Hyalinose segmentaire et focale
Quand rechercher une cause génétique chez l’adulte ?

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Service de Néphrologie
Hôpital Necker Enfants-Malades
Should we look for genetic cause?

Annual incidence of NS
1-3/100,000 in children
0.3/100,000 in adults

80-90% of children are steroid sensitive (≠ genetic cause)

Santin, cJASN. 2011
Should we look for genetic cause?

STEROIDS

SRNS
190 patients

NPHS2 M°
26%

29 patients

Remission
0%

SSNS
124 patients

NPHS2 M°
0%

Immuno suppressive treatment

Ruf, JASN. 2004
Should we look for genetic cause?

SRNS/CNS 91 patients

- Genetic M°: 52%
- No M°: 48%

Remission

- Genetic M°: 0%
- No M°: 68%

Genetic diagnosis can limit drug prescription

Buscher, cJASN, 2010
Should we look for genetic cause?

Genetic diagnostic can help pronosticate renal outcome

Pejorative long term prognosis
ESRD : 71% versus 29%

Low recurrence after kidney transplantation
3-8% versus 20-35%

Buscher, cJASN, 2010
Should we look for genetic cause?

Genetic diagnostic can offer the possibility of genetic counselling

Presymptomatic diagnosis

Prenatal and preimplantation diagnosis
In 10 years, increasing knowledge of the molecular basis of NS has lightened the physiology of podocytes.
Should we look for genetic cause?

Additional genetic causes of NS need to be discovered. Could help define target for specific treatment strategies.
When?

Nephrotic syndrome → Renal Biopsy → Other diagnosis → Search for 2ndary causes of FSGS
When?

No familial history
Steroids
1 mg/kg/d
4 months

Genetic tests
In young adults
SRNS
SSNS
**What should we look for?**

<table>
<thead>
<tr>
<th>ONSET</th>
<th>RENAL HISTOLOGY</th>
<th>GENE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONGENITAL</strong></td>
<td>MGC/FSGS</td>
<td>NPHS1</td>
</tr>
<tr>
<td></td>
<td>Radial dilatation of PT</td>
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<td></td>
<td>DMS</td>
<td>NPHS2* → NPHS1</td>
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<tr>
<td></td>
<td></td>
<td>WT1^/PLCE1</td>
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<tr>
<td><strong>INFANTILE</strong></td>
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<tr>
<td><strong>JUVENILE AND ADULT</strong></td>
<td>FSGS</td>
<td>AR or Sporadic → NPHS2 (p.R229Q)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD → TRPC6/ACTN4/INF2?</td>
</tr>
</tbody>
</table>

*Benoit G, Pediatric Nephrol, 2010, Santin, cJASN. 2011*
What should we look for?

Family FG-FQ
R895C

Autosomal dominant transmission

INF2  TRPC6  α actinin4
Identification of a locus on chromosome 14q32 in autosomal dominant FSGS family (linkage analysis)
Sequencing multiple genes

Missense mutation in INF2
**INF2**: inverted formin 2  
Member of the formin family  
Role in **actin** nucleation, **polymerisation** and **depolymerisation**  
Podocyte actin **cytoskeleton desorganisation**
Major cause of autosomal dominant FSGS in 2 series:
11/93 families (Pollack group)
9/54 families (Antignac group)

≈ 15%

E Brown, Nat Genet. 2010, O Boyer, JASN 2011
<table>
<thead>
<tr>
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<th>Pollack</th>
<th>Antignac</th>
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<tbody>
<tr>
<td>Family Nb</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Patient Nb</td>
<td>72</td>
<td>28</td>
</tr>
<tr>
<td>Origins</td>
<td>North America 90%</td>
<td>Europe 78%</td>
</tr>
<tr>
<td>Pu onset: age (range)</td>
<td>(11-72)</td>
<td>20,5 years old (2-44)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>0%</td>
<td>15%</td>
</tr>
<tr>
<td>Renal biopsy</td>
<td>FSGS</td>
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</tr>
<tr>
<td>ESRD:</td>
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<td></td>
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<tr>
<td>%</td>
<td>53%</td>
<td>70%</td>
</tr>
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<td>Age (range)</td>
<td>(13-67)</td>
<td>36 (20-70)</td>
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</tbody>
</table>

E Brown, Nat Genet. 2010, O Boyer, JASN 2011
Highly variable phenotypes

- Microalb 66 yrs old
- PU 10 yrs old, ESRD 30 yrs old
- PU 24 yrs old

Rare neomutations
1/84 sporadic cases

O Boyer, JASN 2011
Large New Zealand family

Autosomal dominant transmission

High grade proteinuria
3rd or 4th decade
60% progress to ESRD
In 10 years

Winn M Science 2005
Non selective cation channel
Associates with nephrin podocin and CD2AP at the slit diaphragm

TRPC6 mutant enhances calcium influx in vitro
TRPC6

5 mutations in 5 /71 FSGS families

≈ 6 %
Incomplete penetrance

Reiser J Nature genet 2005
α Actinin 4

Autosomal transmission

Actin filament cross linking protein implicated in cytoskeleton dynamics

Kaplan nat genet 2000, Weins JASN 2005
Mild increase in proteinuria excretion in teenage years
Slowly progressive renal dysfunction
ESRD in some individuals

Highly variable phenotype

5 /141 FSGS families
<1% in sporadic cases

Kaplan nat genet 2000, Weins JASN 2005
What should we look for?

Autosomal recessive transmission

NPHS2
Podocine

- *NPHS2* gene identification by positional cloning
- almost exclusively expressed in **podocytes**

- interacts with nephrin and CD2AP

*Boute, Nat genet 2000*
Podocine

• Autosomal recessive disease

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<tr>
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<th>AR SRNS(^{a})</th>
<th>Sporadic SRNS(^{a})</th>
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<tr>
<td>No. of patients (families)</td>
<td>147 (81)</td>
<td>172 (172)</td>
</tr>
<tr>
<td>Two \textit{NPHS2} pathogenic mutations</td>
<td>62 (31)</td>
<td>11 (11)</td>
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<td>2 (1)</td>
<td>6 (6)</td>
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<td>One \textit{NPHS2} mutation + R229Q</td>
<td>6 (3)</td>
<td>1 (1)</td>
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<td>Mutation detection rate (in total)</td>
<td>\textbf{43%}</td>
<td>\textbf{10.5%}</td>
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<tr>
<td>Homozygous R229Q polymorphism</td>
<td>5 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Heterozygous R229Q polymorphism</td>
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<td>11 (11)</td>
</tr>
<tr>
<td>Variants in heterozygous state</td>
<td>3 (2)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>A242V polymorphism</td>
<td>2 (2)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Age at onset (all)</td>
<td>57.6 ± 6.8 months</td>
<td>102.9 ± 8.9 months</td>
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<td>(N = 107)</td>
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<td>(N = 169)</td>
</tr>
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<td>41.2 ± 5.9 months</td>
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<td>69.9 ± 11.5 months</td>
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<tr>
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### Podocine

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**FSGS**

Steroid resistance

ESRD before 10 years of age

very low incidence of post transplant recurrence

*Weber, Kidney Int 2004*
Mr S.
- 24 years old: proteinuria
- 29 years old: Creatinin 99 μmol/l, protU 1.4g/d
- Renal biopsy: FSGS
- Treatment: Steroids, cyclosporin, cyclophosphamid
- 35 years old: ESRD
- 36 years old: Transplantation, no recurrence

Genetic study: NPHS2 855-856del + R229Q variant
R229Q

- Common variant: 1.5% to 13%
- Conserved arginine mutated in glutamine on position 229

- Associated with microalbuminuria in Brazilian population
- Associated with increased FSGS risk in European populations (+20-40%)

- Decreased nephrin binding to the R229Q podocin in vitro

Pereira, KI 2004, Franceschini, genet med 2006   Tsukaguchi JCI 2002
**R229Q**

6/30 FSGS families with *autosomal recessive transmission compound* heterozygous R229Q/NPHS2 mutation

Age range at presentation: **9-36 years old**
Age at ESRD: **26-34 years old**

- **Necker cohort**: 546 patients with SRNS

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<tr>
<th>Clinical feature</th>
<th>(1) R229Q+1 mutation</th>
<th>(2) R229Q+R229Q</th>
<th>(3) 2 mutations</th>
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<tr>
<td><strong>Age at nephrotic syndrome onset</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cases with available information (total)</td>
<td>33 (36)</td>
<td>8 (8)</td>
<td>92 (104)</td>
</tr>
<tr>
<td>Mean ± s.d. (years)</td>
<td>17.3 ± 10.5</td>
<td>6.3 ± 3.8</td>
<td>3.0 ± 3.6</td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td>19 (0–39)</td>
<td>6.8 (0.6–10.7)</td>
<td>1.1 (0–13.7)</td>
</tr>
<tr>
<td><strong>Age at ESRD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases with available information (total)</td>
<td>14 (17)</td>
<td>5 (5)</td>
<td>51 (52)</td>
</tr>
<tr>
<td>Mean ± s.d. (years)</td>
<td>26.4 ± 10.1</td>
<td>10.8 ± 4.4</td>
<td>8.6 ± 5.2</td>
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<tr>
<td><strong>Median (range)</strong></td>
<td>27.9 (9.3–43.5)</td>
<td>11.2 (3.4–14.5)</td>
<td>8.0 (0–26)</td>
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*Tsukaguchi JCI 2002*

*Machuca KI 2008*
• Necker cohort:

- R229Q
- Age at presentation: 17.3 years old
- Age at ESRD: 26.4 years old

- Adult SRNS
  - N = 119
  - Sporadic cases
    - N = 81
    - R229Q/M°
      - N = 9
      - 11%
    - No M°
      - N = 72
  - Familial cases
    - N = 36
    - R229Q/M°
      - N = 6
      - 25%
    - No M°
      - N = 30

Machuca KI 2008
WT1

Transcription factor of the zinc finger family
Gene responsible for:

**Denys-Drash syndrome**
- Male pseudohermaphroditism
- Rapidly progressive glomerulopathy (DSM)
- Risk of nephroblastoma

**Frasier syndrome**
- Male pseudohermaphroditism
- Progressive glomerulopathy
- Risk of gonadoblastoma
7% of sporadic SRNS
3 female patients: isolated FSGS

WT1

16 yrs, Prot 1.5 g/j, Alb 44 g/l, Normal renal function

Rich family history
I1, II1 and II2:
- glomerulopathy
- ESRD (44, 46, 69)

18 yrs old cousin:
- non nephrotic proteinuria

Exon 9 mutation

DNA interaction impairment

Benetti, CJASN 2010
Conclusions

2ndary FSGS

Family history

Autosomal dominant

- INF2
- TRPC6
- Actinin4

Autosomal recessive

- R229Q
- NPHS2

No cause

Steroids

SRNS

SSNS

No cause