Hereditary tubulo-interstitial nephritis

Guillaume Bollée
Service de Néphrologie adulte, Hôpital Necker, Paris
Hereditary TIN in chronic kidney diseases epidemiology

- Annual incidence of ESRD in France: 137 per million
- Overall chronic TIN estimated to account for 3.7%
- Undetermined cause of renal disease: 12.6%
- «Hypertension» and «vascular»: 24.3%

Registre REIN 2006

- Hereditary TIN considered as rare diseases... but likely to be underrecognized

- *UMOD* mutation recently identified in 8/271 patients (3%) with ESRD of unknown cause

Amoroso, ASN congress (abstract) 2008
MCKD
FJHN
Adult NPH

UMOD
HNF1B
MCKD1 locus
NPHP1, NPHP3,...
others
MCKD
FJHN
Adult NPH
...

UMOD
HNF1B
MCKD1 locus
NPHP1, NPHP3,...
others
• *UMOD* gene encoding uromodulin is located to 16p12 (*MCKD2* locus)
• 80% of mutations affect exon 4 which contains a highly cysteine rich sequence and three Calcium-binding EGF domains
• Mutations are likely to cause misfolding and structural destabilization
Mutations found in 22 families:
- 18 (81.8%) in exon 4
- 1 (4.5%) in exon 5
- 3 (13.7%) in exon 8
UMOD mutation

- Autosomal dominant inheritance
- Hyperuricemia and gout
- Chronic renal failure
- Renal cysts

- « Classic syndromes »:
  - FJHN
  - MCKD
  - (rarely GCKD)

- « UMOD associated kidney disease »

- UMOD mutation found in 40% of FJHN/MCKD families

Vyleť’al, Kidney Int, 2006
Wolf, Kidney Int, 2003
Hart, J Med Genet, 2002
Hyperuricemia and gout

- Hyperuricemia occurs in 80% and « early » gout in 45% of patients

  Bleyer, Kidney Int, 2003
  Dahan, JASN 2003

- Age at onset of gout:
  - before 40 years in almost all patients with hyperuricemia
  - frequently during childhood or adolescence

- Hyperuricemia is very early and can be detected in some patients in the first months of life
Analysis of 114 patients with « UMOD » phenotype

<table>
<thead>
<tr>
<th></th>
<th>UMOD mutation</th>
<th>No mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients / families</td>
<td>38 / 21</td>
<td>76 / 65</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.5 (19.5-42.7)</td>
<td>43 (31-53.2)</td>
</tr>
<tr>
<td>Familial history of renal disease (%)</td>
<td>35 (92.1%)</td>
<td>60 (78.9%)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td>43 (26-54)</td>
<td>47 (36-61)</td>
</tr>
<tr>
<td>UA level and renal excretion :</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Uricemia (µmol/l)</td>
<td>519 (494-562) (n=29)</td>
<td>450 (352-550) (n=53)</td>
</tr>
<tr>
<td>- Hyperuricemia (%)</td>
<td>37 (97.4%)</td>
<td>45 (59.3%)</td>
</tr>
<tr>
<td>History of gout (%)</td>
<td>23 (60.5%)</td>
<td>43 (56.6%)</td>
</tr>
<tr>
<td>Either gout or preemptive allopurinol therapy</td>
<td>32 (84.2%)</td>
<td>44 (57.9%)</td>
</tr>
</tbody>
</table>
Age at first gout episode in patients with « FJHN » phenotype

Lower median age at first episode in *UMOD* patients: 22 (16.5-34) vs 30 (22-42) years (*p*<0.05)
Uric acid FE depends on renal function

- Hyperuricemia is related to renal underexcretion with decreased fractional excretion of uric acid
- Renal function must be taken into account for interpreting uric acid fractional excretion
- Normal >6% when GFR is normal

Calabrese, Q J Med, 1990
Underexcretion of uric acid is common in patients with gout.
Low uric acid EF may also be observed in healthy controls.

Low uric acid EF lacks specificity for diagnosis of *UMOD* related disease.

Low uric acid FE was observed in 16/19 patients (84.2%) with *UMOD* mutation and in 23/33 (71.8%) patients without mutation (NS).

*Adapted from Calabrese, Q J Med, 1990*
Chronic renal failure in patients with *UMOD* mutation

- Unspecific features of chronic tubulo-interstitial nephritis

- High inter and intrafamilial variability in the severity:
  - decreased renal function may begin as early as 5 to 10 years
  - some patients older than 50 years keep normal renal function

- Evolution to ESRD:
  - ESRD usually occurs around 40 to 60 years
  - exceptionnally before 20 years
  - later than 70 years in some patients

*Rezende Lima, Kidney Int, 2004*
*Dahan, JASN, 2003*
*Bleyer, Pediatr Nephrol 2005*
*Wolf, Kidney Int, 2007*
Renal function evolution: interfamilial variability

Renal function evolution from diagnosis to last follow-up in 11 patients from 11 families with *UMOD* mutation.
Age at ESRD: intrafamilial variability

Vylet’al, Kidney Int, 2006
Dahan, JASN, 2003
Wolf, Kidney Int, 2003
Renal biopsy findings

- Tubulo-interstitial nephritis with minimal or moderate inflammation
- Focal intracytoplasmic inclusions in tubular cells may be observed
- EM demonstrates material accumulation in ER

Nasr, Kidney Int, 2008
• UMOD mutation is associated with:
  - loss of normal regular apical expression of uromodulin in TAL
  - diffuse intracellular staining for uromodulin in a subset of tubules which are sometimes cystic

Dahan, JASN, 2003
Rampoldi, Hum Mol Genet, 2003
Renal cysts: analysis of 38 patients (21 families)

Renal cysts: 10/38 (26.3%)
  - Bilateral: 3/38 (7.9%)
  - Unilateral: 7/38 (18.4%)

- Cortical: 8/38 (21%)
- Cortico-medullary: 1/38 (2.6%)
- Undetermined: 1/38 (2.6%)
Renal cysts

• Medullary cysts were thought to be a hallmark of *UMOD* associated kidney disease (called MCKD2)

• But renal cysts are observed in only 30% of patients with *UMOD* mutation...

• ... and:
  
  – exact size, number and topography of cysts are not well detailed in many publications
  
  – only 30% of patients with cysts have typical MCKD whereas the pattern is highly variable in others

*Bleyer, Kidney Int, 2003*
*Rampoldi, Hum Mol Gen, 2003*
*Rezende-Lima, Kidney Int, 2004*
*Vylet’al, Kidney Int, 2006*
Urinary level of uromodulin: a diagnostic tool?

Bleyer, Kidney Int, 2004
Dahan, JASN, 2003
Rampoldi, Hum Mol Genet, 2003
Jennings, JASN, 2007
MCKD

FJHN

Adult NPH

...
Renal disease secondary to *HNF1B* mutation

- *HNF1B* gene (17q22) encodes HNF1\(\downarrow\), a transcription factor predominantly expressed by hepatic, renal and pancreatic epithelial cells
- HNF1\(\downarrow\) expression in kidney plays a key role in nephrogenesis
- Disease secondary to *HNF1B* mutation is characterized by autosomal dominant transmission and highly variable phenotype

*References*

Ullinski, *JASN* 2006
Decramer, *JASN* 2007
HNF1B mutation

- Diabetes MODY5
  - frequent but may be absent at diagnosis
- Renal disease
  - cysts
  - multicycstic dysplasia
  - hypoplasia
  - pelvicaliceal dilatation
  - GCKD
  - renal failure
  - « atypical FJHN »
  - unilateral or bilateral
- Others
  - genital abnormalities
  - abnormal liver function
  - others

Bingham, Kidney Int, 2003
Bellané-Chantelot, Ann Intern Med 2004
Ullinski, JASN 2006
<table>
<thead>
<tr>
<th>Age at first consult</th>
<th>Initial eGFR*</th>
<th>Renal cysts</th>
<th>Diabetes</th>
<th>Others signs</th>
<th>Age at last follow-up</th>
<th>Last eGFR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>50</td>
<td>38</td>
<td>bilateral, multiple</td>
<td>Yes (46 y)</td>
<td>gout</td>
<td>51 y</td>
</tr>
<tr>
<td>Patient 2</td>
<td>70</td>
<td>33</td>
<td>unilateral, multiple (7-15mm)</td>
<td>no</td>
<td>gout</td>
<td>30 y</td>
</tr>
<tr>
<td>Patient 3</td>
<td>52</td>
<td>40</td>
<td>bilateral, multiple, medullary</td>
<td>no</td>
<td>-</td>
<td>54 y</td>
</tr>
<tr>
<td>Patient 4</td>
<td>34</td>
<td>62</td>
<td>bilateral, multiple</td>
<td>no</td>
<td>-</td>
<td>36 y</td>
</tr>
<tr>
<td>Patient 5</td>
<td>27</td>
<td>50</td>
<td>bilateral, multiple, medullary (&lt;10mm)</td>
<td>no</td>
<td>-</td>
<td>30 y</td>
</tr>
<tr>
<td>Patient 6</td>
<td>31</td>
<td>31</td>
<td>no cysts, pelvicaliceal dilatation</td>
<td>Yes (38 y)</td>
<td>gout</td>
<td>58 y</td>
</tr>
</tbody>
</table>

(*: ml/min/1.73m²)

6 patients from 4 families with «UMOD like» phenotype
UMOD
HNF1B
MCKD1 locus
NPHP1, NPHP3,...
others

MCKD
FJHN
Adult NPH
...
MCKD1 disease

- A subset of families with autosomal dominant renal disease identical to those secondary to *UMOD* mutation (MCKD2) have been linked to *MCKD1* locus (1q21)

  *Christodoulou, Hum Mol Genet 1998*

- Despite mutation analysis in many candidate genes, the responsible gene causing MCKD1 remains unknown

  *Wolf, Hum Genet 2006*

  *Stavrou, Kidney Int, 2002*
Hallmarks of MCKD1 are very close to MCKD2

• Unspecific features of chronic tubulo-interstitial nephritis

• Progressive renal failure leading to ESRD:
  – ESRD usually occurs around 40 to 50 years
  – exceptionally before 20 years
  – later than 60 years in some patients

• Hyperuricemia (50%) and gout (15%) are common

• Renal cysts have been reported in 40% of patients but number, size and topography are variable and typical MCKD pattern is rare

Cohn, Am J Hum Genet 2000
Stavrou, Kidney Int, 2002
Kiser, Am J Kidney Dis 2004
RENIN mutation : a new cause of hereditary TIN?

• One family with:
  – autosomal dominant TIN (ESRD >50 years in 3/3 patients)
  – mild hyperuricemia (8/15), anemia (8/15) and hyperkalemia
  – small kidneys but no cysts
  – reduced urinary uromodulin excretion and expression on renal biopsy

• Initial study suggested linkage to a new locus on 1q41

• Deletion found in the preprorenin signal peptide (L16REN) (1q32)

Hodanova, Kidney Int, 2005
Zivna, ASHG congress, 2008
MCKD
FJHN
Adult NPH
...

UMOD
HNF1B
MCKD1 locus
NPHP1, NPHP3,...
others
Nephronophthisis

- Autosomal recessive nephropathy mainly affecting children
- Median age at ESRD: 13 years
- Ten genes (*NPHP1-10*) identified
- Most common mutation found is a large deletion in *NPHP1*
- Extra renal disorders may be associated (15%):
  - retinal dystrophy mainly
  - liver fibrosis
  - cerebellar vermis aplasia, brain malformation,…

*Hildebrandt, JASN 2009*
Nephronophthisis: also an adult disease

- Late onset of ESRD was reported in 24 patients in a large pedigree with NPH secondary to *NPHP3* mutation
- ESRD occurred at a median age of 19 (16-25) years

*Omran, Am J Hum Genet 2000*
### Table: Renal Failure Details

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at first consult</th>
<th>eGFR*</th>
<th>Renal cysts</th>
<th>Extra-renal involvement</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>25</td>
<td>16</td>
<td>no</td>
<td>retinal dystrophy, neurological bladder</td>
<td>ESRD at 25y</td>
</tr>
<tr>
<td>Patient 2</td>
<td>22</td>
<td>12</td>
<td>1 cortical (10mm)</td>
<td>no</td>
<td>ESRD at 22y</td>
</tr>
<tr>
<td>Patient 3</td>
<td>22</td>
<td>25</td>
<td>1 cortical (10mm)</td>
<td>no</td>
<td>ESRD at 24y</td>
</tr>
<tr>
<td>Patient 4</td>
<td>19</td>
<td>29</td>
<td>no</td>
<td>retinal dystrophy</td>
<td>eGFR* to 16 at 22y</td>
</tr>
<tr>
<td>Patient 5</td>
<td>23</td>
<td>33</td>
<td>2 unilateral cysts (6-16mm)</td>
<td>no</td>
<td>ESRD at 29y</td>
</tr>
</tbody>
</table>

(*: ml/min/1.73m2)

- We observed 5 patients from 4 families with chronic renal failure secondary to classic large deletion of *NPHP1*

*Bollée, Nephrol Dial Transplant 2006*
TIN
Study genealogic tree
Screen for extra-renal involvement:
- eye
- liver
- urogenital tract
- diabetes
Investigate related individuals

Autosomal recessive (+/- sporadic)
- renal failure < 30 y
- renal cysts +/-
- +/- : retinal dystrophy,…

NPHP1
NPHP3

Autosomal dominant
- gout / hyperuricemia < 40 y
- renal cysts +/-
- no other organ involvement
- uromodulin staining

UMOD
MCKD1
others?

- gout / hyperuricemia +/-
- renal cysts nearly constant
- +/- : diabetes, genital, liver involvement

HNF1B
Screening for *UMOD* mutation at Necker Hospital

128 families / 165 patients screened for *UMOD* mutation

*UMOD* mutation found:
19 families / 35 patients (14.8%)

No *UMOD* mutation found:
109 families / 130 patients (85.2%)
**HNF1B** mutations in patients with « **UMOD** phenotype »

128 families / 165 patients screened for **UMOD** mutation

- **UMOD** mutation found: 19 families / 35 patients (14.8%)
- No **UMOD** mutation found: 109 families / 130 patients (85.2%)

59 families / 61 patients screened for **HNF1B** mutation

- **HNF1B** mutation found: 4 families / 5 patients (6.8%)
- No **HNF1B** mutation found: 55 families / 56 patients (93.2%)
Remerciements

Service de Néphrologie, Hôpital Necker
Bertrand Knebelmann
Aurélie Hummel

Centre de génétique, Université Catholique de Louvain, Bruxelles
Karin Dahan
Yves Pirson

Service de Néphrologie, HEGP, Paris
Christian Jacquot

Service de Néphrologie, Hôpital Bichât, Paris
Florence Vende

Service de Génétique, CHU Bordeaux
Didier Lacombe

Laboratoire de génétique et INSERM U574, Hôpital Necker
Corinne Antignac
Vincent Morinière
Audrey Pawtowski

Laboratoire d’anatomopathologie, INSERM U845, Hôpital Necker
Laure Hélène Noël

Service de Néphrologie, CHU Limoges
Jean-Pierre Charmes

Service de Néphrologie, Hôpital de Dieppe
Catherine Bessin

Service de Néphrologie, Hôpital St Louis, Paris
Marie-Noëlle Peraldi

Service de Néphrologie, Hôpital de Valenciennes
Philippe Vanhille

… and all clinicians and patients participating to our research