UAB P30
CORE A: The Hepato-Renal Fibrocystic Diseases Translational Resource

http://www.arpkdstudies.uab.edu/

Director: Lisa M. Guay-Woodford, MD
Co-Director: William E. Grizzle, MD, PhD

Core A: Components

Clinical Database (patients and families)

Tissue Resource

Genetic Resource

Educational Resource (patients, families and providers)
Core A: Background

- Autosomal recessive polycystic kidney disease (ARPKD) and other hepato-renal fibrocystic diseases (HRFD), while relatively rare recessive disorders, are an important set of childhood inherited kidney disorders.
- Rare disease research requires greater collaboration than the efforts in common diseases where patient resources are routinely available and large repositories can be built locally, as well as nationally.
- The Core Translational Resource provides a bio-repository and resource for investigators; it links basic science, clinical information, patient materials and the patients themselves into a close knit collaboration focused on the hepato-renal fibrocystic diseases.
- Core A will serve as a critical platform for developing future interventional studies, assessing genotype-phenotype correlations, and identifying new disease genes by our Research Base, as well as other members of the research community.

Core A: Specific Aims

**Aim 1:** Expand our knowledge and understanding of HRFD clinical disease, pathology and genetics.

**Aim 2:** Identify genetic mutations in ARPKD and other HRFD patients and assess the disease-causing potential of sequence variants.

**Aim 3:** Establish an annotated, updated, multi-media resource to provide information regarding the diagnosis, management, family impact, and genetics of hepato-renal fibrocystic disease spectrum of disorders, particularly ARPKD.
Aim 1: Rationale / Approach

Aim 1: Expand our knowledge and understanding of HRFD clinical disease, pathology and genetics.

Rationale:

Clinical Database: The observational cohort established in the HRFD Clinical Database will allow analyses of perinatal morbidity and mortality; characterization of the clinical disease course; correlations between renal and extra-renal disease progression; and analysis of long-term survivors.

Tissue Resource: The study of recessive HRFD requires adequate supplies of high quality samples from diseased kidneys, livers and other phenotypically affected tissues -- the supply of these human tissues is currently very limited.

Aim 1: Clinical Database

Developed a REDCap-based framework to import the clinical datasets to Children's National.

REDCap is a secure web application designed exclusively to support secure data capture and database management for research studies.

The REDCap application is supported by the Clinical and Translational Science Institute at Children’s National (CTSI-CN).

The **REDCap Consortium** is composed of **1,783 institutional partners 98 countries**, including all CTSA institutions in the US.
Core A Clinical Database (n = 73)

Demographics

Gender
- Male
- Female

Race
- Caucasian
- Black
- Hispanic
- Asian
- Other

Survival
- Alive
- Deceased

Family History
- Yes
- No
- Unknown

Core A Clinical Database (n = 73)

Clinical Features

- Chronic Lung Disease
- Growth Retardation
- Hyponatremia
- Hypertension
- Renal Insufficiency
- Esophageal Varices
- Variceal Bleeds
- Cholangitis

Renal
- Liver
Core A Clinical Database (n = 73)

Renal Imaging Results

- Ultrasound: n=132
- CT Scans: n=16
- MRI: n=12

Renal Pathology

- Autopsy: 10
- Nephrectomy: 13
Aim 1: Clinical Database

Recruitment Strategies

• Core A is actively promoting the HRFD Clinical Database:
  • Professional societies
  • Patient advocacy groups
    • PKD Foundation Registry with >100 ARPKD patients/families.
    • Parent co-leaders of ARPKD Chapter engaged in promoting Core A activities.
  • Brochure describing the Clinical Database and the other Core functions.
Estimating the ARPKD incidence [Cerner Health Facts® data]

Estimated Incidence (annualized):
1:18,660 live births; 172 new ARPKD neonatal survivors/year.

<table>
<thead>
<tr>
<th>Year</th>
<th>HF patients with ARPKD (&lt; 1-mo)</th>
<th>HF (&lt; 1-mo)</th>
<th>NVS</th>
<th>HF/NVS</th>
<th>ARPKD incidence in HF</th>
<th>Estimated US ARPKD (&lt;1 mo)</th>
<th>Adjusted estimate: US ARPKD (&lt;1-mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>12</td>
<td>219,425</td>
<td>3,999,388</td>
<td>5.49%</td>
<td>1:18,285</td>
<td>219</td>
<td>176</td>
</tr>
<tr>
<td>2011</td>
<td>11</td>
<td>226,609</td>
<td>3,953,590</td>
<td>5.73%</td>
<td>1:20,601</td>
<td>192</td>
<td>155</td>
</tr>
<tr>
<td>2012</td>
<td>13</td>
<td>222,233</td>
<td>3,952,841</td>
<td>5.62%</td>
<td>1:17,095</td>
<td>231</td>
<td>186</td>
</tr>
<tr>
<td>AVG</td>
<td>12</td>
<td>222,756</td>
<td>3,968,606</td>
<td>5.61%</td>
<td><strong>1:18,660</strong></td>
<td><strong>214</strong></td>
<td><strong>172</strong></td>
</tr>
</tbody>
</table>

Calculated incidence data = estimated incidence derived from genetic studies.

Calculated incidence data = estimated incidence derived from genetic studies.

Estimating the ARPKD prevalence [Cerner Health Facts® data]

Estimated prevalence (annualized):
1.5 per 100,000 or ~1,800 ARPKD patients in the US

<table>
<thead>
<tr>
<th>Year</th>
<th>HF ARPKD patients (0-29 yrs)</th>
<th>HF (0-29 yrs)</th>
<th>US population (0-29 yrs)</th>
<th>HF/US population (0-29 yrs)</th>
<th>ARPKD patients (0-29 yrs)</th>
<th>Annualized prevalence (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>63</td>
<td>4,488,306</td>
<td>126,025,383</td>
<td>3.56%</td>
<td>1,769</td>
<td>1.40</td>
</tr>
<tr>
<td>2011</td>
<td>69</td>
<td>4,759,037</td>
<td>126,252,347</td>
<td>3.77%</td>
<td>1,830</td>
<td>1.45</td>
</tr>
<tr>
<td>2012</td>
<td>73</td>
<td>4,552,080</td>
<td>126,452,548</td>
<td>3.60%</td>
<td>2,028</td>
<td>1.60</td>
</tr>
<tr>
<td>AVG</td>
<td>68</td>
<td>4,599,808</td>
<td>126,243,426</td>
<td>3.64%</td>
<td><strong>1,868</strong></td>
<td><strong>1.48</strong></td>
</tr>
</tbody>
</table>

*corrected for US population

Manuscript in preparation
Aim 1: Clinical Database

Based on our experience to date and the calculated prevalence data, we propose that for the current grant cycle: reasonable enrollment target is 50 new participants per year.

Therefore, by 2020, we project that the Database will include 300 patients.

Aim 1: Rationale / Approach

Aim 1: Expand our knowledge and understanding of HRFD clinical disease, pathology and genetics.

Rationale:

Clinical Database: The observational cohort established in the HRFD Clinical Database will allow analyses of perinatal morbidity and mortality; characterization of the clinical disease course; correlations between renal and extra-renal disease progression; and analysis of long-term survivors.

Tissue Resource: The study of recessive HRFD requires adequate supplies of high quality samples from diseased kidneys, livers and other phenotypically affected tissues -- the supply of these human tissues is currently very limited.
Aim 1: Tissue Resource

- IRB-approved protocol to establish a state-of-the-art tissue resource that collects HRFD tissues from consented patients throughout North America.
  - Standardized procedure for tissue collection and mailers with all required reagents sent to institutions collecting tissues.
  - Informed consent obtained by staff at CNMC.
  - Tissues banked in the UAB Tissue Collection Facility with all samples assigned a unique identifier and subjected to quality control examination.

- **Current status:**
  - 14 patients have donated tissue and provided consent, allowing tissue to be added to the Core A Tissue Resource.
  - Established a collaboration with CNMC pathology to collect normal kidney and liver specimens from autopsies of children < 1 year of age.

Aim 2: Rationale / Approach

Aim 2: Identify genetic mutations in ARPKD and other HRFD patients and assess the pathogenicity of sequence variants.

**Rationale:**

- The HRFD comprise at least 10 different disorders with defects in > 150 genes.
- While clinically distinct, several of the HRFD share many of the same causative genes.
- There is wide variability within each disorder, even among affected siblings.
- Therefore, single-gene analysis for HRFD is inefficient and prohibitively expensive. Next generation sequencing (NGS) technologies allow high-throughput sequence analysis of all the protein-coding regions of genomic DNA (i.e. the whole exome) with mutation detection for known HRFD genes, as well as the identification of new HRFD-associated genes.
Established the HRFD DNA Biobank within the CTSI-CN Biorepository

- The CTSI-CN Biorepository provides support for investigators in establishing project-specific biobanking resources under strict Standard Operating Procedures.
- Under informed consent from patients and their parents (patient/parent trios), Core A:
  - Sends a blood collection kit to a family-identified physician
  - Arranges for return of the blood samples to CNMC for DNA extraction and storage in the HRFD DNA Biobank using a unique identifier.
- To date, DNA samples collected for 15 patients, of which 6 are patient-parent trios.

Duke Task Force for Neonatal Genomics: Genome / Exome Sequencing and Return of Results (Collaboration with Dr. Nicholas Katsanis)

- Core A provides detailed phenotypes of HRFD patients and DNAs from the HRFD DNA Biobank.
- Whole-exome sequencing (WES) will be performed on 25 patient/parent trios from Core A per year.
  - To date, 6 patient parent trios are in the process of recruitment / analysis by Duke
  - The primary goal is to identify alleles of obvious pathogenic potential and have these confirmed by Sanger sequencing in a CLIA-certified laboratory.

Aim 3: Rationale / Approach

Aim 3: Establish an annotated, updated, multi-media resource to provide information regarding the diagnosis, management, family impact, and genetics of hepato-renal fibrocystic disease spectrum of disorders, particularly ARPKD.

Rationale:

- For rare diseases, the web as a resource for reliable health information is fraught by limited evidence-based content that is not always pertinent to a family’s or physician’s needs.
- In addition, there is limited information to guide families and their physicians about what it means to participate in clinical research studies.
Aim 3: Progress

ARPKD CLINICAL CARE CONSENSUS CONFERENCE, MAY 07-08, 2013:


FUNDING SUPPORT: PKD Foundation.

Core A: Future Directions

Aim 1:
- Expand recruitment to Core A Clinical Database; target: 50 patients per year.
- Continue tissue sample collection (kidney and liver) and banking with priority for HRFD patients who have functioning kidneys at the time of surgical kidney resection or death (autopsy); target: tissue samples from 10 HRFD patients per year.
- Collect normal kidney and liver samples for autopsies of children <1 year of age; target: tissue samples from 5 autopsies per year.

Aim 2:
- Expand HRFD DNA Biobank.
- Perform whole-exome sequencing (WES) on 25 patient/parent trios per year.

Aim 3:
- Provide an annotated, regularly updated, multi-media resource regarding the diagnosis, management, family impact, and genetics of HRFD, as well as a guide and links to participating in clinical research studies/trials (Core A LMS: CystKids).
DISCUSSION

Core A: Access to data / resources

Aim 1:
- Clinical Database:
  - Request to Core A for cohorts of patients with specific disease features
  - Core A will generate a REDCap report
- Tissue Resource:
  - Request to Core A will require: SAC review (resource distribution); IRB approval (if both clinical data and tissue sample requested)

Aim 2:
- DNA Biobank:
  - Request to Core A will require: SAC review (resource distribution); IRB approval (if both clinical data and DNA samples requested)
- Genetic Data:
  - Core A will generate a REDCap report