PKHD1 genetics: implications for clinical diagnosis and management

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Autosomal Recessive Polycystic Kidney Disease Symposium
Sponsored by the PKD Foundation
15th IPNA Congress, New York City
August 29, 2010
Objectives

• Overview: autosomal recessive polycystic kidney disease.

• Autosomal recessive polycystic kidney disease: genetic data.

• Considerations in gene-based testing.

• Using gene-based testing in clinical practice.
Autosomal recessive PKD

- Incidence: 1:20,000
- Molecular genetics
  - *PKHD1*
- Renal disease
  - 1° collecting ducts
  - very large kidneys
- Other associations
  - biliary dysgenesis and fibrosis
## ARPKD: clinical variability

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<tr>
<td>Prenatal dx</td>
<td>46%</td>
<td>23%</td>
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<td>Hyponatremia</td>
<td>26%</td>
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<td>Hypertension</td>
<td>65%</td>
<td>76%</td>
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<td>Chronic renal insufficiency</td>
<td>42%</td>
<td>86%</td>
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<td>Growth retardation</td>
<td>24%</td>
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<td>Chronic lung disease</td>
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<tr>
<td>Portal hypertension</td>
<td>15%</td>
<td>44%</td>
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</table>

Objectives

- Overview: autosomal recessive polycystic kidney disease.
  - Autosomal recessive polycystic kidney disease: genetic data.
- Considerations in gene-based testing.
- Using gene-based testing in clinical practice.
ARPKD genetics

- In all patients with typical ARPKD or isolated congenital hepatic fibrosis, disease locus linked to chr 6p12
- To date, no evidence for additional loci
ARPKD genetics

PKHD1 gene

465 kb gene; 86 exons, 67 exons in the longest open reading frame
Mutations: 44% missense

In selected cohorts - mutations identified in 81-87% patients

Adeva et al. (2006) Medicine (Baltimore) 85: 1-21  81%
Bergmann et al. (2005) Hum Mutat 25: 225-231  80%
Losekoot et al. (2005) Hum Genet 118: 185-206  87%
ARPKD mutational analysis

- As of August 15, 2010 -- 702 entries
  - 311/702 (44%) missense
  - 191/702 (27%) splice site
  - 76/702 (11%) deletion
  - 54/702 (7%) nonsense
  - 30/702 (4%) insertion/duplication

Mutation Database Autosomal Recessive Polycystic Kidney Disease (ARPKD/PKHD1)
Human Genetics, Aachen University, Germany

http://www.humgen.rwth-aachen.de/
Gene copy number alterations

- Screened 16 ARPKD probands with only one PKHD1 mutation detected
- Three germ-line deletions detected
  - Homozygous deletion Ex 1-37
  - Heterozygous deletion Ex 61-67
  - Heterozygous deletion Ex 21-22

ARPKD: genotype-phenotype correlations

- Two chain-terminating mutations are more frequently associated with perinatal demise, whereas at least one amino acid substitution is more commonly associated with a non-lethal presentation.
  
  [Bergmann et al. (2005) Kidney Int. 67: 829-848]

- Mutational analysis in 78 children/adults with ARPKD/CHF – no patients with two truncating mutation identified, even among those presenting in the first 30 days of life.
  

- In 73 children/adults with ARPKD/CHF – no correlation between kidney size or function and PKHD1 mutations.
  
Denamur et al. correlated the severity of renal and hepatic histopathology with *PKHD1* mutational types in 54 fetuses (medical pregnancy termination) and 20 neonates who died shortly after birth. In this cohort, 55.5% of the mutations truncated fibrocystin. The severity of cortical collecting duct dilatation, and renal cortical and hepatic portal fibrosis increased with gestational age. When adjusted to gestational age, the extent of collecting duct dilatation (cortex and medulla), but not portal fibrosis, was more prevalent in patients with severe genotypes. 

**Conclusion:** the presence of two truncating mutations of the *PKHD1* gene is associated with the most severe renal forms of prenatally detected ARPKD.

*Denamur et al. (2010) Kidney Int. 77: 350-358*
ARPKD: clinical variability within families

- Significant variability in ARPKD-related morbidities observed in 11/20 sibships
  
  \cite{Deget1995}

- Significant differences survival and disease severity demonstrated in 20/48 sibships
  
  \cite{Bergmann2005}

- Within-family variability in survival and ARPKD-related morbidities. In one sibship, affected children homozygous for delEx1-37. Two sibs suffered perinatal demise while their 8 yo brother has CKD and severe congenital hepatic fibrosis.
  
  \cite{Guay-Woodford2019}
## Factors modulating PKD disease expression

<table>
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<tr>
<th>Genetic factors</th>
<th>Mechanism</th>
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<tr>
<td>Genetic heterogeneity</td>
<td>single gene, <em>PKHD1</em></td>
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<td>Allelic heterogeneity</td>
<td>limited genotype-phenotype</td>
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<tr>
<td>Allelic variation in other genes</td>
<td>modifier genes</td>
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</tbody>
</table>
ARPKD is a complex trait

Discontinuous trait

Continuous trait

\[ y_{ij} = \mu + [G_i] + E_j + I_{ij} + \varepsilon \]
Objective:

Use the cpk mouse as a model system to identify genes that modulate the renal and biliary phenotypes in recessive PKD.

Table 1: Murine models of polycystic kidney disease

<table>
<thead>
<tr>
<th>Model</th>
<th>Transmission</th>
<th>Gene</th>
<th>Protein</th>
<th>Human PKD phenocopy</th>
<th>Cilia expression</th>
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<td>AR</td>
<td>Cys1</td>
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<td>ARPKD</td>
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<td>AD/AR</td>
<td>Bicc1</td>
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<td>MKS/ARPKD</td>
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<td>AR</td>
<td>Pkh1d</td>
<td>fibrocystin</td>
<td>ARPKD</td>
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</tbody>
</table>

**Kif12**: candidate modifier of \( cpk \) \((Mocpk)\)

**A.**

![Diagram of kinesin structure]

**B.** Comprehensive informatic analyses of kinesin-like sequences in 19 eukaryotes determined that kinesin-12 is a member of the Kinesin 16 family (a new kinesin family predicted to have cilia/flagellar functions)


**C.**

![Imaging results showing kinesin localization]
Cystoproteins localize to the cilia/centrosome complex

- Polyductin/fibrocystin
- Cystin
- Kinesin 12

- Polycystin-1
- Polycystin-2
**Pkd1** modulates renal disease severity in **Pkhd1** mutants

A. 

B. 

Garcia-Gonzales et al. (2007) 
From experimental models to human patients
Objectives

- Overview: autosomal recessive polycystic kidney disease.
- Autosomal recessive polycystic kidney disease: genetic data.
- Considerations in gene-based testing.
- Using gene-based testing in clinical practice.
Guidelines for genetic testing

• Clinical laboratory:
  • Examines patient samples and reports results to the provider for the purpose of diagnosis, prevention, treatment of an individual patient.
  • In US, all clinical laboratory testing is regulated through the Clinical Laboratory Improvement Amendments (CLIA).

• Research laboratory:
  • Collects and examines patient samples for the purpose of better understanding disease pathogenesis or to develop a clinical test.
  • Not subject to CLIA regulation.
  • Results not reported to the provider.
Welcome to the GeneTests Web site, a publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons. Use of this Web site assumes acceptance of the terms of use.

At This Site

- **GeneReviews**
  Online publication of expert-authored disease reviews

- **Laboratory Directory**
  International directory of genetic testing laboratories

- **Clinic Directory**
  International directory of genetics and prenatal diagnosis clinics

- **Educational Materials**
  - Illustrated glossary
  - About genetic services
  - PowerPoint® slide presentations

What's New

New Features
- PowerPoint® slide show: Genetic Testing: The Clinician's Perspective
- Array Genomic Hybridization listed in Lab Services

New in GeneReviews
- 23 new listings

Visit **GENETIC TOOLS** — Materials for teaching genetics in primary care settings

http://www.genetests.org
Laboratory Directory

The Laboratory Directory is a voluntary listing of US and international laboratories offering in-house molecular genetic testing, specialized cytogenetic testing, and biochemical testing for inherited disorders. Listings are divided into Clinical Laboratories (which require CLIA certification in the US) and Research Laboratories.

- Includes information on:
  - Laboratory contact personnel
  - Test methodology
  - Staff certification by:
    - The American Board of Medical Genetics
    - The American Board of Genetic Counseling
    - The American Board of Pathology: Molecular Genetic Pathology
  - Laboratory certification
- Searchable by disease name, gene symbol, protein name, clinical disease feature, services, director, location (US state or country), or laboratory name
- Updated in a formal comprehensive process at least once a year
- Revised by the laboratory as needed
- Provides links (when available) to GeneReviews, resources, laboratory Web sites, and OMIM. Links to PubMed are provided from some research laboratories.
The result of your search (below) includes a group of related disorders with your search term in **bold** or an alphabetical listing of the individual entries that match your search term. For more information about search results, see [Interpreting Your Search Results](#).

**Search Result for `ARPKD`**

| ARPKD [Polycystic Kidney Disease, Autosomal Recessive] | Testing | Research | Reviews | Resources |
**Polycystic Kidney Disease, Autosomal Recessive** | ARPKD | Polycystic Kidney Disease, Infantile

<table>
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<tr>
<th>Laboratories offering clinical testing:</th>
<th>Analysis of the entire coding region: Sequence analysis</th>
<th>Analysis of the entire coding region: Mutation scanning</th>
<th>Targeted mutation analysis</th>
<th>Linkage analysis</th>
<th>Prenatal diagnosis</th>
<th>Preimplantation genetic diagnosis</th>
<th>Clinical confirmation of mutations identified in a research lab</th>
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Objectives

• Overview: autosomal recessive polycystic kidney disease.

• Autosomal recessive polycystic kidney disease: genetic data.

• Considerations in gene-based testing.

➢ Using gene-based testing in clinical practice.
ARPKD linkage analysis

Chromosome 6

ARPKD interval
Normal interval

Father
Affected Boy
Unaffected Girl
Unaffected Boy

Mother
ARPKD gene-based analysis

PKHD1 gene

465 kb gene; 86 exons, 67 exons in the longest open reading frame
Mutations: 44% missense

In selected cohorts - mutations identified in 81-87% patients

Adeva et al. (2006) Medicine (Baltimore) 85: 1-21 81%
Bergmann et al. (2005) Hum Mutat 25: 225-231 80%
Losekoot et al. (2005) Hum Genet 118: 185-206 87%
ARPKD: Diagnostic testing - UAB experience

Methods
• Linkage-based testing - 7 microsatellite markers
• Two-tier testing
  ➢ 23 exons contain 80% mutations - US $1,500
  ➢ All 67 exons - US $3,300

Testing (May 2005 to January 2009)
• Probands from >100 unrelated families

Results
• 84.7% mutation detection rate in patients with clinical data c/w ARPKD
• 48% overall mutation detection rate

Messiaen et al. unpublished data
## Hepato-Renal Fibrocystic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene(s)</th>
<th>Renal disease</th>
<th>Hepatic disease</th>
<th>Systemic features</th>
<th>Prevalence</th>
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<tr>
<td>ARPKD</td>
<td><em>PKHD1</em></td>
<td>Collecting duct dilatation</td>
<td>CHF; Caroli disease</td>
<td>no</td>
<td>~1 in 20,000</td>
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<td>ADPKD</td>
<td><em>PKD1</em>; <em>PKD2</em></td>
<td>Cysts along entire nephron</td>
<td>Biliary cysts; CHF</td>
<td>yes - adults</td>
<td>~1 in 1,000</td>
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<tr>
<td>Nephronophthisis (NPHP)</td>
<td><em>NPHP1-NPHP9</em>; <em>NPHP11</em></td>
<td>Cysts at the cortico-medullary junction</td>
<td>CHF</td>
<td>+/-</td>
<td>~1 in 50,000</td>
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<td>Joubert syndrome</td>
<td><em>JBTS1-JBTS9</em></td>
<td>Cystic dysplasia; NPHP</td>
<td>CHF; Caroli disease</td>
<td>yes</td>
<td>~1 in 100,000</td>
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<tr>
<td>Bardet-Biedel syndrome</td>
<td><em>BBS1-BBS14</em></td>
<td>Cystic dysplasia; NPHP</td>
<td>CHF</td>
<td>yes</td>
<td>~1 in 100,000</td>
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<td>Meckel-Gruber syndrome</td>
<td><em>MKS1-MKS6</em></td>
<td>Cystic dysplasia</td>
<td>CHF</td>
<td>yes</td>
<td>~1 in 140,000</td>
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<td>Oral-facial-digital syndrome, Type I</td>
<td><em>OFD1</em></td>
<td>Glomerular cysts</td>
<td>CHF (rare)</td>
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<td>~1 in 250,000</td>
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<td>Glomerulocystic disease</td>
<td><em>PKD1</em>; <em>TCF2</em>; <em>UMOD</em></td>
<td>Enlarged; normal or hypoplastic kidneys</td>
<td>CHF (with <em>PKD1</em> mutations)</td>
<td>+/-</td>
<td>rare</td>
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<td>Jeune syndrome (asphyxiating thoracic dystrophy)</td>
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<td>Cystic dysplasia</td>
<td>CHF; Caroli disease</td>
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<td>Renal-hepatic-pancreatic dysplasia</td>
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<td>Cystic dysplasia</td>
<td>Intrahepatic biliary dysgenesis</td>
<td>yes</td>
<td>rare</td>
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<td><em>PEX1-3;5;6;12;14;26</em></td>
<td>Renal cortical microcysts</td>
<td>Intrahepatic biliary dysgenesis</td>
<td>yes</td>
<td>rare</td>
</tr>
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</table>
ARPKD phenocopies

- ADPKD caused by mutation in *PKD1* or *PKD2*, can (rarely) manifest as a neonatal disease within a family segregating typical ADPKD. Two pedigrees described, each with single proband manifesting massive PKD *in utero*. *PKHD1* gene analysis negative; analysis of *PKD1* identified co-inheritance of a hypomorphic allele in *trans* with an inactivating allele.


- Three children had features typical of ARPKD (enlarged, diffusely microcystic kidneys and early-onset severe hypertension), as well as early-onset chronic anemia, a feature of nephronophthisis, and speech / oculomotor apraxia, suggestive of Joubert syndrome. Gene-based analysis identified *MKS3* mutations.

Pre-implantation testing or genetic diagnosis (PGD)

- Gigarel et al. (2008) Reprod Biomed Online. 16: 152-158

The isolated DNA is amplified by PCR to generate multiple copies of the PKHD1 gene.

The PCR-amplified DNA is sequenced.

The "test" sequence is then compared to the normal PKHD1 sequence to determine whether there is a likely disease-causing change (mutation).
ARPKD:

- Gene-based testing is primarily applied in the context of prenatal testing and pre-implantation genetic diagnosis.
- To date, there is limited evidence for correlations between specific mutations and clinical disease expression.
- The clinical utility of *PKHD1* testing is dependent on the clinical data.
1. UAB Recessive PKD Research and Translational Core Center
   Condition: Autosomal Recessive Polycystic Kidney Disease
   Study: Observational; retrospective
   Recruiting: Yes

2. Evaluation of Autosomal Recessive Polycystic Kidney Disease and Congenital Hepatic Fibrosis (NHGRI)
   Conditions: Autosomal Recessive Polycystic Kidney Disease; Congenital Hepatic Fibrosis; and other related ciliopathies
   Study: Observational; Natural history
   Recruiting: Yes
The University of Alabama at Birmingham Recessive Polycystic Kidney Disease Core Center (UAB RPKDCC) has established a NIDDK-funded, interdisciplinary center of excellence in PKD-related research, with specific emphasis on recessive PKD. Among the five Cores, the UAB RPKDCC includes the ARPKD Clinical and Genetic Resource, a Core resource designed to develop a unique set of clinical, genetic, and educational resources for ARPKD.

The Core has three primary objectives:

1. Establish a comprehensive Clinical Database that includes information from all patients who meet the inclusion criteria for ARPKD.

   **ARPKD Clinical Database**
   - Patient/family information and consent
     - Information (PDF Downloadable)
     - Consent Form (PDF Downloadable)
     - Participant Web Enrollment
   - Physician access (password protected)
     - Information (PDF Downloadable)
     - Physician

2. Establish a Mutational Database which will be capable of linking clinical and mutational information in a searchable format to facilitate genetic analyses (e.g. genotype-phenotype correlations, modifier gene studies), translational studies, and clinical trials.

   **ARPKD Mutational Database** (Authorized medical personnel)
Summary

• With recent advances in molecular genetics, gene-based testing is becoming part of the armamentarium of diagnostic and predictive tools in ARPKD patient management.

• Gene-based testing requires appropriate pre- and post-test counseling.

• Clinical utility of gene-based testing in ARPKD:
  • prenatal diagnosis
  • PGD


