Overview of CAKUT

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1st IPNA-EDTA Master for Junior Classes
Congenital anomalies of the kidney and urinary tract

- Rising detection rate of anomalies of the kidney and urinary tract due to routinely performed pre- and postnatal ultrasound examinations

- Abnormal ultrasound results in 0.2-0.8% of all pregnancies
CAKUT: congenital anomalies of kidney and urinary tract

A congenital nephropathies

1.1 kidney agenesis/hypoplasia
1.2 hypoplasia with dysplasia
1.3 oligomeganephronia

2.1 dysplasia without cysts
2.2 dysplasia with cysts
2.3 multicystic dysplasia
2.4 obstructive forms

B congenital uropathies

1.1 ureteropelvic junction stenosis

2.1 primary non-refluxive megaureter (distal ureter obstruction)
2.2 primary refluxive megaureter
2.3 secondary megaureter with infravesical obstruction (urethral valve, meatus stenosis)

3.1 ureter ectopia with/without doubling malformations of the upper tract
<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (per 1000 live births)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesicoureteral reflux</td>
<td>Frequent, up to 10% postnatally</td>
</tr>
<tr>
<td>Double kidney/ureter</td>
<td>8.0</td>
</tr>
<tr>
<td>Obstruction of kidney or ureter</td>
<td>1.0</td>
</tr>
<tr>
<td>Kidney agenesis/dysplasia</td>
<td>0.8</td>
</tr>
<tr>
<td>Obstruction of bladder or urethra</td>
<td>0.2</td>
</tr>
<tr>
<td>Horseshoe kidney</td>
<td>0.15</td>
</tr>
<tr>
<td>Bladder extrophy</td>
<td>0.06</td>
</tr>
<tr>
<td>Cystic kidneys</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Beetz et al. 1998
Bladder outflow obstruction, kidney agenesis, ARPKD

Oligo/Anhydramnios

Potter facies
Joint contractions
Pulmonary hypoplasia

Survival depends strongly on onset of oligohydramnios

Klaassen et al., *Nephrol Dial Transplant* 2007
Typical clinical signs:

Febrile urinary tract infection
Urosepsis
Back pain, abdominal pain
Abdominal tumor
Hypertension
Vomitting
Non-invasive diagnosis by ultrasound
Kidney obstruction
Kidney dysplasia without cysts
Multicystic dysplastic kidney
Kidney dysplasia is a frequent diagnosis in children with chronic renal insufficiency.
CAKUT with renal insufficiency
Diagnosis of CAKUT in 70% of pediatric CNI patients (n=466)
Kidney survival in CAKUT phenotypes

Sanna-Cherchi et al., *Kidney Int* 2009
CAKUT: Specific aspects

- Frequently combined anomalies
- Uni- or bilateral
- Positive family history in many cases
- Frequently associated with extrarenal manifestations
- Frequently associated with syndromal disease
Early kidney development

Rat/Mouse

- ureteral budding
- Wolffian Duct
- Condensed Mesenchyme
- growth of the ureter & vessels
- 11 d
- 21 d
- disappearance of 'septa'
- Birth

Human

- 35 d
- 40 wk
Molecular mechanism of the regulation of budding

Miyazaki et al., JCI 2000
Ectopic Budding of the Ureter

Kidney dysplasia
Genetic aspects of CAKUT

A Familial clustering observed in ~ 10% of patients
Genetic aspects of CAKUT

A  Familial clustering observed in ~ 10% of patients

B  Monogenic gene *knock-out* of developmental genes in mice results in a phenotype highly reminiscent of human CAKUT

- kidney agenesis
- kidney hypoplasia/dysplasia
- double kidneys
- ureteral anomalies/hydronephrosis
### Knock-out mice with CAKUT phenotype

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Renal phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wt1</strong></td>
<td>transcription factor</td>
<td>bilateral agenesis</td>
</tr>
<tr>
<td><strong>Eya-1</strong></td>
<td>transcription factor</td>
<td>+/-: bilateral aplasia, +/-: hypoplasia</td>
</tr>
<tr>
<td><strong>Lim1</strong></td>
<td>transcription factor</td>
<td>bilateral agenesis</td>
</tr>
<tr>
<td><strong>Foxc1/2</strong></td>
<td>transcription factor</td>
<td>double kidneys, hydroureter, hypopl.</td>
</tr>
<tr>
<td><strong>Pax2</strong></td>
<td>transcription factor</td>
<td>+/-: bilateral agenesis, +/-: hypoplasia</td>
</tr>
<tr>
<td><strong>Bmp-4</strong></td>
<td>secreted signal molecule</td>
<td>+/-: hypo/dysplasia, hydronephrosis</td>
</tr>
<tr>
<td><strong>Bmp-5</strong></td>
<td>secreted signal molecule</td>
<td>hydronephrosis</td>
</tr>
<tr>
<td><strong>Bmp-7</strong></td>
<td>secreted signal molecule</td>
<td>dysplasia</td>
</tr>
<tr>
<td><strong>Fgf-7</strong></td>
<td>secreted signal molecule</td>
<td>+/-: hypoplasia</td>
</tr>
<tr>
<td><strong>Wnt4</strong></td>
<td>secreted signal molecule</td>
<td>dysplasia</td>
</tr>
<tr>
<td><strong>Gdnf</strong></td>
<td>secreted signal molecule</td>
<td>+/-: unilat. agenesis, bilat. dysplasia</td>
</tr>
<tr>
<td><strong>Ret</strong></td>
<td>receptor tyrosine kinase</td>
<td>+/-: bilat agenesis</td>
</tr>
<tr>
<td><strong>Agtr2</strong></td>
<td>angiotensin receptor</td>
<td>unilat aplasia/dysplasia</td>
</tr>
<tr>
<td><strong>Adams-1</strong></td>
<td>metalloproteinase/disintegrin</td>
<td>hypo/dysplasia, hydronephrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+/-: proximal ureter stenosis</td>
</tr>
</tbody>
</table>
CAKUT-phenotype due to combined deletion of *Foxc1/Foxc2*

Homozygot Foxc1-/-  Compound-heterozygot Foxc1-/-Foxc2-
Nephrogenic duct (ND)-specific knock-out of *Gata3*

![Control vs. Gata3<sup>ND/-/-</sup> comparison](image)

CAKUT phenotype in 53% of $Bmp4^{+/-}$ pups

60% kidney hypoplasia/dysplasia
32% UVJ/hydronephrosis
8% bifid ureter/double kidneys

Miyazaki et al., JCI 2000
Mutation analysis in candidate genes *BMP4* and SIX2

- 250 pediatric patients from Europe with renal hypodysplasia (RHD)
  
- 150 controls (race-matched)
Results of mutational analysis in **BMP4** and **SIX2**

<table>
<thead>
<tr>
<th>Index Patient</th>
<th>Herkunft</th>
<th>SIX2 Mutation (Nukleotide)</th>
<th>SIX2 Mutation (Aminosäuren)</th>
<th>Ultraschallbefund</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Polen</td>
<td>402 C-&gt;T</td>
<td>Leu43Phe (het)</td>
<td>DYS(l)/VUR(r)</td>
</tr>
<tr>
<td>P2</td>
<td>Polen</td>
<td>997 C-&gt;T</td>
<td>Pro241Leu (het)</td>
<td>CYS-DYS(r,l)/VUR(r,l)</td>
</tr>
<tr>
<td>P3</td>
<td>Deutschland</td>
<td>997 C-&gt;T</td>
<td>Pro241Leu (het)</td>
<td>CYS-DYS(r,l)</td>
</tr>
<tr>
<td>P4</td>
<td>Italien</td>
<td>997 C-&gt;T</td>
<td>Pro241Leu (het)</td>
<td>HYPO(r)/VUR(r)</td>
</tr>
<tr>
<td>P5</td>
<td>Portugal</td>
<td>1100-1101 GG-&gt;AA</td>
<td>Asp276Asn (het)</td>
<td>CYS-DYS(r,l)/ HYPO(r)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMP4 m Mutation (Nukleotide)</th>
<th>BMP4 Mutation (Aminosäuren)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P6</td>
<td>Polen</td>
<td>272 C-&gt;G</td>
</tr>
<tr>
<td>P7</td>
<td>Deutschland</td>
<td>272 C-&gt;G</td>
</tr>
<tr>
<td>P8</td>
<td>Turkei</td>
<td>347 C-&gt;G</td>
</tr>
<tr>
<td>P9</td>
<td>Turkei</td>
<td>450 C-&gt;G</td>
</tr>
<tr>
<td>P10</td>
<td>Turkei</td>
<td>450 C-&gt;G</td>
</tr>
</tbody>
</table>

**a** Patients n= 250 ; controls n= 150

**b** DYS=dysplasia, VUR = vesico-ureteral reflux, CYS-DYS=cystic dysplasia, HYPO=hypoplasia, AGEN=agenesis, l=left, r=right
Morpholino knock down of six2.1 and bmp4 is associated with disruption of normal pronephros development

Weber/Taylor et al., JASN 2006
Some genes have been assigned to specific developmental steps.

Ruf et al., *PNAS* 2004
Jenkins et al., *JASN* 2005
Jenkins et al., *NDT* 2006
Wu et al., *AJHG* 2007
Weber/Taylor et al., *JASN* 2008
Weber et al., *AJHG* 2011
Saisawat et al., *Kidney Int* 2013
Schild et al., *NDT* 2013
Vivante et al., *JASN* 2013
Sanna-Cherchi et al., *NEJM* 2013
Shukrun et al., *PLoS One* 2014
Hwang et al., *Ped Nephrol* 2014
Extrarenal malformations/symptoms in 28%
Results of the ESCAPE study

Mutational analysis in 99 patients CAKUT:

PAX2:

EYA1:

SIX1:

SALL1:

HNF1B:

Severe prenatal renal anomalies associated with mutations in \textit{HNF1B} or \textit{PAX2}:

Madariaga et al., \textit{CJASN} March 2013

- Analysis of \textit{HNF1B} and \textit{PAX2} in 103 fetuses (91 families) with termination of pregnancy due to severe congenital anomalies of the kidney
HNF-1β

- Tissue specific transcription factor
- Expressed in pancreas, liver and kidney
- In the kidney, expression was observed in the developing ureter and tubular system
- First mutations in the human $HNF1B$ gene were identified in patients with MODY5, then in Renal cysts and diabetes (RCAD) syndrome

Source: Journal of Molecular Endocrinology (2001) 27, 11–29
Renal cyst and diabetes syndrome RCAD

- Diabetes mellitus (MODY5)
- Pancreatic atrophy/exocrine dysfunction
- Kidney cysts – cystic dysplasia
- Genital anomalies (uterus bicornis)
- Elevated liver enzymes
- Hyperuricemia
- Hypomagnesemia

HNF1-β specifically regulates the transcription of the γ-subunit of the Na+/K+-ATPase FXYD2 in the DCT

Adalat et al., JASN 2009
HNF1B mutations were identified in 25/80 patients with predominant cystic RHD (30%)
High prevalence of *HNF1B* mutations in bilateral anomalies

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>TCF2 Molecular Abnormality</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>80</td>
<td>25</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td></td>
<td>0.2 (0 to 14)</td>
<td>0.1 (0 to 12)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>53/27</td>
<td>17/8</td>
<td>36/19</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>multicystic dysplasia</td>
<td>32</td>
<td>8/25 (32%)</td>
<td>24/55 (44%)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cysts</td>
<td>57</td>
<td>21/25 (84%)</td>
<td>36/55 (65%)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cortical cysts</td>
<td>51</td>
<td>21/25 (84%)</td>
<td>30/55 (55%)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bilateral cortical cysts</td>
<td>22</td>
<td>16/25 (64%)</td>
<td>6/55 (11%)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>microcysts (&lt;10 mm)</td>
<td>40</td>
<td>21/25 (84%)</td>
<td>19/55 (35%)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperechogenicity/poor</td>
<td>64</td>
<td>22/25 (88%)</td>
<td>42/55 (76%)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticomedullary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>differentiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bilateral hyperechogenicity</td>
<td>39</td>
<td>20/25 (80%)</td>
<td>19/55 (35%)</td>
<td>&lt;0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypoplasia</td>
<td>60</td>
<td>15/25 (60%)</td>
<td>45/55 (82%)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bilateral hypoplasia</td>
<td>25</td>
<td>10/25 (40%)</td>
<td>15/55 (27%)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dilation</td>
<td>23</td>
<td>8/25 (32%)</td>
<td>15/55 (27%)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bilateral abnormalities</td>
<td>54</td>
<td>25/25 (100%)</td>
<td>25/55 (45%)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ulinski et al., JASN 2006
**HNF1B**

- 6/24 patients of the total cohort with cystic lesions have a mutation in *HNF1B* (25%)

- in contrast: only 2/76 patients without cystic lesions (3%)
HNF1B analysis in 104 CAKUT patients

- 81 patients with renal hypodysplasia
- 39 patients with kidney dysplasia with cysts
- 9 patients with \textit{HNF1B} mutation: all dysplasia with cysts (8 bilateral)
Anomalies of the \textit{TCF2} Gene Are the Main Cause of Fetal Bilateral Hyperechogenic Kidneys

Stéphane Decramer,*‖ Olivier Parant,† Sandrine Beaufils,‡ Séverine Clauin,‡ Cécile Guillou,‖ Sylvie Kessler,† Jacqueline Aziza,§ Flavio Bandin,*‖ Joost P. Schanstra,* and Christine Bellanné-Chantelot‖


62 fetuses with bilateral hyperechogenic kidneys

- 18/62 (29%) → positive \textit{HNF1B (TCF2)} mutation analysis  
  → 15/18 whole gene deletions(83%)

- 34/62 → ARPKD/ ADPKD/ tubulopathy
18 fetuses with *HNF1B* mutation:

- 11/18 (61%) → prenatal cysts (unilateral in 8 pat, bilateral in 3 pat)
- 17/18 (94%) → postnatal cysts within the first year
- 15/18 (83%) → progression to bilateral cysts
HNF1B nephropathy: autosomal dominant mode of inheritance
Phenotypic variability in *HNF1B* mutation carriers

Renal cysts, CRI
uterus bicornis

Vester et al., *Ped Nephrol* 2010
Phenotypic variability in *HNF1B* mutation carriers

Clinical diagnosis in mother and girl: ADPKD – with early manifestation, resembling ARPKD in renal ultrasound in the girl

Mutational analysis: PKD1 negative, PKD2 negative, HNF1B positive: heterozygous del Ex1-9

Kidney cysts

3 wks old, oligohydramnios hypertension, large kidneys with small cysts
Incomplete penetrance, oligogenic inheritance

• Mutations in most CAKUT associated genes are inherited in an autosomal dominant manner (e.g. *HNF1B, PAX2, EYA1, RET, DSTYK*)

• Penetrance is frequently incomplete

• **Exception:**

  - autosomal recessive inheritance of mutations in *ITGA8* in fetuses with bilateral kidney agenesis, anhydramnios, Potter Sequenz

    Humbert et al., *AJHG* (2014)

  - autosomal recessive inheritance of mutations in the renin angiotensin system (RAS)

    Gribouval et al., *Nat Genet* (2005)
Renal tubular dysgenesis (RTD): Mutations in components of the renin angiotensin system

<table>
<thead>
<tr>
<th>AR</th>
<th>1q32</th>
<th>REN</th>
<th>Renin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>17q23</td>
<td>ACE</td>
<td>Angiotensin-Converting Enzyme</td>
</tr>
<tr>
<td>AR</td>
<td>1q42-q43</td>
<td>AGT</td>
<td>Angiotensin I</td>
</tr>
<tr>
<td>AR</td>
<td>3q21-q25</td>
<td>AGTR1</td>
<td>Angiotensin II Receptor, Typ I</td>
</tr>
</tbody>
</table>

Phenotype: severe developmental defect of proximal tubules, anuria, ROH

36. wks of gestation

Gribouval et al., Nat Genet 2005; Gribouval et al., Hum Mutat 2012; Plazanet et al., Ped Nephrol 2014
Renal tubular dysgenesis (RTD): Mutations in components of the renin angiotensin system

**CAVE**

Correlation between fetal nephropathy and maternal treatment with ACE inhibitors or AT2-receptor blocker!

*(in utero-exposition  →  secondary RTD)*

Gribouval et al., *Nat Genet* 2005; Gribouval et al., *Hum Mutat* 2012; Plazanet et al., *Ped Nephrol* 2014
The phenotypic spectrum of CAKUT is broad. The renal prognosis is largely dependent on the phenotype of anomaly.

Family history is positive in about 10-15%. Mouse model studies support a genetic contribution.

Mutations in \textit{PAX2} and \textit{HNF1B} seem to be a relevant cause of CAKUT in a subset of patients.

High detection rate of \textit{HNF1B} mutations in bilateral cystic dysplasia (23-25\%) and hyperechogenic large kidneys (29\%) in antenatal ultrasound.

Renal function and progression of renal insufficiency can be very variable, also within the same family.

Family analysis and genetic counseling can be important in CAKUT patients (frequently autosomal dominant disease, extrarenal symptoms).
Establishment of ESPN Working Groups

- Transplantation
- Dialysis
- CKD-MBD
- CAKUT/UTI/Bladder dysfunction
- Inherited renal disorders
- Nephrotic syndrome
- Immune-mediated disorders

CME I of the ESPN WG CAKUT: Thu Sept 18th, 9-10:30, Infante Hall

Meeting of the ESPN WG CAKUT: Thu Sept 18th, 16-17:15, Arquivo Hall

http://www.esp-nephrology.org