Genetics of Nephrotic Syndrome

DRAGoN Study
Deciphering Diversities:
Renal Asian Genetics Network

RAPIDS
Renal Alliance for Precision Diagnosis in Singapore

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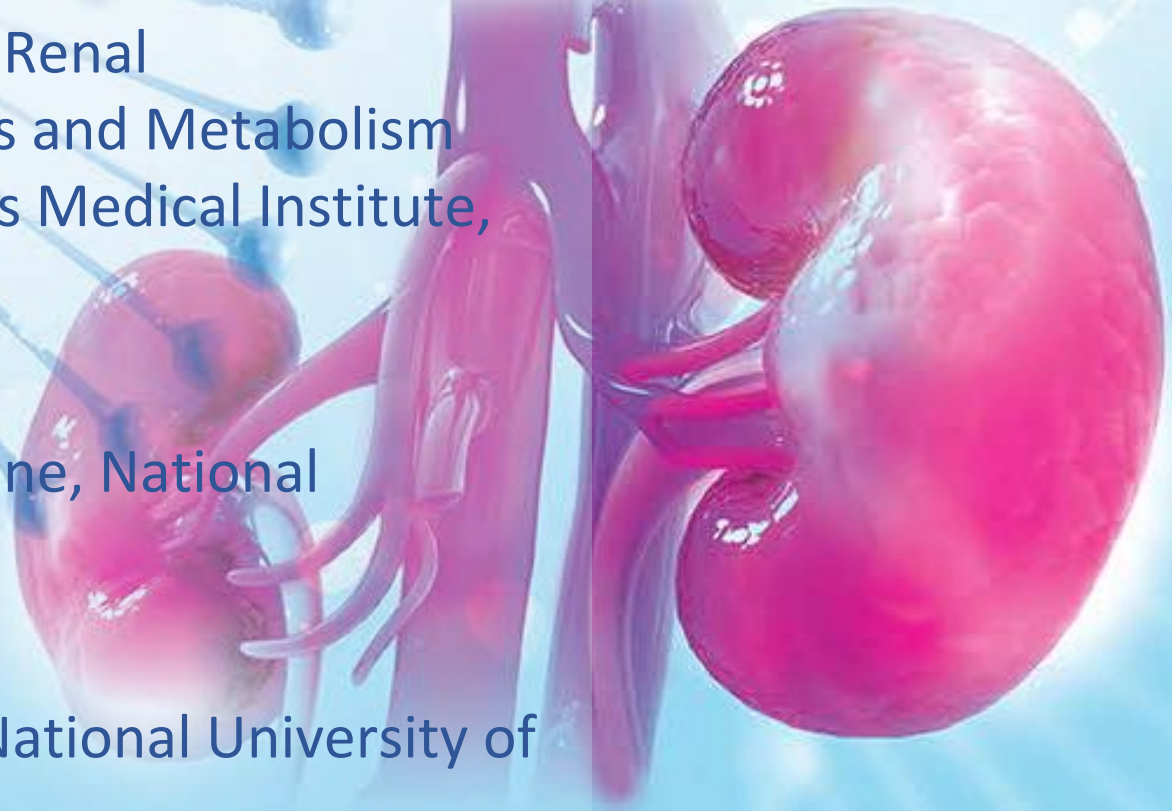


DISCLOSURES

- No conflicts of interest

Rare genetic condition

Straits Times, 10 Nov 2025

- 6 years old: Edema over a few days, nephrotic syndrome
- Steroid resistant

- Biopsy: FSGS
- Resistant to calcineurin inhibitors, MMF
- Progressed to kidney failure in 2 years by 8 years old

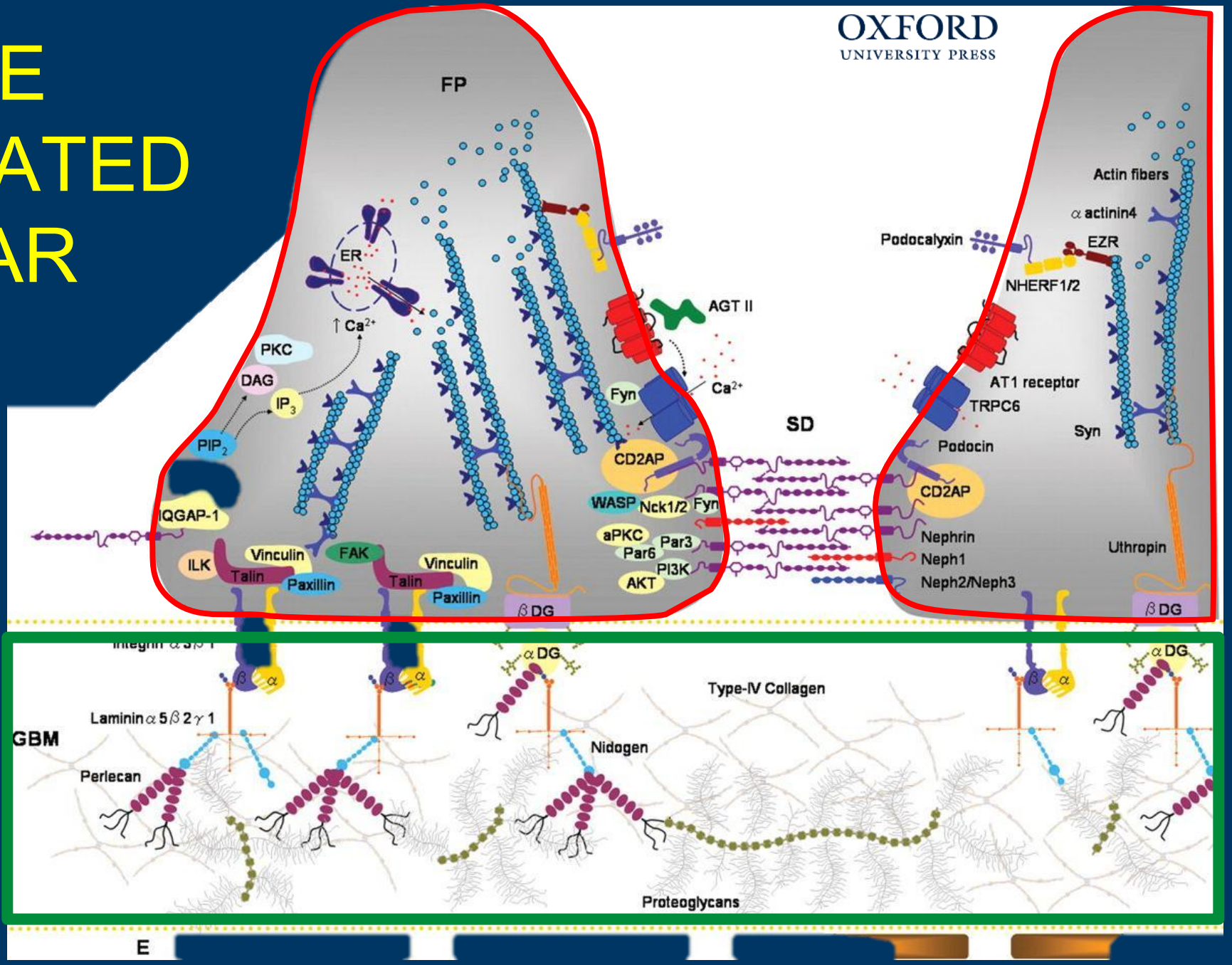
- 16 years old today: just received a deceased donor transplant two days ago!

WHY IS THIS A POSSIBLE GENETIC CASE?

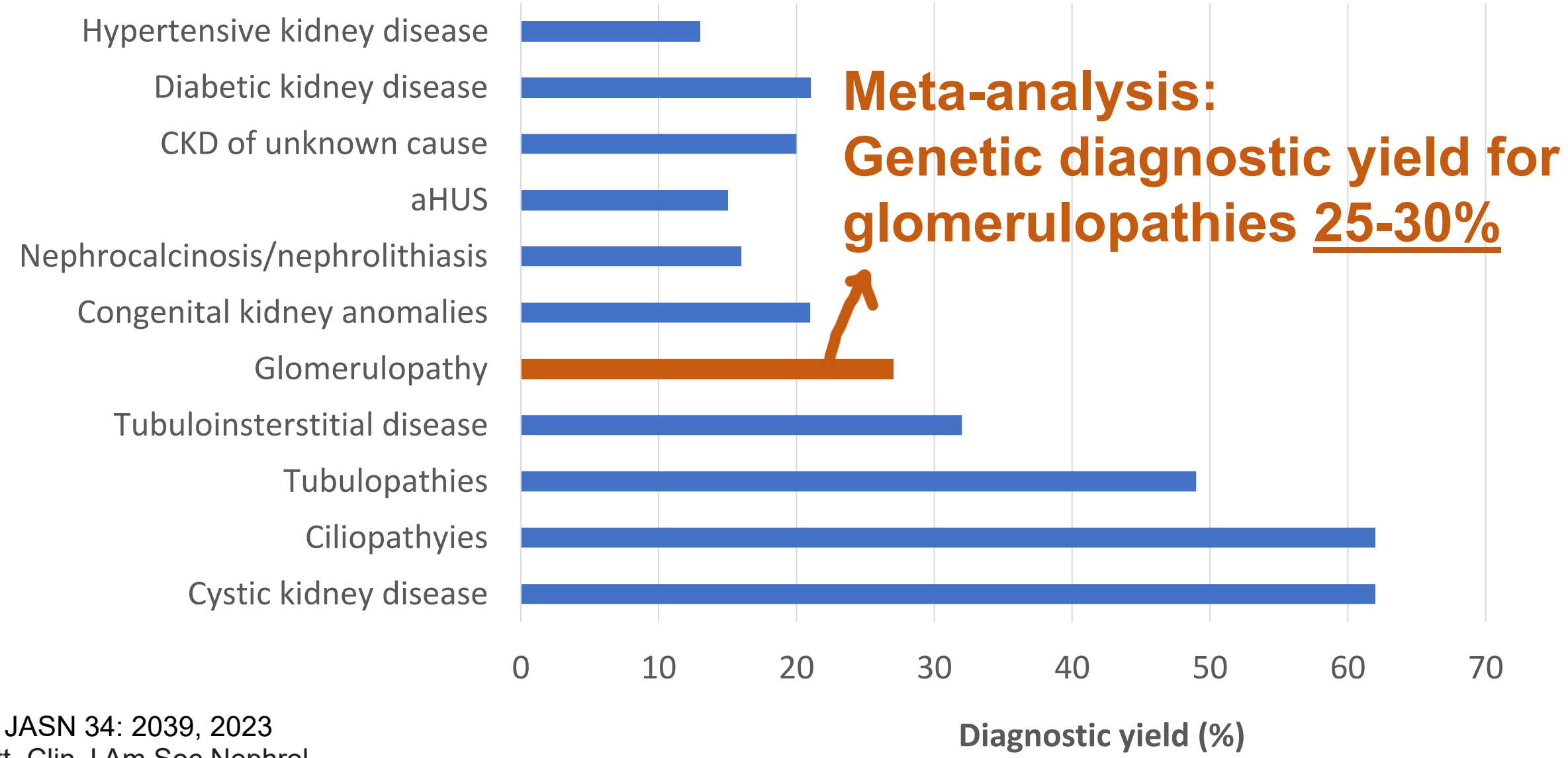
Genetic testing: Heterozygous pathogenic variant in *TRPC6* gene

> 80 PODOCYTE GENES IMPLICATED IN GLOMERULAR DISEASES

6-8 genes account for 80% of the cases



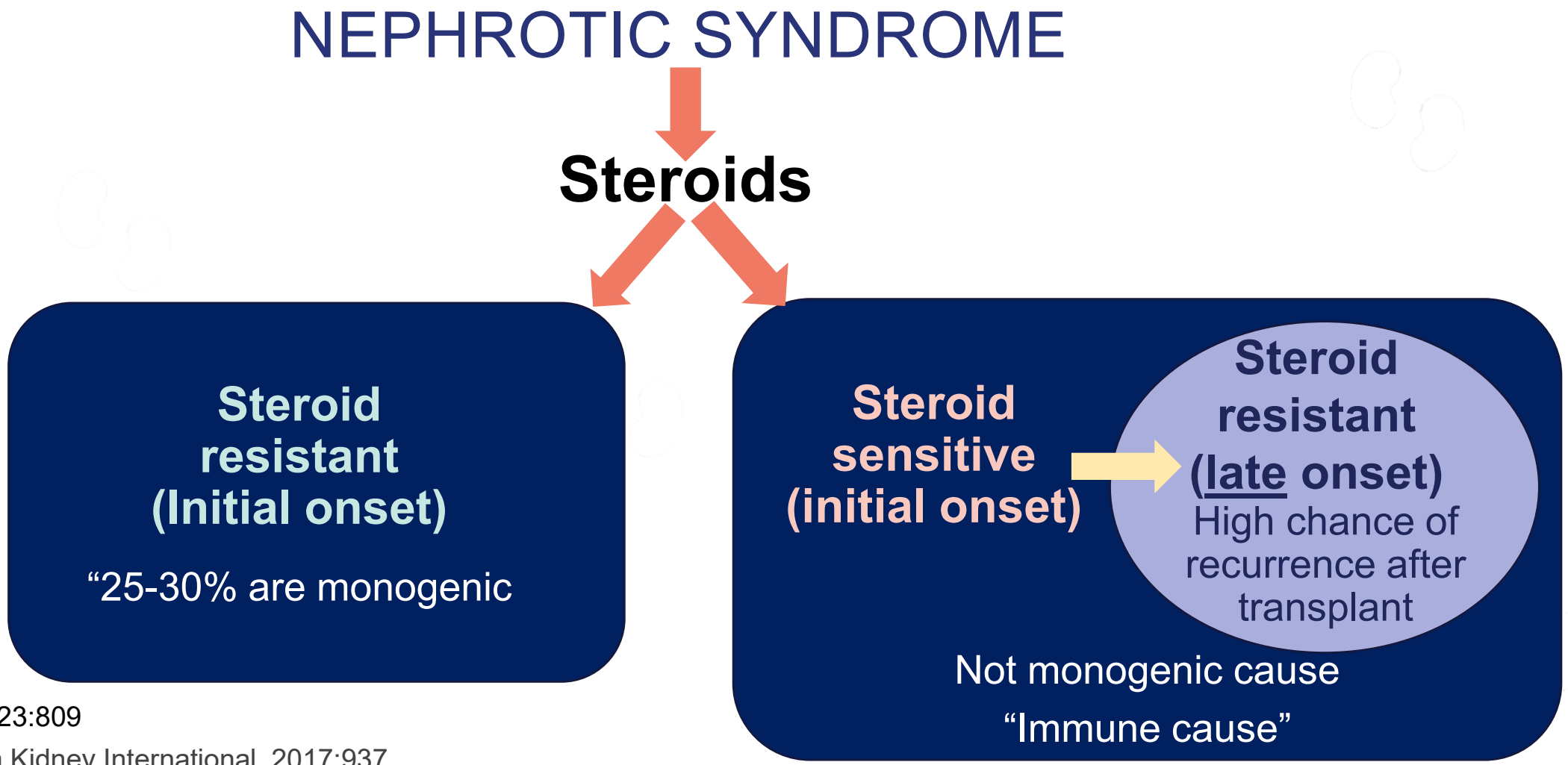
Hum Mol Genet, 2009, R185



Dahl. JASN 34: 2039, 2023
Schott. Clin J Am Soc Nephrol.

What are the clues to a genetic diagnosis in Nephrotic Syndrome?

Initial-onset steroid resistance is a clue, but not late-onset



Lancet. 2023:809

Bierzynska Kidney International. 2017:937

GENETIC-FIRST APPROACH

Steroid-resistance
(4 weeks of steroid treatment)

↓

Genetic testing in 5th week

Positive genetic result in 2 weeks

↓

No need biopsy at 7th week

Negative / uncertain genetic result

↓

Kidney biopsy at 7th week

Pediatric Nephrology
https://doi.org/10.1007/s00467-020-04519-1

GUIDELINES

Check for updates

IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome

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Received: 21 December 2019 / Revised: 7 February 2020 / Accepted: 21 February 2020

Resistance to multiple immunosuppressives may suggest a genetic cause

KDIGO 2025 guideline

Genetic testing for all pati nt nephrotic syndrome
Especially those r uppressives

Are monogenic cases really resistant to immunosuppression?

Beware of poor drug adherence or inadequate drug dosages

Cyclosporin acts directly on podocytes

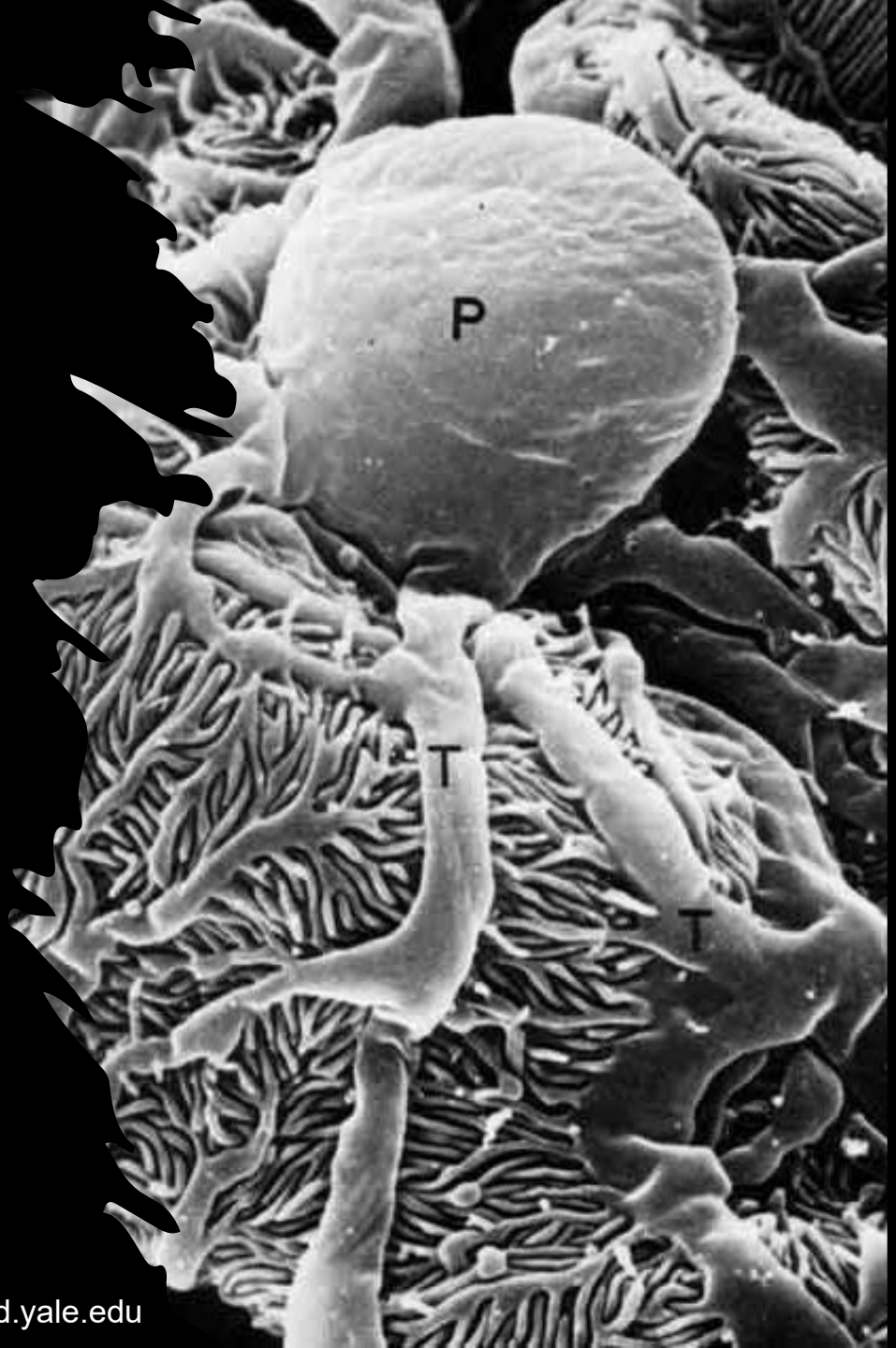
Blocks the calcineurin-mediated dephosphorylation of synaptopodin

↓

Prevents deactivation of synaptopodin

↓

Stabilizes the actin cytoskeleton



Faul, Nat Med, 2008

Image from medcell.med.yale.edu

A multicenter retrospective study of calcineurin inhibitors in nephrotic syndrome secondary to podocyte gene variants.

Kidney International(2023)103:962

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Retrospective study

141 children with monogenic SRNS

37 paediatric nephrology cent

CNI treatment fo ≥3 months

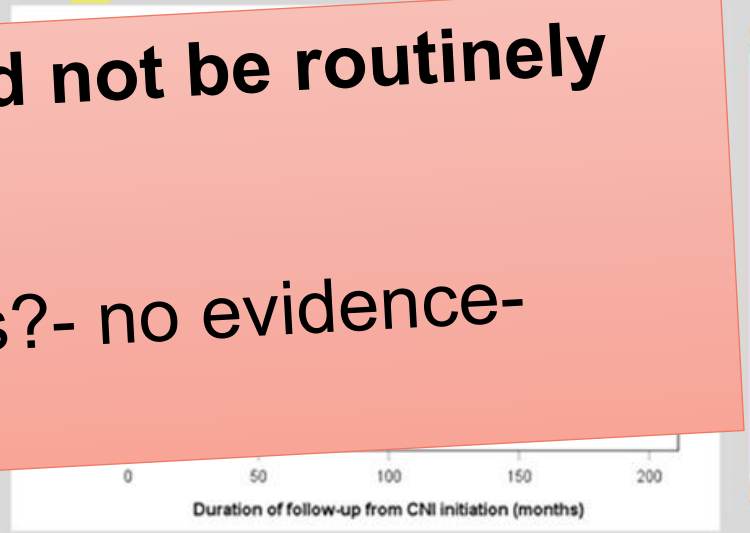
All variants reviewed for pathogenicity

Response to treatment (partial or full) definition as per IPNA Clinical Practice Recommendations

Median follow-up after CNI onset= 42 months

27.6% partial or full response at 6 months

75% lower risk for kidney failure at last visit



Higher serum albumin at CNI onset associated with increased odds of response at 6 months (OR 1.16)

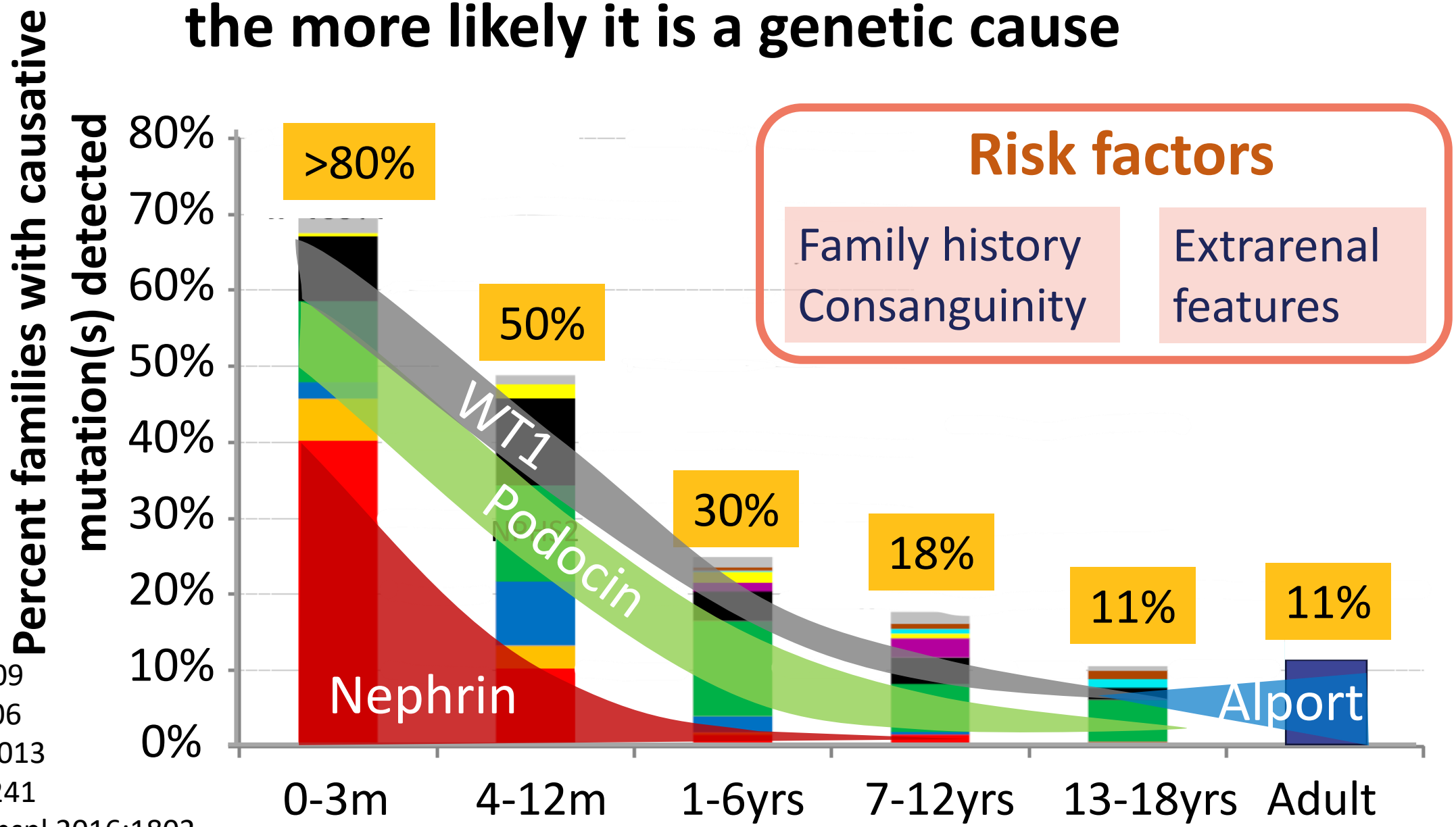
Immunosuppression should not be routinely used in monogenic SRNS

Trial of CNI in selected cases?- no evidence-based recommendations

Malakasioti et al., 2022

CONCLUSION: A trial course of CNI in children with monogenic SRNS under close monitoring could be considered as response to treatment conveys a benefit in long term kidney outcome

The younger the age of onset, the more likely it is a genetic cause



Risk factors

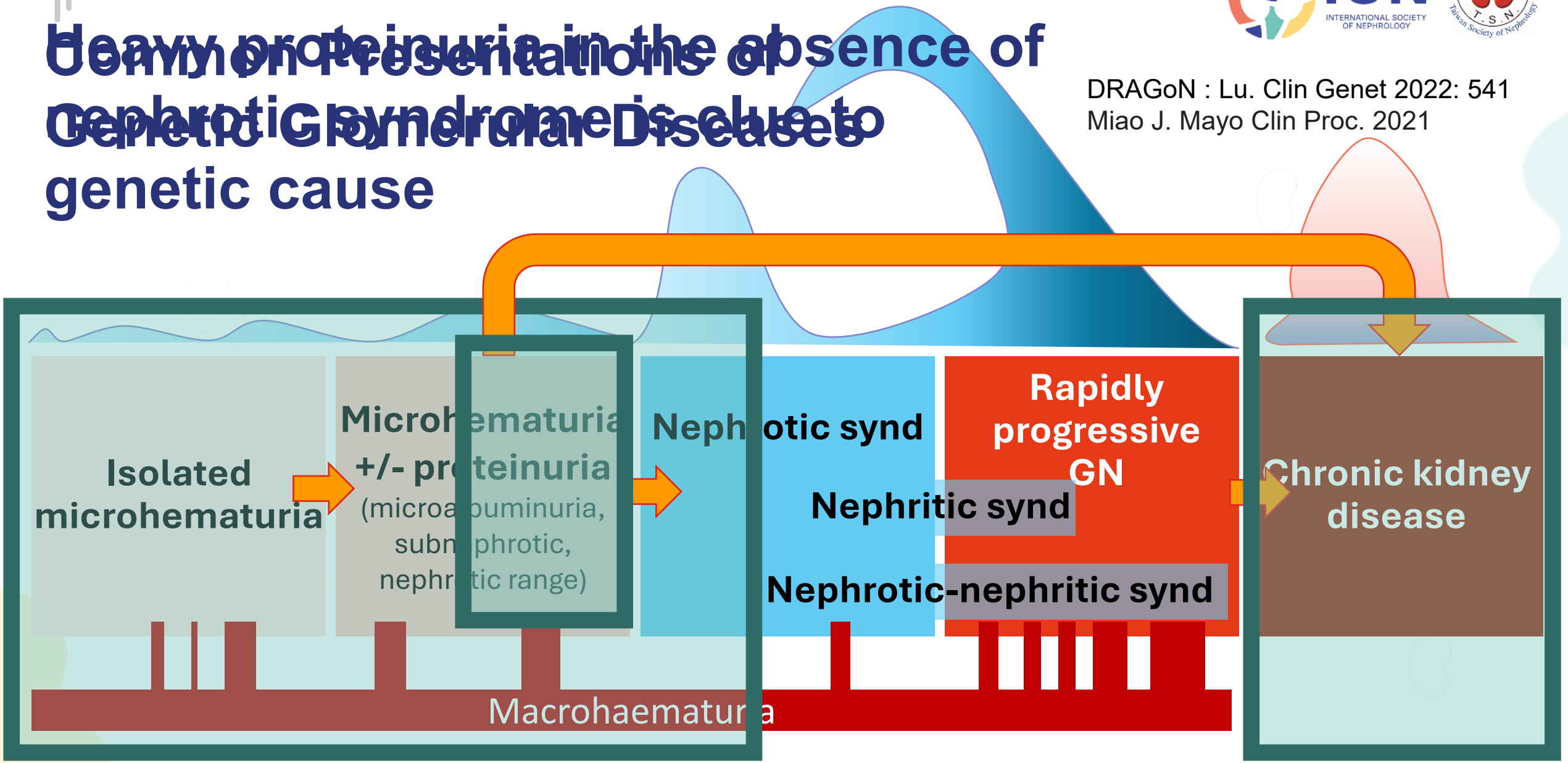
- Family history
- Consanguinity
- Extrarenal features

JASN 2014
Lancet 2023:809
Kid Int 2013:206
Kid Int. 2018:1013
Kid Int 2025:S241
Nephr Dial Transpl 2016:1802

Heavy proteinuria in the absence of nephrotic syndrome is due to genetic cause

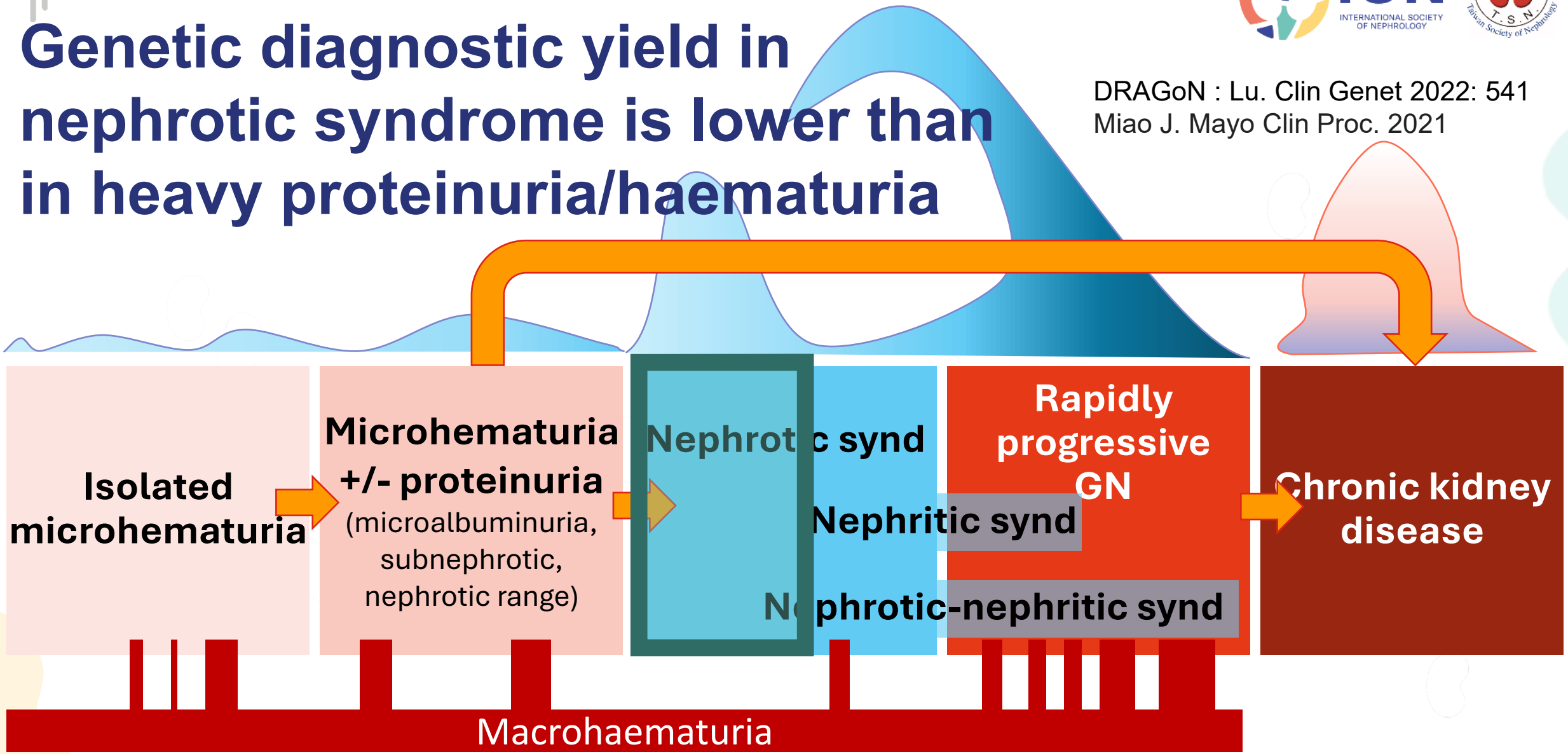
Common presentations of Genetic Glomerular Diseases

DRAGoN : Lu. Clin Genet 2022: 541
Miao J. Mayo Clin Proc. 2021



Genetic diagnostic yield in nephrotic syndrome is lower than in heavy proteinuria/haematuria

DRAGoN : Lu. Clin Genet 2022: 541
Miao J. Mayo Clin Proc. 2021



Do patients with Alport syndrome present with nephrotic syndrome?

Young children

Steroid-resistant nephrotic synd

FSGS

Severe variants

X-linked (male)
Autosomal recessive
Digenic

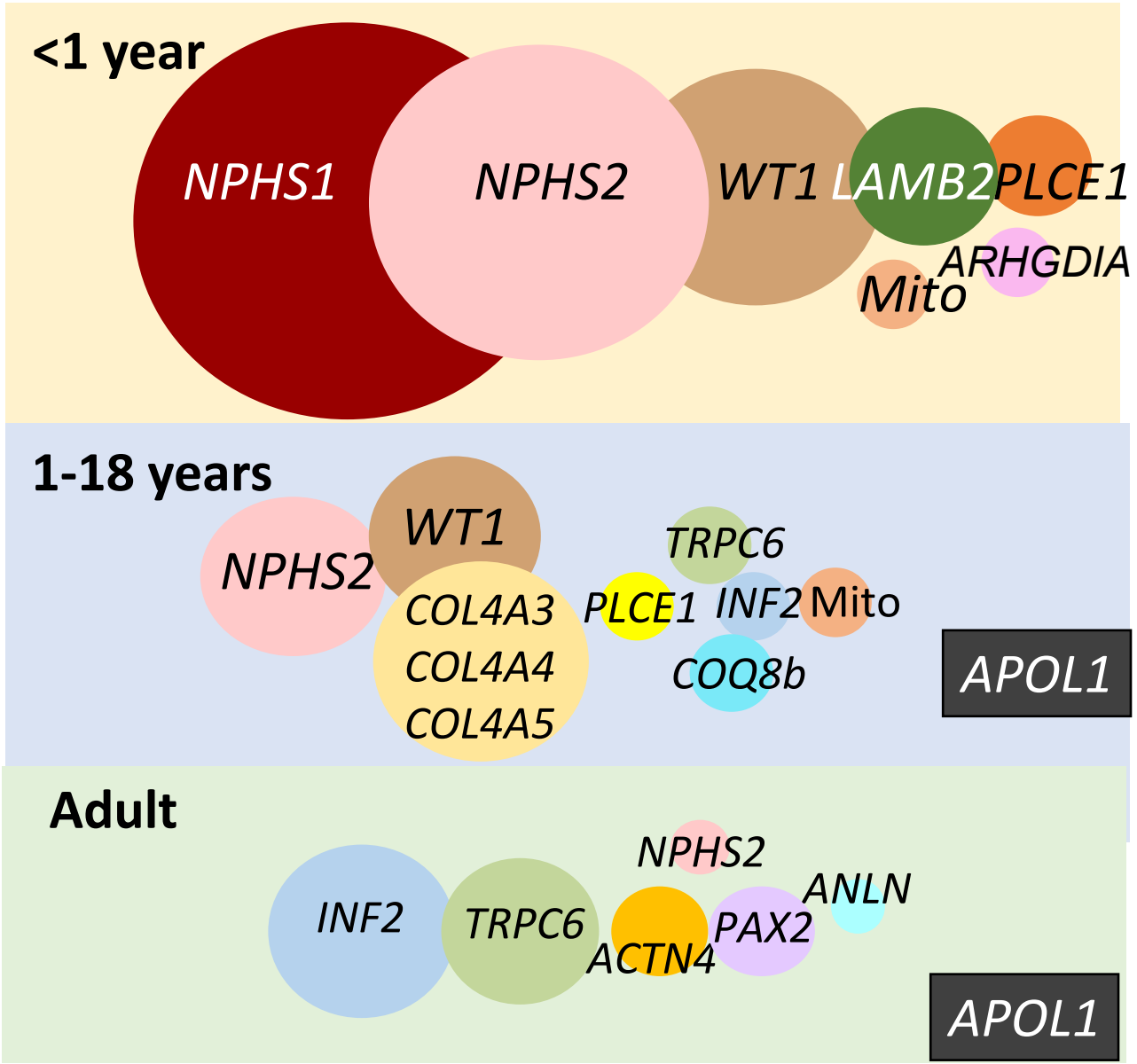
Truncating variants

Beware of the child with autosomal dominant Alport syndrome + nephrotic syndrome

Clin Nephrol. 2025:CN111767.
Pediatr Nephrol 2025:393
Transplant Immunology. 2023:101941
Pediatr Nephrol. 2024:3205

Adult patients with nephrotic syndrome

Typically not Alport syndrome

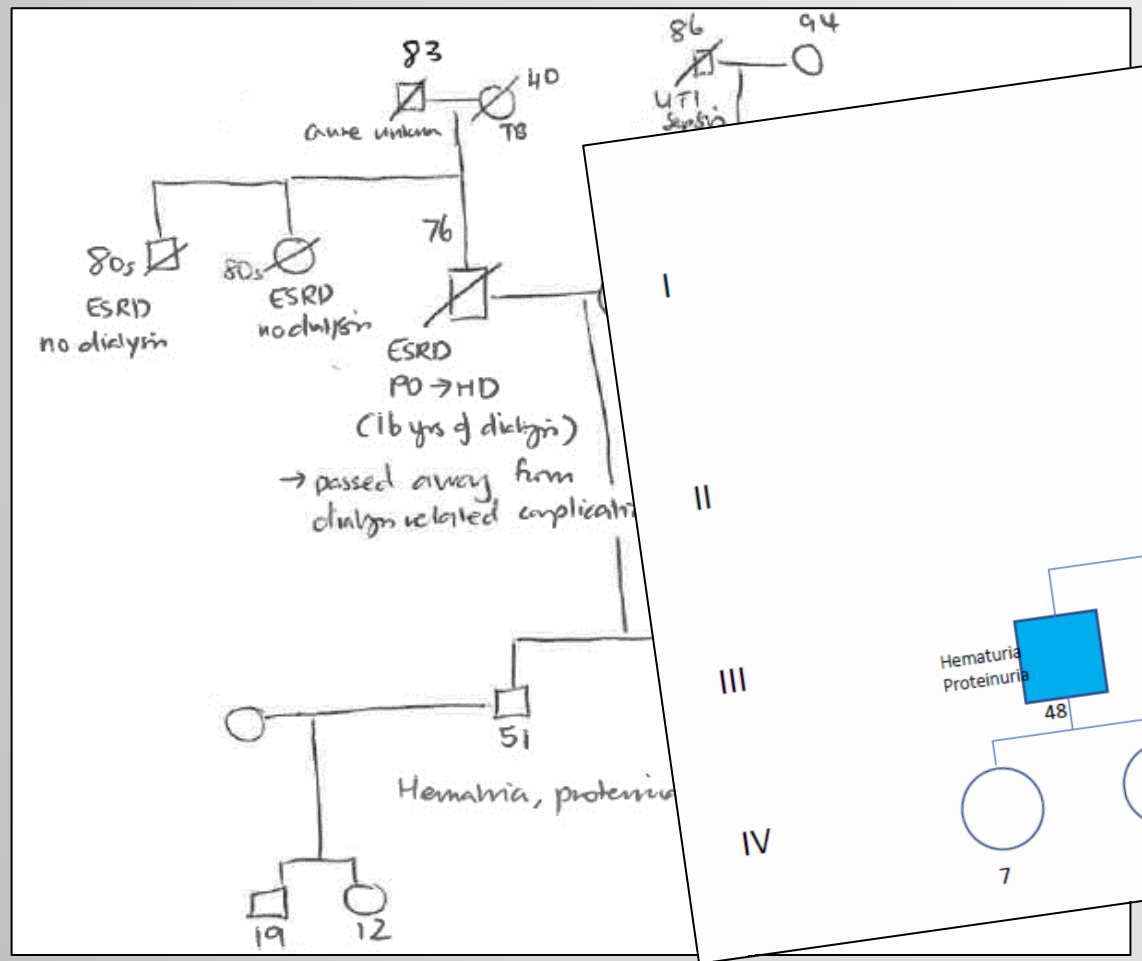


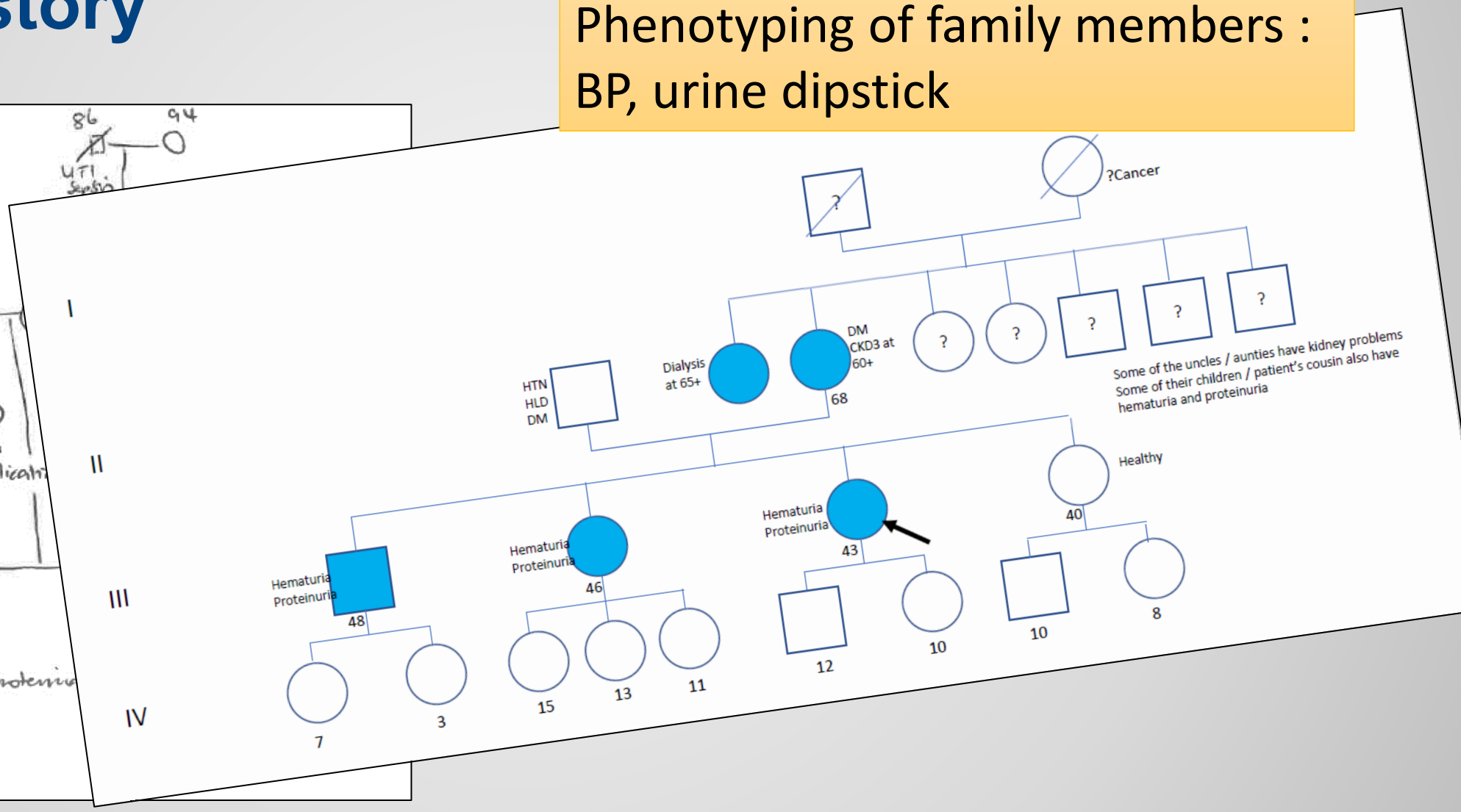
Liu, Front Med, 2017
Sadowski, JASN 2014

Think "Genetic": Family History

3-generation
Renal and non-renal features

Phenotyping of family members :
BP, urine dipstick





5 year old with nephrotic syndrome

History of
Ichthyosis
Hypoadrenalism, Hypothyroidism,
Immunodeficiency

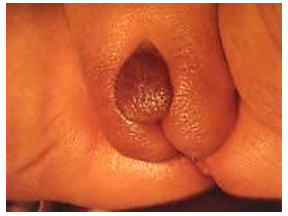
Resistant to steroids, and multiple immunosuppression

Sphingosine-1-phosphate lyase insufficiency syndrome (SPLIS)

Defects in Sphingosine-1-phosphate lyase (*SGPL1*)

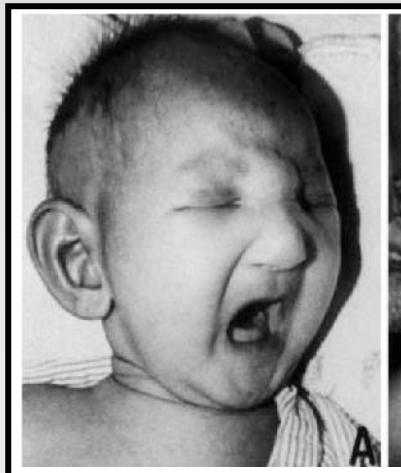
Lovric S. J Clin Invest. 2017:912
Prasad R. J Clin Invest. 2017:942

Think “Genetic”: Extrarenal



Denys Drash / Frasier

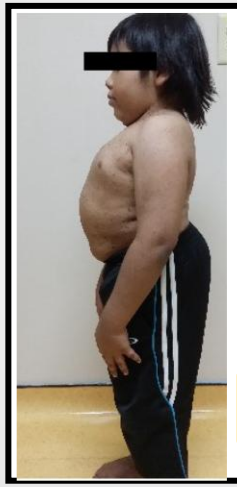
WT1



Galloway-Mowat syndrome

WDR73

The obvious



Schimke immuno-osseous dysplasia

SMARCAL1

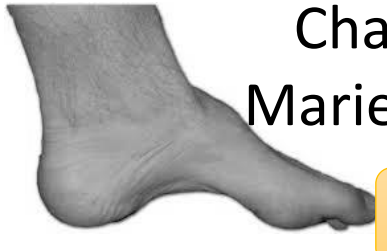
Epidermolysis bullosa

ITGB4

Sphingosine-1-phosphate lyase insufficiency syndrome (SPLIS)

SGPL1

Ichthyosis
Adrenal insufficiency
Immunodeficiency
Neurological deficits



Charcot-Marie-Tooth

INF2

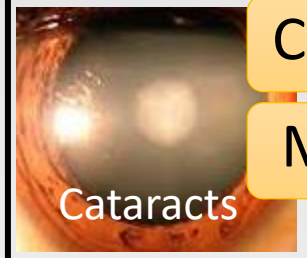
Mandibuloacral dysplasia

ZMPSTE24

Lipska-Ziętkiewicz, PloS one, 2017
Kambham, Am J Kidney Dis, 2000
Esposito, Hum Mol Genet, 2013
Pedagogos, Ped Nephrol 1995
Lin, Ped Nephrol 2001
Weaver KN. GeneReviews

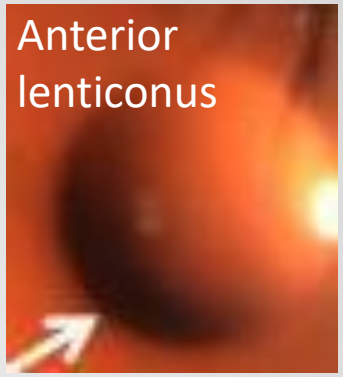
The not-so-obvious

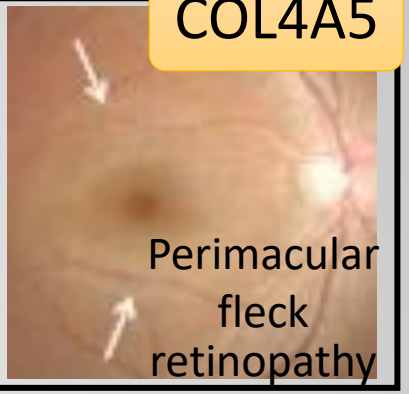
Eye



COL4A5

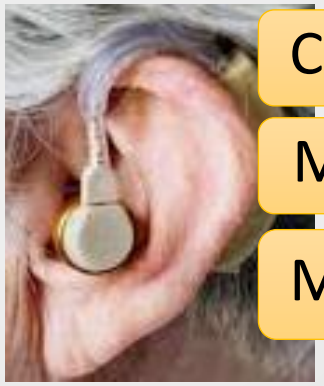
MYH9





COL4A5

Hearing



COL4A3,4,5

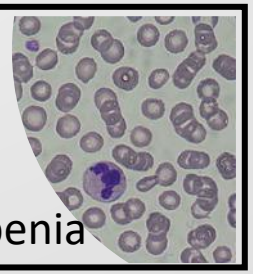
MYH9

Mitochondrial

Lab tests

MYH9

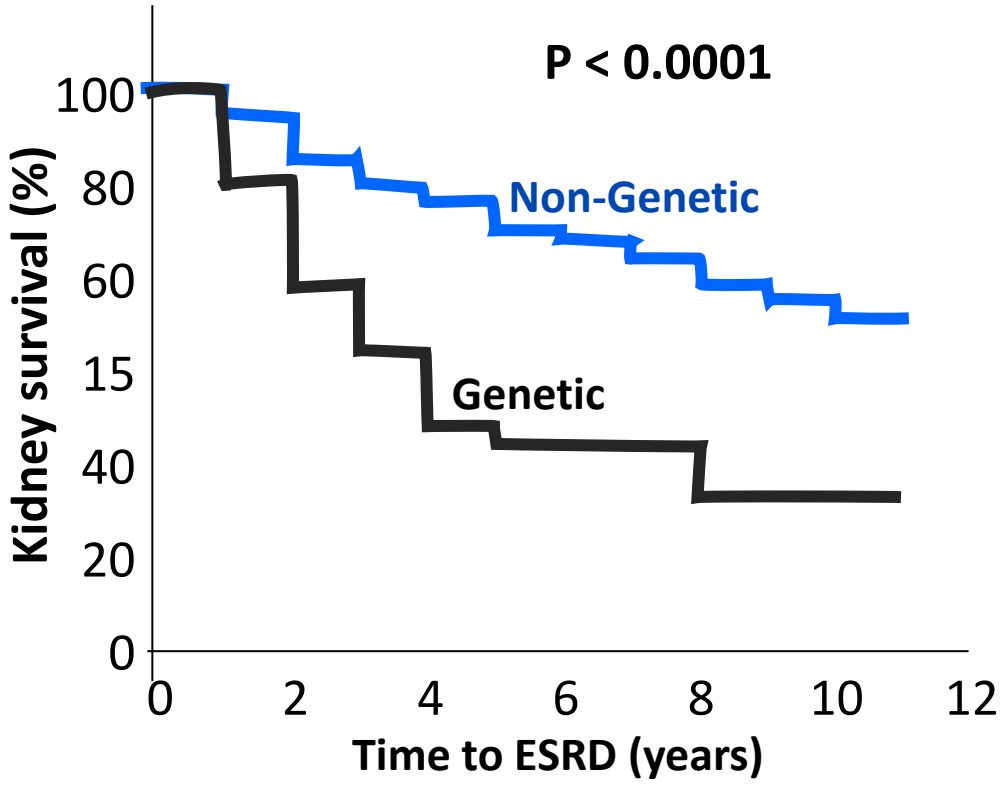
Macro-thrombocytopenia



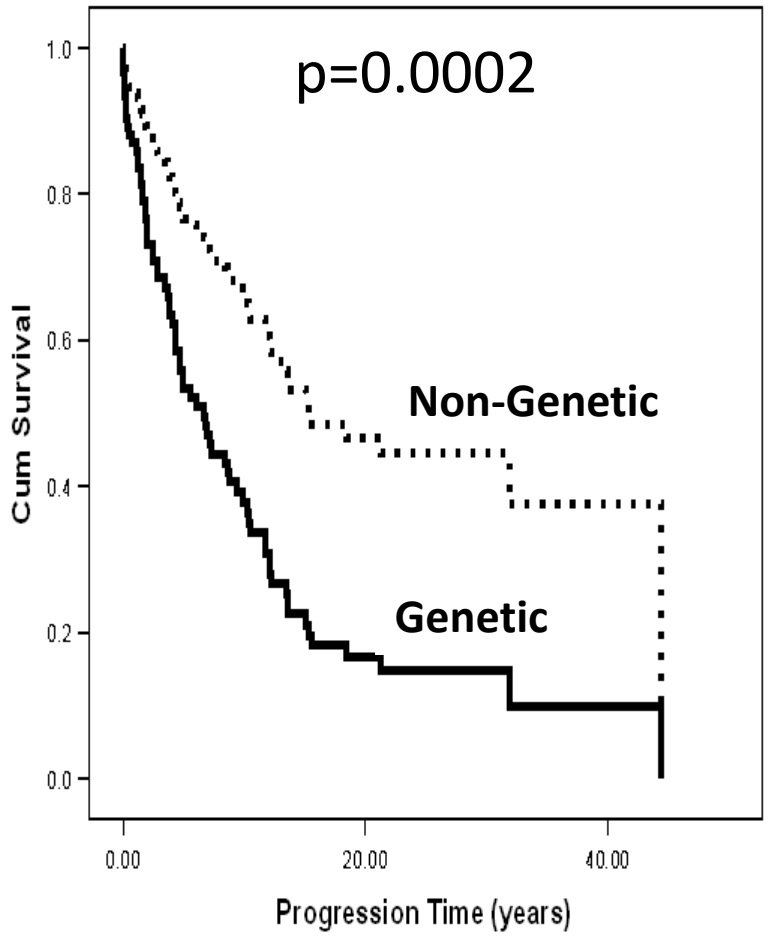
Mitochondrial

Lactate acidosis
Diabetes mellitus

Those with genetic causes progress more rapidly to kidney failure



Bierzynska, Kidney International (2017) 91, 937



Lu L, Ng KH et al. Clin Genet. 2022:541

What are the clues to a genetic diagnosis in Nephrotic Syndrome?

Resistance to immunosuppression

Extrarenal features

Age of onset

Rapid CKD progression

Family history

Why is it important to know your patient has a genetic cause?

Have the conviction and articulate the utility well

- Provides closure
- Reproductive options
- Cascade testing
- Accurate diagnosis

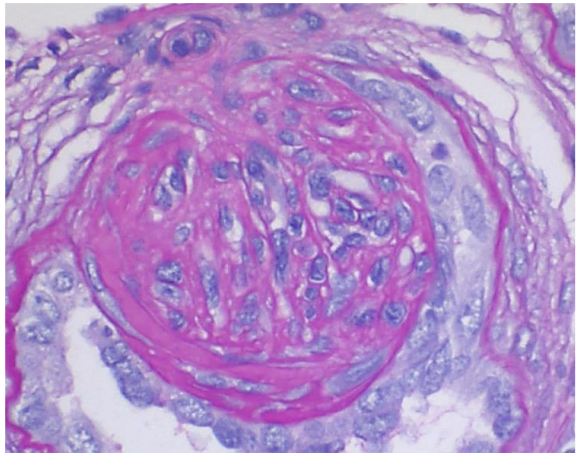
Re-classification in 17%

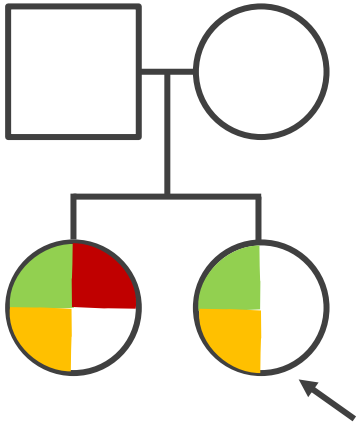
- Avoid diagnostic odyssey including biopsy
- Tailored immunosuppression strategies
- Gene-specific treatment
- Transplant planning
- Extrarenal surveillance

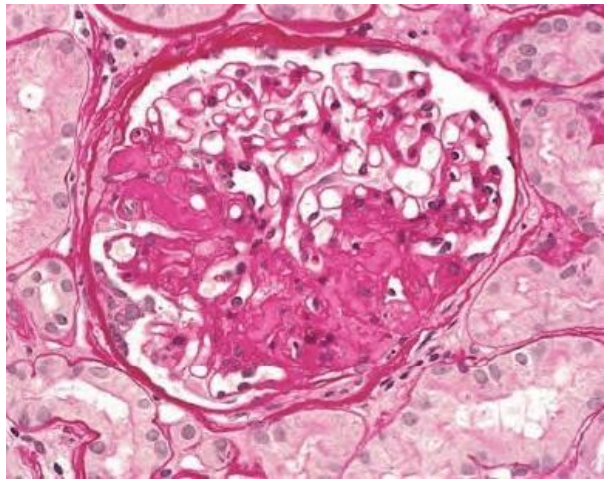
RAPIDS

Schott. Clin J Am Soc Nephrol. 2024

NUHS National University Health System







Nephrotic syndrome +
microscopic haematuria +
hypertension at 24yrs old

Biopsy: **Diffuse mesangial sclerosis**

No immuno-suppressants

Kidney failure by 26 years old

Subnephrotic proteinuria at 19 yrs old
eGFR 96, no hypertension
Biopsy: **FSGS**
GBM thick and thin segments

Steroid / CNI / MMF resistant
Kidney failure by 26 years old

Two COQ8B heterozygous mutations, likely pathogenic

Compound heterozygous for Co-enzyme Q10 deficiency

Use of CoQ_{10} in CoQ_{10} deficiency
COQ2, COQ6, COB8b

- Dose: 30-50 mg/kg/day, 3 divided doses (maximum 1500 mg/day for adolescents and 2400 mg/day for adults)

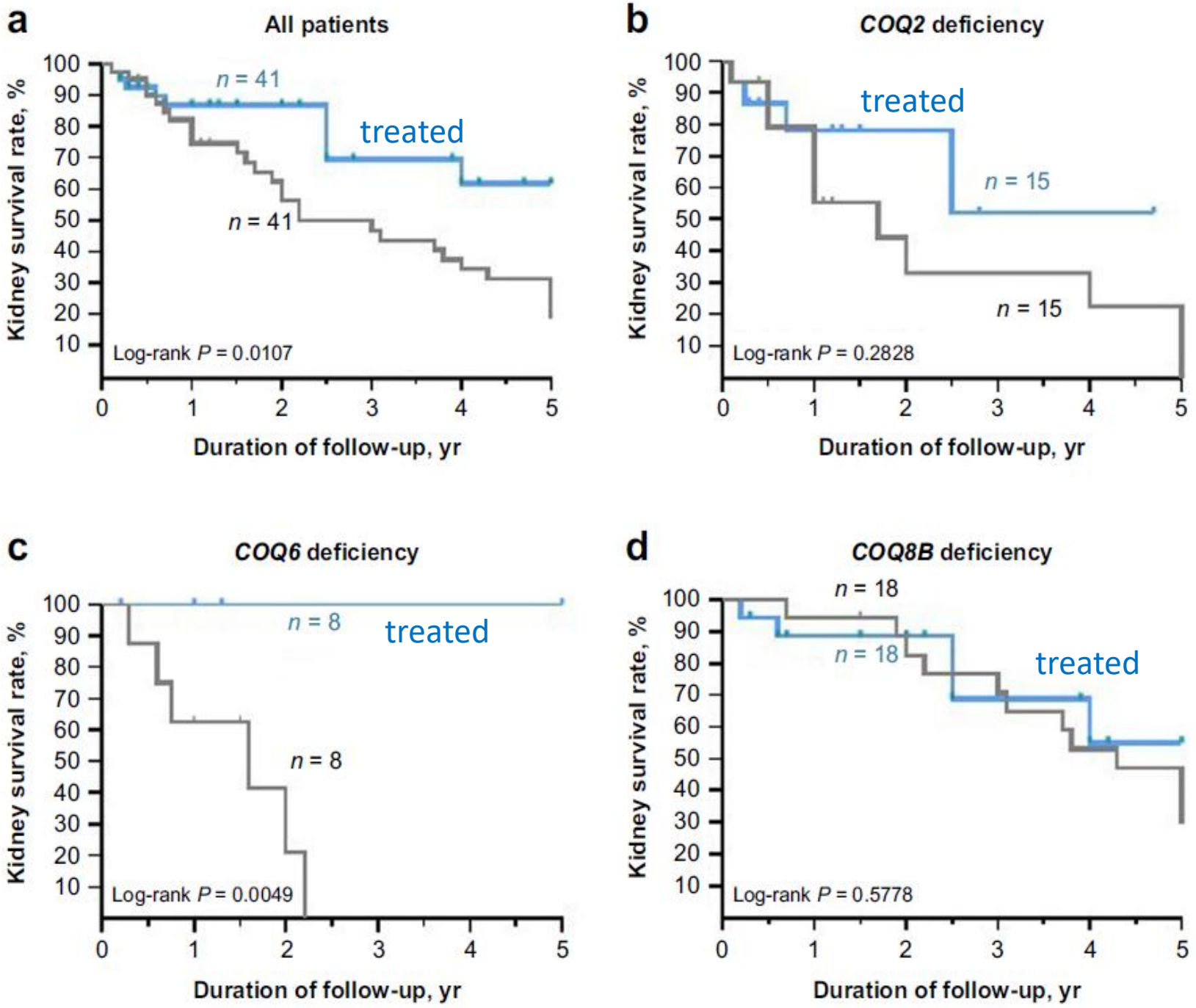
- Optimal dose and formulation is unclear
  - Ubiquinol : Reduced, active form (more “potent” at the same dosage)
  - Ubiquinone : Oxidized form, needs to be converted in the body to the active form
- Expected proteinuria improvement in 4-6 weeks
- Maximal effect in 6 months

- Consider as therapeutic trial (waiting / no genetic results)
- Discontinue if no improvement after 4-6 weeks
- Improvement in kidney condition in 43-56%

Schijvens AM. Kidney Int Rep. 2020: 2146

NUS National University of Singapore

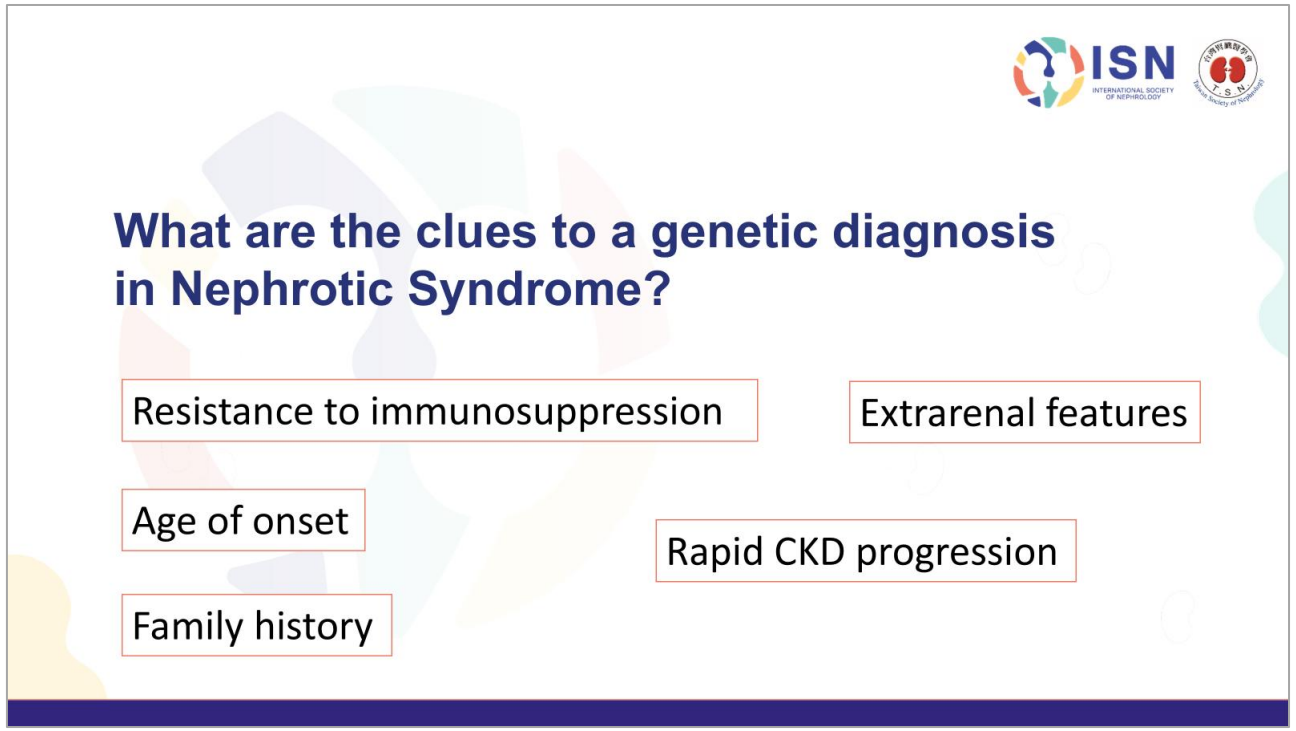
COQ10 supplements can significantly improve kidney survival in patients with Coenzyme Q10 deficiency associated glomerulopathy



Kidney International (2022) 102, 604-

TAKE HOME MESSAGES

1. Look for clues that suggest a genetic cause: “Think genetic”



2. New paradigm of genetic testing over kidney biopsy

TAKE HOME MESSAGES

3. Know how to articulate the utility of a genetic diagnosis
   - Avoid biopsy, tailored immunosuppression
   - Directed therapy
   - Transplant planning

Our DRAGoN team

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RAPIDS

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RAPIDS

NUHS
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