Kongenitala nefroser och genetik

Christer Holmberg
Hospital for Children and Adolescents
University of Helsinki
Helsinki, FINLAND

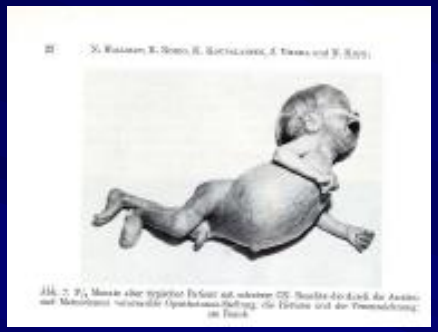
Clinical classification of nephrotic syndrome (NS)

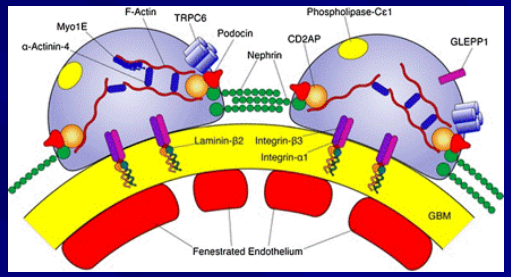
- Onset of symptoms
  - Congenital NS (0-3 months)
  - Infantile NS (4-12 months)
  - Childhood NS (> 12 months)

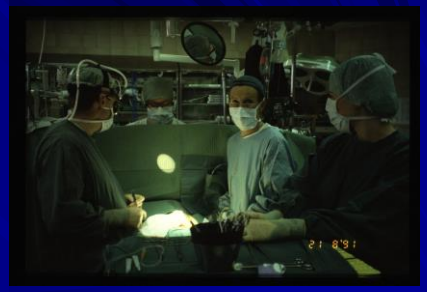
  - Congenital + infantile = early onset NS

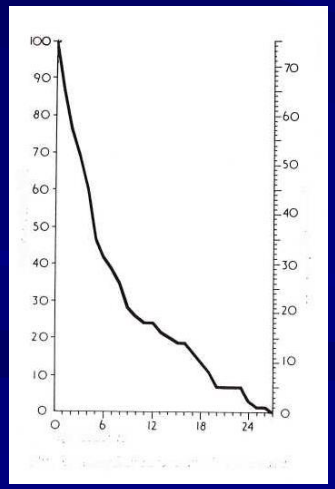
- Response to therapy
  - Steroid sensitive NS
  - Steroid resistant NS

1950----------2017




F-Actin
TRPC6
Phospholipase-Cε1
Myo1E
Podocin
CD2AP
GLEPP1
α-Actinin-4
Nephrin
Laminin-β2
Integrin-β3
Integrin-α1
GBM
Fenestrated Endothelium

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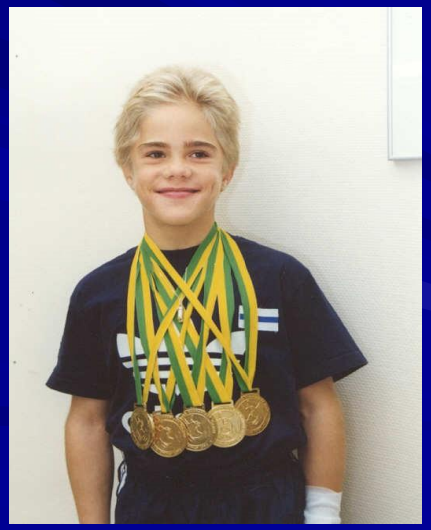


CNS - history

TABLE I. CNSY CASES REPORTED IN LITERATURE

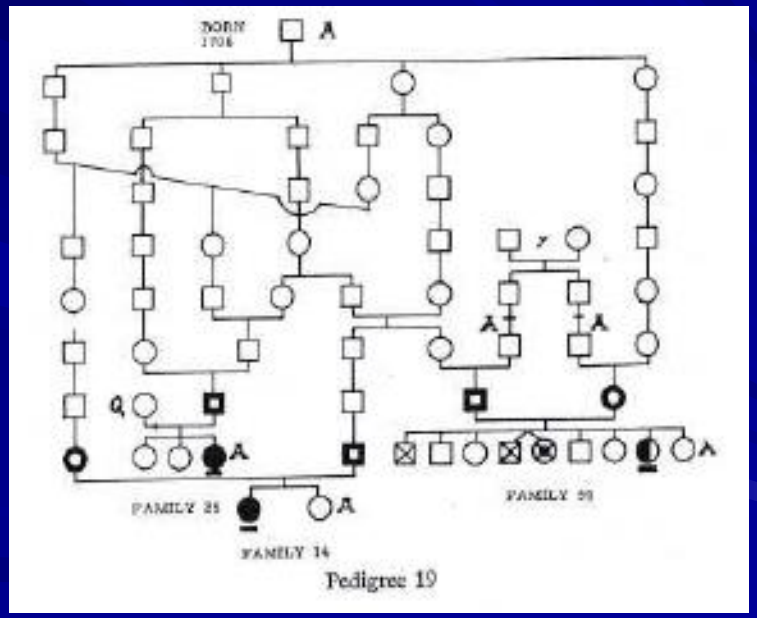
YEAR	AUTHORS	NUMBER OF CASES
1942	Gautier and Miville	1
1950	Lyttle and Goettsch	1
1951	Fanconi et al.	3 (siblings)
1954	Kunstadter et al.	1
1954	Eiben et al.	1
1954	Frischknecht et al.	1
1957	Giles et al.	3 (2 siblings)
1957	Hudson (cited by Giles)	2 (siblings)
1957	Dobbs and France (cited by Giles)	1
1957	Vernier et al.	1
1957	Gruskay and Turano	3 (siblings)
Total		18

- Hallman, Hjelt, Ahvenainen, 1956
- 8 patients
- Clinical picture defined

CNS – etiology??

- infection, nephrotoxic, immunological lesion??
- genetic??
  - several siblings
  - Giles et al. 1957 (intermarriage)
  - Hereditary!!

- Norio, 1966
  - 57 evident CNS families



- Autosomal recessive inheritance

CNS - dialysis

Acta Pædiat Scand 61: 1–4, 1972

THE LOW-WEIGHT GROUPS AND HAEMODIALYSIS

TOM AHOLA, HELINÄ BJÖRKMAN, PAAVO MÄKELÄ, MIKKO PASILA, JUSSI VILSKA and NIILO HALLMAN

From the Children's Hospital, University of Helsinki, Helsinki, Finland

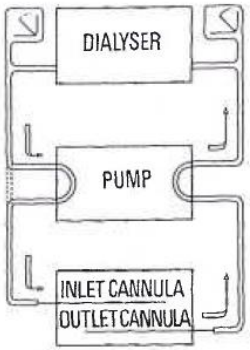


Fig. 2. The extracorporeal blood circulation. The tube indicated with a dotted line shows the conventional route for dialysis.

Table 2. *The treated infants*

Patient	Age (mo.)	Weight (kg)	Surface area (m^2)	Diagnosis	Indication	No. of dialysis	Outcome
R. A.	17	12.6	0.52	Tubular necrosis	Anuria Hyperpotassemia Hypertension	2	Recovery
L. J.	24	11.5	0.50	Stenosis inf. et valv. a. pulm.	Anuria post operat.	1	Recovery
A.-M. P.	13	9.8	0.44	Hemol. uremic syndrome	Anuria	5	Recovery
H. P.	18	11.4	0.49	Hemol. uremic syndrome	Anuria	2	After 3 months residual haematuria + proteinuria
T. K.	2	4.0	0.23	Cong. nephrosis	Bilateral nephrectotomy	6	Died of septic infection
J. G.	23	6.8	0.32	Cong. nephrosis	Bilateral nephrectomy	9	Died after a transplantation attempt
P. T.	4.5[a]	3.2[a]	0.21[a]	Cong. nephrosis	Bilateral nephrectomy	50+	Under regular dialysis

[a] Values at bilateral nephrectomy.

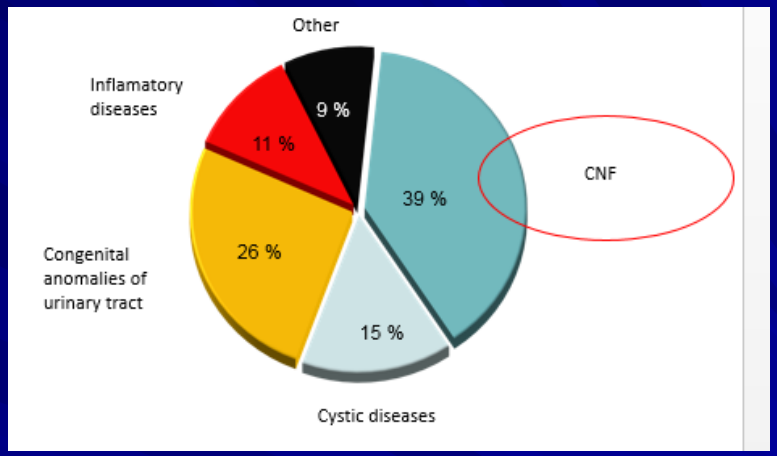
Acta Pædiat Scand 61

CNS – Renal Transplantation

- - Hoyer, Lancet 1973
- -Mahan et al., 1984
  - 41 pts 24 treated after 1971
  - steroids, cytotoxics….no effect
  - agressive nutrition, 8 bilateral nephrectomy
  - 44% family history, 22% Finnish anc.
  - 2 year PS 80%, GS 71%
  - height -3,1 SD, 80 % normal school

Renal transplantations in children

- Helsinki
  - 1986 renal 298
  - 1987 liver 141
    - combined 12
  - 1991 heart 84
  - 2007 lung 4
  - 2009 intestine 4



- 107 CNF patients transplanted

CNS - Renal transplantation

Jahnukainen et al. 2016

Table 4. One- and three-yr graft survival in pediatric KTx recipients

	One-yr graft survival			Three-yr graft survival		
	1982—1993	1997–2012	p value	1982—1993	1997–2012	p value
Age at KTx <2 yr						
LD	92	95.5	0.233	88	95.5	0.076
DD	70	94.6	<0.001	60	94.6	<0.001
Age at KTx 2–5 yr						
LD	83	95.6	0.006	82	90.6	0.063
DD	81	91.5	0.039	69	89	<0.001
Age at KTx 6–16 yr						
LD	90	99.1	0.013	81	96.1	<0.001
DD	77	91.9	0.006	69	88.3	0.002

Hölttä et al., 2016

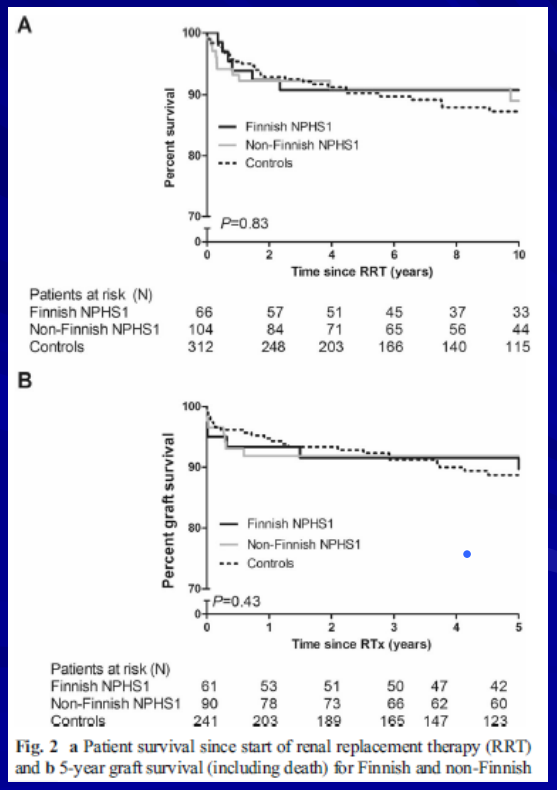


Fig. 2 a Patient survival since start of renal replacement therapy (RRT) and b 5-year graft survival (including death) for Finnish and non-Finnish

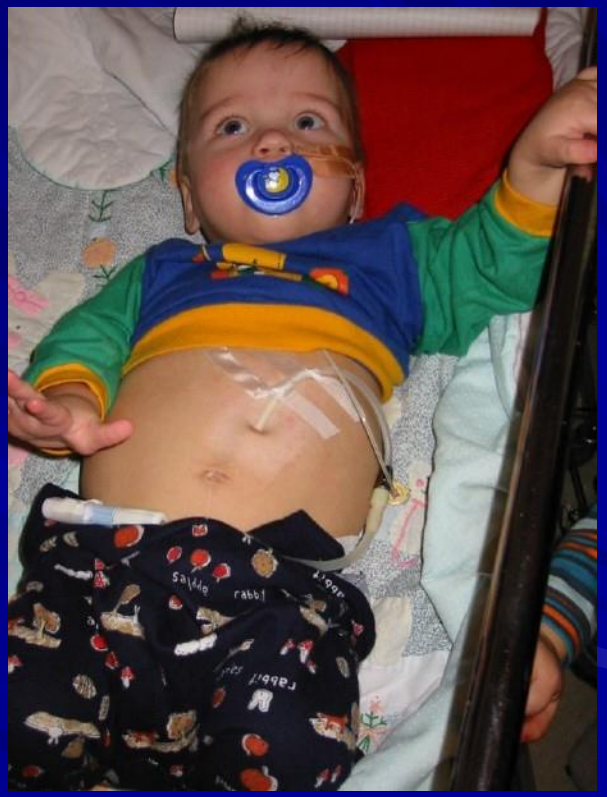
Natural history without therapy

- Reduced growth and development
- Infections
- Thrombotic events
- Sudden death
- Renal failure
- (Wilms tumor/s)

CNS – Renal Transplantation

- Treatment:
  - nutrition
  - albumin
  - anticoagulation
  - thyroxin
  - treatment of infections
  - vitamins

Dialysis:



Nephrectomy?

Parenteral protein supplementation

- Depends on the protein losses
- Intravenous albumin infusions
  - 20 % albumin infusions+furesis 0.5 mg/kg
  - infusions started x3-4 /day,
  - One infusion (6-8 h) at night
  - Albumin amount 1-4 gr/kg/d
    - Oedem, blood pressure, weight gain
    - P-albumin, >15 g/l
- Central vein catheter
  - At the age of 2-3 weeks in CNF

Medical management

- Hypothyroidism
  - Heavy proteinuria leads to losses of TBG, T4,T3
  - Clinical significance somewhat open
  - Thyroxin substitution 6.25-50 ug/d
  - TSH follow-up
- Thrombotic events
  - Anti-coagulants (AT III) lost into urine
  - Warfarin therapy
    - In CNF started at the age of 2-3 weeks
  - AT III (50 u/kg)
    - before surgical procedures

Nutrition

- Optimal nutrition
  - Breast milk/normal formula 100-130 ml/kg/day
  - 100-130 kcal/kg/day
  - proteins 4 g/kg/day
  - lipid supplementation (rapeseed/sun flower oil)
  - A,D,E and water soluble vitamins
  - calcium, magnesium (potassium) supplementation

  - Nasogastric tube or gastrostomy often required

ACEinhibitor and indomethacin therapy

- Primary therapy:
  - ACE-inhibitor (captopril 1-5 mg/kg/d)
- If pure response:
  - ATII blocker added (losartan 0.3-1.4 mg/kg/d)
- If pure response:
  - Indomethacin added (1-5 mg/kg/d)
- Renal function !
- Patients with severe genetic mutations (truncated protein, no expression) hardly response

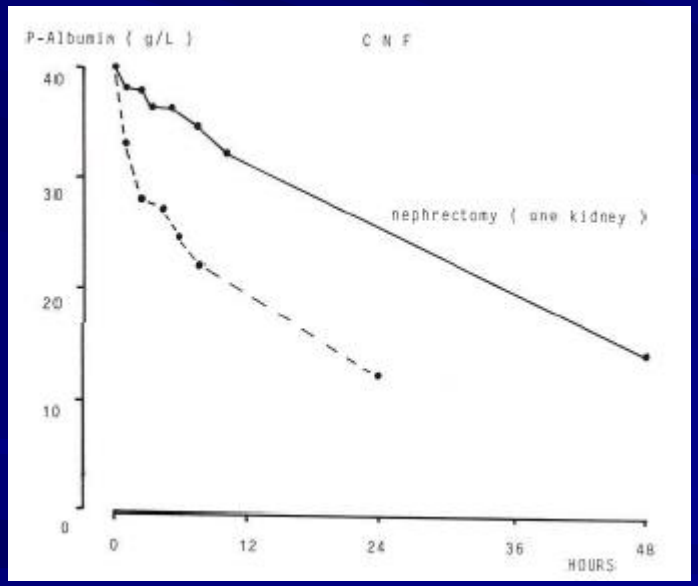
Therapy if severe proteinuria

- Nephrectomy – dialysis – renal transplantation
  - to reduce protein loss and correct its consequences; corrects protein deficiency, improves growth, corrects coagulation defect, hypothyreosis and risk for severe infections
  - to improve quality of life for the child and its family, can be at home
  - unilateral nephrectomy??
  - BUT: terminal renal failure, dialysis and medication

CNS - nephrectomy

Unilateral

Coulthard et al.,1989



Bilateral

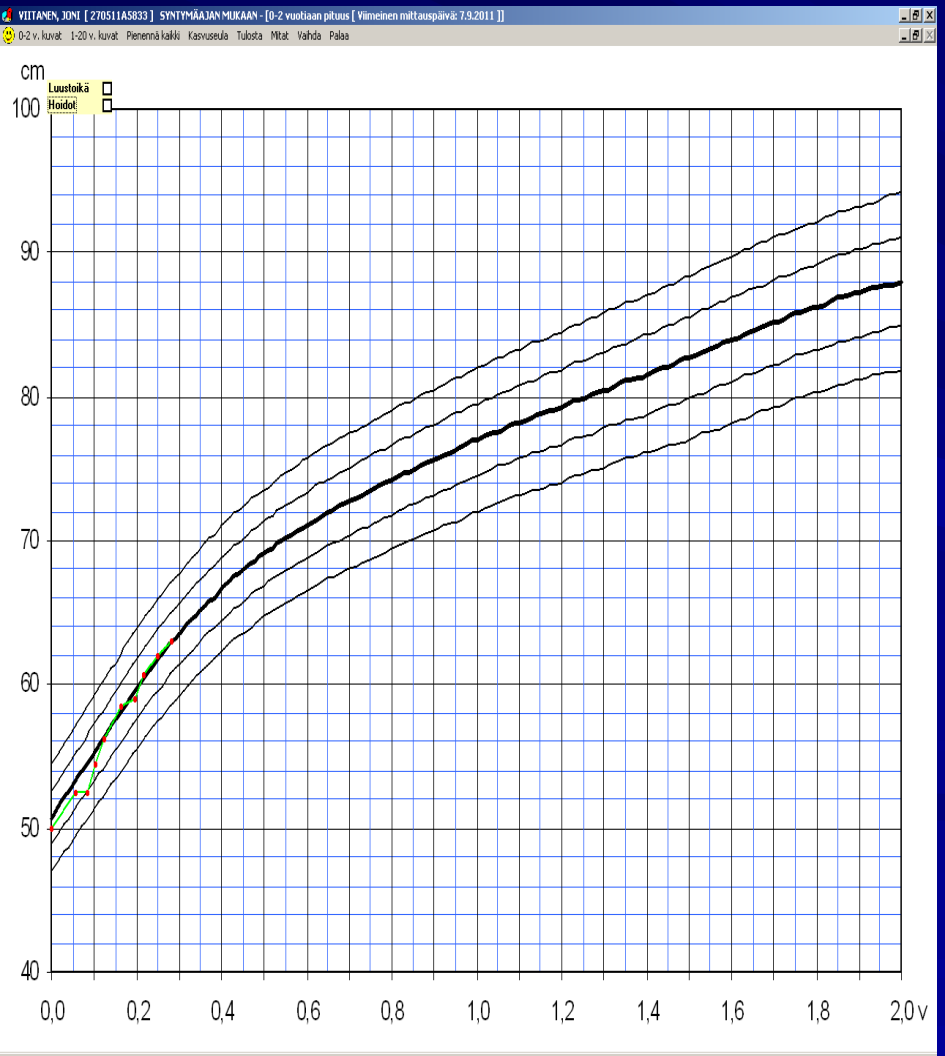
Holmberg et al., 1995

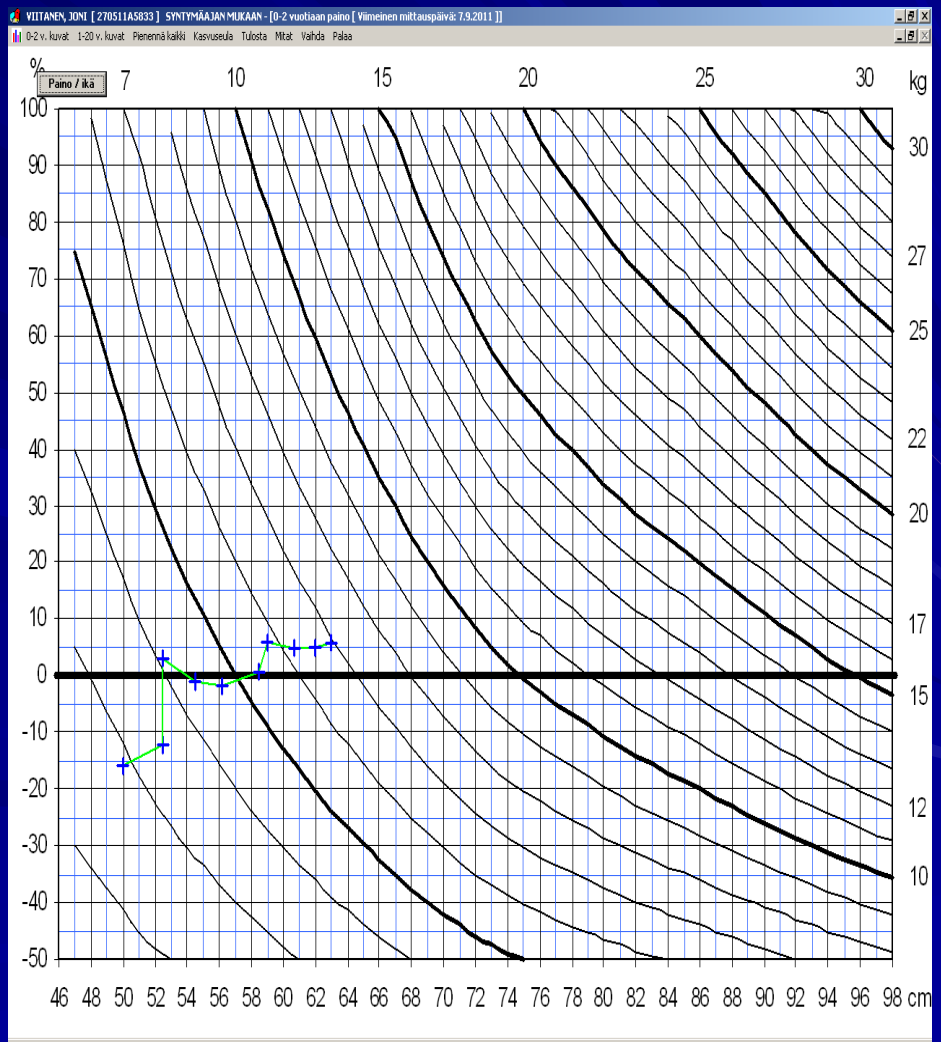
- When severe protein loss
- No reaction to medication
- Reduced growth and QOL for patient and family
- Complications
- Experienced centre

Nephrectomy

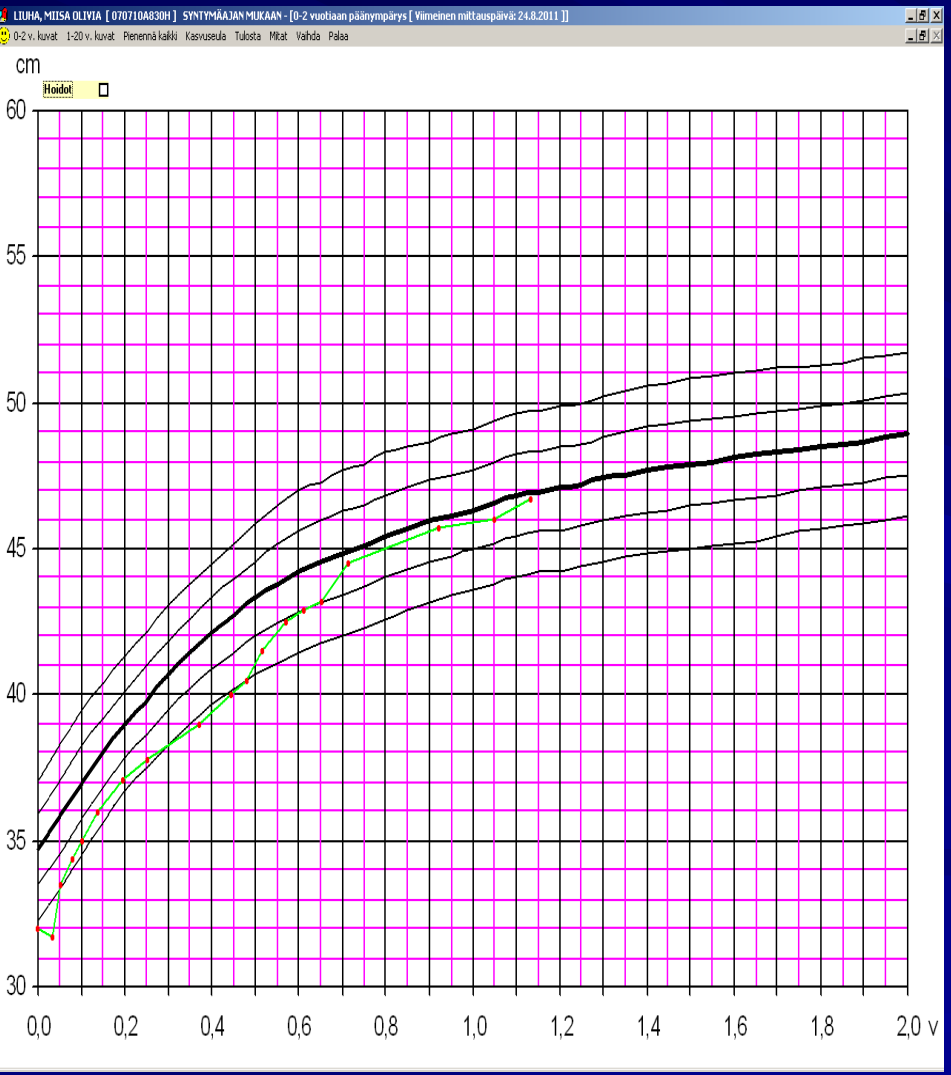
- No nephrectomy needed
  - Development of renal failure and fibrosis reduces proteinuria
- Unilateral nephrectomy
  - To reduce protein losses
  - Improvment of quality of life
  - Used in some centers with good results
- Bilateral nephrectomy + dialysis
  - To stop massive proteinuria + complications
- In Denys-Drash
  - To prevent (treat) Wilm´s tumor

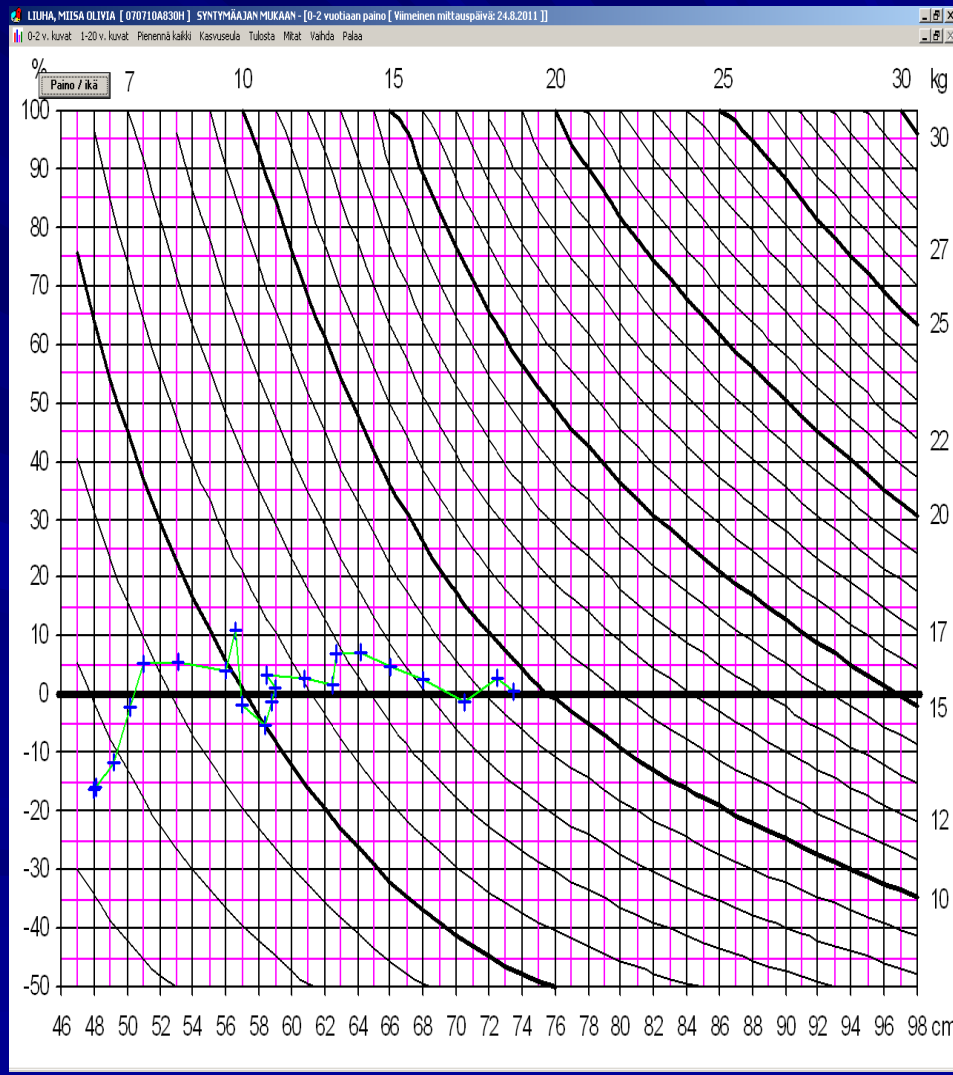
Growth in a Finnish NPHS1 patient diagnosed at birth





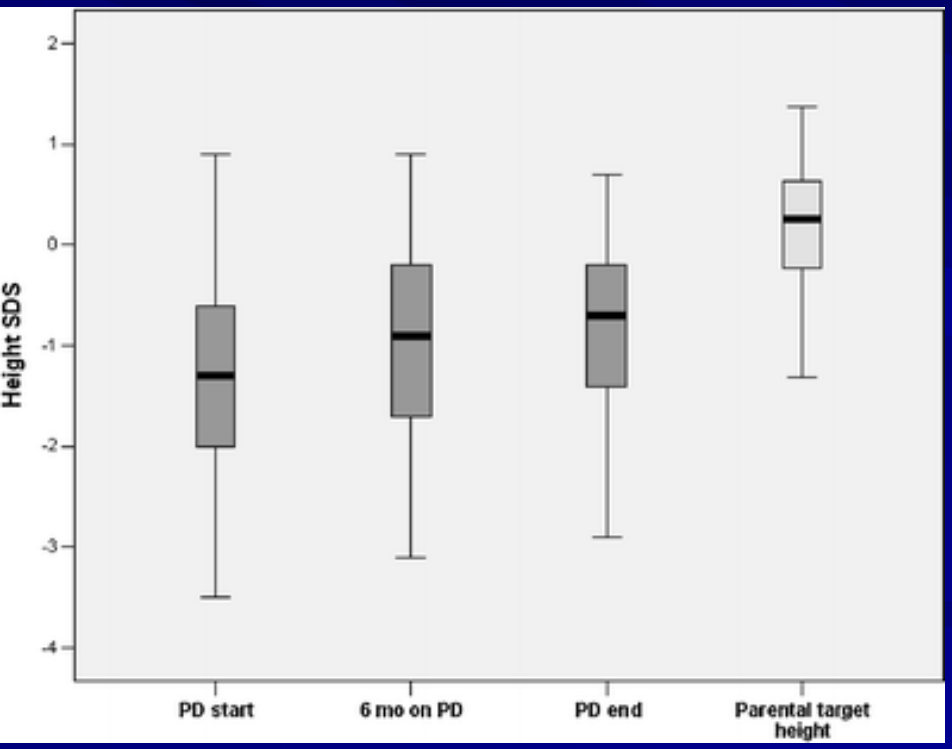
Growth in a Finnsh NPHS1 patient diagnosed at 5 months of age





Growth and puberty after renal transplantation

Growth of 23 CNS children on PD



-109 children transplanted at a mean age of 4,5 years:

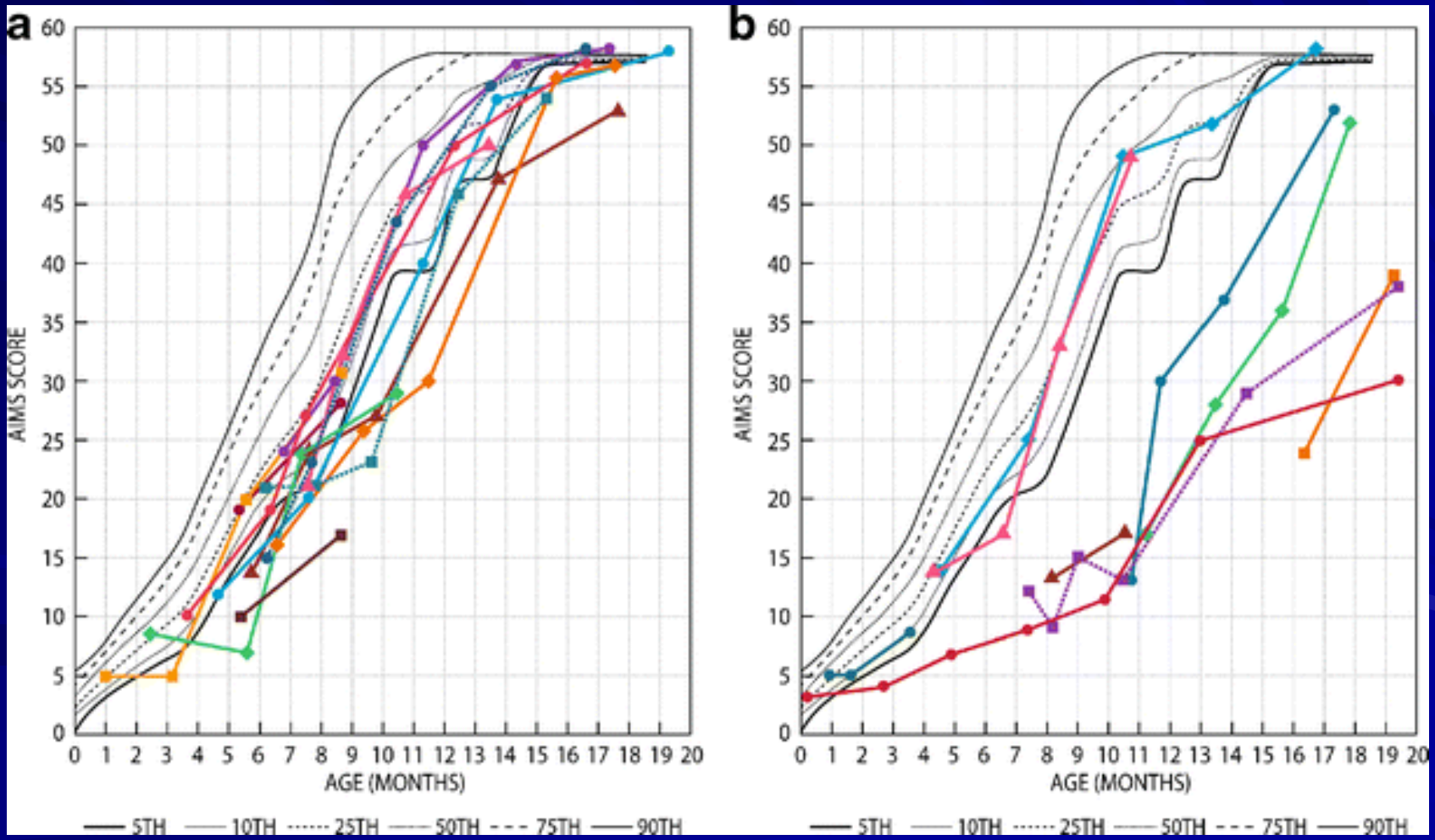
- normal puberty

- final height

  boys 169 cm (- 1.2 SD)

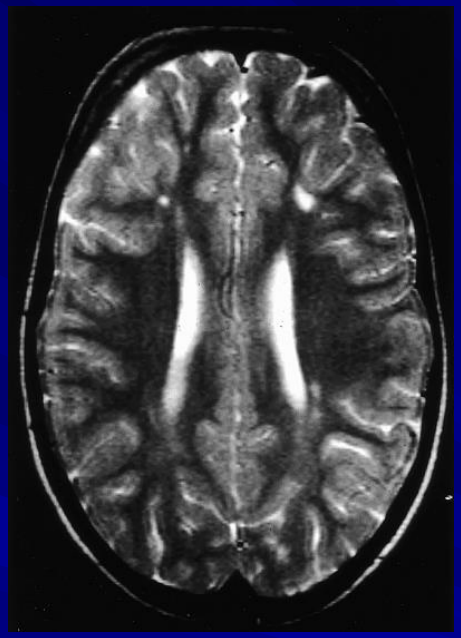
  girls 154 cm (-1.7 SD)

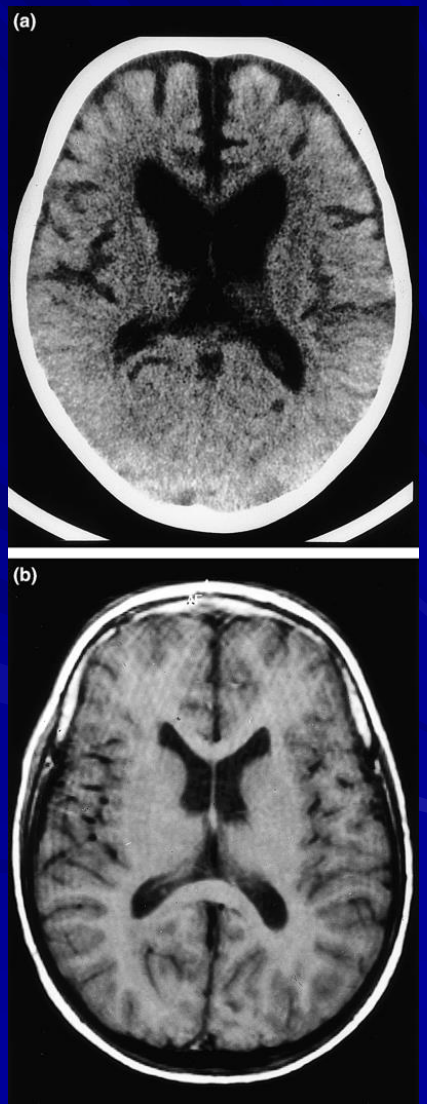
Neuromotor development in 23 CNS children with and without comorbidity



CRF in infancy; neurological outcome

- Valanne et al. 2004
  - 33 pts/29 NPHS1 Tx>5y
  - 54% ischemic lesions in vascular border zones/haemodynamic crises
  - 15% reversible athrophy
- Qvist et al. 2002
  - 79% normal school
  - 76% normal motor perf.
- Laakkonen et al, 2011
  - 21 pts/15 NPHS1 CCPD at 0.59y
  - 52% comorbidity or risk factor for abnormal dev.
  - 30% normal, 43% minor imp. and 29% major imp. (all comorb. or risk factor)





Neurodevelopmental outcome of 21 CNS children

- 29 % normal
- 43 % minor impairment
- 29% major impairment

All attended full time school

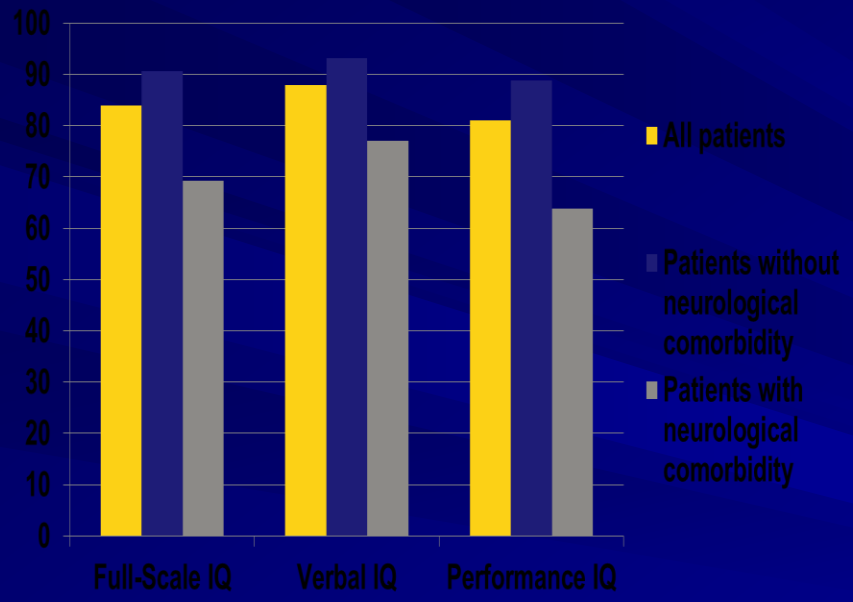
Quality of life??

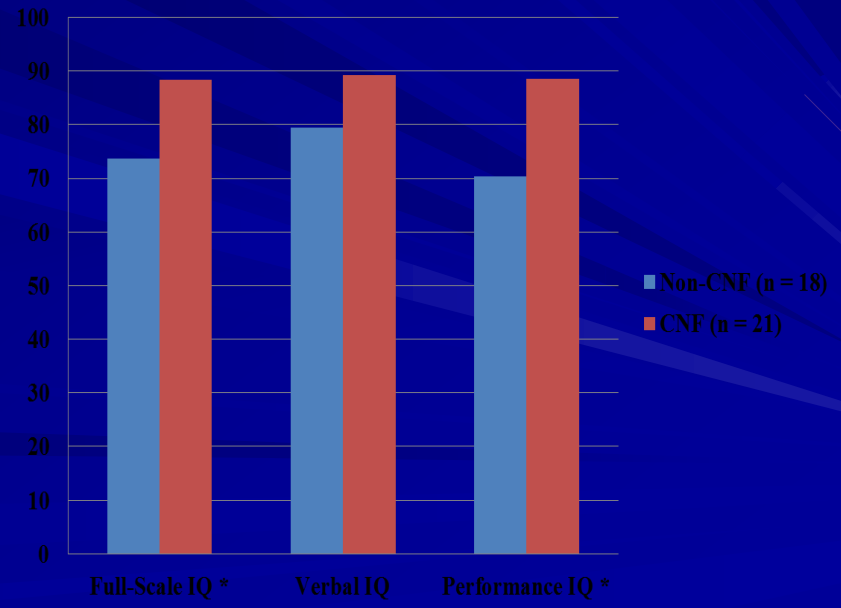
- Early CNS patients had neurological problems (no anticoagulation!) and 54% arterial border zone infarcts

- 21 pts treated 1987-1995, > 50% CNS assessed for HRQL at 6 y and adults (21y) and CBCL and ASR:
  - 52 % secondary level or vocational education (N=66%)
  - ASR normal range
  - HRQL 0.94/controls 0.97, = as in all chronically sick pts.
  - some visuomotor and verbal impairment = test and support!!
  - those with early arterial border zone infarcts did as well as the others!!

Neoropsychological development; comorbidity and CNF

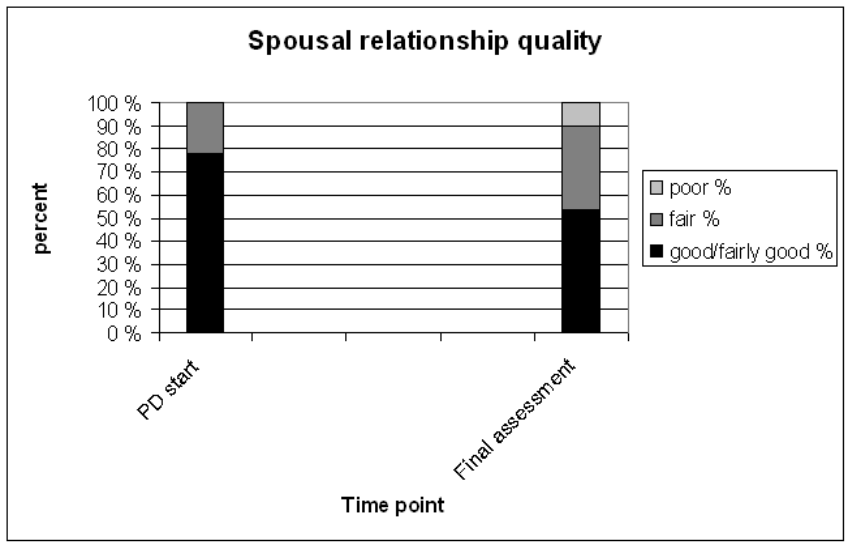
Haavisto et al,, 2012,2013

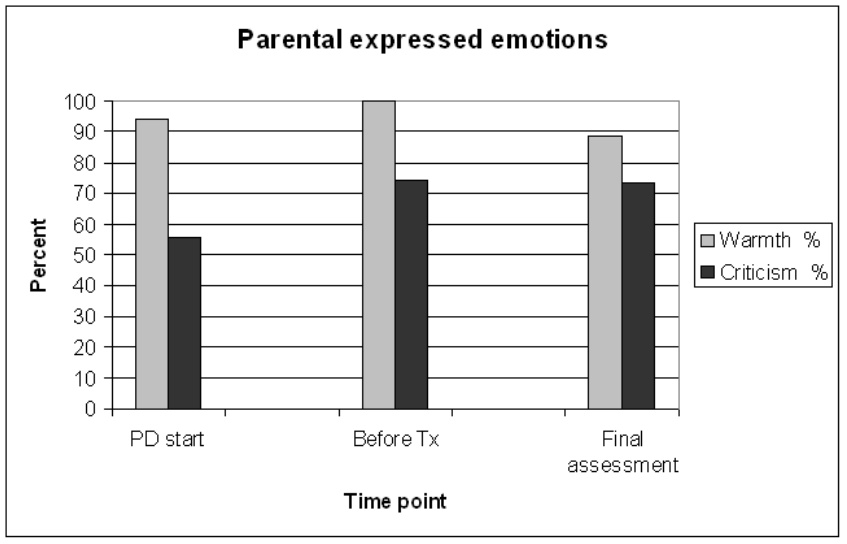




Infants in PD; family coping

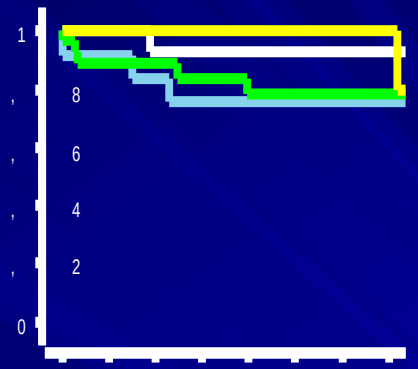
Laakkonen et al., 2014



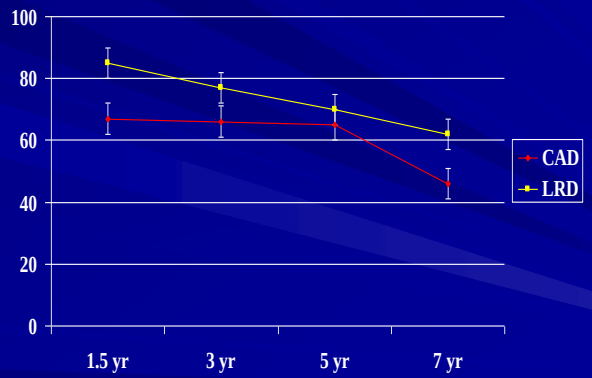


Kidney transplantation

- Results in infants as good as in older children
  - US: DD allograft survival 93 % at 3 years
  - LD allograft survival 95 % at 3 years
  - Scandinavia: All survivals in infants equal to older children

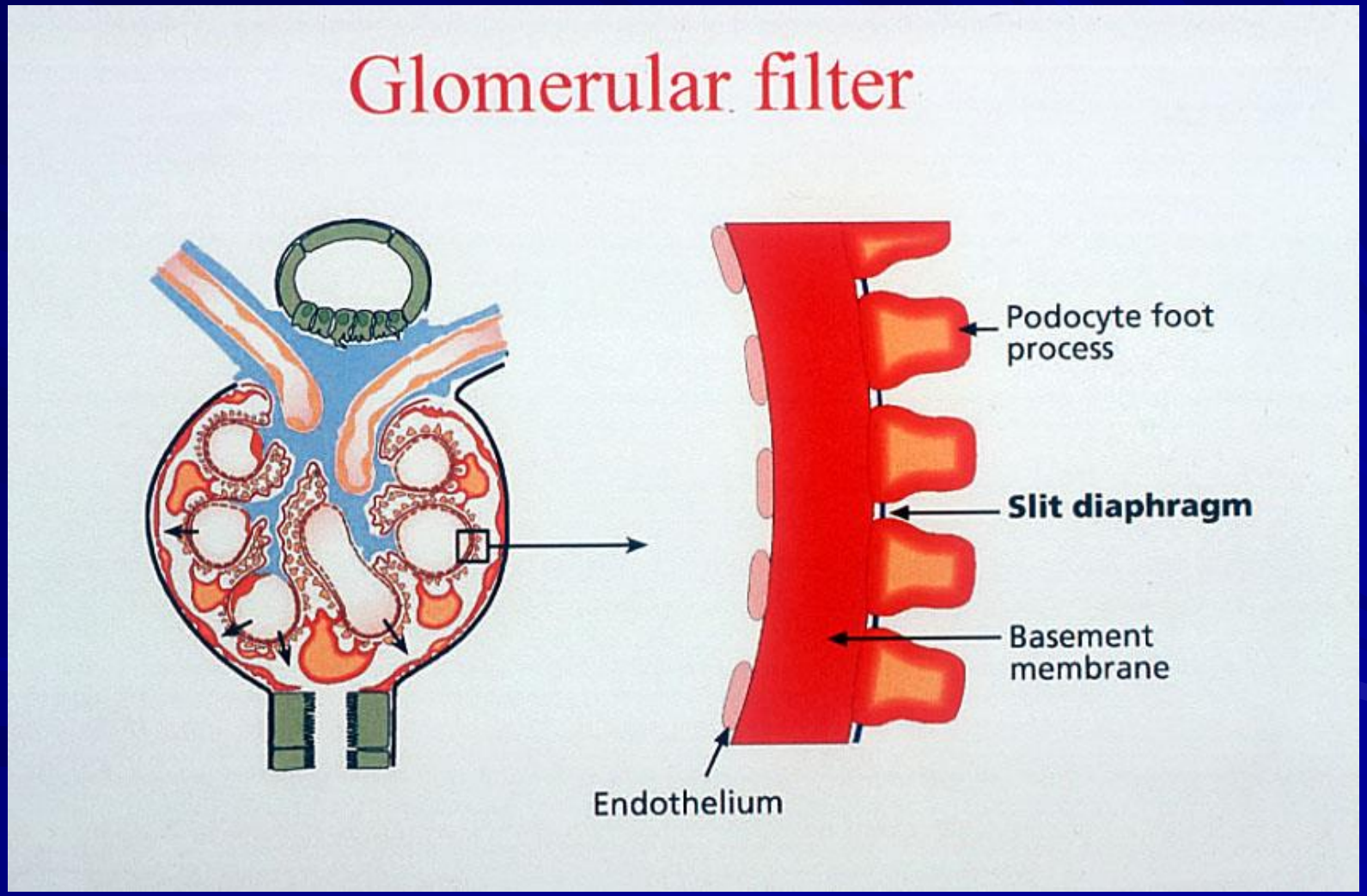


- Extraperitoneal placement possible when recipient weight 9-10 kg
  - 1.5 x fluids during the early weeks



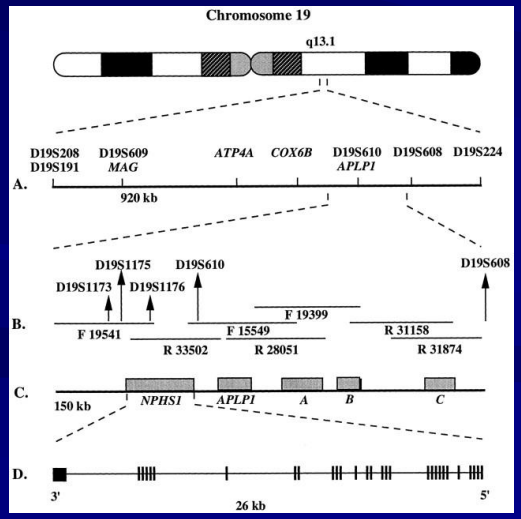
- Genetic diseases do not show recurrence
  - An exception is a CNF child with two severe truncating mutations (Fin-major homozygotes)

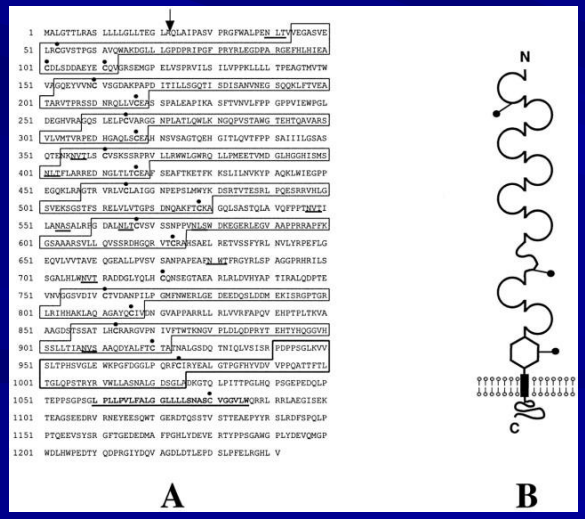
What is wrong in CNF??

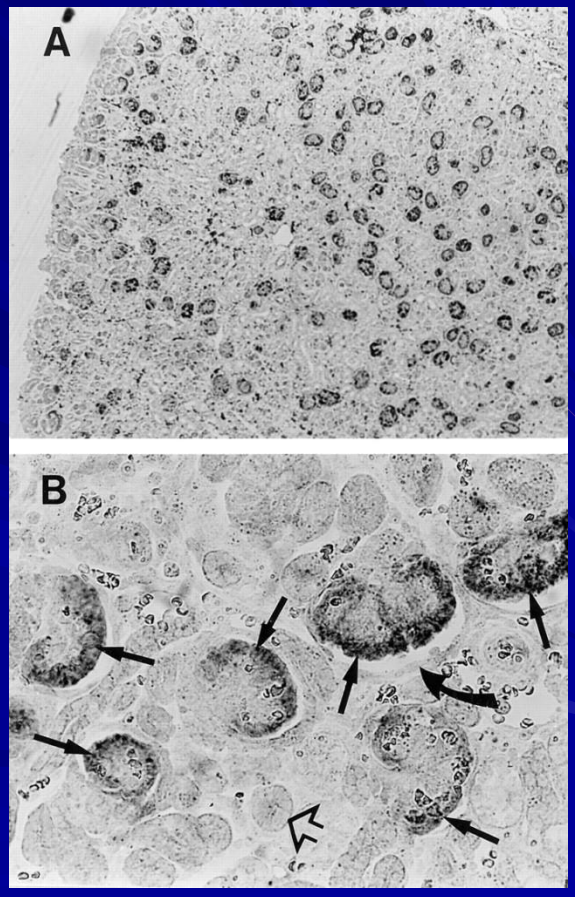


Gene for Congenital Nephrotic Syndrome

- Kestilä et al. Cell, 1; 575-582, 1998

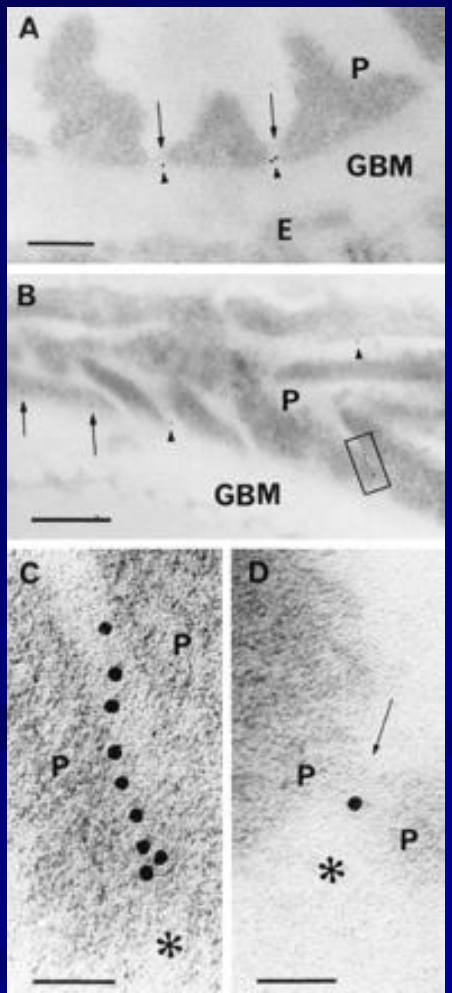


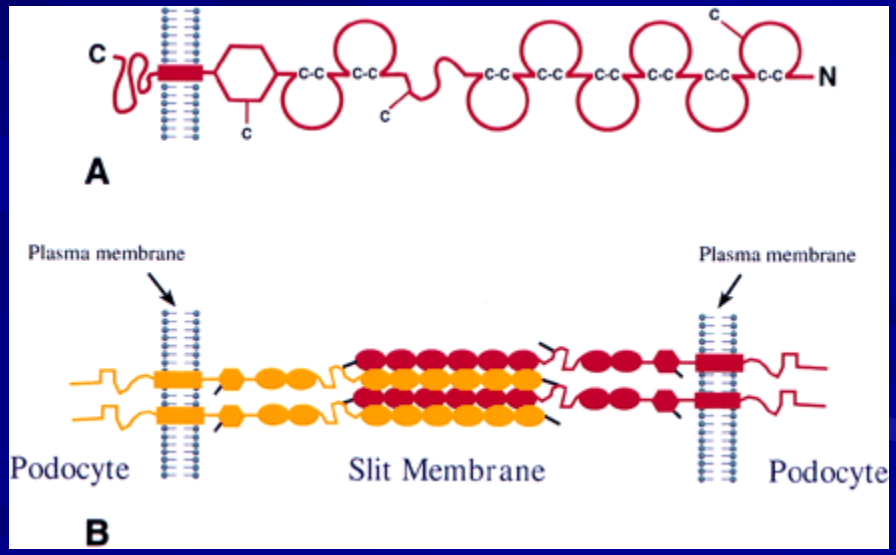




Nephrin is located at the slit diaphragm

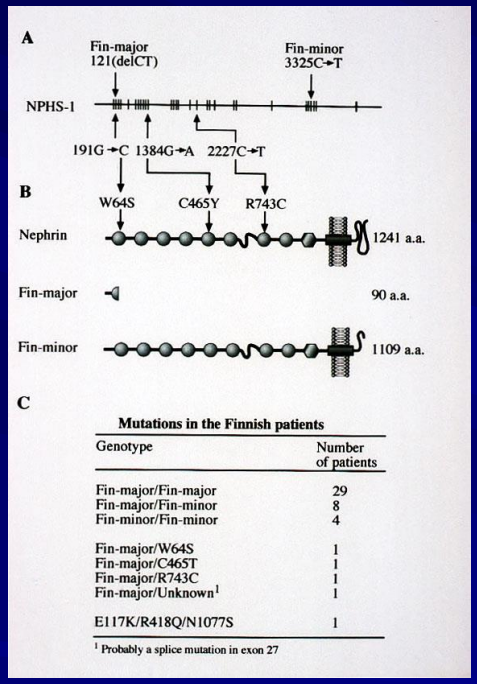
- Ruotsalainen V, Ljungberg P et al., PNAS 96;7962-7, 1999





Nephrin in CNF??

- Kestilä, Lenkkeri, Ruotsalainen, Ljungberg et al., 1999

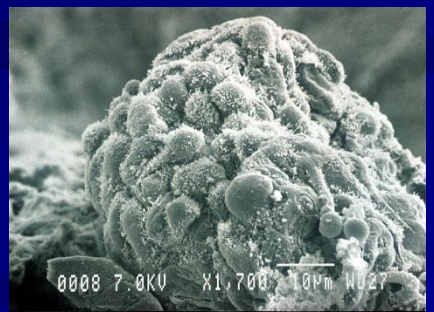


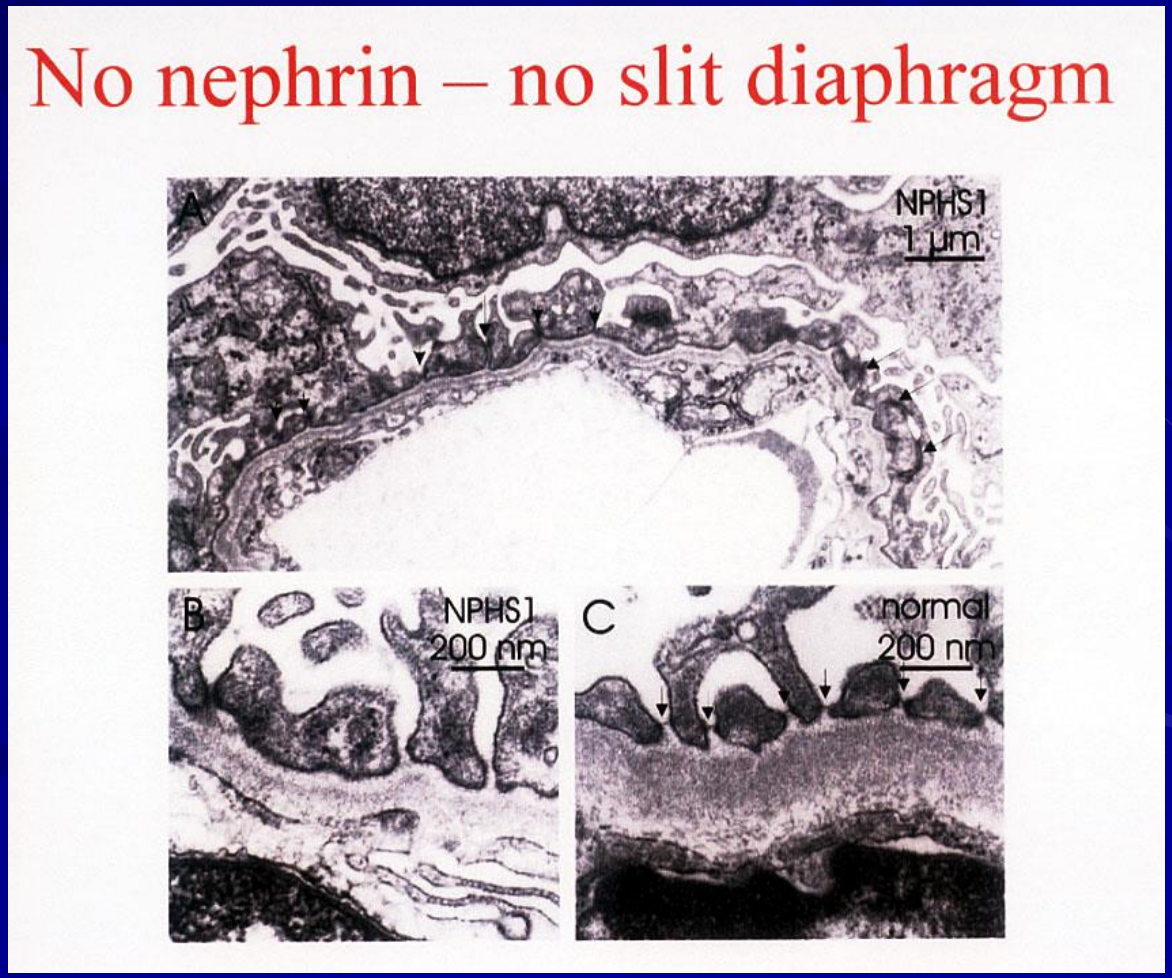
C

Mutations in the Finnish patients

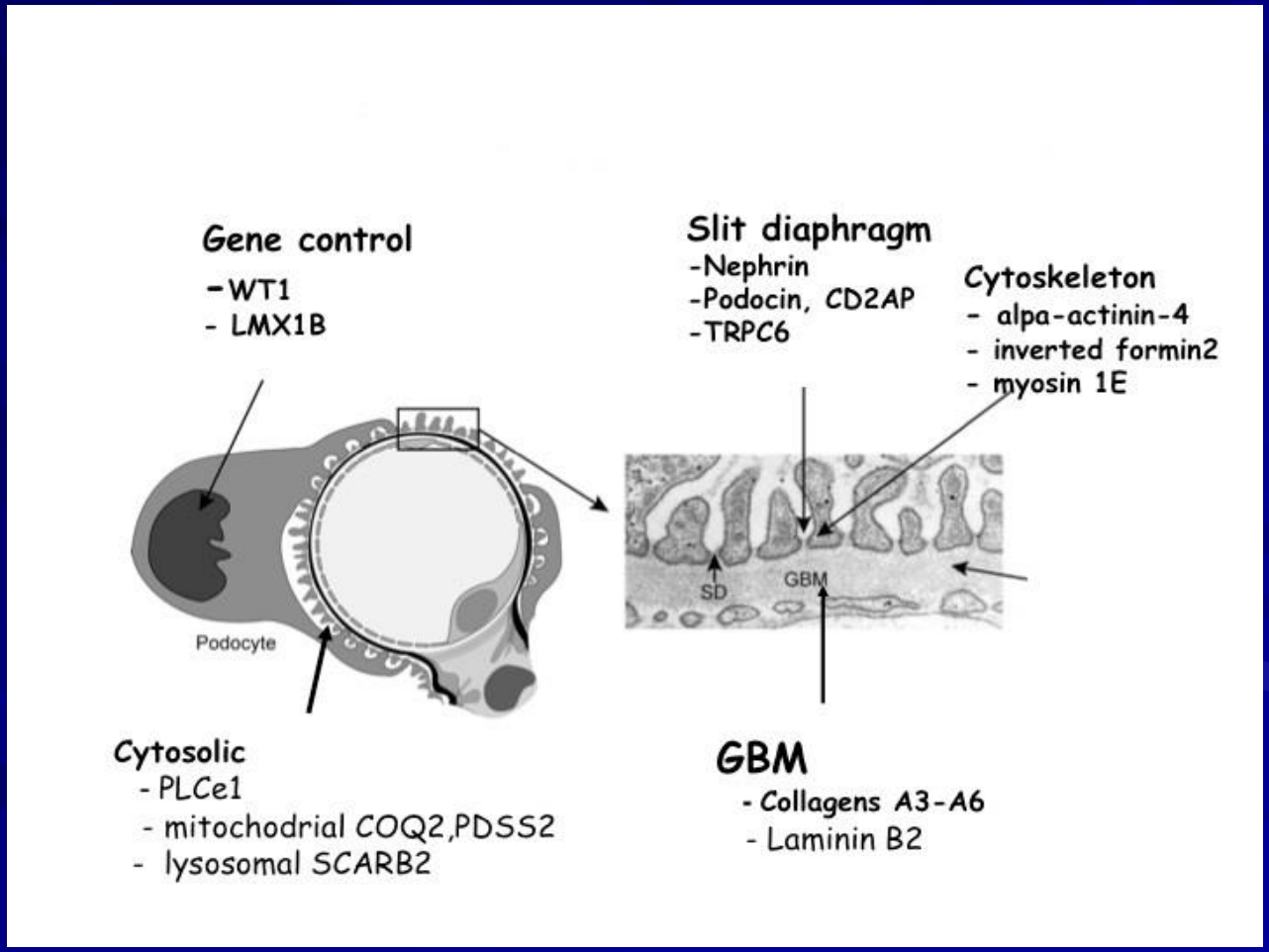
Genotype	Number of patients
Fin-major/Fin-major	29
Fin-major/Fin-minor	8
Fin-minor/Fin-minor	4
Fin-major/W64S	1
Fin-major/C465T	1
Fin-major/R743C	1
Fin-major/Unknown[1]	1
E117K/R418Q/N1077S	1

[1] Probably a splice mutation in exon 27

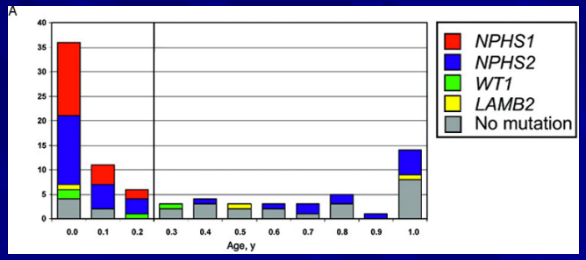




Podocyte Gene Mutations known today



Congenital Nephrotic Syndrome

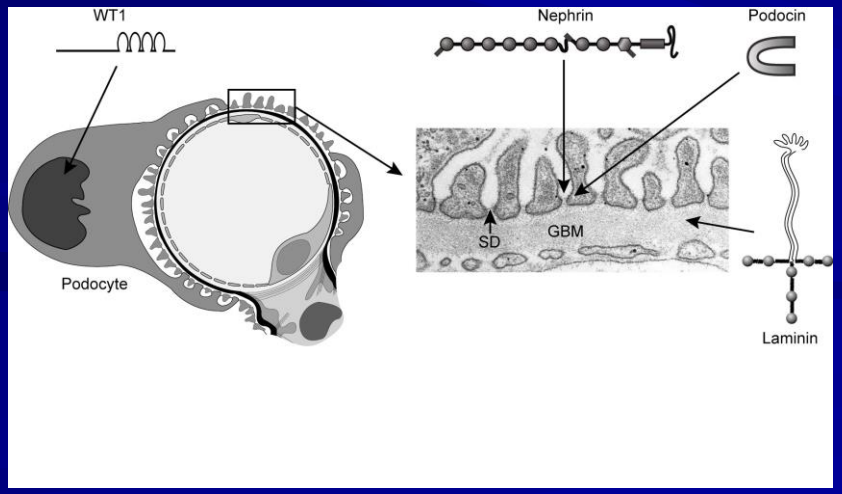


- **Primary forms:**
  - Nephrin gene (*NPHS1*) mutations (CNF,NPHS1)
  - Podocine gene (*NPHS2*) mutations
  - Phospholipase C epsilon 1 gene (*PLCE1*) mutations (NPHS3)
  - Wilms tumor suppressor 1 gene (*WT1*) mutations (Denys-Drash, Frasier, isolated NS)
  - Laminin β2 gene (*LAMB2*) mutations (Pierson syndrome, isolated NS)
  - Laminin β3 gene (LAMB3) mutations (Herlitz junctional epidermolysis bullosa)
  - Lim homebox transcriptionfactor 1β gene (*LMXB1*) mutations (Nail-patella syndrome)
  - Decaprenyl diphosphate synthase subunit 2 gene (*PDSS2*) mutations (Leigh syndrome with nephropathy)
  - Primary coentzym Q2 gene (*COQ2*) muatations (*COQ2* nephropathy)

Etiology of NS in the first year

Monogenic disorders
(Podocytopathies)

Nephrin	(NPHS1, CNF)	- isolated, severe NS
Podocin	(NPHS2)	- isolated, steroid resistant NS
PLCe1	(NPHS3)	- isolated , early onset NS
WT1		- Denys-Drash, Frasier, isolated NS
Lamininβ2	(Lamb2)	- Pierson syndrome, isolated NS



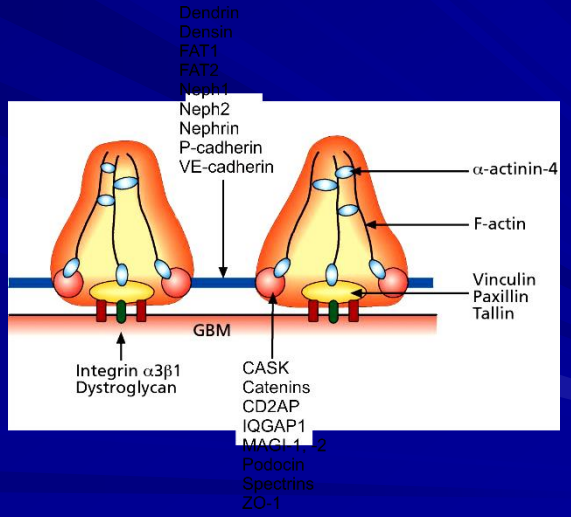
Etiology of NS in the first year

Genetic syndromes

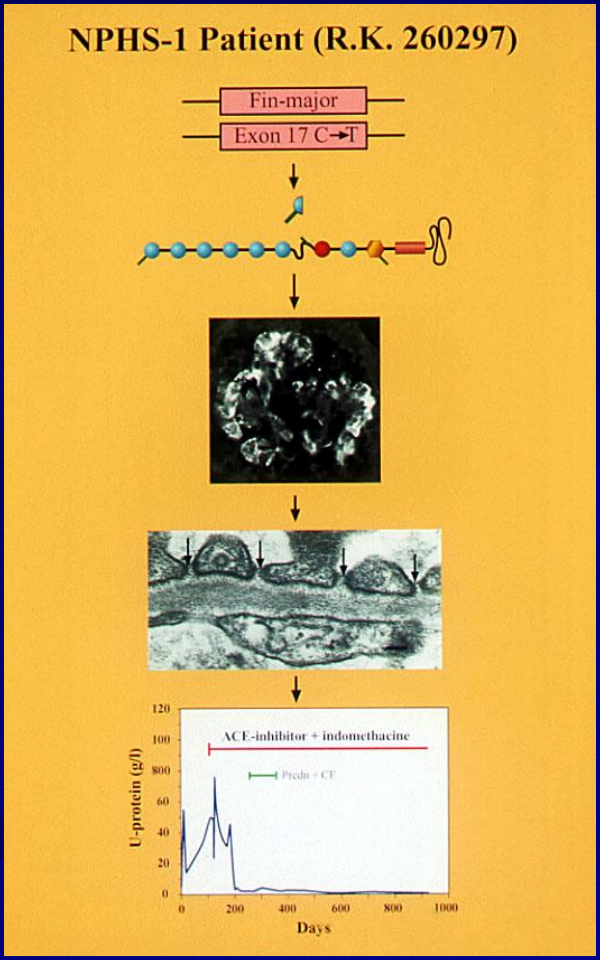
- Mowat-Galloway syndrome
- Mitochondrial cytopathy
- Nail-Patella syndrome
- Glycosylation type I disorder
- Herlitz junctional epidermolysis bullosa

Familial (and sporadic)

- Gene defect not yet known



Treatment in less severe mutations



- Lahdenkari et al Kidney Int, 2004
  - 25 adults MCNS as chidren
  - 5 NPHS1 heterozygotes
  - 1 Fin-major and Arg800Cys

- Schoeb et al. 2010:
  - 67 CNS/36 NPHS1
  - 3/11 steroids +
  - 9/34 ACE-inhibitors +
  - 8/28 ACE + indomethacin +

Should other medications be tried??

- Steroids, Cyclosporine ?? Not only immunosuppressants but also effects on the podocyte!!
- Probably no effects on primary mutation caused CNS, especially < 1 years of age. Severe mutations/less severe ones??
- Minimal change/FSGS no mutation and early infant CNS??
- Medications to reduce development of ESRD???

CNS; Recurrent Nephroses after Renal Transplantation

- Kuusniemi AM et al., Transplantation, 2007
  - 23 episodes/19 grafts in 13/65 pts. 1986-2006
  - All Fin-major homozygotes, 73% anti-nephrin antibodies

- Holmberg and Jalanko, Pediatr Nephrol, 2014

Table 2

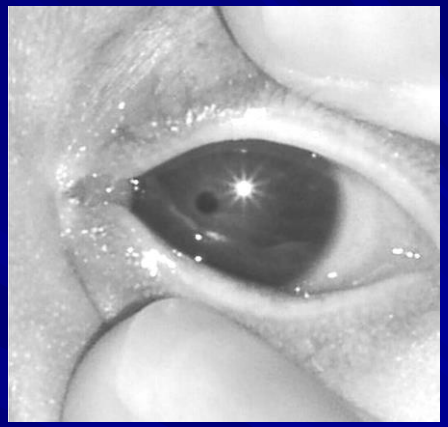
Treatment and outcome of the last six Finnish CNS patients with recurrence of proteinuria and nephrotic syndrome after RTx

Patient	Mutation	dgn	RTx, age	Re-nephrosis (no)	Time after RTx (mo)	Therapy	Outcome (+ time since last remission in bold)
1 UTI, polyoma, rejections	Fin-major homozygote	at birth	1y 7mo	1)	51	MP, Cyclo, PE	**Remission 7y 7mo**
2	Fin-major homozygote	at birth	2y 4mo	1) 2) 3) 4) 5) 6)	4, 5 12 23 26 31 40	MP, Cyclo, PE MP, Cyclo, PE MP, Cyclo, PE MP, Cyclo, PE, ACE MP, Cyclo, PE, ACE MP, Rituxi x4, ACE	Remission " " " **Remission 6y**
3	Fin-major homozygote	at birth	1y 1mo	1) 2)	40 42	MP, Cyclo, PE ACE MP, Rituxi x4 ACE	Remission after 1mo **Remission 5y 6mo**
4	Fin-major homozygote	at birth	2y 10mo	1) 2)	4 5 20	MP, PE, Rituxi x4 Cyclo MP, PE, *Bortezomibi x4* Rituxi x1	Remission after 12mo still γ-glob. infusions **Remission 3y 7mo**
5 H1N1	Fin-major homozygote	at birth	1y 4mo	1) 2)	32 60	MP, Cyclo, PE +Rituxi x2 +ACE +*Bortezomibi x4* +Rituxi x1 MP, Rituxi x4 ACE	U-prot: 1.5 g/l Transplant nephropathy, HD
6	Fin-major homozygote	at birth	1y 8mo	1)	13 14	MP, Cyclo, PE Rituxi x2	Remission after 11mo **Remission 4y 6mo**

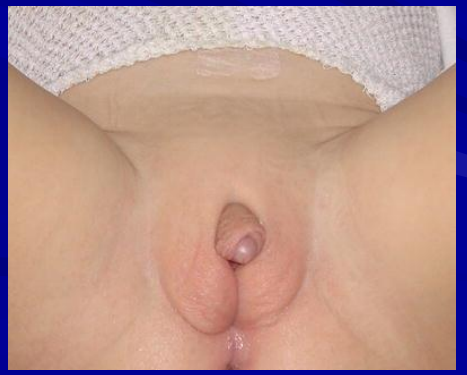
RTx renal transplantation, *y* year, *mo* month, *MP* methylprednisolone, *Cyclo* cyclophosphamide, *PE* plasma exchange, *ACE* angiotensin-converting enzyme inhibition, *Rituxi* Rituximab, *CNS* congenital nephrotic syndrome, *UTI* urinary tract infection

Diagnostics of CNS

- Placenta
  - > 25 % of birth weight
    - Intrauterine proteinuria



- Neurological findings (Mowat-Galloway, Pierson)
  - Muscular hypotony common in NS
  - Microcephaly, seizures, retardation
- Ocular findings (Pierson)
  - Microcoria, embryotoxon, cataract, etc.



- Genitals (WT1)
  - Ambiguous
- Cardiac findings
  - -LVH quite common in hypoproteinemia
  - - Malformations reported in NPHS2 -patients

Renal biopsy

Histology

-Does not reveal the etiology

NPHS1: MI, FSGS, MCNS, DMS

NPHS2: FSGS,MCNS, CNF, MPGN

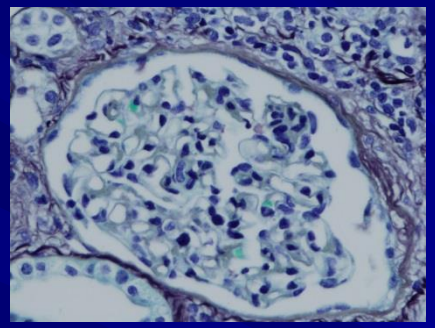
WT1 and PLCe1 : DMS, FSGS

Lamb2: DMS

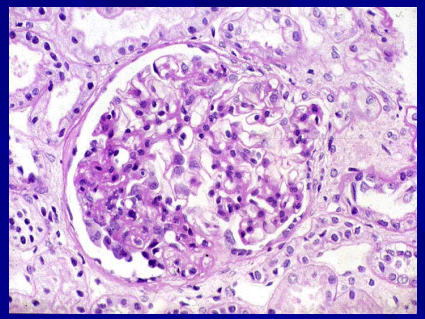
-Findings vary from glomerulus to glomerulus

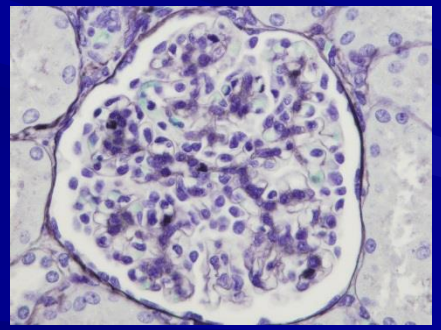
-Tells about the progression
-The amount fibrosis etc.

Minimal change

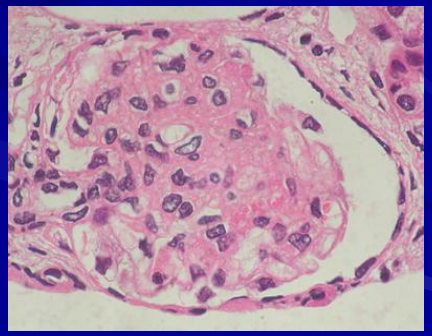


FSGS





Mesangial increase (MI)



DMS

Diagnostics of CNS (histology)

- **Congenital**
  - radial dilatation of PT — *NPHS1*
  - MGC/FSGS — *NPHS2, NPHS1*
  - DMS — *WT1, PLCE1*
- **Infantile**
  - MGC/FSGS — *NPHS2, NPHS1, WT1, PLCE1*
  - DMS — *WT1, PLCE1*
- **Childhood**
  - MGC/FSGS — *NPHS2, NPHS1, WT1, PLCE1*
  - DMS — *WT1, PLCE1*
- **Juvenile**
  - FSGS — AR or Sporadic — *NPHS2*
    AD — *ACTN4, TRPC6*

Gene analysis

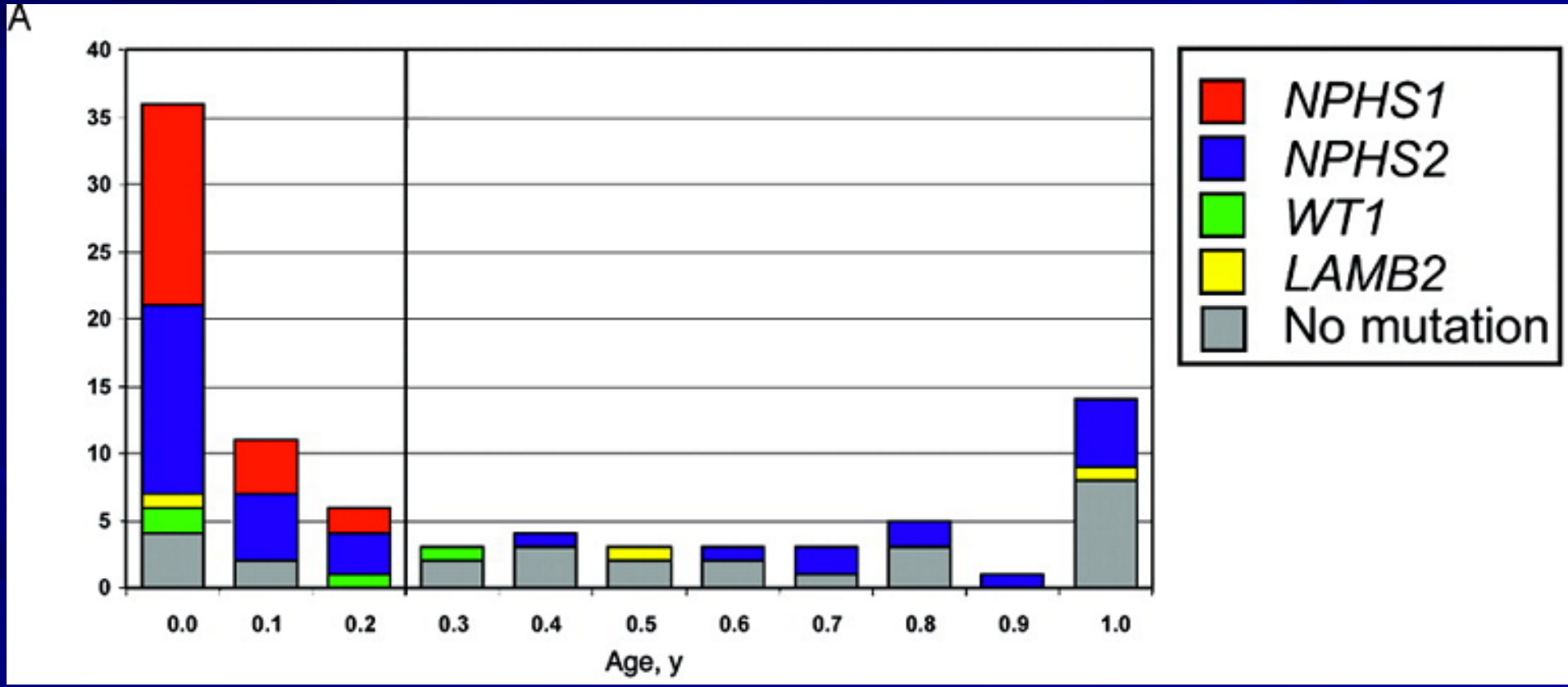
- Diagnostics
  - Reveals etiology
  - Guides for further studies
    - WT1: sex chromosmes, wilms´
    - Pierson: ocular and neurological studies
- Management
  - Genetic disorders resistant to immunosuppressives
    - Avoidance of unnecessary therapies
  - Evaluation of the possible effect of therapy
    - "Mild mutation": Missense (amino acid change)
    - "Severe mutation": Deletion, non-sense, frame shift

Gene analysis

- Evaluation of the success of transplantation
  - Recurrence risk in the graft is low in genetic diseases
  - Choosing donor: LRD vs. CAD
- Genetic counseling
  - Prenatal diagnosis of the next child in the family
    - Analysis is fast if a mutation is already known
- Analyses available
  - Athena Diagnostics, Helsinki (Jalanko)
  - NPHS1 (nephrin), NPHS2 (podocin), WT1, Lamb2 (laminin),
  - a-Actinin-4, TRCP6

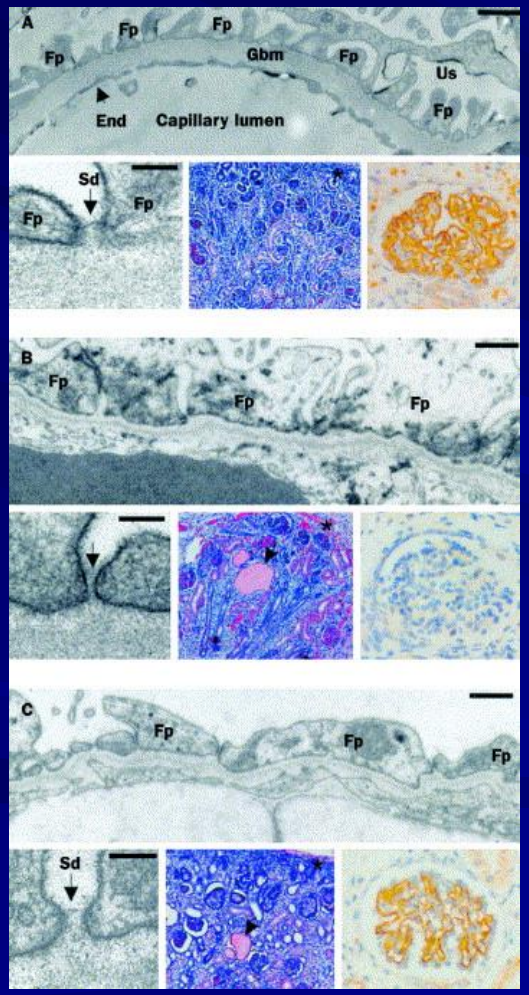
Nephrotic syndrome in the first year of life

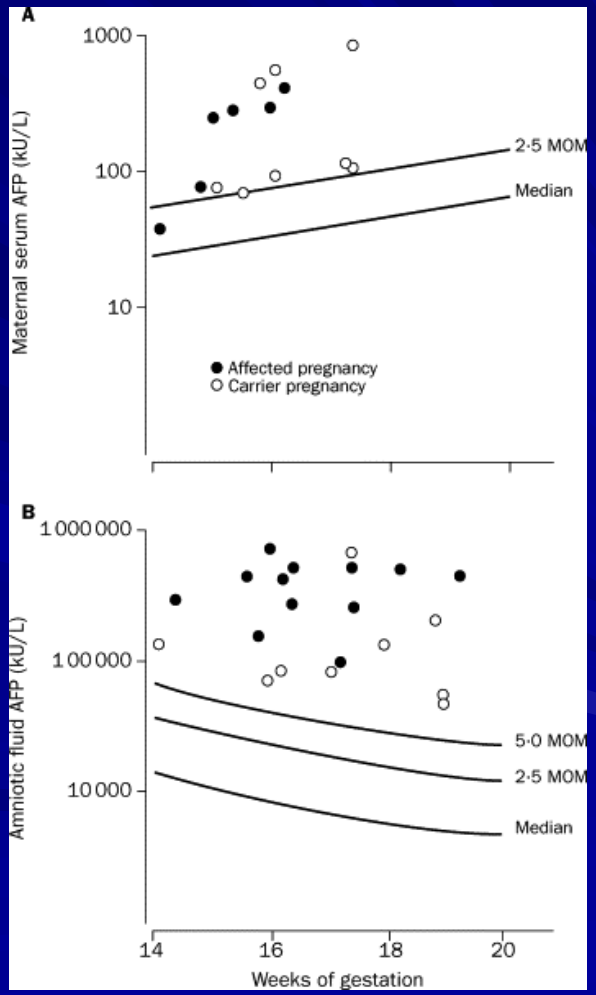
Hinkes et al. 2007



CNS; Prenatal Diagnosis?

Patrakka et al., *Lancet*, 2002





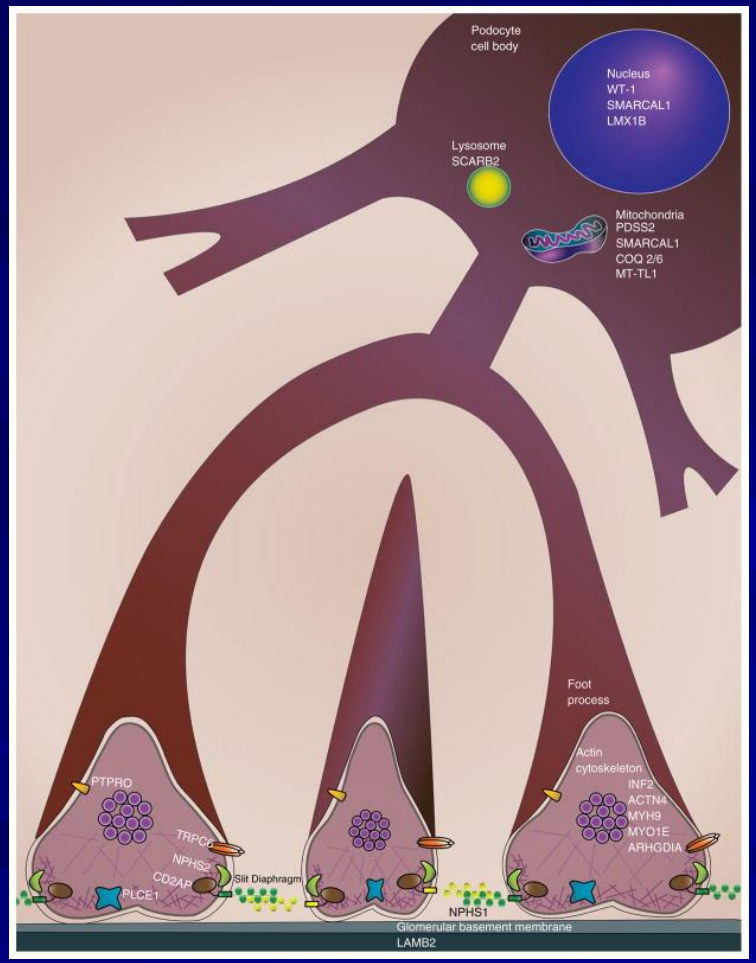
CNS Summary

- Severe and mild primary forms
- Comorbidities important for long-term outcome
- Normal growth and development if early diagnosis and therapy and no comorbidities – Final height in boys -1.2 SD and girls -1.7 SD, normal puberty! (Tainio et al. Transplantation 2011)

- 25 years of pediatric transplantation in Helsinki (>400 pts, >200 kidneys – 100 CNS)

doctors+patient

Podocyte gene mutations

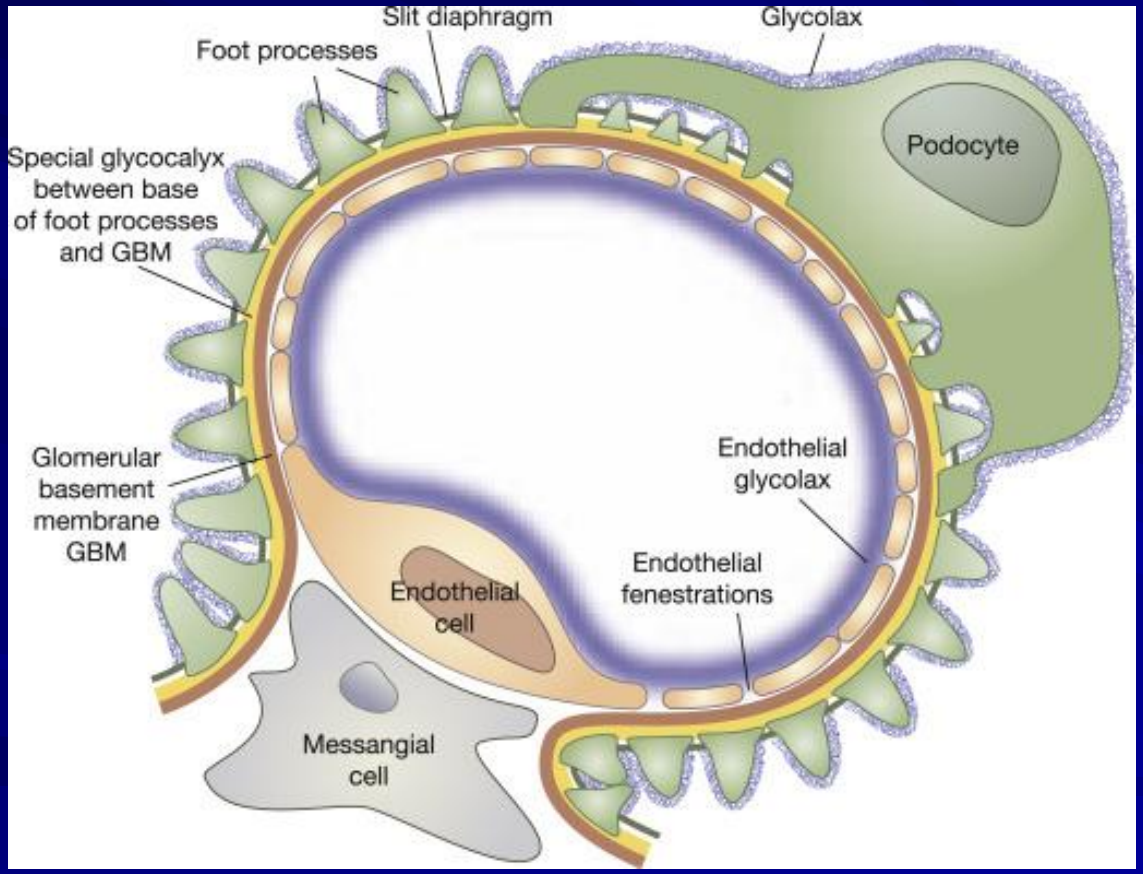


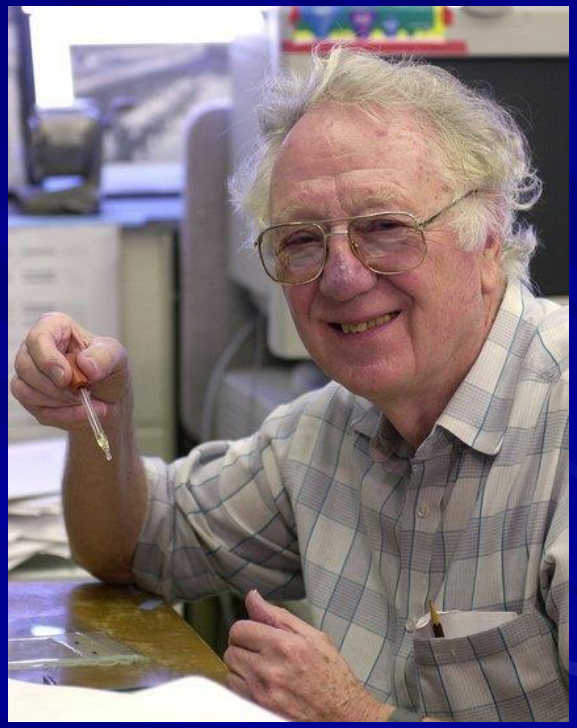
- Induce injury to effects on the podocyte's structure, actin cytosceleton, calcium signalling and lysosomal and mitochondrial function

The Glomerular filtration barrier

PNAS, 2017

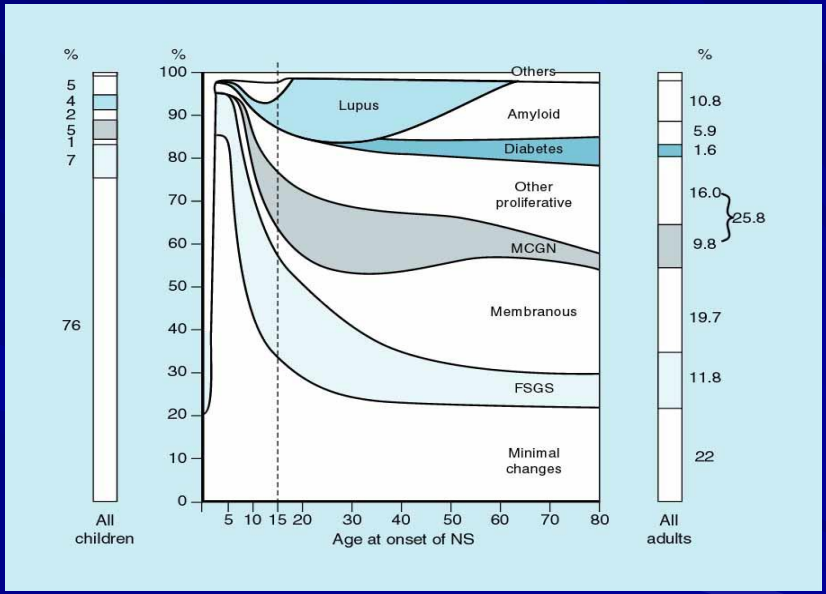
Oliver Smithies, Nobel prize 2007





NS Classification

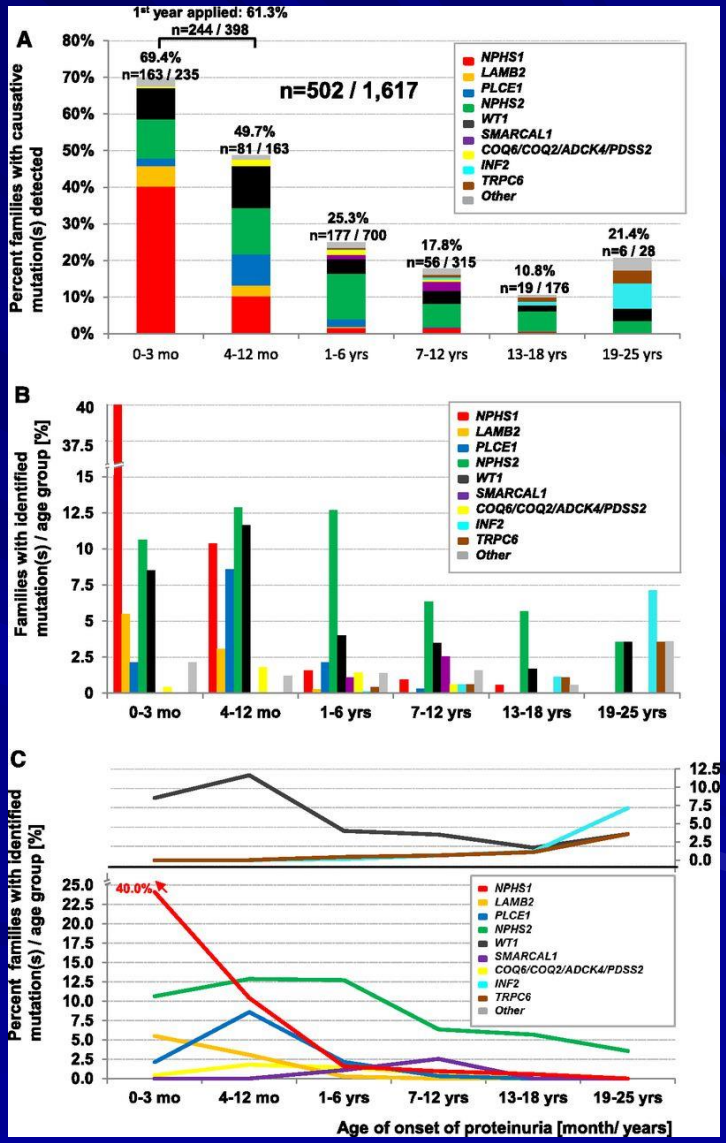
- *Podocytopaties*
  - NPHS1, NPHS2, PLCE1
- *Syndromes*
  - WT1, LAMB2, TRCP6, PDSS2,ARGHDIA, LMX1B, OCRL, LAMB3
  - Galloway-Mowat
- Secondary causes
  - Infections
  - Immunological
  - *Idiopathic NS*



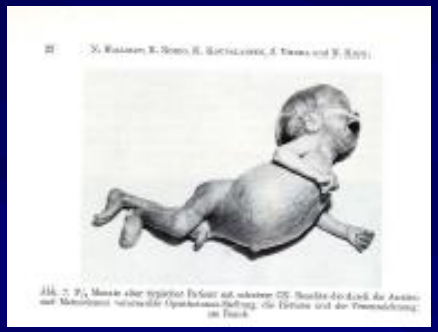
SRNS

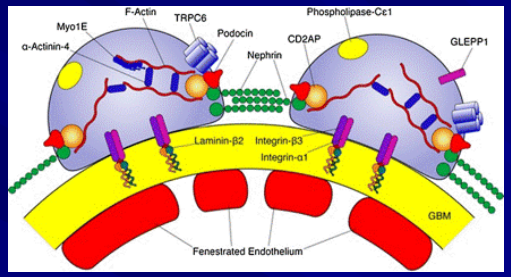
(Sadowski 2015)

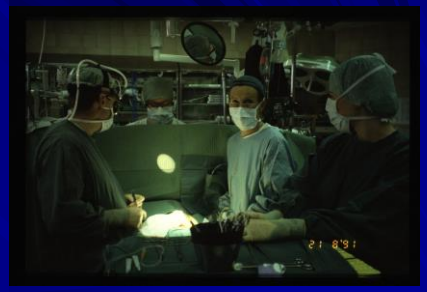
- 12-15%
- 50% ESRD
- FSGS
- 29.5% genetic
- >27 genes known
- *no recurrence after Tx* (other 10-50%)

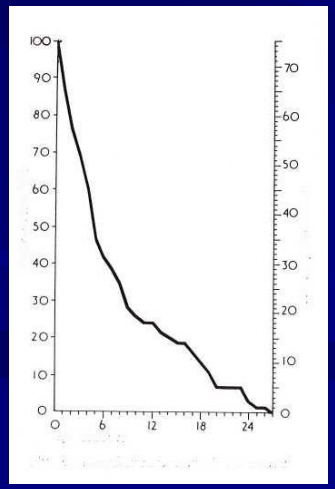


1950----------2017




F-Actin
TRPC6
Phospholipase-Cε1
Myo1E
Podocin
CD2AP
GLEPP1
α-Actinin-4
Nephrin
Laminin-β2
Integrin-β3
Integrin-α1
GBM
Fenestrated Endothelium

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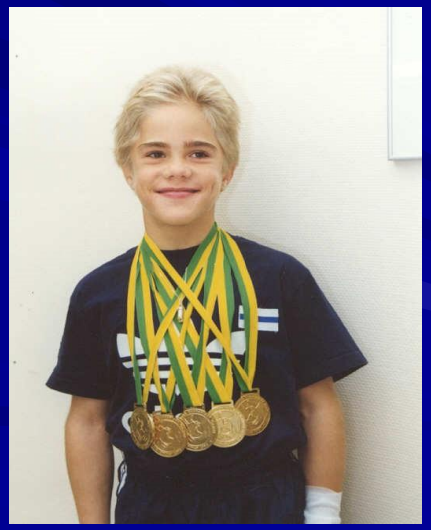

Conclusions

- Nephrotic syndrome in an infant is rare
- Infections are possible and treatable cause in newborns
- Genes are responsible for NS in most infants
- Renal histology does not reveal the etiology
- Genetic testing is available and important
- RAS-inhibitors should be tried in most cases
- New drugs are needed