ERKNet
The European Rare Kidney Disease Reference Network

Clinical implications of genetics: nephrotic syndrome

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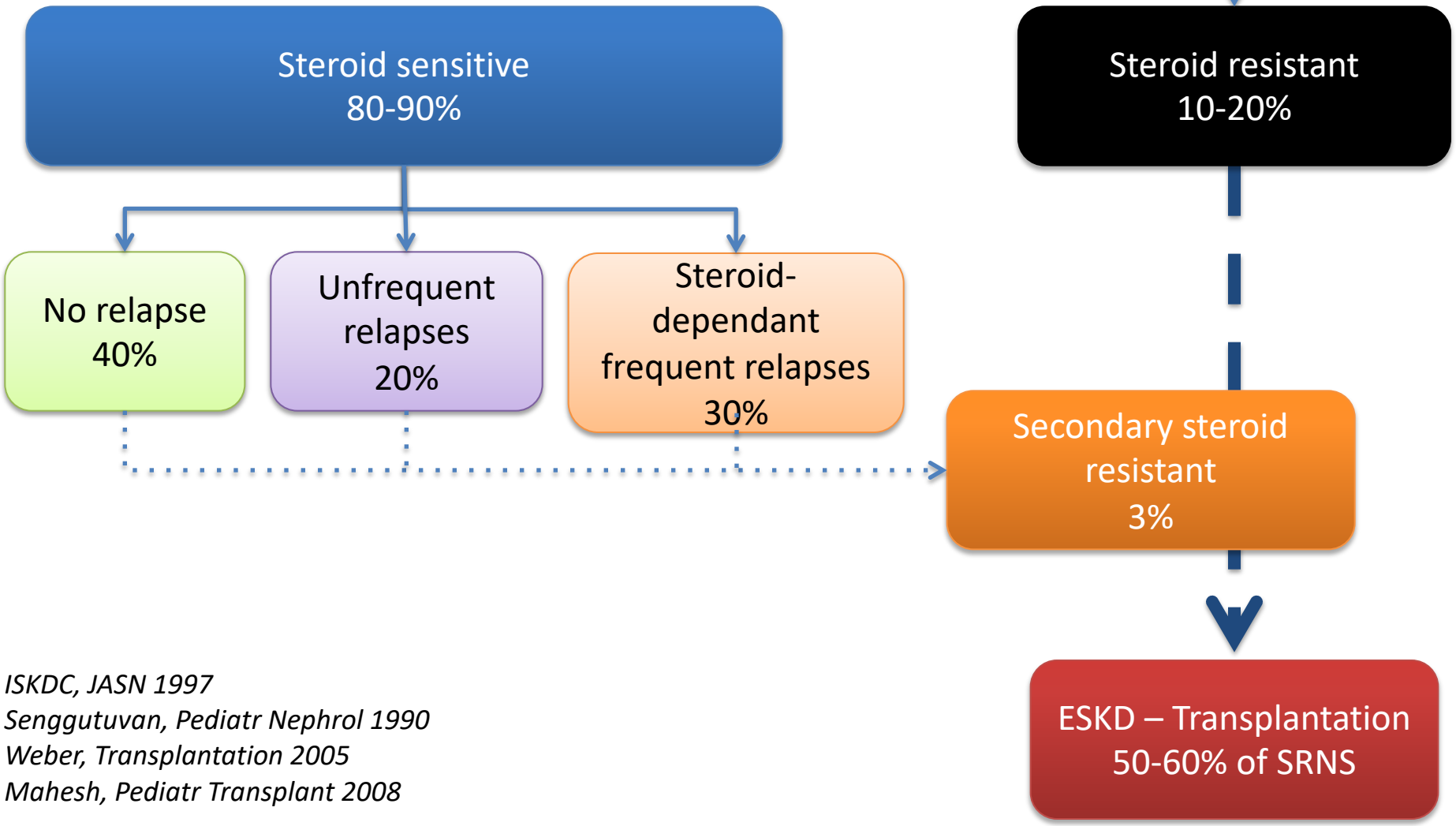
ERN ORKiD FILIÈRE ORPHAN KIDNEY DISEASES imagine INSTITUT DES MALADIES GÉNÉTIQUES UNIVERSITÉ PARIS DESCARTES

Idiopathic nephrotic syndrome in children

Pu/creatinine U > 200 mg/mmol, albuminemia < 25 g/l



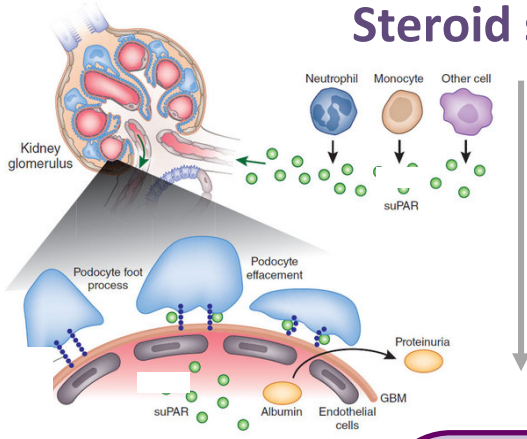
ISKDC, JASN 1997
Senggutuvan, Pediatr Nephrol 1990
Weber, Transplantation 2005
Mahesh, Pediatr Transplant 2008

Different etiologies of nephrotic syndrome (NS)

Idiopathic NS

Circulating factor

Steroid sensitive



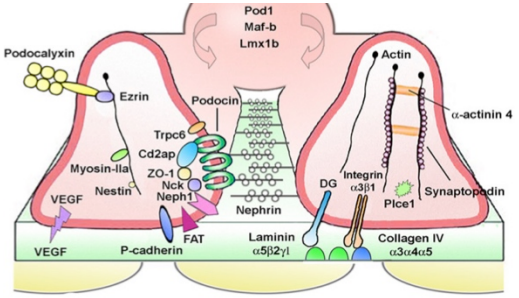
Shankland et al. Nature Med, 2011

Steroid resistant

Complete remission with intensified immunosuppression

Recurrence after RTx

Podocyte proteins



Dysimmune NS

↓

Circulating factor of glomerular permeability ?

Monogenic NS

↓

Structural anomalies of the glomerular filtration barrier

- Congenital NS
- Steroid resistant NS
- AD FSGS

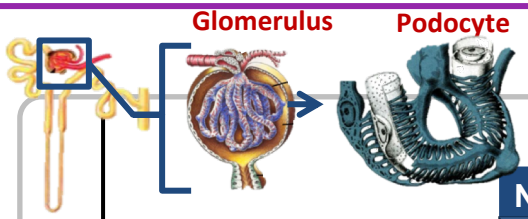
No monogenic cause

Partial remission may be observed with CNIs

Dorval, Pediatr Nephrol 2017

Néphron

Molecular bases of nephrotic syndrome



> 50 genes mutated in hereditary nephrotic syndrome

Cell body

Major foot process

Minor foot process

Nuclear proteins

LMNA
NXF 5
LMX1B
SMARCAL
PAX2
WT1
NUP205
NUP93
NUP107
XPO5

Lysosomal proteins

SCARB2

Mitochondrial proteins

ADCK4
COQ2
COQ6
MTTL1
PDSS2

Urinary space

Microtubular proteins

WDR73
TTC21B

Others

PTPRO
EMP 2
DAG
IP3
PLCE1

Actin-regulating and associated proteins

Rho
CDC42
KANK1,2,4
ARHGDIA
ARHGAP2
RAC
ACTN4
INF2
MYH9
ANLN
MYO1E

Slit diaphragm

Podocin
FAT1
Nephrin
TRPC6
Ca^{2+}
CD2AP
CD2AP
MAGI2
CRB2

Proteins of the extra-cellular matrix

CD151
ITGA3
ITGB4
COL4A3-4-5
LAMB 2

Glomerular basement membrane

Endothelial cell

Capillary lumen

Clinical implications of genetics: nephrotic syndrome

- **Make a diagnosis**
  - rule-out differential diagnoses
  - Identify potential syndromic forms with specific management
- **Provide genetic counseling**

- **Provide adequate therapeutic management**
- **Discover personalized treatments**

- **Evaluate the risk of recurrence after transplantation**
- **Select potential intra-familial kidney donors**

Clinical implications of genetics: nephrotic syndrome

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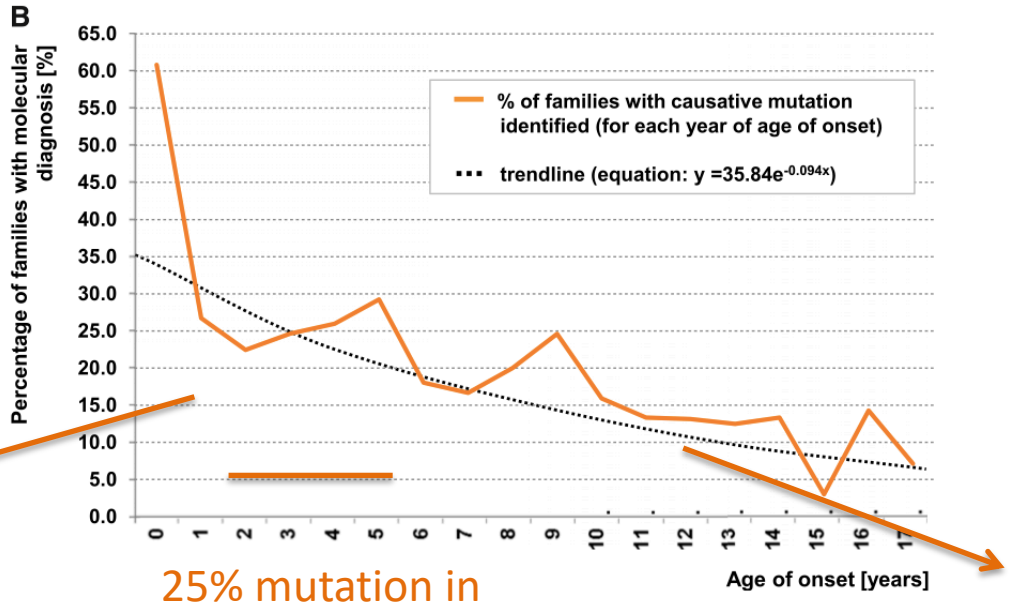
What is the proportion of children with SRNS and identified causative mutations by next generation sequencing techniques?

- 10-15%
- 25-30%
- 35-40%
- 45-50%

Targeted sequencing – Next Generation Sequencing (NGS) panel sequencing or WES in SRNS

- 1783 families with SRNS < 25 yrs : Sanger and targeted NGS of 27 genes
- **29.5% disease causing mutations in a single gene**
- 49.5% in consanguineous families and only 25% in non consanguineous families



61% mutation in CNS and infantile NS

25% mutation in children 2-5 yrs at NS onset

10% mutation in children > 12 yrs at NS onset

Sadowski et al. JASN, 2014

Whole Exome Sequencing of Patients with Steroid-Resistant Nephrotic Syndrome

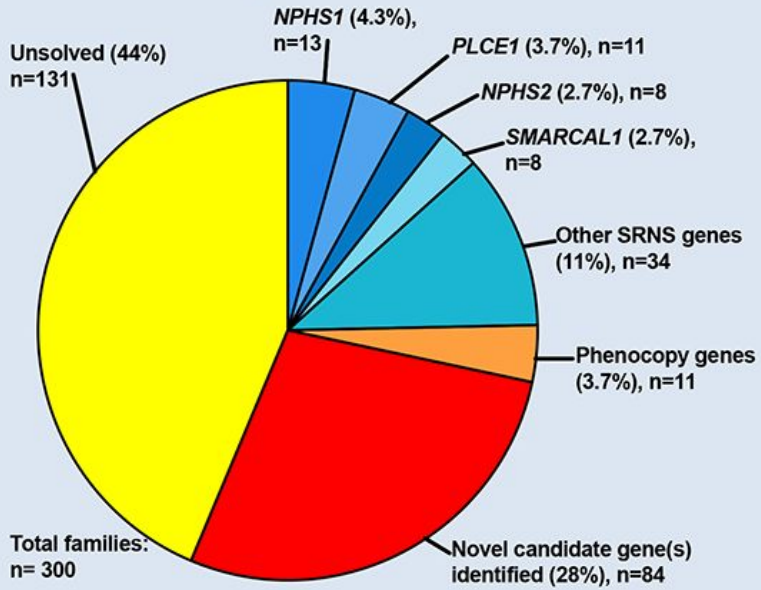
METHODS

335 individuals from **300** families with steroid resistant nephrotic syndrome

Whole exome sequencing performed

Variant calling and filtering

OUTCOMES: 25% of families had a causative mutation detected in candidate genes

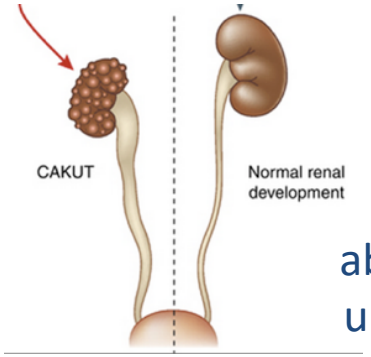


CONCLUSION A potentially causative genetic mutation can be identified in many patients with steroid-resistant nephrotic syndrome.

Jillian K. Warejko, Weizhen Tan, et al. Whole Exome Sequencing of Patients with Steroid-Resistant Nephrotic Syndrome. CJASN doi: 10.2215/CJN.04120417.

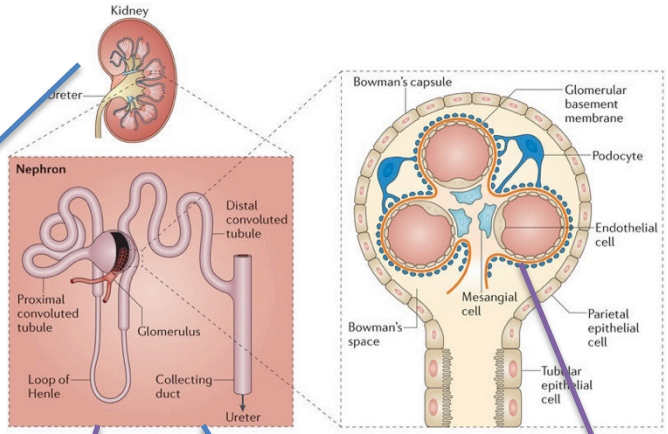
CJASN
Clinical Journal of American Society of Nephrology

1) Rule out differential diagnoses



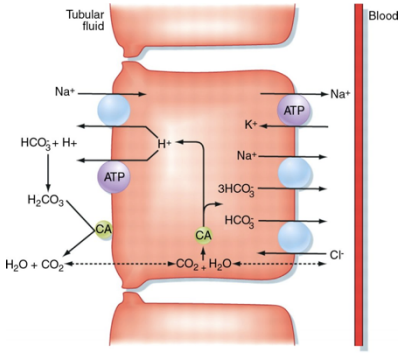
CAKUT
PKD

abN kidney ultrasound
LMW Pu



Glomerular diseases (SRNS, Alport)

Albuminuria +/- Hu

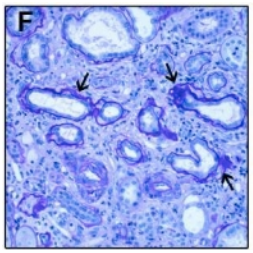


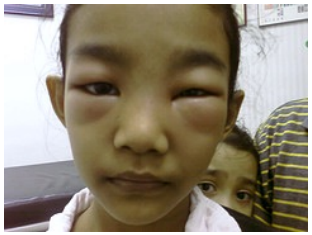
Tubulopathies

Ion perturbances
LMW Pu

Ciliopathies (NPH)

Urinary sodium loss
Polyuria, LMW Pu





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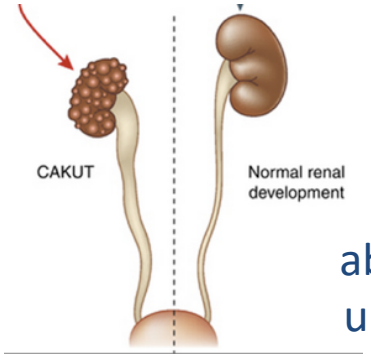
Which of the following diseases may present as SRNS with FSGS lesions on kidney biopsy (MCQ, check all that apply) ?

- renal-coloboma syndrome (*PAX2* mutations)
- Dent's disease (*CLCN5* mutation)
- Nephronophthisis (*TTC21B* mutation)
- Alport syndrome (*COL4A3-5* mutation)
- None of the above

1) Rule out differential diagnoses



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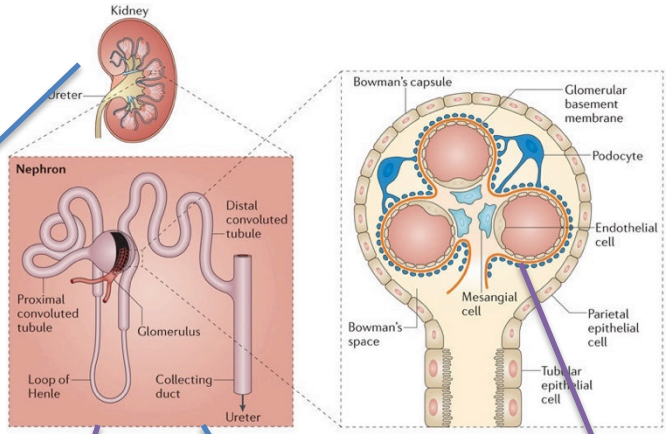

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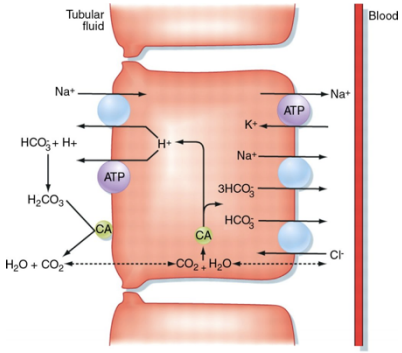

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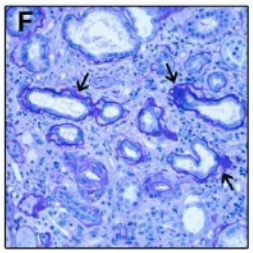
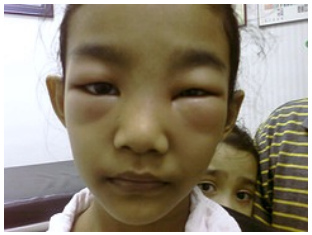
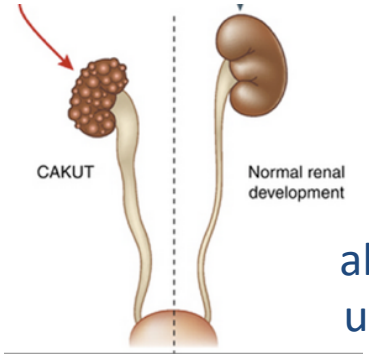




1) Rule out differential diagnoses



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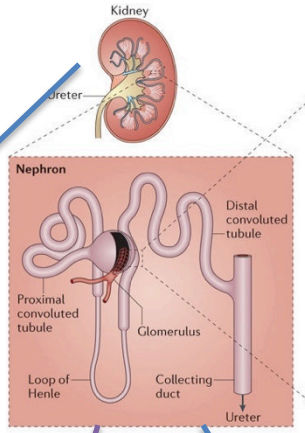
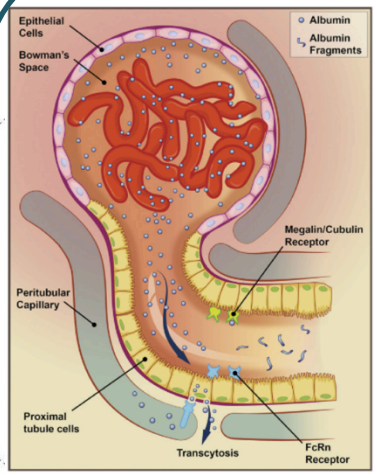
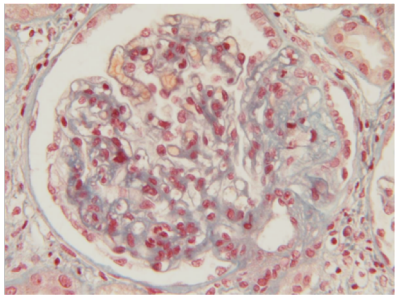




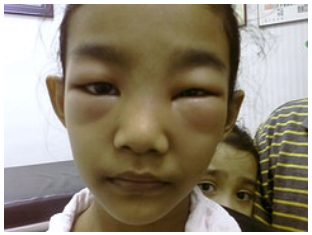
*** Albumin filtration greater than previously thought**



*** Chr nephropathies may => FSGS (non specific lesion)**

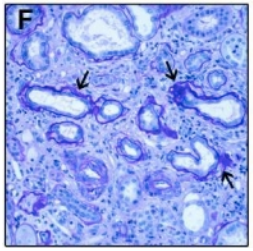
Glomerular diseases
SRNS
Alport

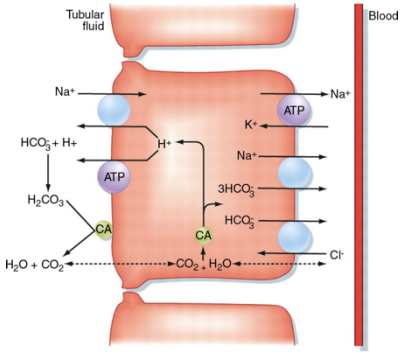
Albuminuria +/- Hu



Ciliopathies

Urinary sodium loss
Polyuria, LMW Pu





Tubulopathies

Ion perturbances
LMW Pu

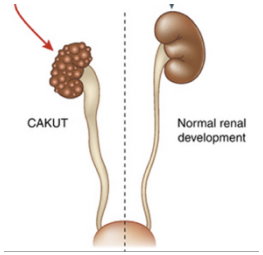
Dickson et al. JASN, 2014

1) Rule out differential diagnoses/phenocopies

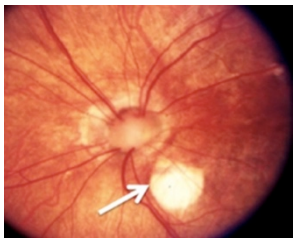
PAX2 (CAKUT)

⇒ CAKUT and papillo-renal syndrome

⇒ in 4% of adult-onset familial SRNS/FSGS and no extra-renal features

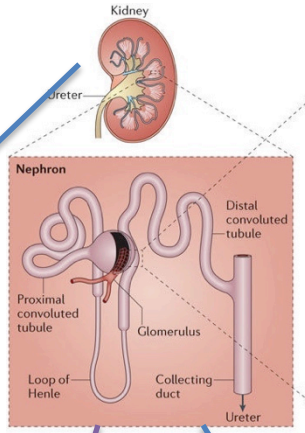


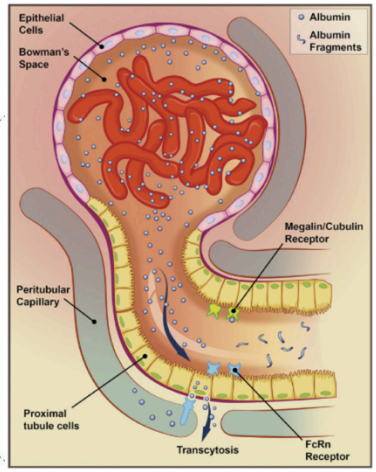
CAKUT

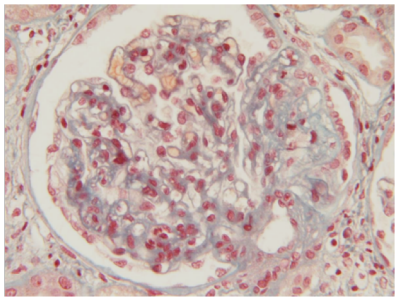


coloboma

Barua et al, *JASN* 2014





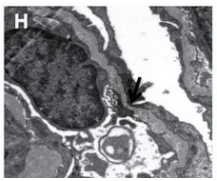


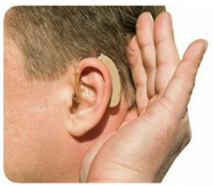
FSGS (non specific lesion)

COL4A3-5 (Alport)

⇒ Heterozygous *COL4A3* mutation in ~10% AD-SRNS/FSGS families

No known deafness before genetic testing





Malone et al., *KI* 2014

Tubulopathies

- *CBN* (cubilin) (Megaloblastic anemia)
- *OCRL* and *CLCN5* (Dent)

=> Chronic albuminuria and FSGS

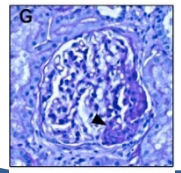
Ovuncet al, *JASN* 2011

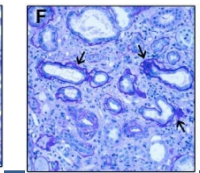
TTC21B (ciliopathy)

- AlbU (1-7 g/l) et HBP ++
- ESKD 22 yrs

⇒ SRNS and nephronophtisis

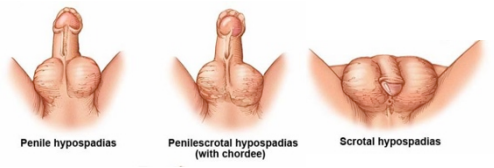
- Magrheb and Portugal



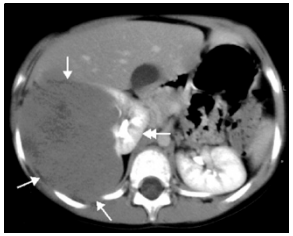


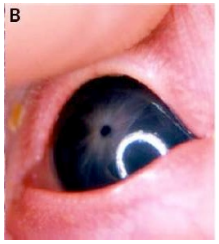
Huynh Cong E et al., *JASN* 2014

2) Identify potential syndromic forms with specific management

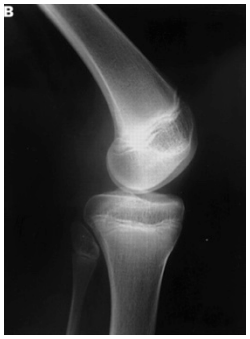


DDS and Frasier Sd

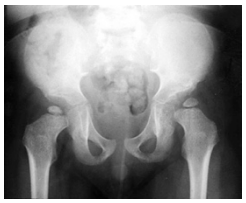


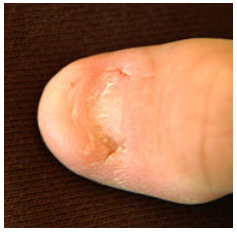


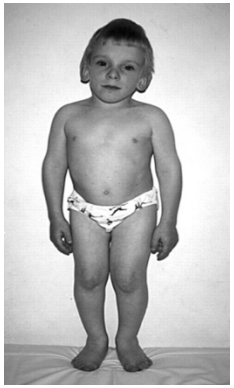
Pierson Sd



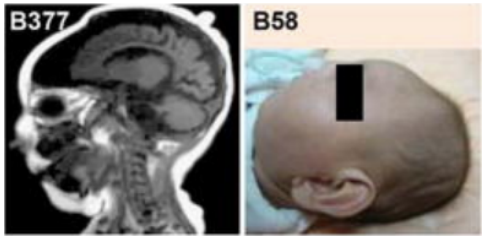
Nail Patella







Schimke



Galloway Mowatt

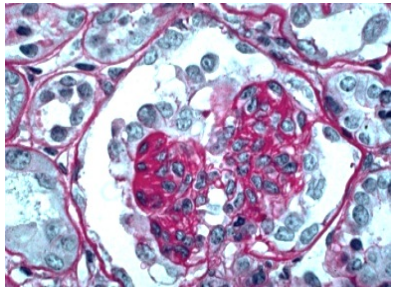
Mitochondrial disease

CMT

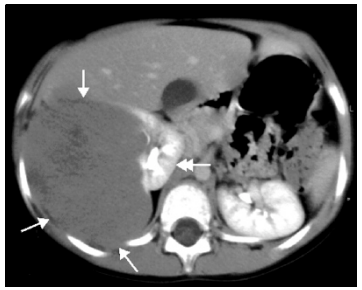
May develop immunodeficiency
=> Should not be given IS

WT1 mutations in syndromic or non-syndromic AD-SRNS

Denys Drash

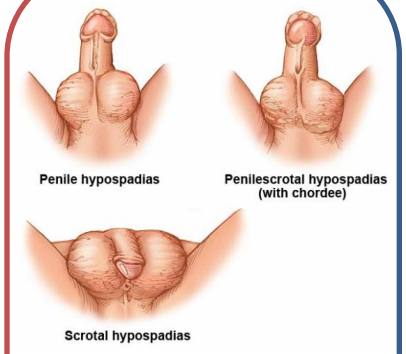


DMS



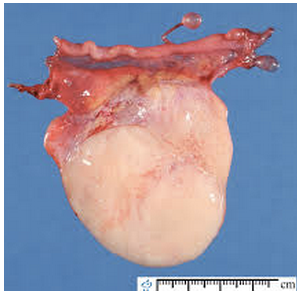
Wilm's

Mutation in exons 8 and 9

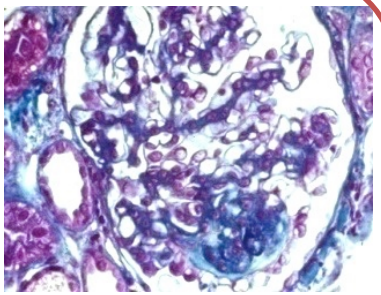


Male pseudo-hermaphroditism

Frasier



Gonadoblastoma
Streak gonades



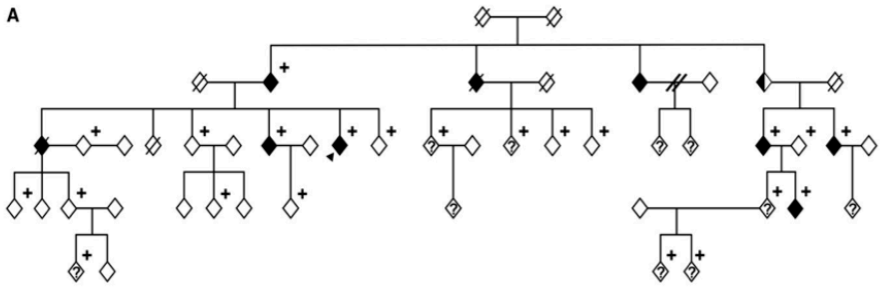
FSGS

Splice site mutation in intron 9

Mutation in exons 8 and 9 in **5% girls with non syndromic SRNS**

onset 3 yrs (0.1 – 6.9) and rarely in males

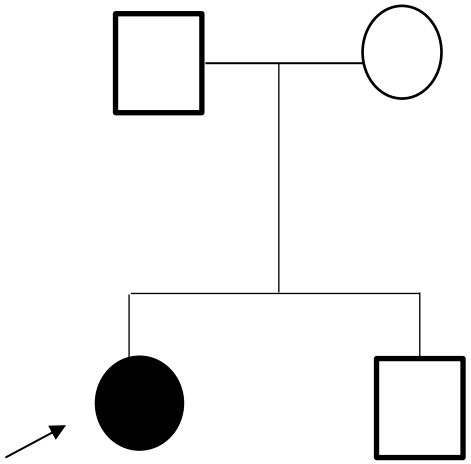
Identification of one mutation segregating with the disease in 2 large families (with > 5 males) with FSGS (onset 16-30 yrs)



Monitor kidney US/3 months

Karyotype (phenotypic girls)

Hall G et al., *JASN 2015*



17 yrs
Nephrotic syndrome at 15 years
Primary amenorrhea

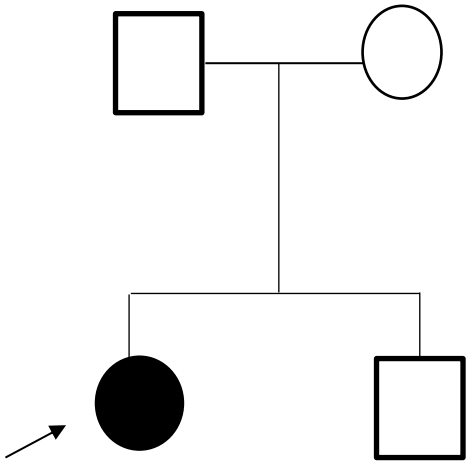
Chromosomal sex: 46, XY
WT1 mutation c.1432+2T>C (Frasier)

Clinical implications in this patient?

ERKNet
The European
Rare Kidney Disease
Reference Network

What are the clinical implications in this patient (MCQ, check all that apply)?

- Refer to an endocrinologist
- Refer to a surgeon for gonadal removal
- Abdominopelvic US every 6 months
- Refer to a psychologist
- 50% risk of having a child with SRNS



17 yrs
Nephrotic syndrome at 15 years
Normal puberty

Chromosomal sex: 46, XX
WT1 mutation c.1432+2T>C (Frasier)

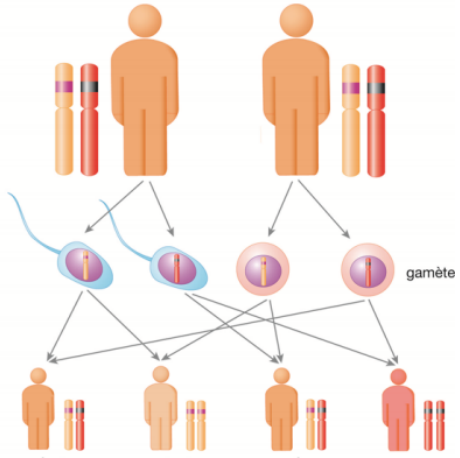
Genetic counselling in this patient?

ERKNet
The European
Rare Kidney Disease
Reference Network

What is the genetic counselling for this patient ?

- 25% risk of having a child with SRNS
- 50% risk of having a child with SRNS
- risk of having a child with gonadoblastoma
- risk of having a child with Wilm's tumor
- risk of having a child with male-to female sex reversal

3) Provide genetic counselling



Autosomal recessive

Unaffected parents
Frequent consanguinity

***NPHS2* (podocin) +++**

***NPHS1* (nephrin)**

***PLCE1 – NPHS3* (PLCE1)**

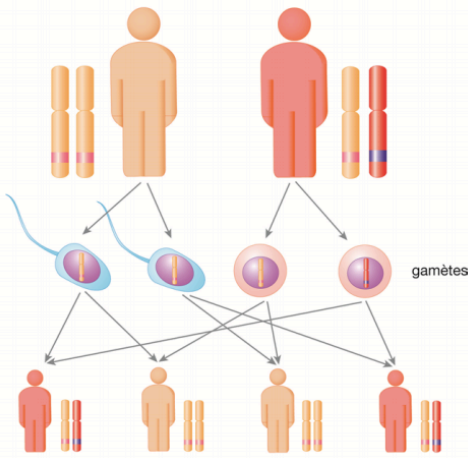
MYO1E (myosin 1E)

PTPRO (GLEPP1)

NUP93, 107, 205

KANK1,2,3

XP05



Autosomal dominant

One affected parent
Incomplete penetrance ++

WT1

***INF2* (inverted formin 2)**

TRPC6 (TRPC6)

ACTN4 (alpha-actinin 4)

LMX1B (LMX1B)

ARHGAP24

ARHGDIA

ANLN

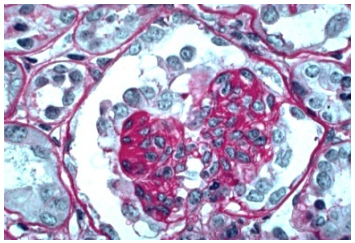
NPHS3 (*PLCE1*) mutations (AR) have an incomplete penetrance

- Onset : 2 mo (CNS) to 4 yrs (SRNS)
- FSGS or DMS
- ESKD < 7 yrs
- **INCOMPLETE PENETRANCE**

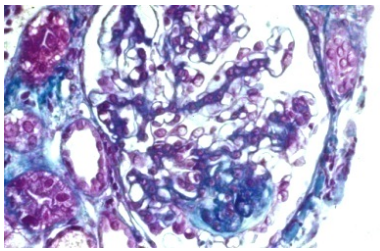
⇒ Oligogenic inheritance*?*

⇒ *Modifier genes?*

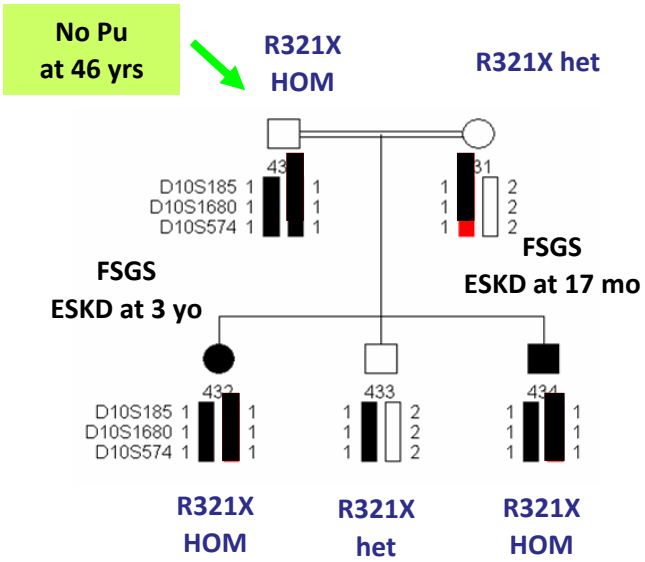
⇒ *environnemental factors?*

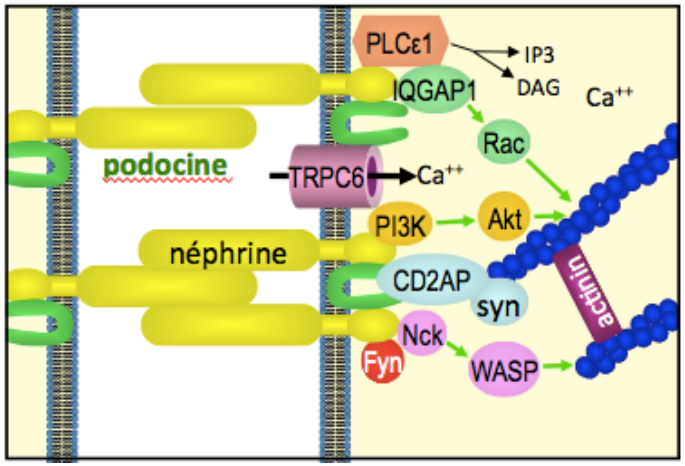


Diffuse mesangial sclerosis



FSGS





Cytoplasmic protein
Podocyte signalling cascades

Hinkes et al., Nat Genet 2006
Boyer et al., J Med Genet 2010

NPHS2 mutations (podocin) are the 1st cause of autosomal recessive steroid-resistant nephrotic syndrome

AR-SRNS

NS ≅ 4 years, ESKD ≅ 10 years

> 110 mutations

- 42% familial cases
- 10% sporadic cases

R138Q (32%): retained in the endoplasmic reticulum

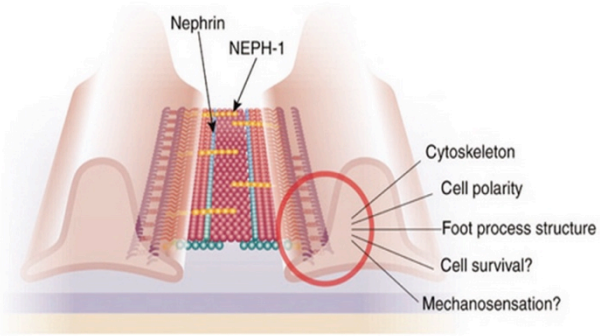
Age at Dx 2 years < 10 years for mutants located at the plasma membrane

Congenital NS

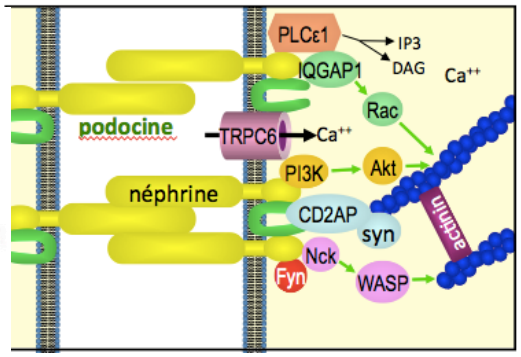
15-40 % of cases (ESKD ≅ 6 years)

Late onset NS/Pu

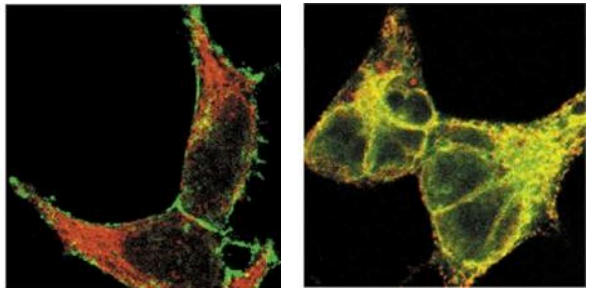
p.R229Q + 1 specific pathogenic mutation 19% of adult NS (Pu ≅ 25 years, ESKD ≅ 32 years)



Slit diaphragm protein

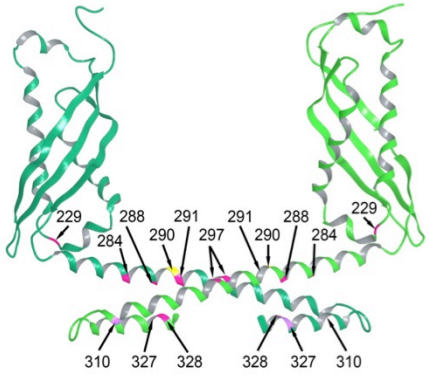


Linked to the cytoskeleton



WT **R138Q**

Podocine **Calnexin (RE)**



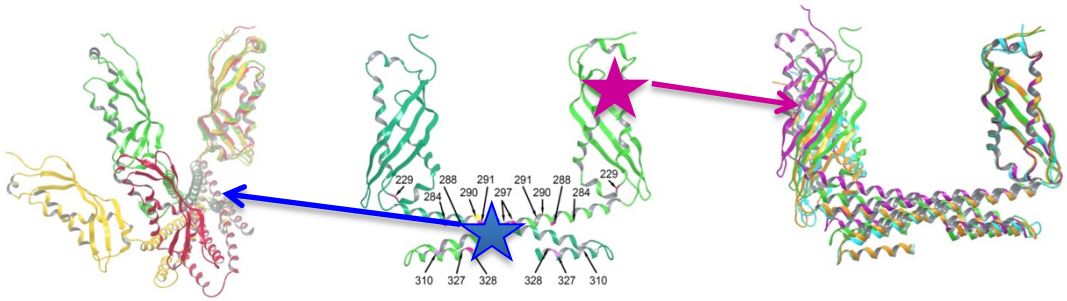
Homodimer

Boute et al., Nat Genet 2000
Roselli et al., Traffic 2004

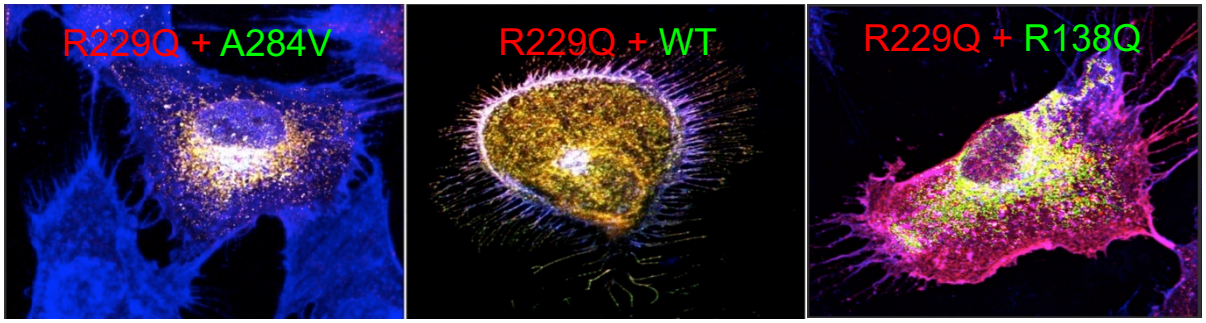
Boute, Nat genet 2000
Bouchireb, Boyer et al., Hum Mut 2014

The effect of the p.R229Q *NPHS2* variant depends on the 2nd mutation

Pathogenic dimers
[**p.R229Q**];[**C-terminal** mutation]

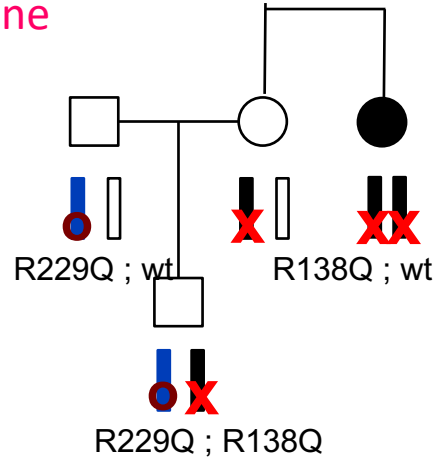


Non pathogenic dimers
[**p.R229Q**];[**N-terminal** mutation]



Podocin retained in the cell
SRNS/FSGS

Podocin at the plasma membrane
unaffected

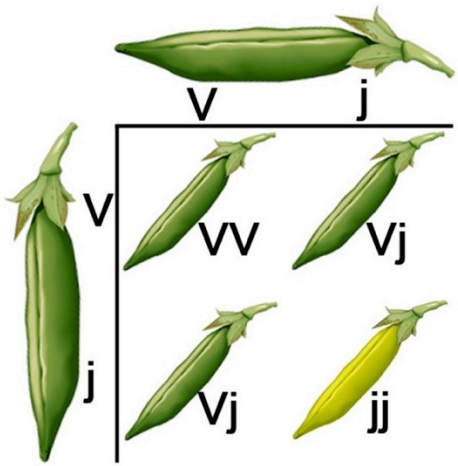


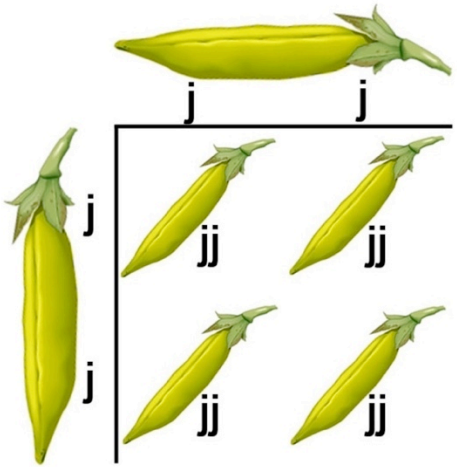
➔ [**p.R229Q**];[**N-terminal mutation**] DO NOT EXPLAIN NS => **immune NS?**

➔ **Genetic counselling**: A couple carrying an *NPHS2* N-term mutation (exons 1–6) in one member and R229Q in the other is not at risk of having an affected child

Tory et al, Nat Genet 2014

The effect of the p.R229Q *NPHS2* variant depends on the 2nd mutation





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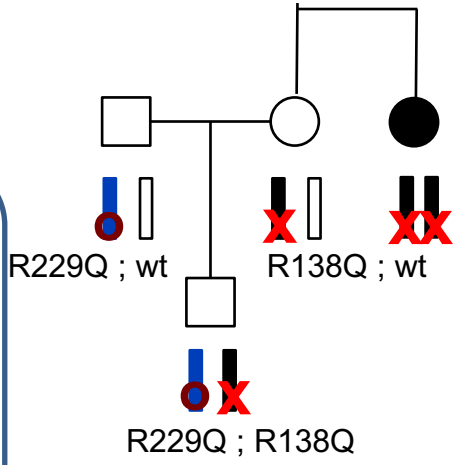


Tory et al, Nat Genet 2014

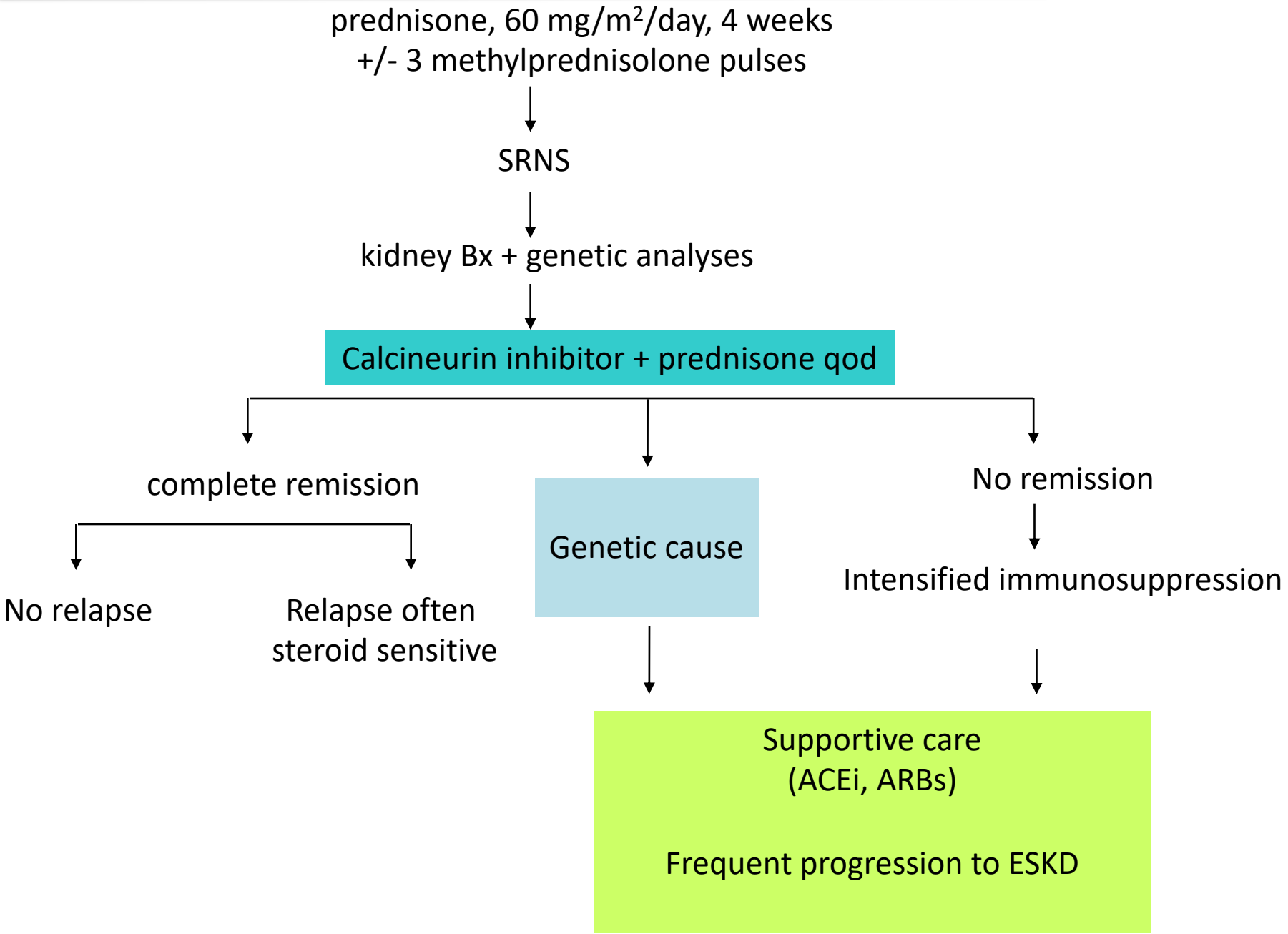
Clinical implications of genetics: nephrotic syndrome

- Make a diagnosis
- Provide genetic counseling

- Provide adequate therapeutic management
- Discover personalized treatments

- Evaluate the risk of recurrence after transplantation
- Select potential intrafamilial kidney donors

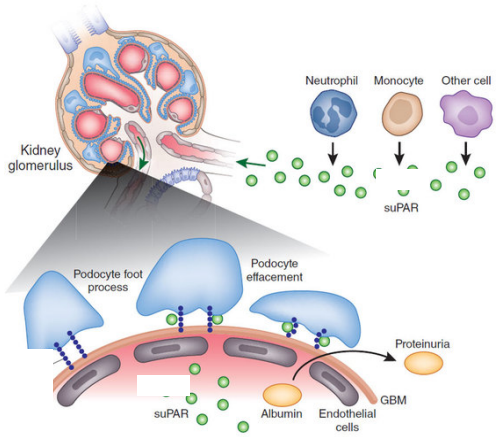
4) Provide adequate therapeutic management



Do mutated patients benefit from ciclosporine?

1. Effects on the immune system

- T-helper cells : downregulates of transcription of cytokine gene: IL-2
- inhibits the proliferation of cytotoxic T-cells and B-cells in response to T-helper cell signaling.



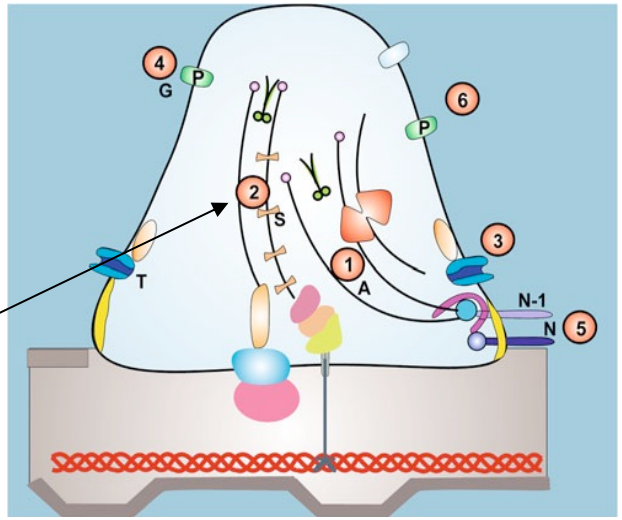
2. Direct anti-Pu effect

By altering glomerular hemodynamics

3. Direct podocyte-stabilizing effect

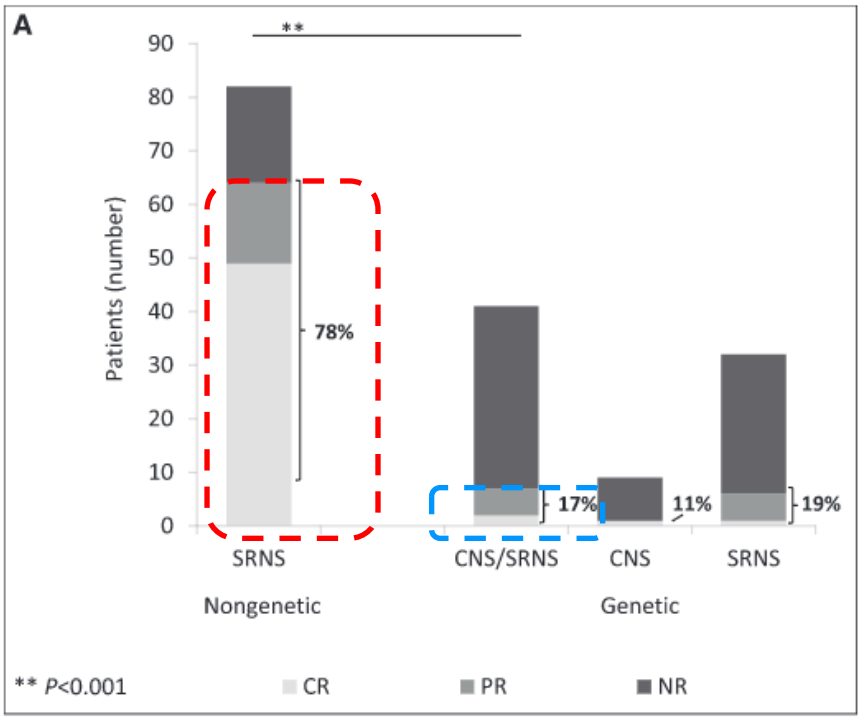
By blocking the calcineurin-mediated dephosphorylation of synaptopodin

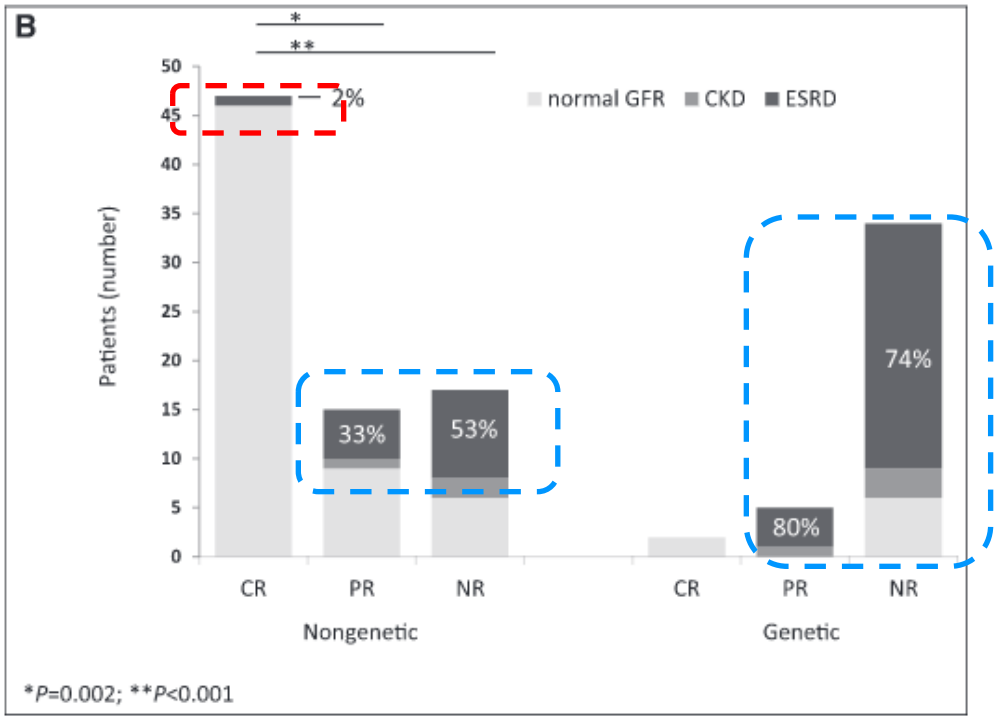
(that stabilizes the podocyte actin cytoskeleton by regulating of RhoA GTPases)



Gbadegesin et al. Ped Nephrol 2010
Faul et al,. Nat Med 2008

Most patients without any identified mutation respond to CNI and have a preserved renal function



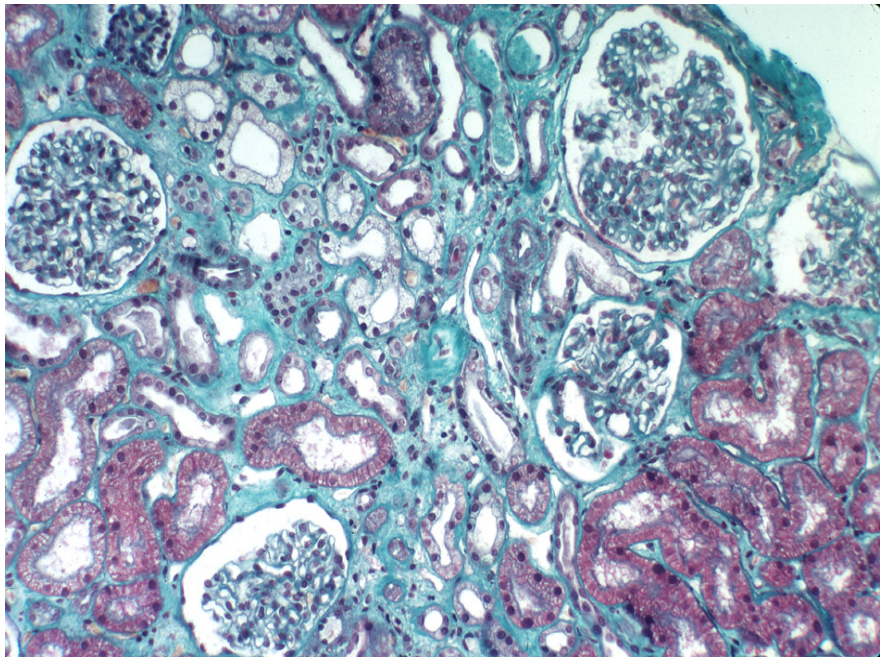


- 231 SRNS and CNS, 131 with identified mutation
- 78% CR or PR in non mutated patients vs 17% PR only in mutated patients
- 2% ESKD if CR vs. 33% or 53% in case of PR or no remission, and 74% in mutated pts

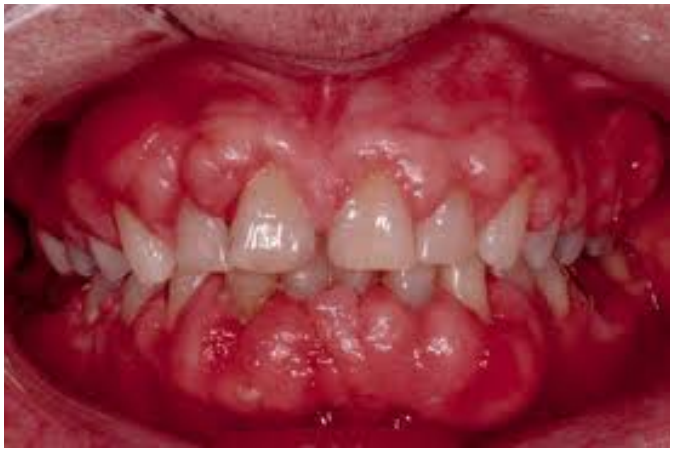
➥ **achieving complete remission is a major goal**

Buscher et al, CJASN 2015

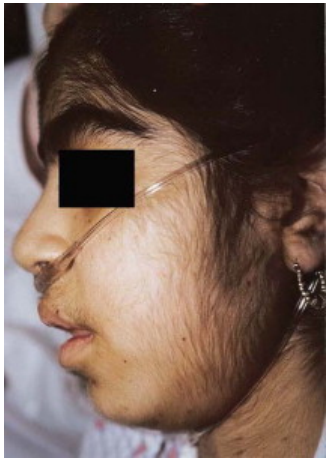
However, prolonged exposure to CNIs may have significant burden



nephrotoxicity



gum hypertrophy



hyperpilosity

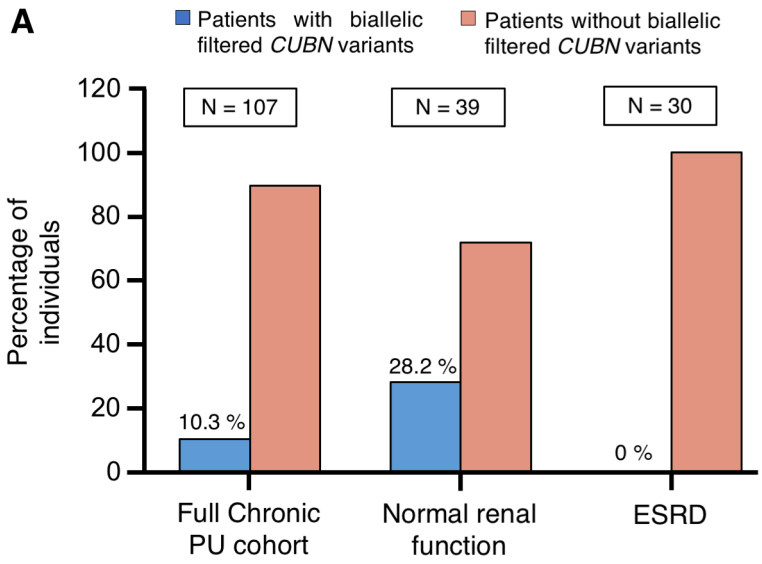
Picture courtesy of Marie Claire Gubler

4) Provide adequate therapeutic management
Do all mutated patients need ACEi?

➢ **Imerslund-Gräsbeck syndrome (IGS)**
***CUBN* gene mutations**
– Vitamin B12 malabsorption (anemia)
– **Proteinuria**

➢ **GWAS:** frequent variants associated with Pu

➢ **NGS: 49 biallellic cubilin mutations in**
- **14/759 (18%) pts** with suspected genetic cause for SRNS, AS, CAKUT, PKD, TIN (France)
- **13/1350 (10%)** with suspected genetic cause for SRNS, AS (Germany)
- **12/107 (11%) with chronic Pu** (France)



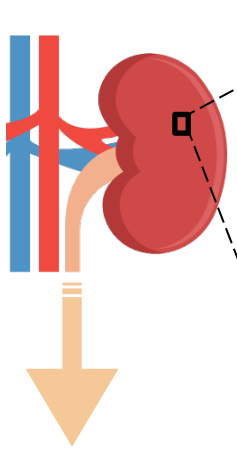
- Average age at onset of Pu: 10.9 years
- chronic Pu 0.5 to 3g/24h (>50% albumin)
- **Bx: MCD**
- **Normal eGFR 17 years then a lot of LTFU**
- **No effect of ACEi : indicated ?**

JCI The Journal of Clinical Investigation

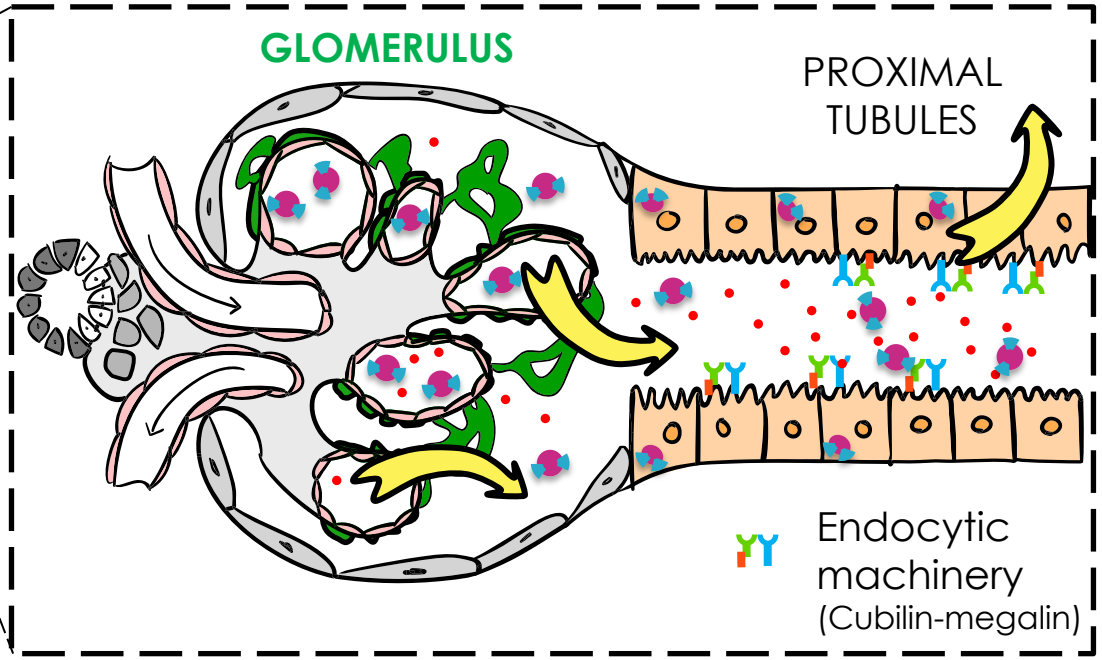
Human C-terminal *CUBN* variants associate with chronic proteinuria and normal renal function

Bedin M, Boyer O, … Antignac C, Simons M. JCI 19

PROTEIN HANDLING BY THE PROXIMAL TUBULE



NORMAL
final urine

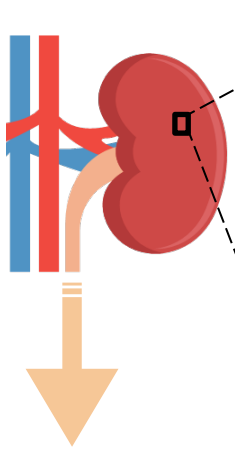


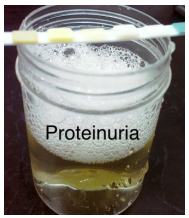
Capillary lumen:
large+small proteins
30–50g/L albumin

Tubular lumen:
small proteins
15–20mg/L albumin

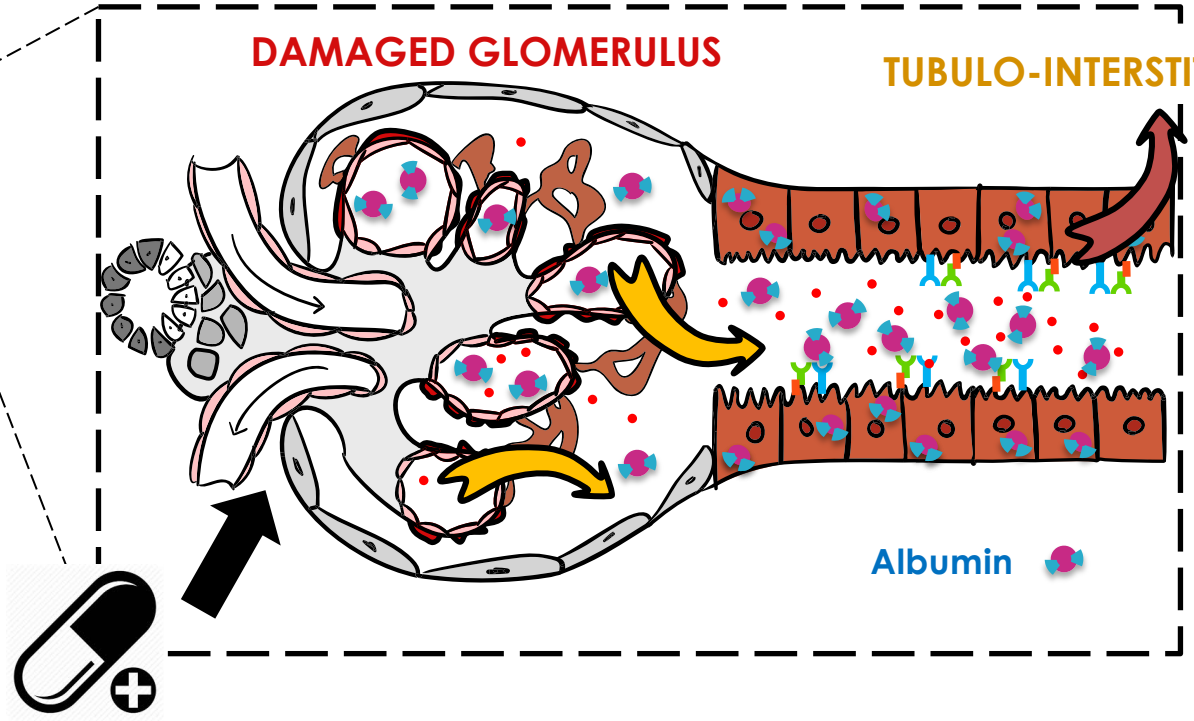
Bedin M, Boyer O, … Antignac C, Simons M. JCI 19

GLOMERULAR DAMAGE AND NEPHROTIC SYNDROME





ABNORMAL
final urine:
PROTEINURIA



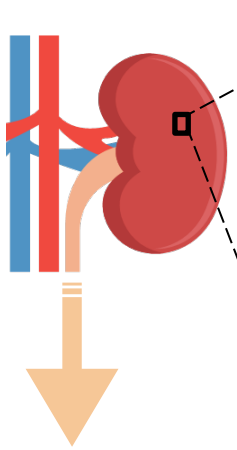
Glomerular defects lead to **tubular injury and inflammation** due to the overload with **albumin**

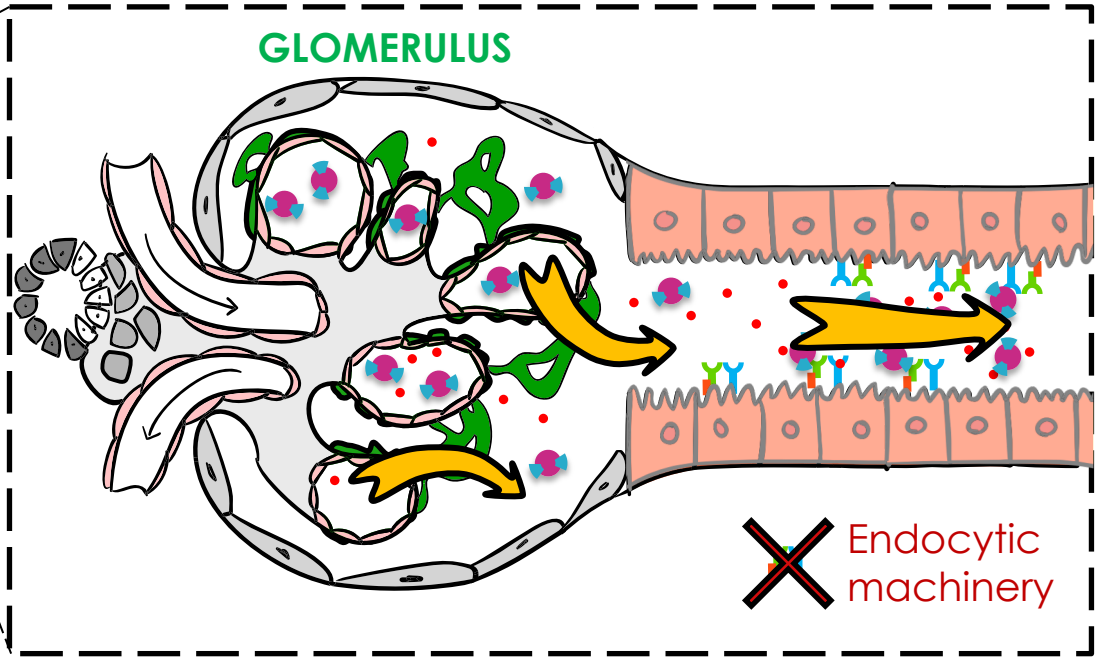
CHRONIC KIDNEY DISEASE

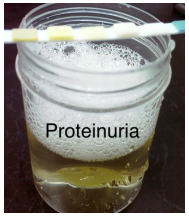
ACEi => reduce albumin overload => nephroprotection

Bedin M, Boyer O, … Antignac C, Simons M. JCI 19

CUBN MUTATIONS







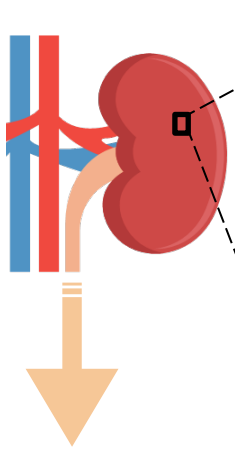
ABNORMAL
final urine:
PROTEINURIA

Glomerular barrier still functional but loss of endocytic machinery
Albuminuria

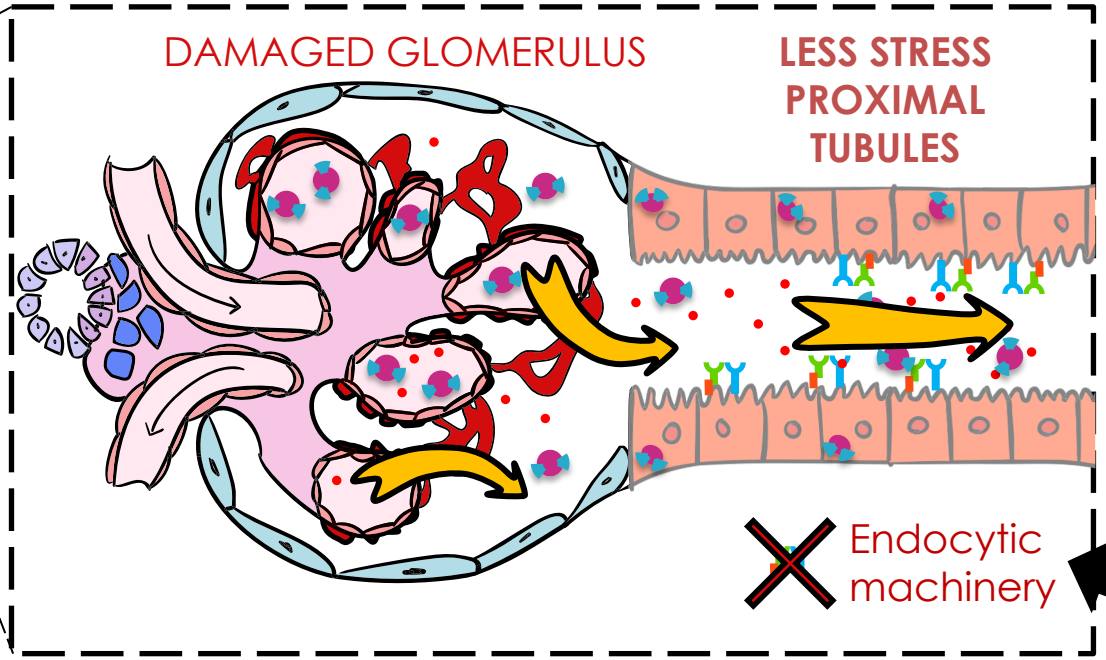
No tubulo-interstitial damage
NORMAL RENAL FUNCTION

Bedin M, Boyer O, … Antignac C, Simons M. JCI 19

CUBN PROTEINURIA PROTECTION AGAINST KIDNEY DISEASE ?



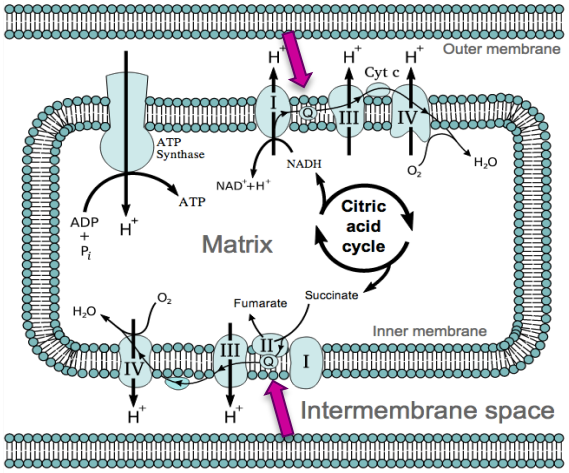
ABNORMAL
final urine:
PROTEINURIA

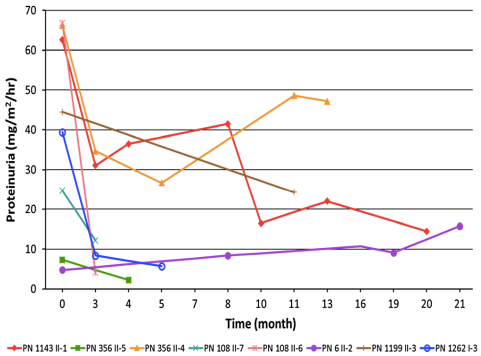


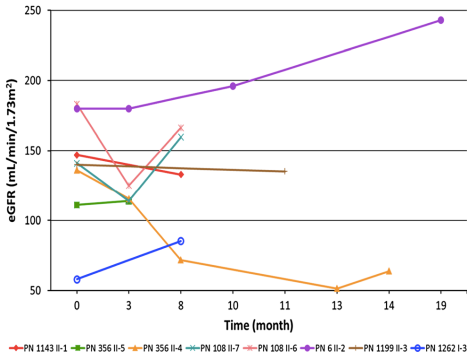
Reduced uptake of albumin could protect proximal tubular cells

Bedin M, Boyer O, … Antignac C, Simons M. JCI 19

5) Discover personalized treatments
Genes involved in coenzyme Q_{10} (CoQ_{10}) biosynthesis







Atacama et al., Ped Nephrol 2017

Gene	Kidney phenotype	Extra-renal features	COQ10 effects
COQ2	CNS, SRNS (FSGS)	Encephalopathy, MOF	?
PDSS2	Congenital/infantile NS	Deafness, MR, Leigh	?
COQ6	CNS, SRNS (FSGS/DMS)	± Deafness, seizures, ataxia	↓ Pu ± deafness
COQ8 (ADCK4)	CNS, SRNS (FSGS): median age at Dx 14.1 yrs (11-17) At ESKD: 14-18 yrs	1 heart disease, 1 MR/15 **Mostly isolated SRNS**	↓ Pu

Heeringa et al., JCI 2011
Ashraf et al., JCI 2013
Kormaz et al., JASN 2015

5) Discover personalized treatments: chaperons ?
NPHS2 mutations (podocin)

AR-SRNS

NS ≅ 4 years, ESKD ≅ 10 years

> 110 mutations

- 42% familial cases

-10-30% sporadic cases

R138Q (32%): retained in the endoplasmic reticulum

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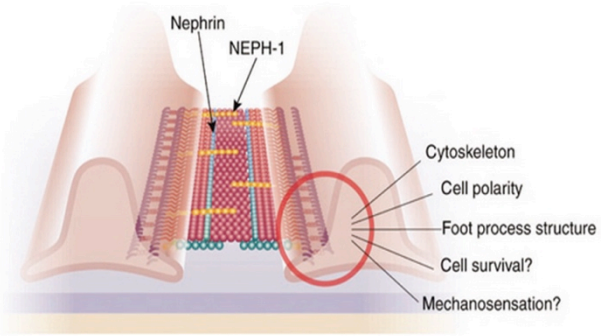
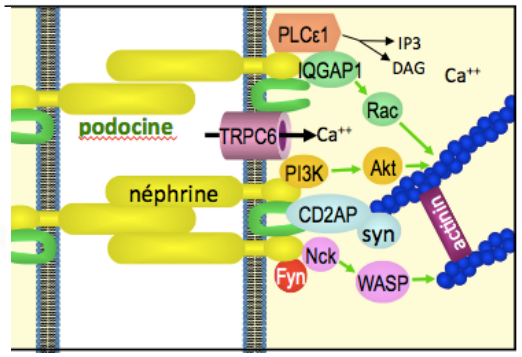
Late onset NS/Pu

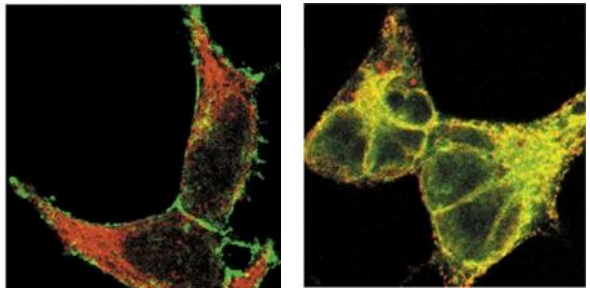
p.R229Q + 1 specific pathogenic mutation 19% of adult NS (Pu ≅ 25 years, ESKD ≅ 32 years)



Slit diaphragm protein

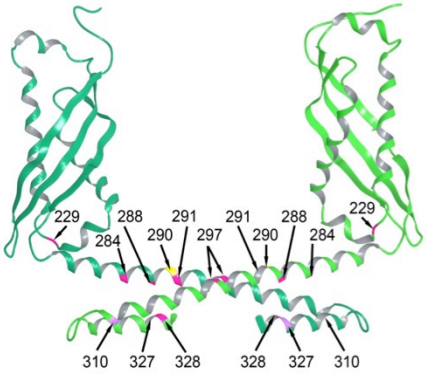


Linked to the cytoskeleton



WT **R138Q**

Podocine **Calnexin (RE)**



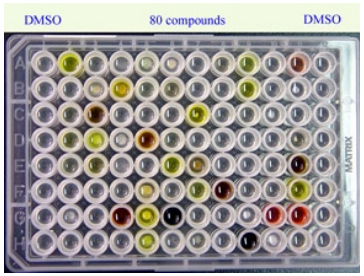
Homodimer

Boute et al., Nat Genet 2000
Roselli et al., Traffic 2004

Boute, Nat genet 2000
Bouchireb, Boyer et al., Hum Mut 2014

5) Discover personalized treatments: chaperons ?

Screening compound librairies



Prestwick, Chembridge
Plateforme Biophenics, Curie
Faculté de pharmacie, Strasbourg

membrane

Golgi

COP II

ERAD

Calnexine

RE

Protéasome

Clinical implications of genetics: nephrotic syndrome

- Make a diagnosis
- Provide genetic counseling

- Provide adequate therapeutic management
- Discover personalized treatments

- Evaluate the risk of recurrence after transplantation
- Select potential intra-familial kidney donors

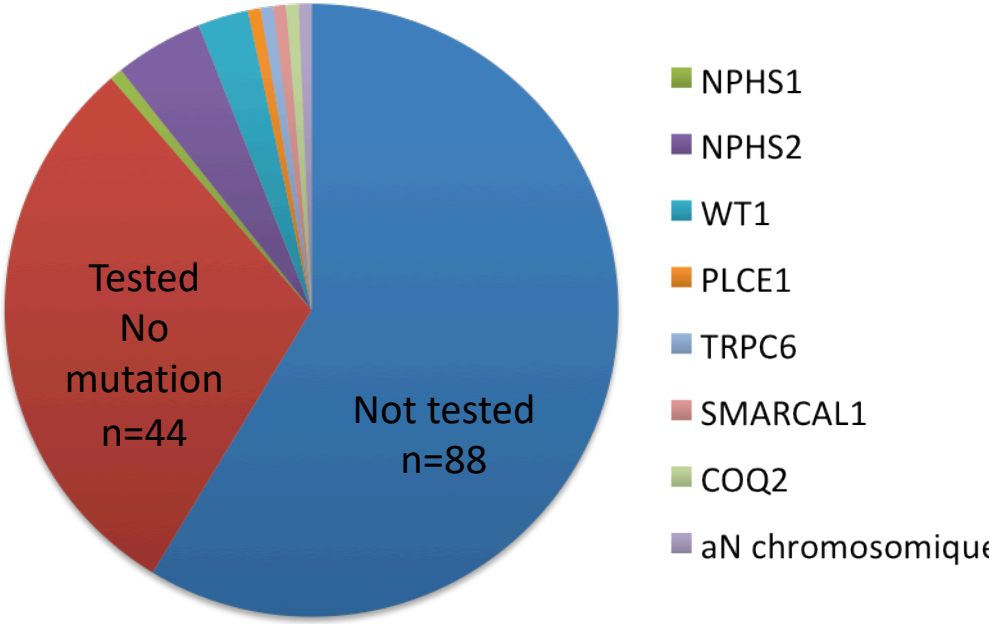
6) Evaluate the recurrence risk after RTx

Moin Saleem, Bristol, UK

- **150 transplanted patients** (1e graft) for SRNS between 1981 and 2012

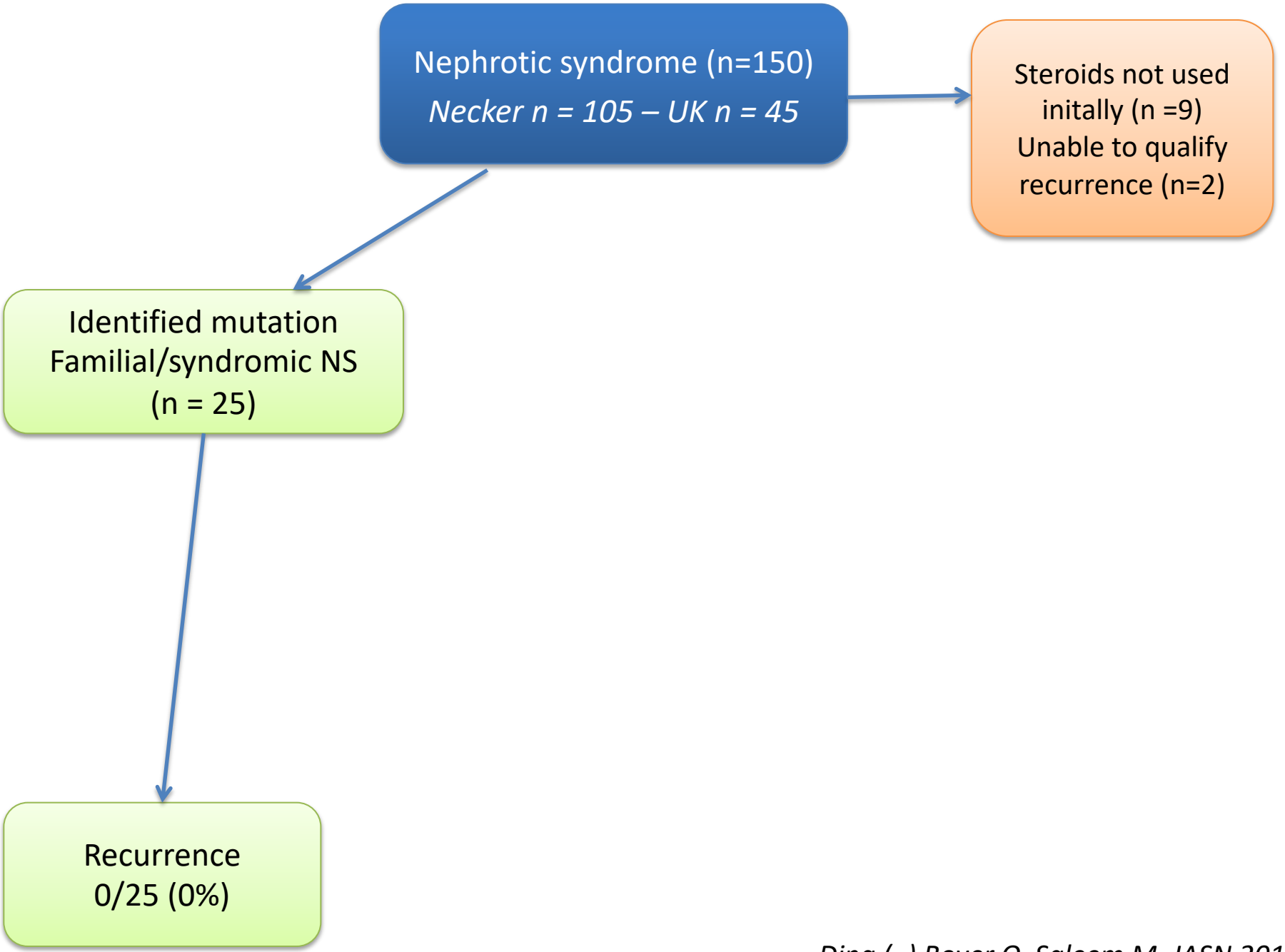
- 105 from Necker – 45 from 2 UK centers (Bristol, London)

- Median age at diagnosis: 4.0 yrs (0.3-15.5)
- Median time to ESKD: 3.0 yrs (0-17 yrs)
- Median age at Tx: 11.5 yrs (2.5-23.5)
- 18 patients with identified gene mutations
- 7 familial cases/syndromic cases

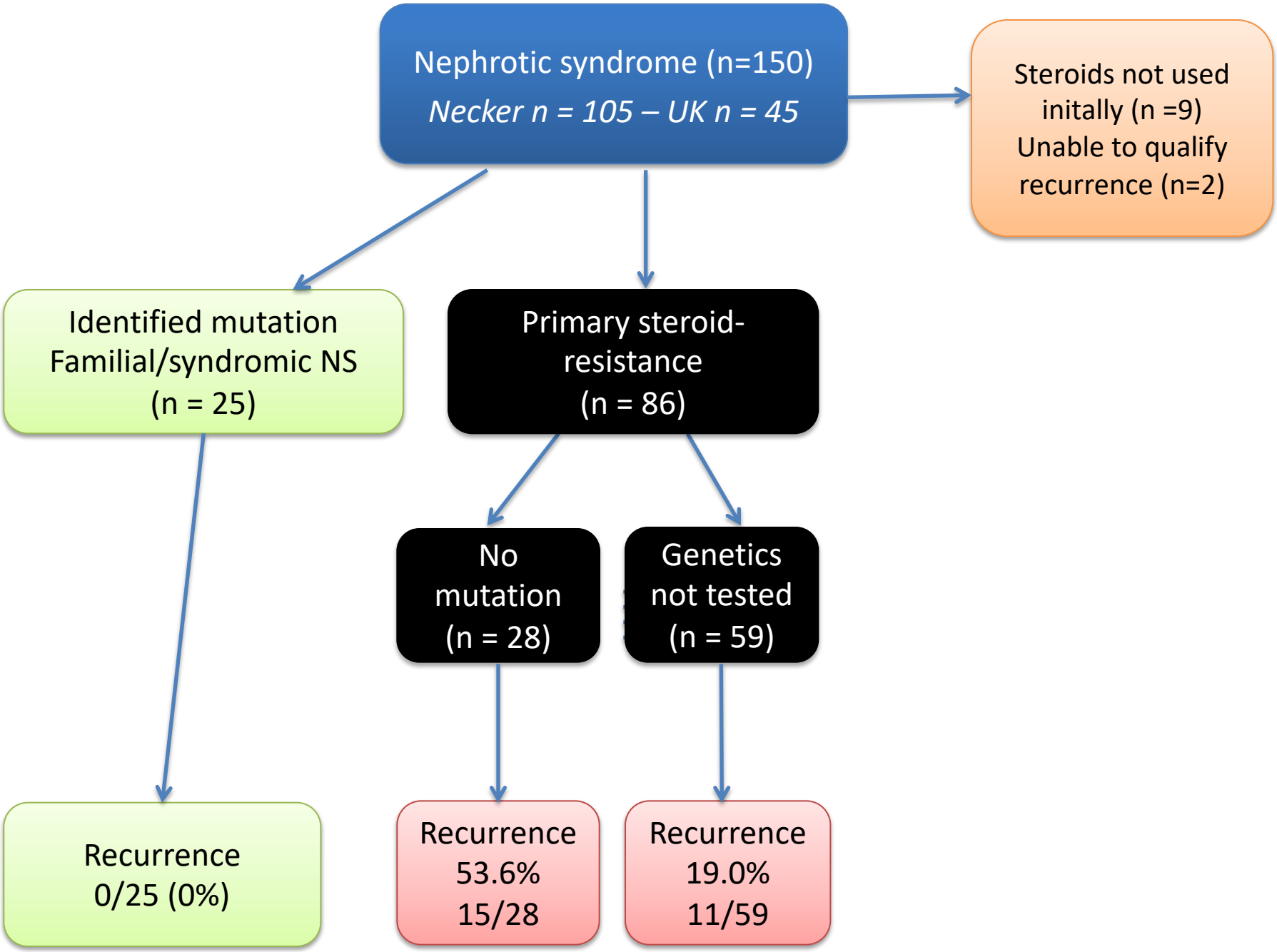


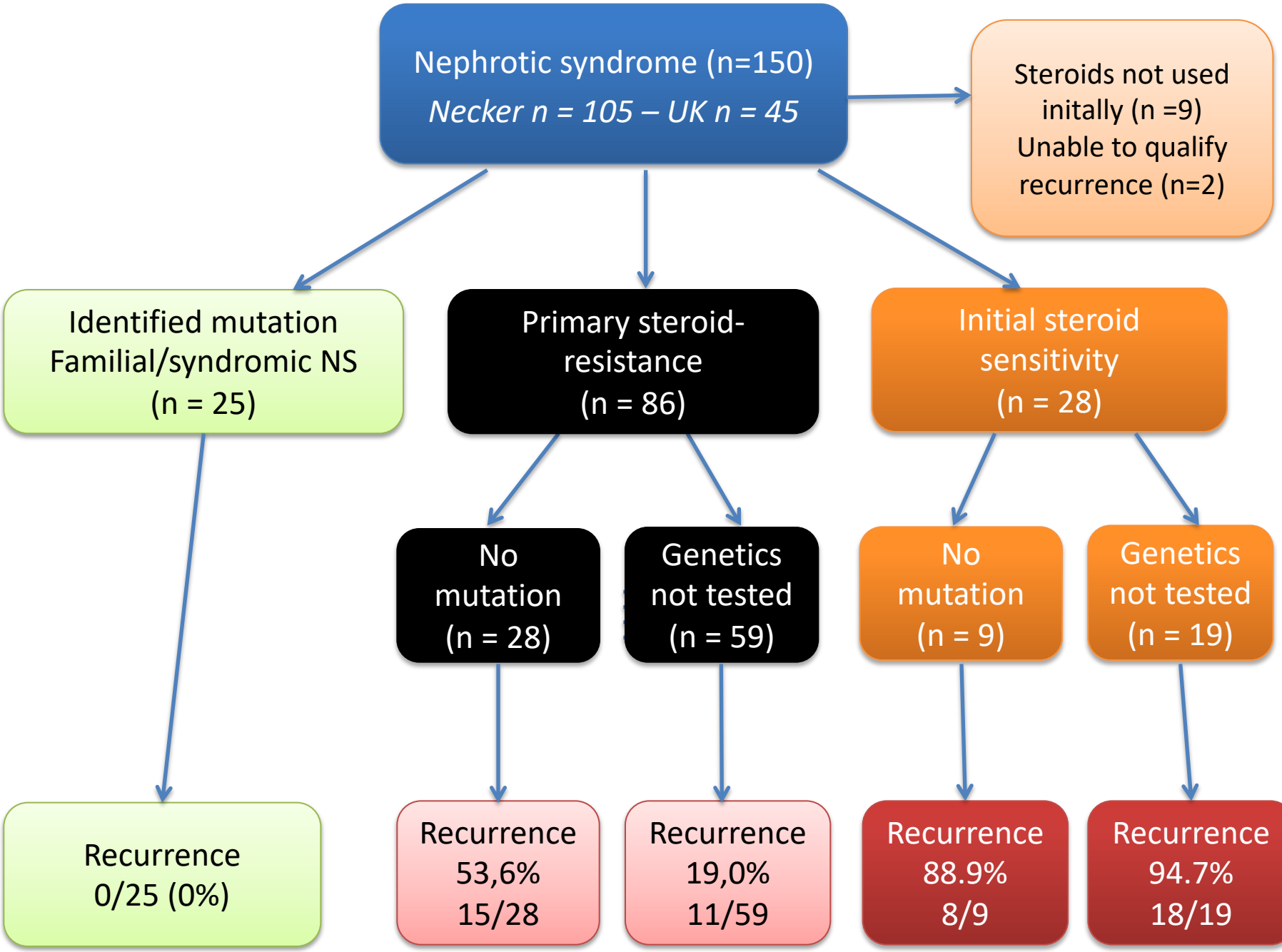
Recurrence rate after Tx 38%
Double rate of Post-Tx complications

Ding (..) Boyer O, Saleem M, JASN 2014



Ding (..) Boyer O, Saleem M, JASN 2014


Nephrotic syndrome (n=150)
Necker n = 105 – UK n = 45
Steroids not used initally (n =9)
Unable to qualify recurrence (n=2)
Identified mutation Familial/syndromic NS (n = 25)
Primary steroid-resistance (n = 86)
No mutation (n = 28)
Genetics not tested (n = 59)
Recurrence 0/25 (0%)
Recurrence 53.6% 15/28
Recurrence 19.0% 11/59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No mutation (n = 9)
Genetics not tested (n = 19)
Recurrence 0/25 (0%)
Recurrence 53,6% 15/28
Recurrence 19,0% 11/59
Recurrence 88.9% 8/9
Recurrence 94.7% 18/19

6) Evaluate the recurrence risk after RTx

2 major factors predict the risk of recurrence

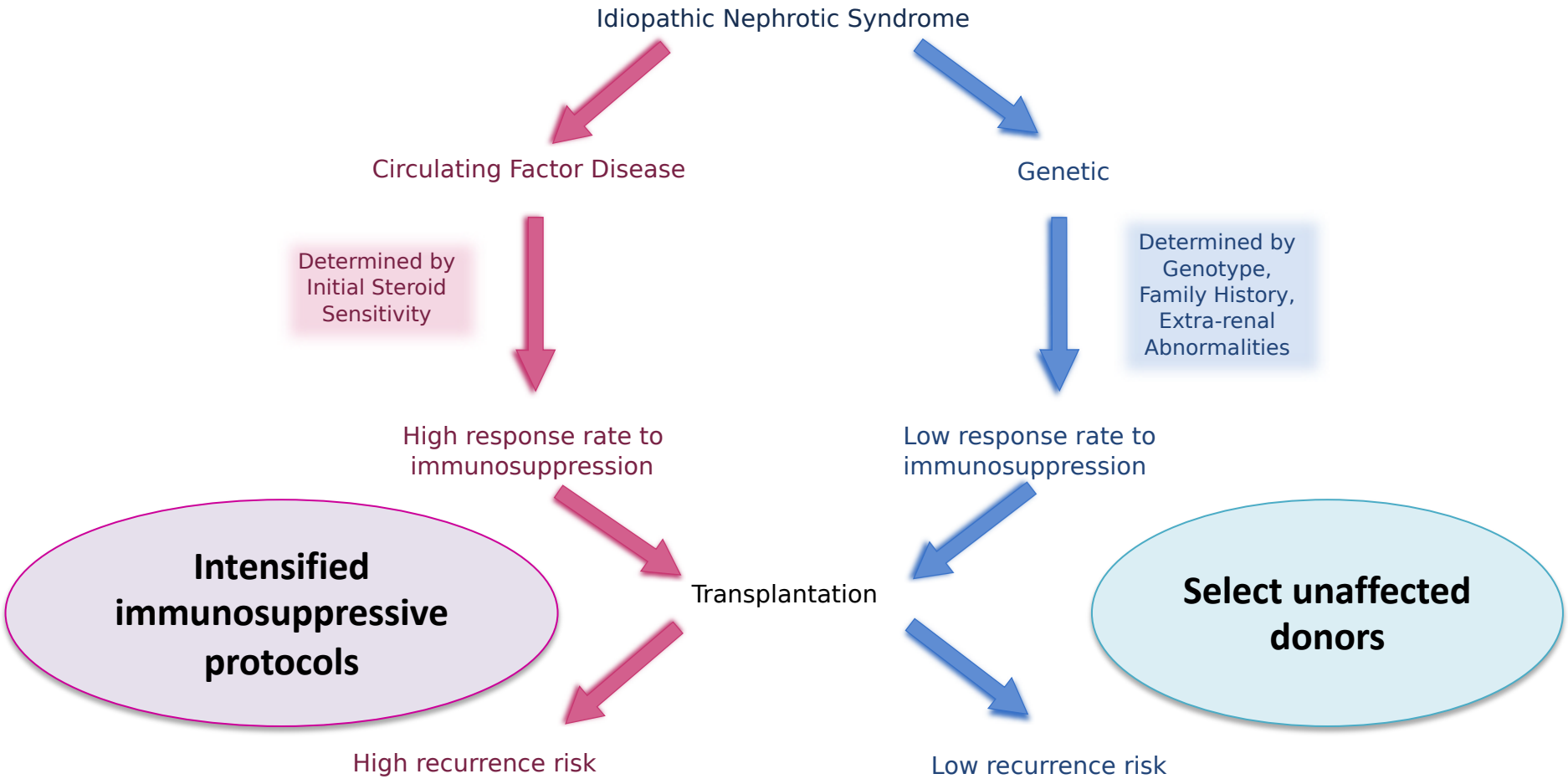
- Genetic origin : very low risk
- Initial steroid sensitivity : very high risk

Table 2. ORs for post-transplant recurrence in children with nongenetic/nonfamilial SRNS

Characteristic	OR (95% CI)	*P* Value
Age of diagnosis <6 yr	0.88 (0.40 to 1.90)	0.84
Time to ESRF <3 yr	0.68 (0.31 to 1.47)	0.44
Age of first transplant <12 yr	0.74 (0.36 to 1.53)	0.47
Time on dialysis <2 yr	0.56 (0.26 to 1.19)	0.18
African-European race	0.92 (0.24 to 3.61)	>0.99
Living donor transplant	6.00 (1.24 to 29.06)	0.02
Steroid sensitivity	30.00 (6.62 to 135.86)	<0.001

Ding (..) Boyer O, Saleem M, JASN 2014

6) Evaluate the recurrence risk after RTx
7) Select unaffected donors



Ding (..) Boyer O, Saleem M, JASN 2014

Clinical implications of genetics: nephrotic syndrome

- Make a diagnosis
  - Some non-podocyte related diseases may mimic SRNS
  - Search and follow extra-renal features
- Provide genetic counselling
  - monogenic diseases
  - Issue of incomplete penetrance
  - Issue of interallelic influence of mutations
- Avoid inefficient immunosuppressive treatments with potential side effects
  - but complete remission with CNI in a subset of patients?
- Discover personalized treatments: COQ10, anti-cubilin? Chaperons?
- Predict a low risk of recurrence after transplantation
- Select potential intra-familial kidney donors

Acknowlegdments

Imagine Institute - Necker

Olivier Gribouval
Géraldine Mollet
Kalman Tory
Guillaume Dorval
Sophie Saunier
Marie-Claire Gubler
Corinne Antignac

Pediatric Nephrology - Necker

Marie-Josèphe Tête
Patrick Niaudet
Rémi Salomon

Imagine Genomic Core Facility

Christine Bole-Feysot

Bioinformatic Core Facility

Patrick Nitschké

All the clinicians who referred the patients

Collaborations

Franz Schaefer (Heidelberg)
Beata Lipska (Gdansk)

ERKNet

The European
Rare Kidney Disease
Reference Network

Next webinar

Fabry disease: new great imposter

Olivier LIDOVE

Paris (Hôpital de la Croix St Simon), France

Tuesday December 3rd 4 pm CET