Podocytopathies

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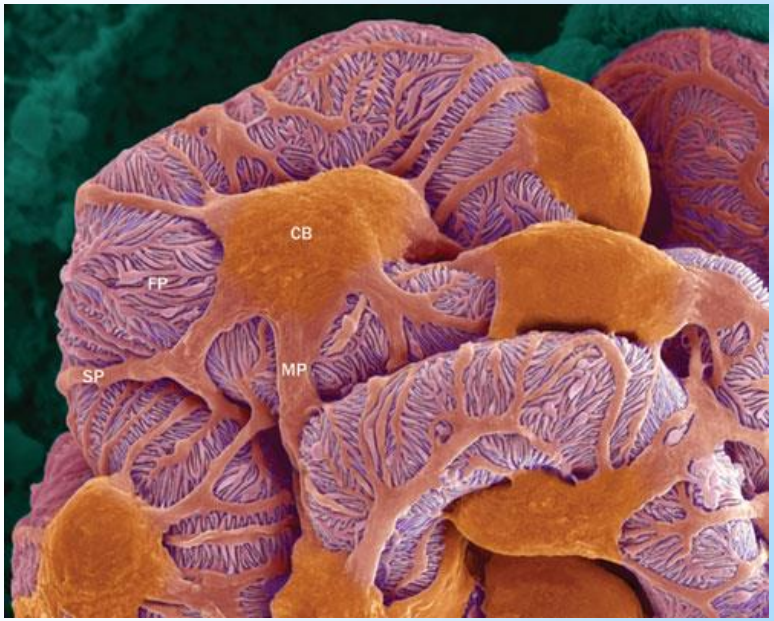
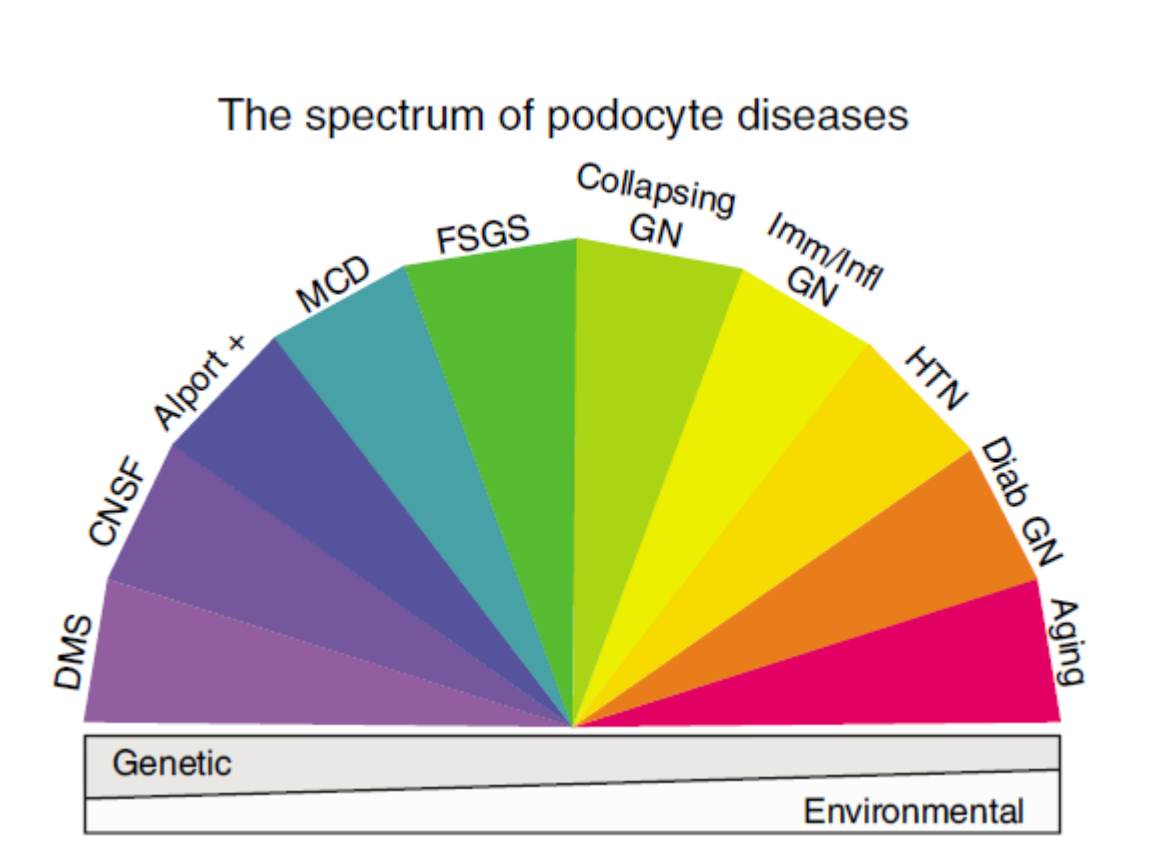


Podocytopathies Spectrum



Wiggins, Kidney International 2007

Podocytopathies

* Hereditary podocytopathies have increasingly been recognized to be involved in the development of SRNS.

* In general, hereditary podocytopathies are associated with a poorer renal outcome than the non-genetic variants.

* They require a different approach with respect to the applied therapeutic strategies as most patients do not respond to immunosuppressive agents.

(Büscher and Weber, Eur J Pediatr 2012)

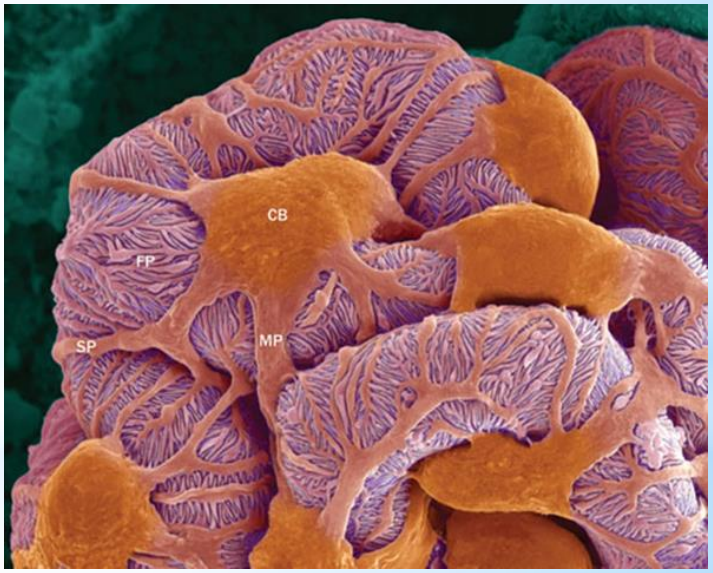
PODOCYTES

* Highly specialized, terminally differentiated epithelial cells.
* Covered by negatively charged glycocalyx.
* Podocytes consists of 3 segments:

cell body, major processes, foot processes.

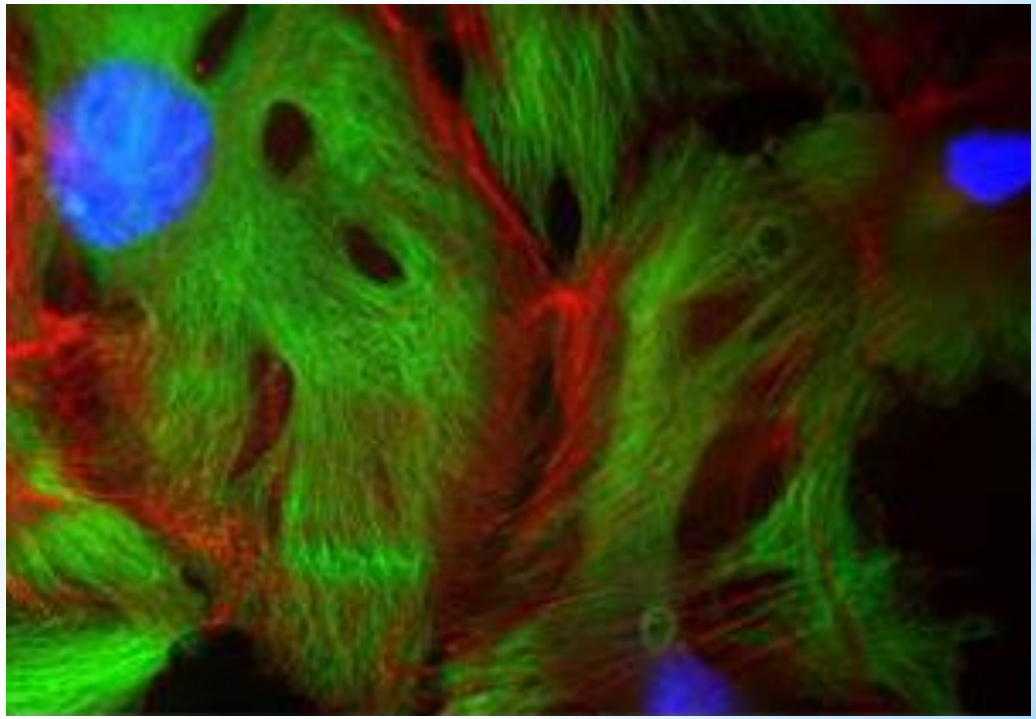
* Adjacent foot processes form pores covered by an extracellular membrane with a“zipper-like” structure,

the slit diaphragm



* Podocytes are polarized cells with rich **actin cytoskeleton.**
* **Microfilaments**, intermediate filaments and **microtubules**.
* Podocyte FPs contain a dense network of actin filaments

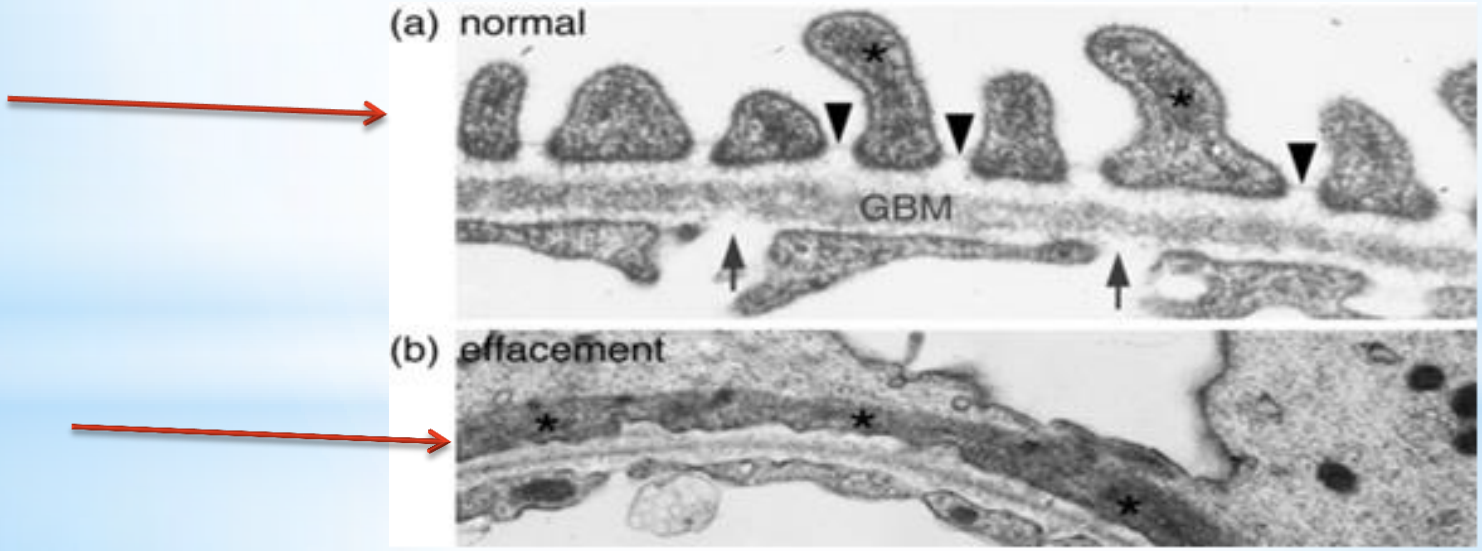
* Connected by Linker proteins to SD and GBM.



Pavenstadt et al., Physiological reviews 2003

* Variations in the podocyte actin cytoskeleton can be caused by both genetic and acquired problems.

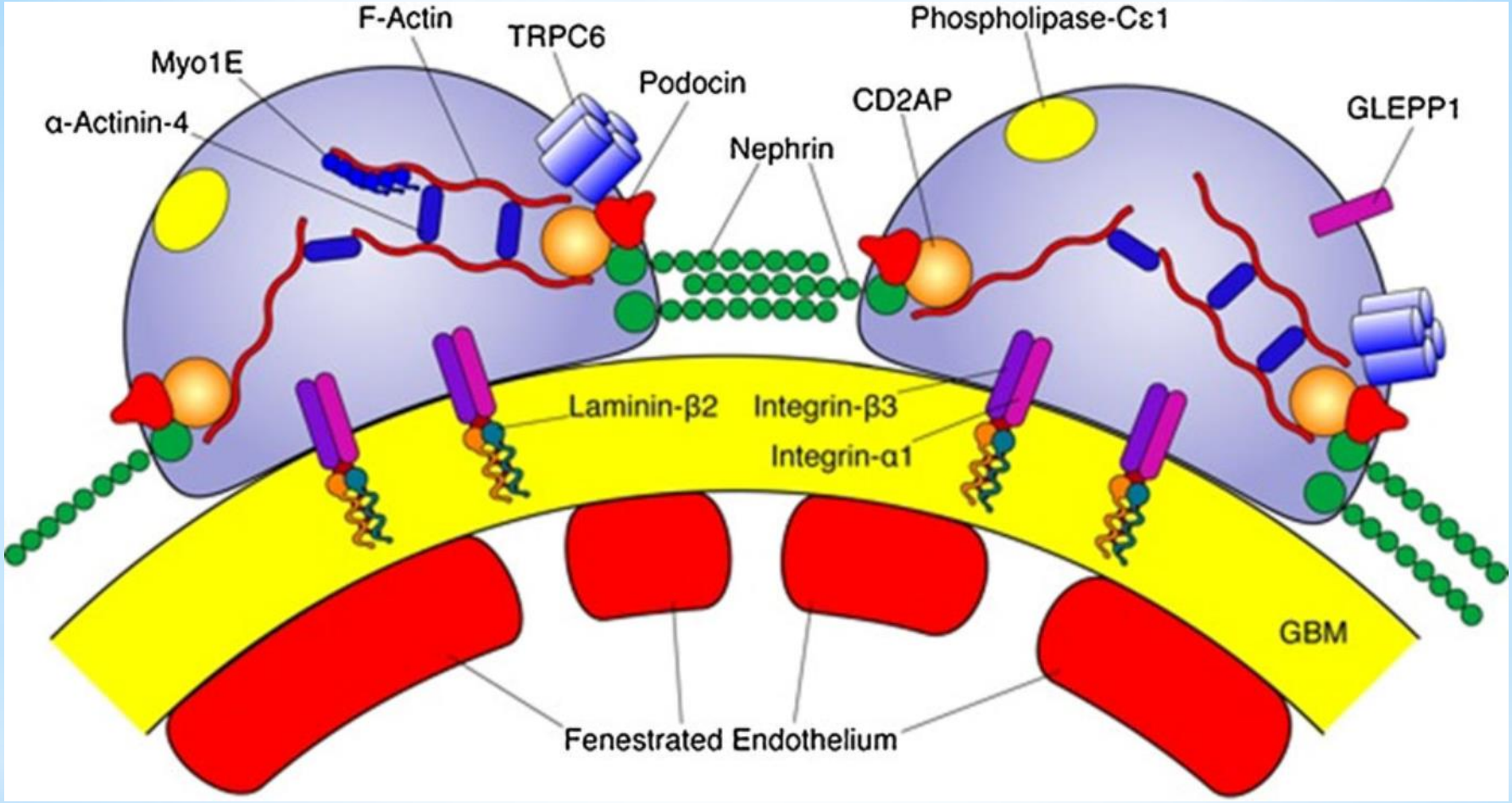
* Podocyte injury and repair are very important aspects. Flattening of the actin filaments is related to podocyte foot processes effacement.



(Mathieson, Clin Kidney J 2012)

Podocyte proteins

* In the last years, knowledge of the genetic defects associated with nephrotic syndrome provided new insight in the structure and function of the podocyte slit membrane and the development of nephrotic syndrome.
* The regulation of this actin-based morphology is achieved through slit diaphragm proteins, such as nephrin and podocin, via adapter proteins, including CD2AP and Nck, which link directly to actin filaments.
* The signalling pathways leading from the slit diaphragm to actin regulation are becoming clearer, and much of the signalling traffic passes via important regulators of actin dynamics, the Rho GTPases.



This slit diaphragm which represents the only cell–cell contact between podocytes, together with the highly dynamic foot processes of the podocyte is the central structure for the barrier function of the glomerulus.

(Büscher and Weber, Eur J Pediatr 2012)

Table 1 Hereditary forms of SRNS

Gene	Locus	OMIM	Inheritance	Protein	Function	Phenotype
LAMB2	3p21	150325	AR	Laminin β2	Linkage podocyte/GBM	Pierson syndrome; isolated DMS
MyoE1	15q21	601479	AR	Myosin E1	Structural integrity of podocyte	Infantile SRNS (FSGS)
Nuclear protein						
WT1	11p13	607102	AD	Wilms tumor 1	Mediator of podocyte differentiation	Denys-Drash-S., Frasier S., WAGR S., isolated FSGS/DMS
LMX1B	9q34	602575	AD	LIM-homeodomain protein	Podocyte differentiation	Nail-patella syndrome
					cytoskeleton	
TRPC6	11q21-22	603652	AD	Transient receptor potential cation channel 6	Mediation of calcium influx; cell signaling	Predominately late-onset SRNS (FSGS); incomplete penetrance
PLCe1	10q23	608414	AR	Phospholipase Cε1	Podocyte signaling	Early-onset SRNS with DMS or FSGS
PTPRO (GLEPP-1)	12p12	600579	AR	Protein tyrosine phosphatase receptor type O (glomerular epithelial protein 1)	Regulation of glomerular pressure and permselectivity	Infantile/adolescent SRNS (FSGS/MCN)
Cytoskeleton						
ACTN4	19q13	604638	AD	α-Actinin 4	Crosslinkage of f-actin	Late-onset SRNS; incomplete penetrance
INF2	14q32	610982	AD	Inverted formin 2	Actin-regulating protein; influence on actin polymerization and -depolymerization	Adolescent/adulthood SRNS (FSGS)

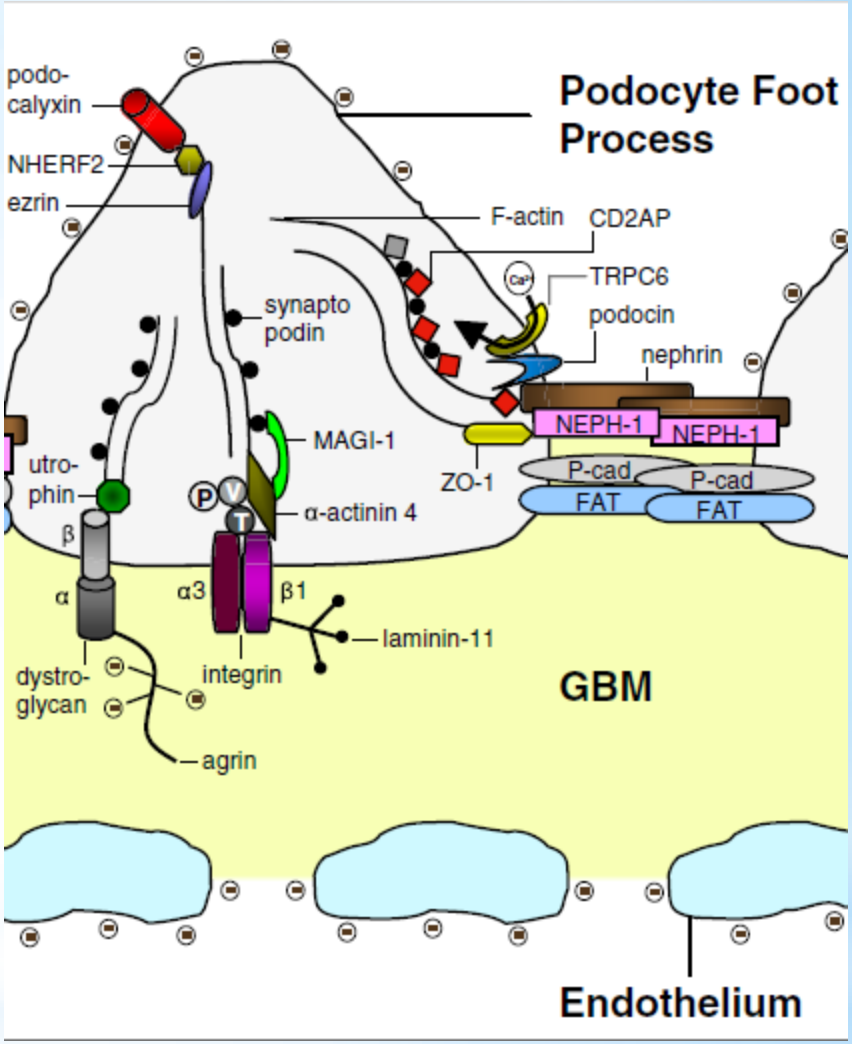
(Büscher and Weber, Eur J Pediatr 2012)

Cyclosporin in hereditary podocytopathies

* Cyclosporine stabilizes the actin cytoskeleton in the podocyte.

* Cyclosporine protects synaptopodin from cathepsin l-mediated degradation.

* Synaptopodin is an important regulator of podocyte function.



Löwik et al., Eur J Pediatr 2009

Hereditary Podocytopathies

* Mutations in the corresponding podocyte genes result in the disintegration of this complex network with:
  * Foot process effacement,
  * Loss of the slit diaphragm,
  * And subsequent proteinuria.
* Depending on the mutated protein, podocyte damage is caused by:

  -The alteration of podocyte function,

  -Integrity, or

  -The altered expression of podocyte-specific proteins due to alteration of nuclear transcriptional factors.

Mitochondrial cytopathies

* Rare as a cause of nephrotic syndrome
* But are very important to recognise as interventional treatment to modify the disease may be possible.

* Mutations affect the co-enzyme Q10 biosynthesis pathway, and this enzyme can be orally supplemented.

* In fact, mutations that cause MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) and CoQ10 deficiency can also cause FSGS in isolation.

(Yamagata et al., J Am Soc Nephrol 2002)

Mutations responsible for CoQ10 deficiency:

*COQ2:

- Codes for a protein involved in the biosynthetic pathway
- May cause isolated nephropathy (collapsing glomerulopathy or crescentic glomerulosclerosis)—or with an encephalopathy.

*PDSS2:

- Codes for the first enzyme in the pathway
- Has been described in a case of severe Leigh's syndrome with seizures, hypotonia, cortical blindness and nephrosis.

*COQ6:

- Has been reported in 13 individuals from seven families.
- Causing early onset SRNS and sensorineural deafness.
- Two of these individuals were treated with COQ10 supplementation orally and appeared to respond with a lowering proteinuria.

(Saleem, Pediatr Nephrol 2013)

Indications of genetic testing in NS

* SRNS (including congenital nephrotic syndrome) displays considerable genetic heterogeneity, with 24 genes currently linked to this disorder.
* Genetic testing is indicated in all cases of congenital, infantile and childhood onset SRNS.
* In familial SRNS and SRNS presenting in the first 2 years of life, identifiable mutations are present in 95% of cases.
* This percentage decreases to around 40%–60% in children under 5 years, and in older children with sporadic disease, the incidence of genetic mutations is estimated to be 20%

(Rood et al., Nephrol Dial Transplant 2012)

Potential benefits of genetic testing

1) Aids in diagnosis esp in fuzzy phenotype.
2) Limiting medication exposure, or identifying a best treatment.
3) Helps in determining risk of recurrent disease in kidney transplantation.
4) Risk assessment in candidate living related kidney donors.
5) Prenatal diagnosis.
6) Motivate screening I other family members.

New technologies

* It is better to sequence all genes (or at least all coding sequences-the exome) than to test for a specific gene only.
* SRNS is a genetically heterogeneous disease where the chance of genetic mutation is high but requires sequencing of multiple genes.
* Now next generation sequencing analysis of pediatric SRNS patients is accurate and revealing.

(McCarthy et al., Clin J Am Soc Nephrol 2013)

* NGS involve obtaining multiple short reads of sequence from all components of a library that may be created using individual's entire genomic DNA, or DNA from the exome.
* The number of reads of a particular segment is called its coverage.
* Several software platforms are available for processing data and filter them before giving the final output to the researcher.
* Now filtering the long list of variants to reach the potentially causative mutation is the main challenge.
* Shared information held in open-access collections of accurate data on specific genetic disorders.

Sporadic or acpuired podocytopathies

* There is overwhelming evidence, both clinical and experimental, that certain forms of SRNS are caused by an abnormality of the **circulating plasma**.

* Recurrence of proteinuria within hours of a new graft being transplanted in patients with SRNS.
* Glomerular swelling after exposure to disease plasma.

* A study of SRNS by Wei et al. identified raised levels of soluble urokinase receptor **(suPAR)** in two-thirds of patients with primary FSGS and a higher level of suPAR in pre-transplant FSGS patients who subsequently went on to develop recurrent disease.

* suPAR is a cellular receptor for urokinase, which can be cleaved from its anchor and released into the circulation.

* In a comprehensive set of animal and cellular experiments, circulating suPAR, via activation of podocyte β3 integrin, was demonstrated to cause an FSGS-like glomerulopathy.

* This result identifies suPAR as a circulating factor that may cause FSGS, with the prediction that removal of this protein by plasmapheresis or antibody columns would be a therapeutic option in patients with high serum levels.

* Currently, there are several studies on the cell biology level and animal models based on different hypotheses of how circulating factor or factors are affecting the filtration barrier.

(Wei et al., Nat Med 2011, *Saleem, Pediatr Nephrol 2013)*

THANK YOU