Mayo Classification TKV) and crucial phenotypic features (obesity, hypertension, age at onset) to accurately predict progression.

1. Genomic Foundation: Establishing Baseline Risk

PKD1 and PKD2 mutations establish the initial disease severity and progression trajectory, forming the essential blueprint for subsequent clinical decisions.

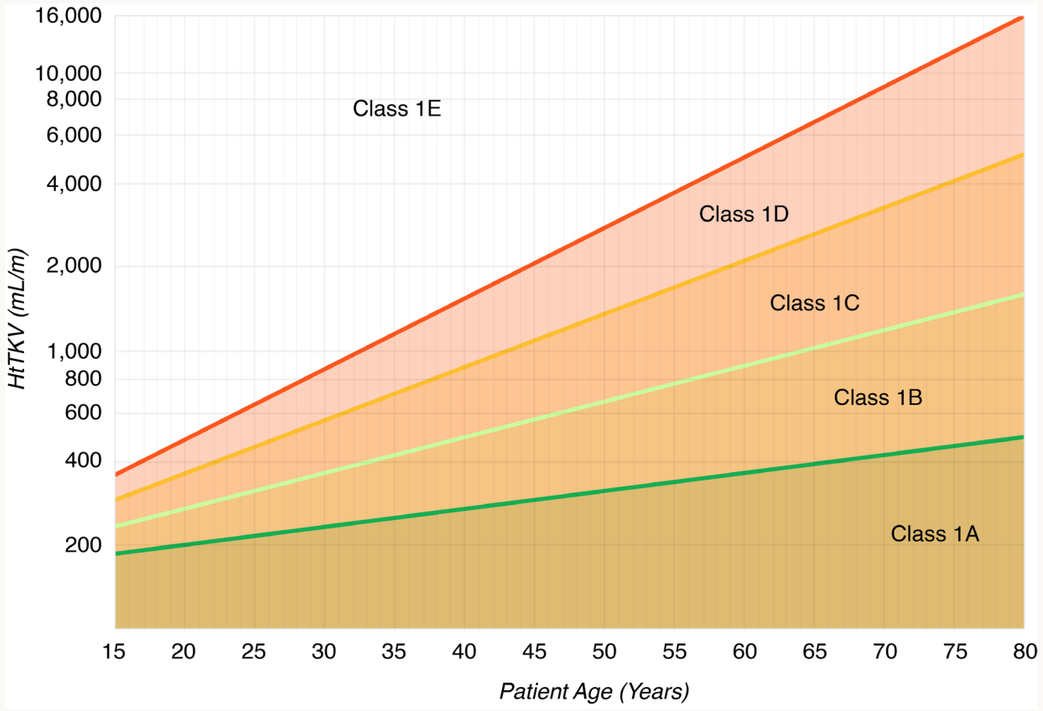
> "*ADPKD stands as the archetype for personalized nephrology—the blueprint for seamlessly integrating **genotype with intermediate phenotypes** to drive optimized clinical management*."
>
> — **Lanktree et al., Nature Reviews Nephrology (2017)**

eGFR and TKV trajectories



Mayo Imaging Classification System for ADPKD

The Mayo Imaging Classification (MIC) is a risk stratification tool that uses total kidney volume (TKV) to predict kidney outcomes in autosomal dominant polycystic kidney disease (ADPKD). It assigns patients to five classes (1A–1E) based on height-adjusted TKV measurements.



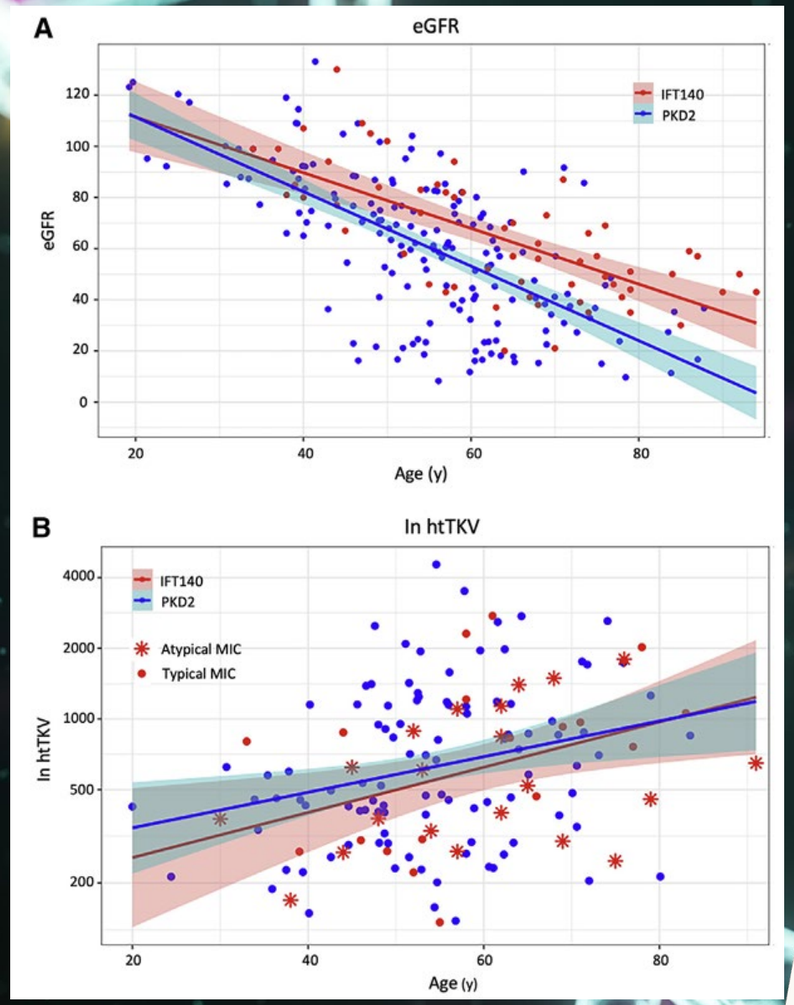
Good Correlation with eGFR

Mayo Class	Expected eGFR Decline	Clinical Category
1A–1B	<1 mL/min/year	Slow progressor
1C	2–3 mL/min/year	Moderate
1D–1E	>3–5 mL/min/year	Rapid progressor

MIC Limitations

Limitation	Consequence
Excludes atypical cases	Can’t classify ~10% of patients
Lacks genetic input	Misses genotype-specific prognosis
Imaging variability	Risk of misclassification
Not ideal for extremes (young/CKD5)	Reduced predictive accuracy
Ignores modifiers	Incomplete picture of progression risk

Genotype Strongly Predicts Time to Kidney Failure



Senum et al. (2022) *American Journal of Human Genetics*

55.3y

PKD1 - Truncating

Median age at ESKD

60.8y

PKD1 - NT1

Fully penetrant nontruncating

66.2y

PKD1 - NT2

Hypomorphic mutations

74.4y

PKD2

Milder genetic form

>74.4y

IFT140

Mildest genetic form

Strengths

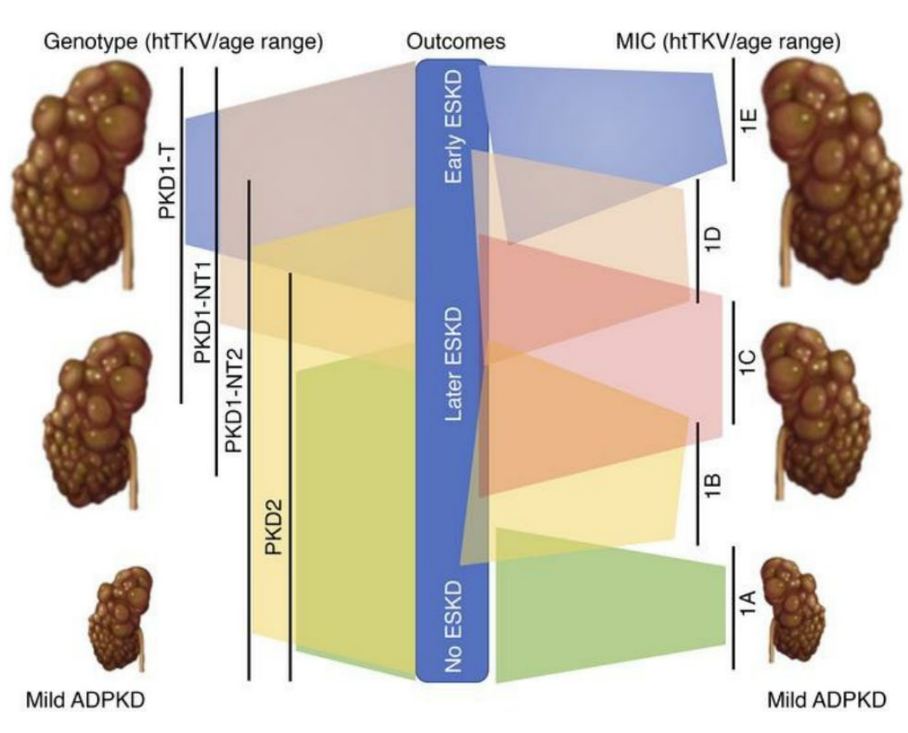
Predicts functional endpoints; stable one-time test; supports cascade testing and counseling

Limitations

Less predictive for structural growth; **variants of uncertain significance**; cost and access barriers

Combined Genotype and Imaging: Maximum Predictive Power

Multivariate analysis revealed that genotype significantly improved imaging-based predictions, and vice versa. Models incorporating both parameters achieved exceptional discriminatory ability.



Lavu et al. (2020)

Combined Genotype and Imaging: Maximum Predictive Power

Multivariate analysis revealed that genotype significantly improved imaging-based predictions, and vice versa. Models incorporating both parameters achieved exceptional discriminatory ability.

Predictive Model	Endpoint	C-index	Interpretation
Genotype alone	ESRD	**0.824**	Strong predictive power for renal survival (PKD1T > NT > PKD2).
MIC alone	ESRD	**0.830**	Slightly higher accuracy; stronger separation between imaging classes (1A–1E).
Combined (Genotype + MIC)	ESRD	**0.845**	**Best discrimination** — integrating imaging and genetics gives the most accurate prediction.
Combined (Genotype + MIC)	eGFR < 50% / ESRD	**0.765**	Also improves prediction of functional decline vs either model alone.

Lavu et al. (2020)

Kuwait ADPKD National Clinic: Integrating Precision Medicine into Patient-Centered Care

Established in 2023 at Mubarak Al Kabeer Hospital, Kuwait's National ADPKD Clinic represents a pioneering approach to comprehensive polycystic kidney disease management in the Gulf region.

A Patient-Centered Care Philosophy

Individualized Treatment Plans

Every patient receives personalized care based on their unique genetic profile, kidney function trajectory, and quality of life considerations.

Family-Focused Approach

Genetic counseling extends beyond the individual patient to include family screening, education, and reproductive planning support.

Shared Decision-Making

Treatment decisions are made collaboratively, ensuring patients understand their options and participate actively in their care journey.

The clinic's philosophy prioritizes not just clinical outcomes, but the overall wellbeing and empowerment of patients and their families throughout the disease trajectory.

Kuwait's National ADPKD Clinic: Precision Medicine in Action

126

Patients Enrolled

Established a comprehensive patient cohort across 36 families.

88.9%

Molecular Diagnosis Yield

This high success rate was rigorously documented in CKJ 2023.

69%

Novel Variants Identified

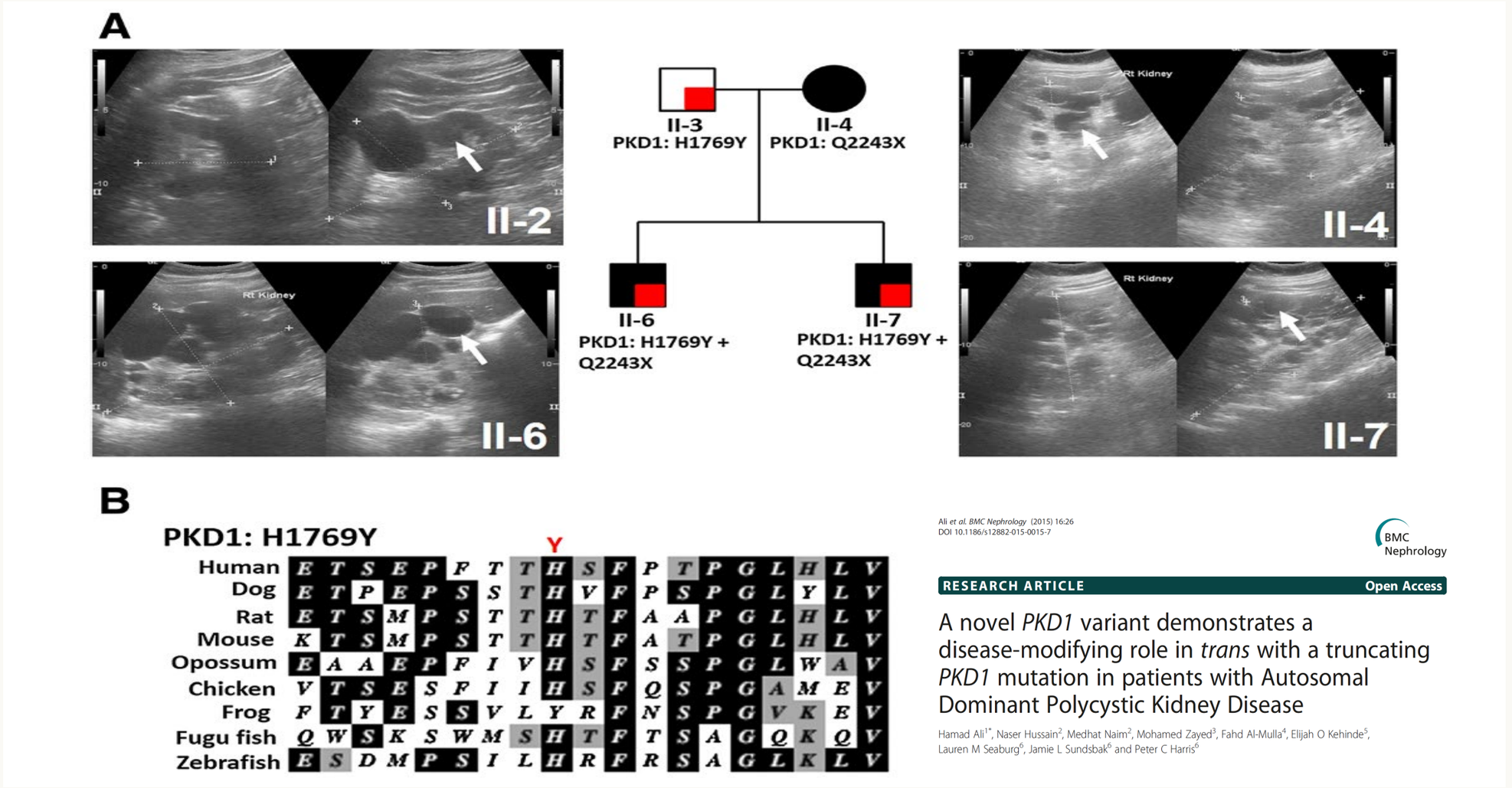
These findings significantly expand the regional genetic reference database.

This joint initiative, established by the Dasman Diabetes Institute and Mubarak Al-Kabeer Hospital, represents the pioneering precision ADPKD program within the Gulf region.

Genetic Architecture Defined: Analysis revealed a distinct regional distribution of mutations: 77.8% PKD1, 15% PKD2, and 2.8% IFT140.

Kuwait's program proves that personalized medicine for ADPKD is not a distant vision—it is actively transforming patient care today.

Attempts to add Genetics to ADPKD practice



Ali *et al. BMC Nephrology* (2015) 16:26
DOI 10.1186/s12882-015-0015-7

BMC Nephrology

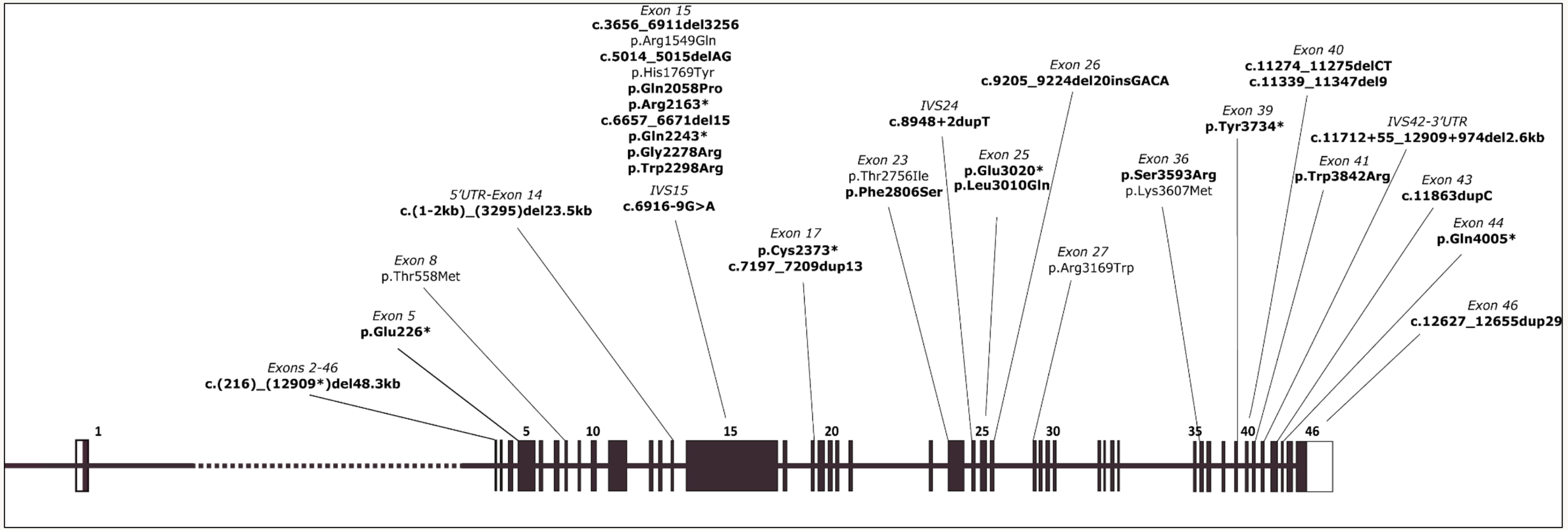
RESEARCH ARTICLE Open Access

A novel *PKD1* variant demonstrates a disease-modifying role in *trans* with a truncating *PKD1* mutation in patients with Autosomal Dominant Polycystic Kidney Disease

Hamad Ali[1*], Naser Hussain[2], Medhat Naim[2], Mohamed Zayed[3], Fahd Al-Mulla[4], Elijah O Kehinde[5], Lauren M Seaburg[6], Jamie L Sundsbak[6] and Peter C Harris[6]

Ali et al., 2015 *BMC Nephrology*

Kuwait's National ADPKD Clinic



ORIGINAL ARTICLE

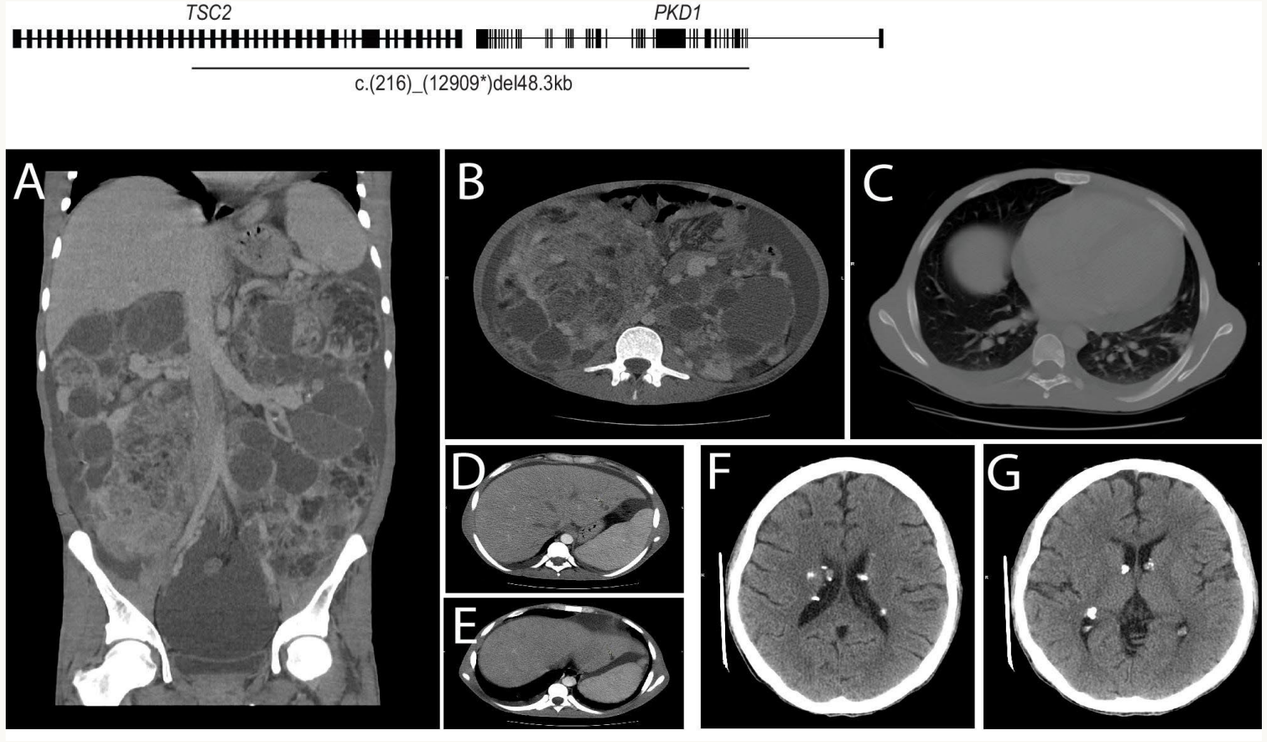
The genetic landscape of autosomal dominant polycystic kidney disease in Kuwait

Hamad Ali[1,2], Medhat Naim[3], Sarah R. Senum[4], Ali AlSahow[5], Yousif Bahbahani[3,6], Mohamed Abu-Farha[7], Jehad Abubaker[7], Anwar Mohammad[7], Adel Al-Hunayan[8], Akram M. Asbeutah[9], Mohamed Zayed[10], Sriraman Devarajan[11], Naser Hussain[3], Sumi Elsa John[2], Arshad Channanath[2], Thangavel Alphonse Thanaraj[2], Mohammad Al-Ali[12], Mustafa AlMousawi[13], Fahd Al-Mulla[2] and Peter C. Harris[4]

Ali et al., 2023 *Clinical Kidney Journal*

Kuwait's National ADPKD Clinic
Atypical cases

- A case with the TSC2-PKD1 contiguous syndrome.
- Detected in a 25-year-old male patient with early renal insufficiency (eGFR 9.8 ml/min/1.73 m2).
- Radiologic analysis revealed renal angiomyolipoma, pulmonary lymphangioleiomyomatosis and bilateral subependymal calcified nodules
- Patient showed multiple skin lesions including fibrous cephalic plaques, hypopigmented macules, angiofibroma and shagreen patches on the lower back.

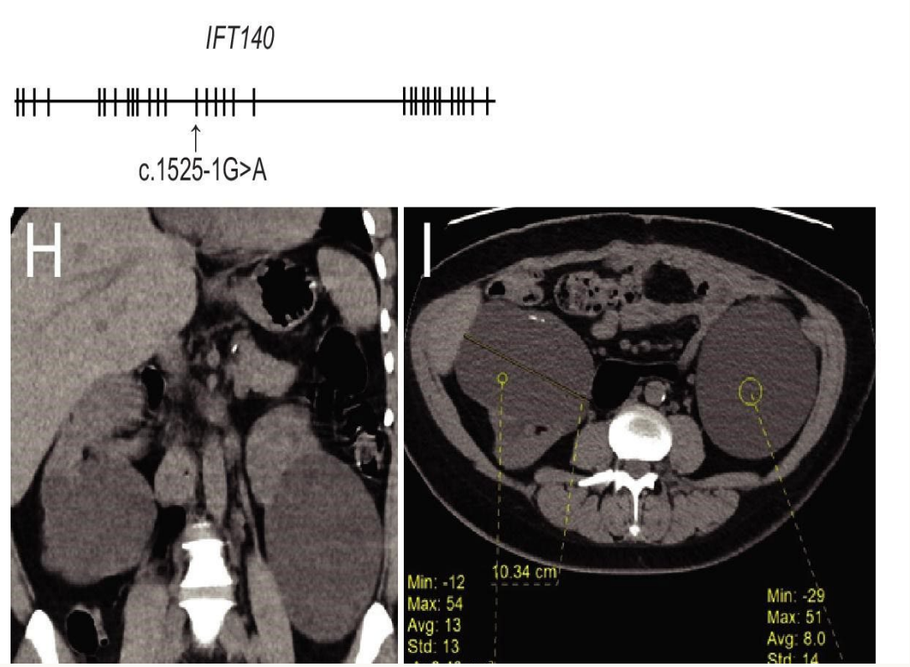


Ali et al., 2023 *Clinical Kidney Journal*

Kuwait's National ADPKD Clinic

Atypical cases

- A splicing pathogenic variant at a conserved site.
- This variant was detected in a 44-year old female with normal eGFR and htTKV of 876 ml/m.



Ali et al., 2023 *Clinical Kidney Journal*

Comprehensive Services: From Diagnosis to Treatment

01

Genetic Testing & Diagnosis

Comprehensive genetic analysis identifies specific PKD1/PKD2 mutations, establishing definitive diagnosis and informing prognosis.

02

Risk Stratification

Mutation type (truncating vs. non-truncating) combined with clinical parameters guides treatment intensity and monitoring frequency.

03

Tolvaptan Therapy Management

Eligible patients receive treatment with careful monitoring for efficacy and side effects, optimizing disease modification.

04

Annual Surveillance

MRI-based kidney volume assessments track disease progression and treatment response, enabling data-driven care adjustments.

Tolvaptan: The First and Only Approved Therapy for ADPKD

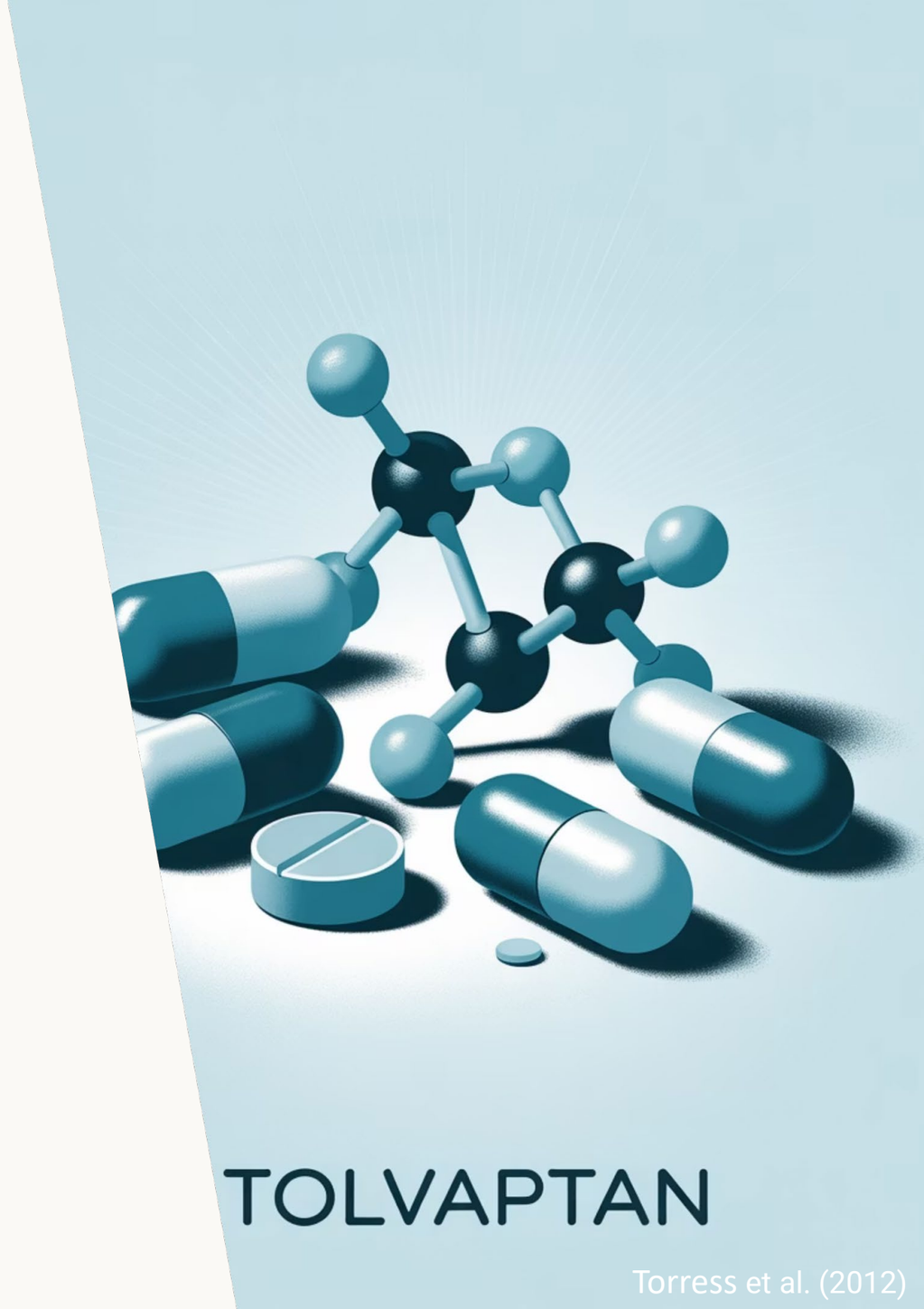
Mechanism of Action: Tolvaptan is a vasopressin V2 receptor antagonist. By blocking vasopressin signaling, it reduces intracellular cAMP in renal tubular cells, which slows cyst fluid secretion and cellular proliferation in kidney cysts.

TEMPO 3:4 Trial (3 years)

35%
eGFR Decline Rate Reduction

49%
TKV Growth Rate Reduction

The subsequent REPRISE trial decisively **confirmed these sustained benefits** in patients with later-stage CKD 3-4, firmly establishing Tolvaptan's efficacy across the broad ADPKD disease spectrum.

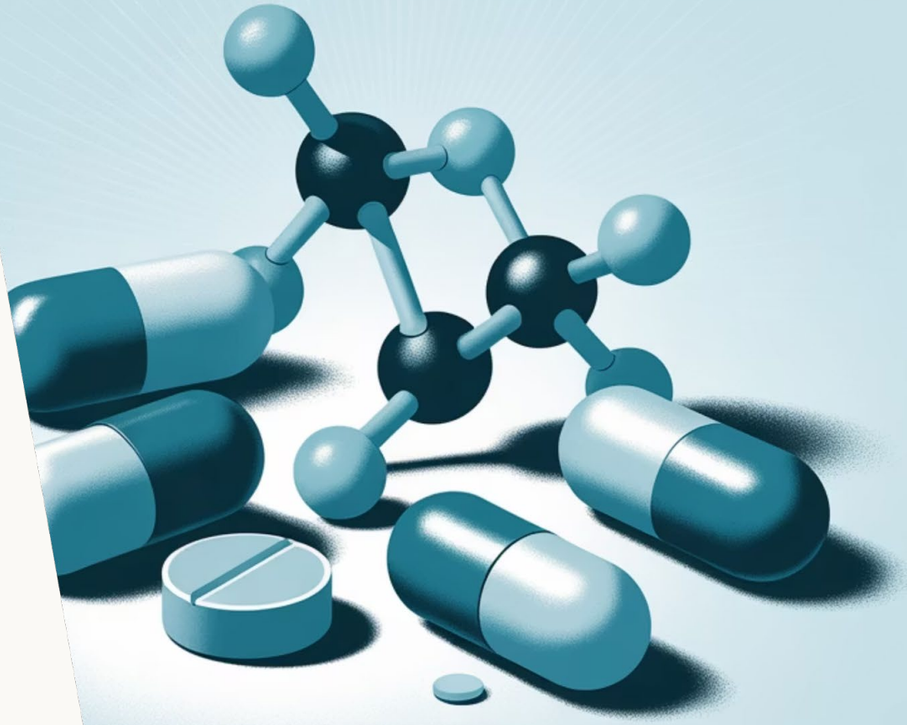


Torress et al. (2012)

Patient Selection: Who Gains the Greatest Benefit from Tolvaptan?

Category	Typical Profile of “Tolvaptan Responders”	Expected Outcome
Rapid progressors	eGFR decline ≥ 3 ml/min/yr, TKV ≥ 750 ml	~30% slower eGFR loss
Younger adults	18–50 years, CKD 2–3	Delayed kidney failure onset
High-risk genotype	PKD1 truncating, PROPKD ≥ 6	Strongest slowing effect
Imaging risk class	Mayo Class 1C–E	Validated progression markers
Good liver tolerance and adherence	Able to maintain hydration and monitoring	Sustained long-term benefit

Tolvaptan provides the most benefit in ADPKD patients aged 18–50 years with preserved kidney function (CKD 2–3), high total kidney volume or Mayo class 1C–E, and/or a PKD1 truncating variant—i.e., those at greatest risk of rapid progression.



Torress et al. (2012)

Optimizing Tolvaptan Therapy: Understanding Genotype Response

85%

PKD1 Truncating Mutations

These mutations drive the most aggressive disease course, where Tolvaptan delivers the greatest absolute therapeutic benefit for rapid progressors.

65%

PKD1 Non-truncating Genotypes

Patients with these genotypes demonstrate a moderate, yet clinically significant, therapeutic response relative to their slower baseline progression rate.

45%

PKD2 Variants

The typically indolent disease course in PKD2 results in a smaller absolute risk reduction, but personalized treatment remains a consideration.

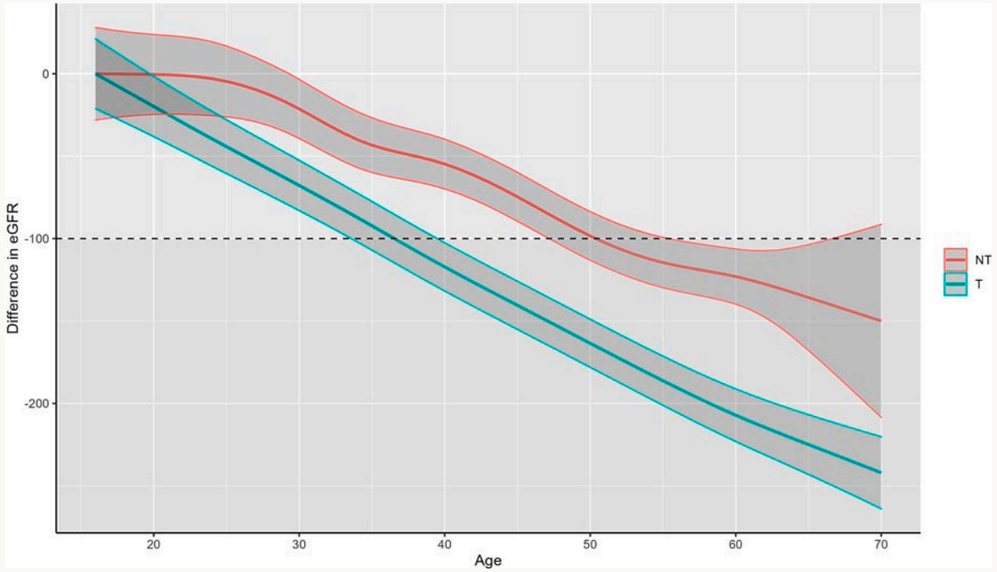
0%

IFT140/GANAB/DNAJB11 (Rare Variants)

These rare ADPLD and ADPKD variants often present with a mild phenotype, meaning Tolvaptan initiation is generally unwarranted.

Clinic Experience : PKD1 Truncating Mutations Accelerate Kidney Function Decline in ADPKD

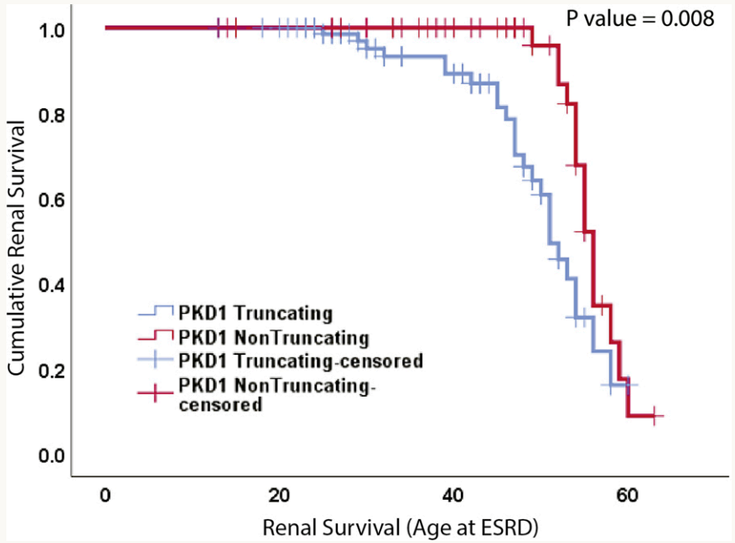
Local Population
Tailor management
Refine prognosis



42
PKD1 Patients

6.6 years
(1 to 12 years) Follow up

34% faster
eGFR Decline Rate PKD1 Truncating vs. NT



51 Years
ESRD
PKD1 Truncating Patients

56 years
ESRD
PKD1 Non-Truncating Patients

Ali et al. 2024 *American Journal of Nephrology*

Navigating Tolvaptan Scarcity: A Genetic Solution

The Challenge

Limited medication access: Initially only 10 patients approved, recently expanded to 15.

Sourcing difficulties: Unable to establish direct contact with Otsuka Pharmaceuticals.

Complex supply chain: Currently sourcing through Kuwait Embassy's health office in London.

The Genetic-Guided Solution

Faced with medication scarcity, the clinic developed an innovative **Mutation-Informed Criterion (MIC)** prioritization system that combines genetic and clinical data to identify patients who will benefit most from treatment.

This evidence-based approach ensures that limited Tolvaptan supplies reach patients with the highest risk for rapid disease progression, maximizing therapeutic impact across the population.

Precision Medicine: Combining therapeutic approaches

01

Patient Selection

Prioritize initiation of therapy in younger patients with *PKD1* truncating mutations (Mayo Clinic Classification C-E), especially when access or resources are limited.

02

Safety Monitoring

Mandate rigorous safety protocols, including intensive hydration management and diligent, regular surveillance of liver function tests.

03

Adjunctive Therapies

Evaluate the use of GLP-1 receptor agonists and SGLT2 inhibitors to achieve additional metabolic and potential synergistic benefits in ADPKD management.

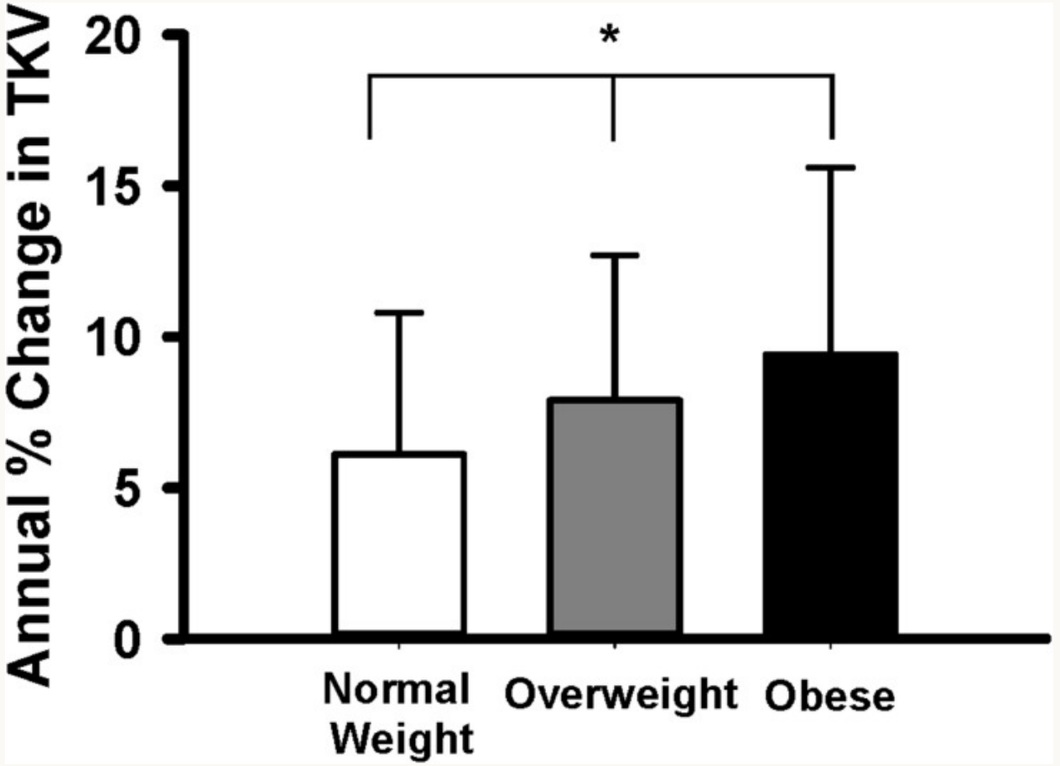
Emerging clinical data strongly support the synergistic potential of combination approaches that target multiple, distinct pathophysiological pathways in ADPKD.

Precision Lifestyle Interventions: Targeting Obesity to Slow ADPKD

Obesity affects 40–45% of adults with ADPKD and represents a modifiable driver of disease progression. Epidemiologic data demonstrate that elevated BMI correlates independently with accelerated kidney growth and earlier renal decline.

Annual % change in TKV:

- Normal weight: 6.1%±4.7%,
- Overweight: 7.9%±4.8%
- Obese: 9.4%±6.2%
- Earlier onset of hypertension and metabolic complications



Mechanistic links include increased vasopressin secretion, RAAS activation, oxidative stress, renal lipotoxicity, and chronic inflammation—all amplifying cyst expansion.

Nowak et al. (2017)

Balancing Promise and Caution

Ali *et al. BMC Nephrology* (2025) 26:279
https://doi.org/10.1186/s12882-025-04217-w

BMC Nephrology

COMMENT Open Access

Can GLP-1 receptor agonists slow the progression of Autosomal Dominant Polycystic Kidney Disease?

Hamad Ali[1,2,3,4*], Barrak Alahmad[2,5] and Fahd Al-Mulla[2]

Potential Benefits

- Weight loss slows TKV growth and eGFR decline
- Blood pressure reduction and CV protection
- Anti-inflammatory and anti-fibrotic effects
- May improve tolvaptan tolerability by reducing metabolic load
- Visceral fat reduction may enhance tolvaptan efficacy

Critical Concerns

- No direct human ADPKD trial data yet
- Potential cAMP elevation—opposing tolvaptan mechanism
- Dehydration risk with GI side effects (nausea, vomiting)
- Unknown drug interactions with tolvaptan
- AKI risk in patients with reduced renal reserve

> *"Metabolic health is kidney health —obesity amplifies cyst growth. Targeting modifiable disease drivers represents the next frontier in ADPKD management ."*

Ali et al. 2025 *BMC Nephrology*

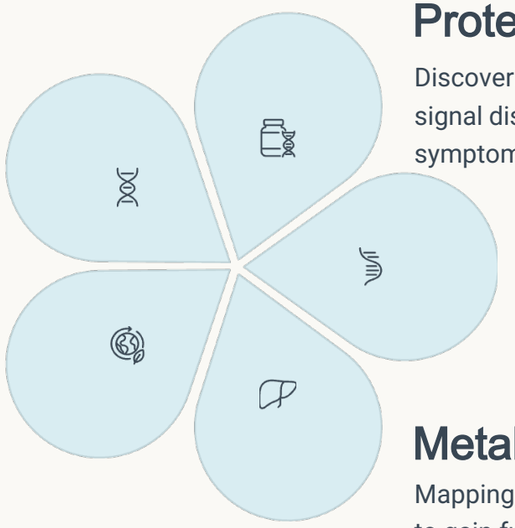
Integrating AI and Multi-Omics Accelerating Precision Medicine in ADPKD

Genomics

Unlocking precise **variant classification** and leveraging ancestry-specific data for personalized risk assessment.

Exposomics

Identifying critical **environmental and lifestyle modifiers** that interact with genetics to influence disease onset and progression.



Proteomics

Discovering **early tubular injury biomarkers** that signal disease progression before clinical symptoms appear.

Transcriptomics

Utilizing dynamic **miRNA panels** to accurately measure current disease activity and monitor therapeutic response.

Metabolomics

Mapping specific **metabolic pathway signatures** to gain functional insight into pathophysiological mechanisms.

Biomarker Discovery Revolution

AI identifies novel biomarkers that surpass traditional measures

01

Beyond eGFR and TKV

Multi-parameter predictive signatures outperform single metrics

02

Early Detection

Specific miRNAs, metabolites, and protein panels flag rapid progressors

03

Pre-Structural Damage

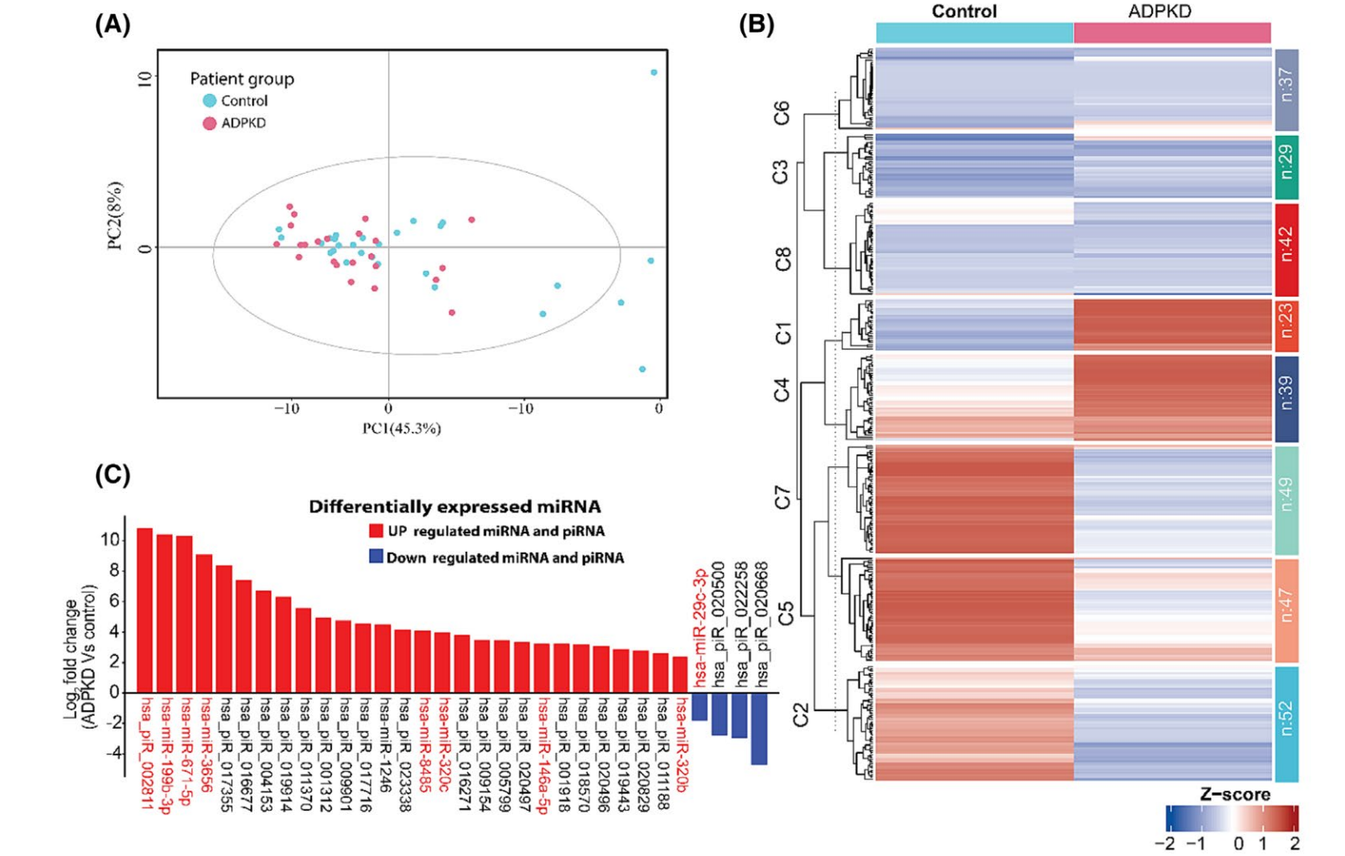
Identify risk before kidney damage becomes visible

04

Refined Patient Selection

Optimize Tolvaptan eligibility and future therapy targeting

Multi-OMICS and ADPKD



Ali et al. 2024 *Journal of Gene Medicine*

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“Science is the art of building bridges —across borders and across ideas — turning distance into dialogue and curiosity into shared progress.” Chat GPT