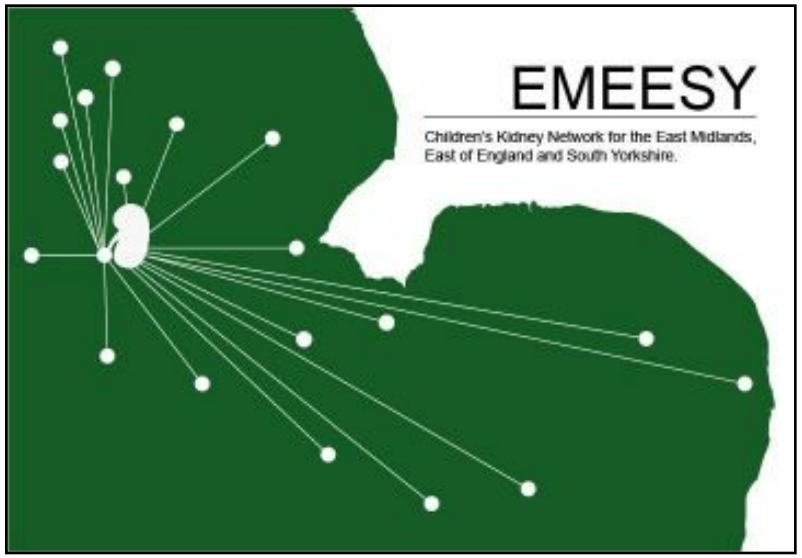
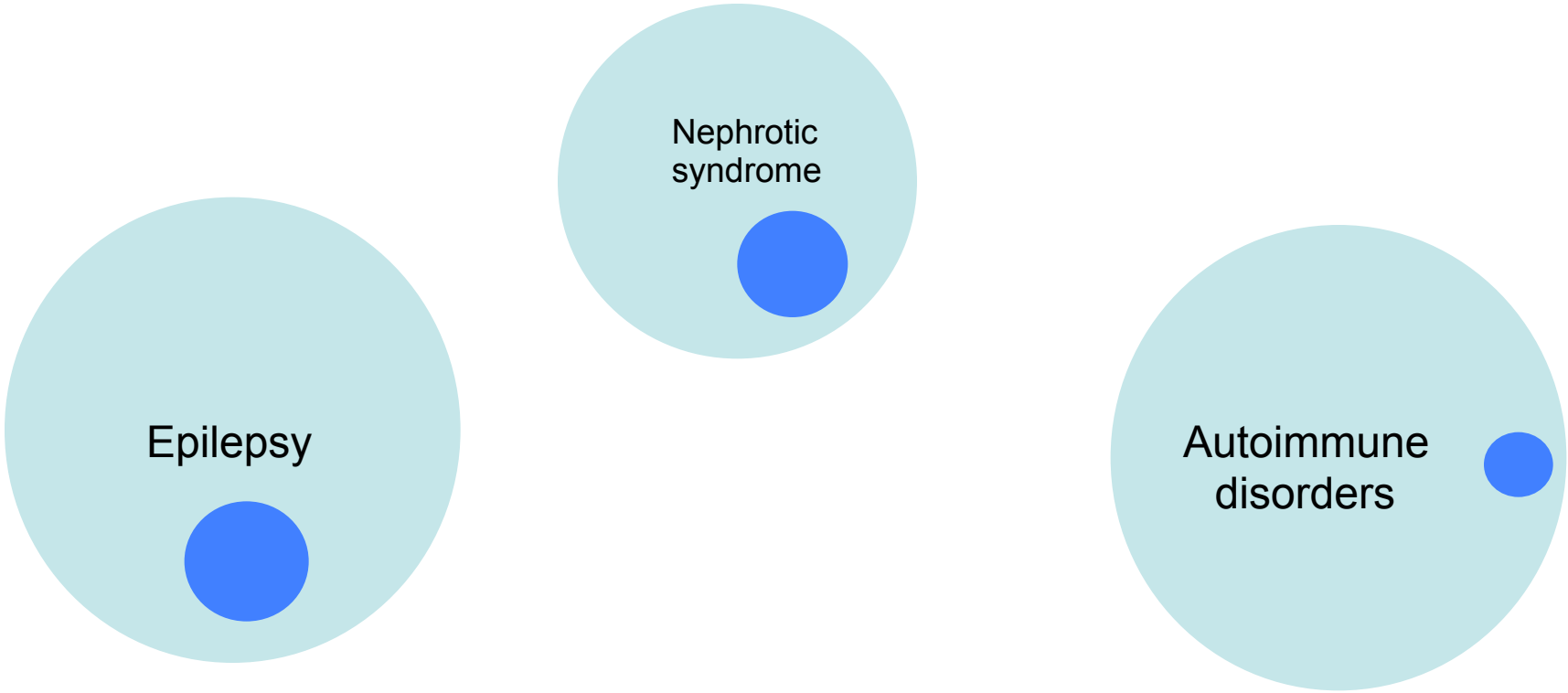


EMEESY Network Annual Education Day

Sedgebrook Hall
16th October 2015

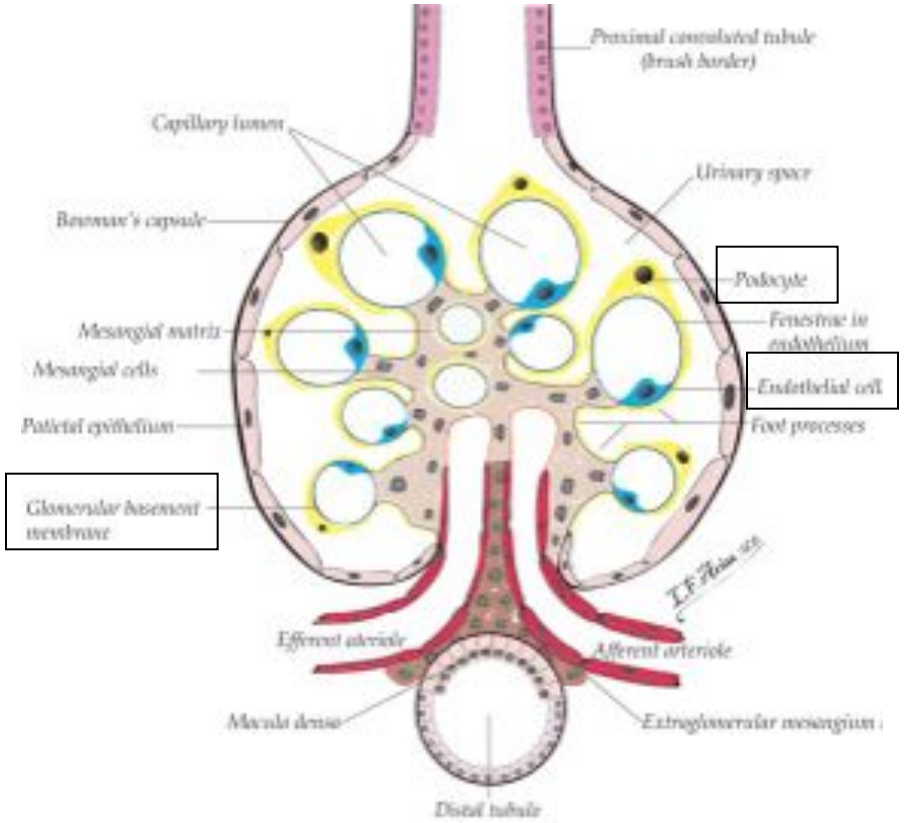
Steroid-resistant nephrotic syndrome

What can genetics tell us?



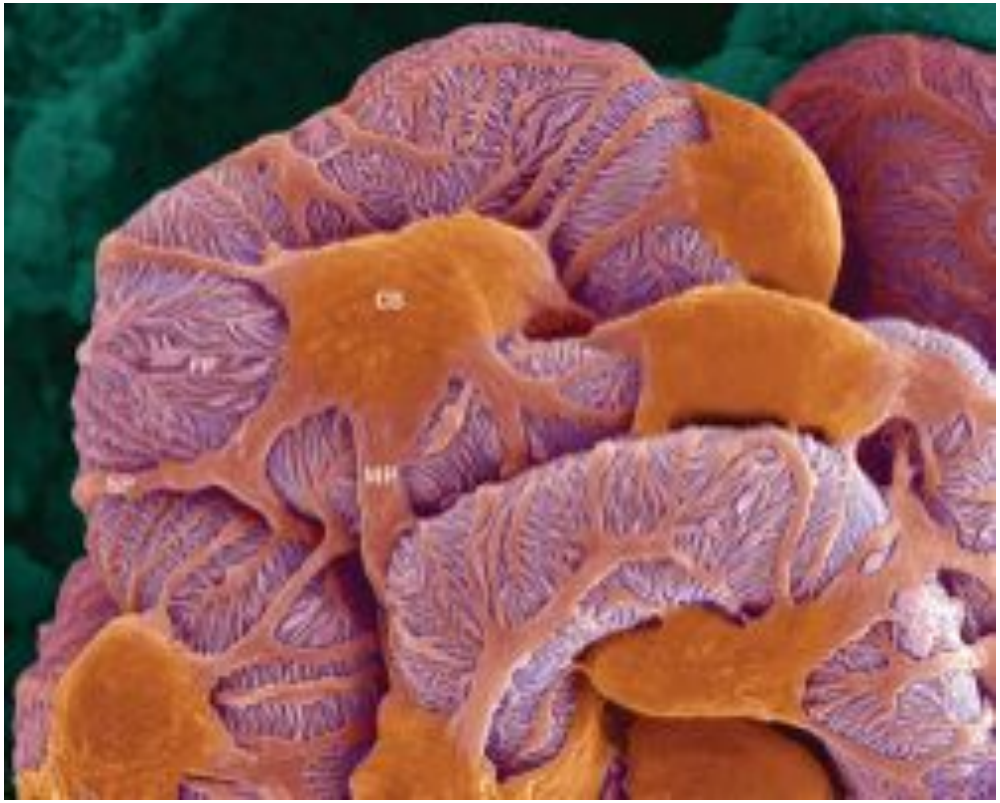
Nephrotic syndrome

- Failure of glomerular filtration barrier
  - Severe proteinuria
    - oedema
    - ↓ albumin
    - ↑ lipids



~20% steroid resistant
Majority have FSGS

A scanning electron micrograph of podocyte cells in a glomerulus demonstrates the cell body, major processes, secondary processes and the finely interdigitating foot processes

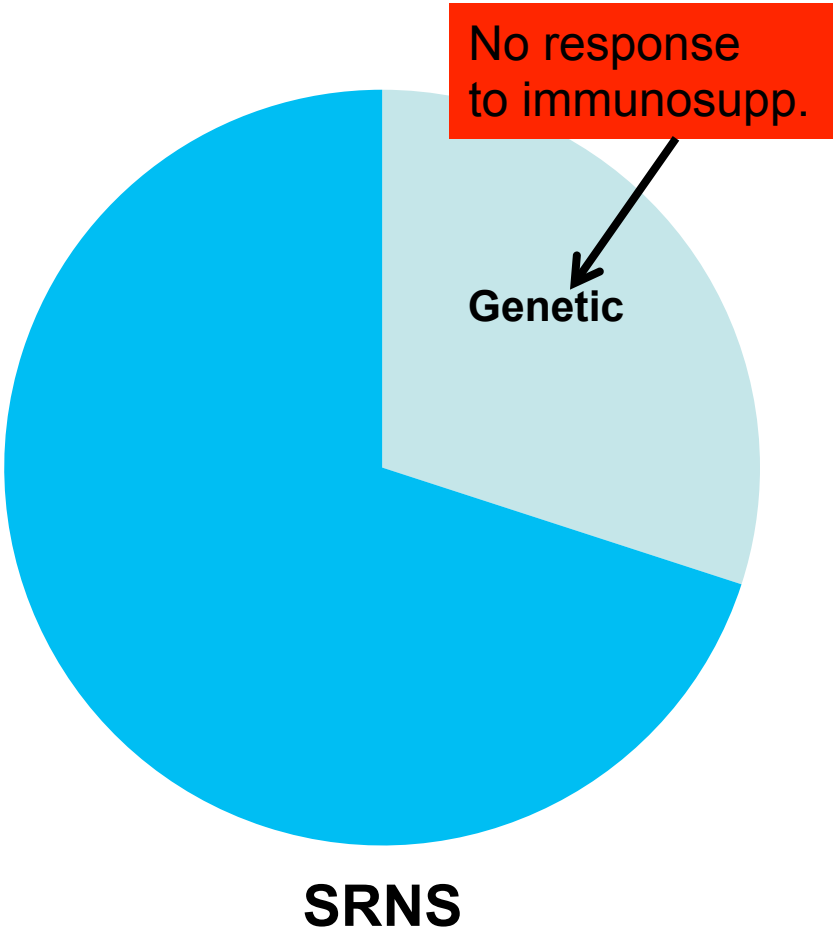


Welsh, G. I. & Saleem, M. A. (2011) The podocyte cytoskeleton—key to a functioning glomerulus in health and disease
Nat. Rev. Nephrol. doi:10.1038/nrneph.2011.151

nature REVIEWS NEPHROLOGY

Steroid-resistant nephrotic syndrome

- Definition
  - No urinary remission after 4 weeks of optimum dose steroids
- Next step
  - Cyclosporin A (immunosuppressive)



Clues to genetic SRNS

Clinical

- Young age
  - 0-3 mo (congenital NS)
  - 3-12 mo (infantile NS)
- Genital abnormalities (either gender)
- Check karyotype in young girls with FSGS

- Other
  - Wilm's tumour
  - Nail abnormalities

Genetic testing

- SRNS gene panel
  - 37 genes (~Nov 2013)
  - Turnaround 4-6 weeks (if urgent)
    - Otherwise 12 weeks
  - About £612

  - Panel due for update
  - Several new genes in last couple of years
    - *CRB2, NUP107, ACDK4, EMP2, WDR73*

Genes causing SRNS

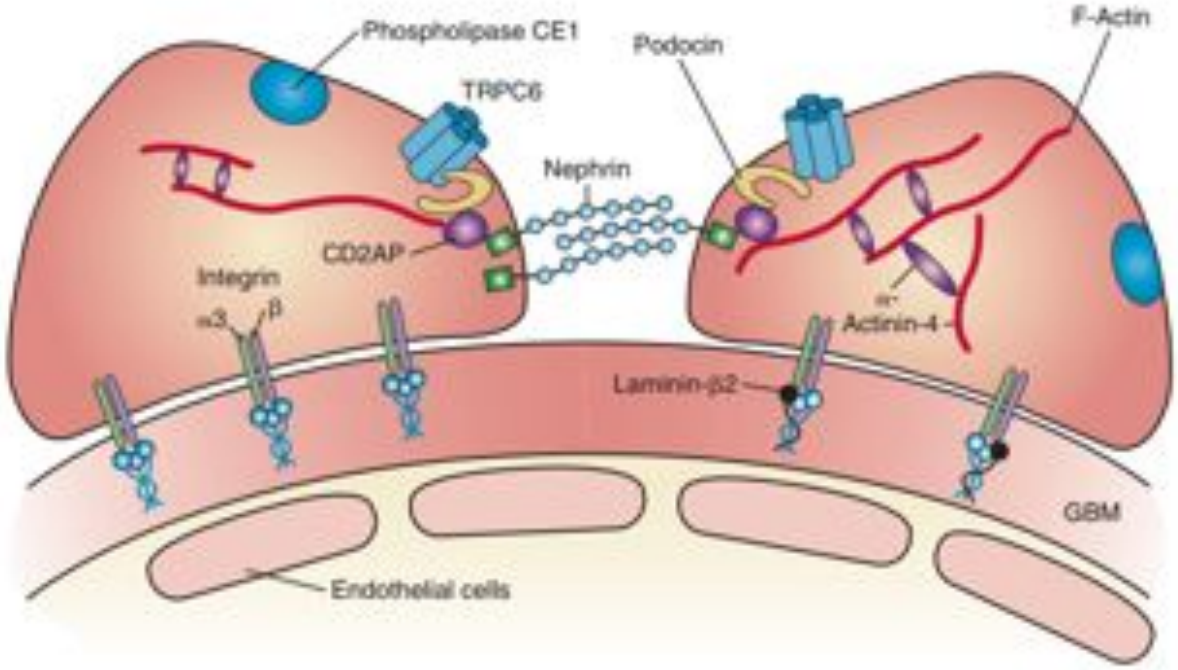


Figure 13-2 Schema of a podocyte foot process cross section depicting important components involved in hereditary nephrotic syndrome.

NPHS1 (Nephrin)
NPHS2 (Podocin)
WT1 → Denys-Drash, Frasier synd, Isolated DMS
PLCe1 (Phospholipase CE1)
CD2AP
TRPC6
LAMB2 (Laminin-β2)- Pierson syndrome

From: Geary D and Schaefer F (eds). Comprehensive Pediatric Nephrology. Elsevier. Burlington 2008

Syndromic SRNS

- 5.5 yr old girl
- Presented with SRNS at 3.5 yr
- Renal biopsy showed focal segmental glomerulosclerosis

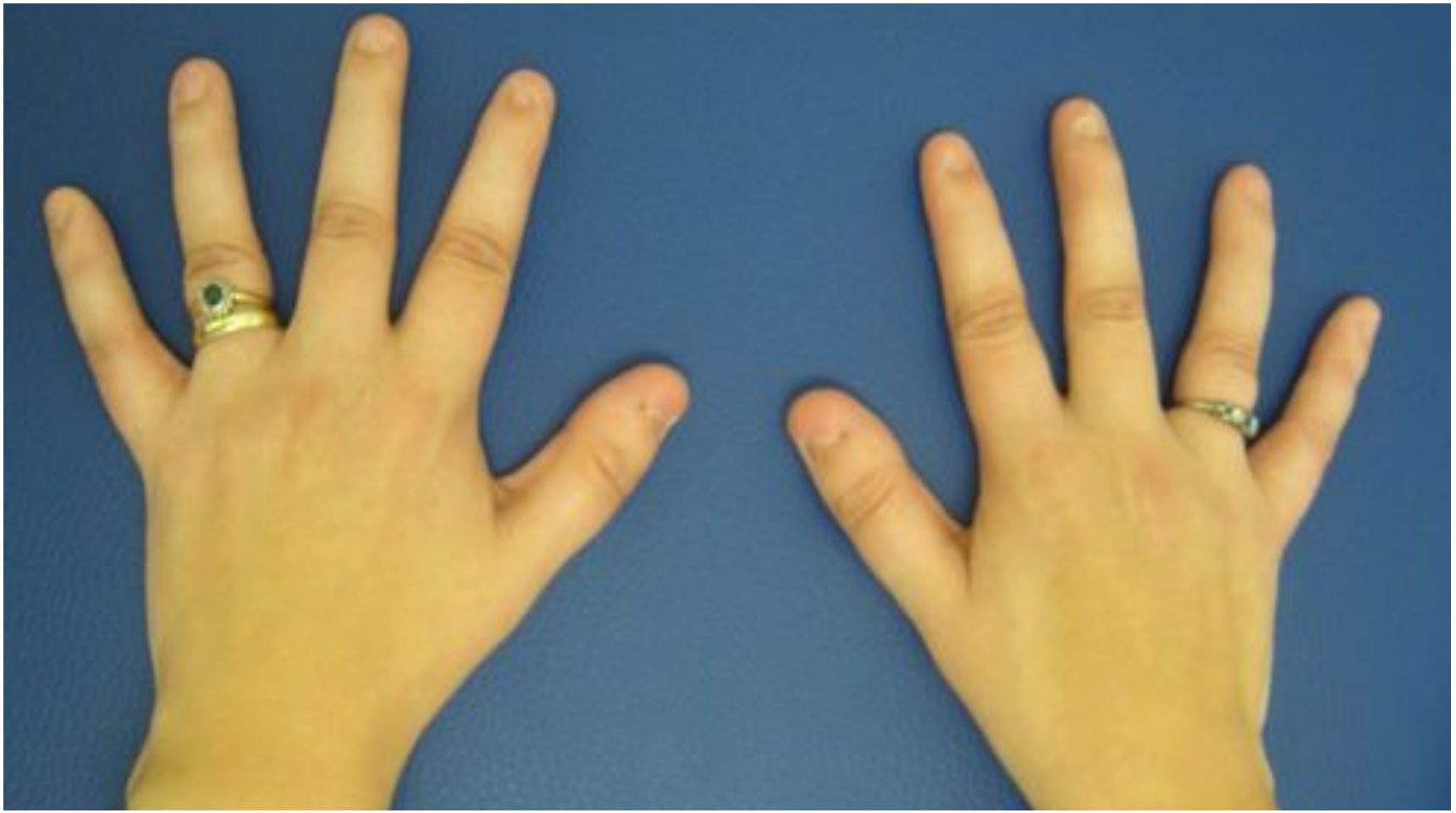
- No significant FH
- No other medical problems

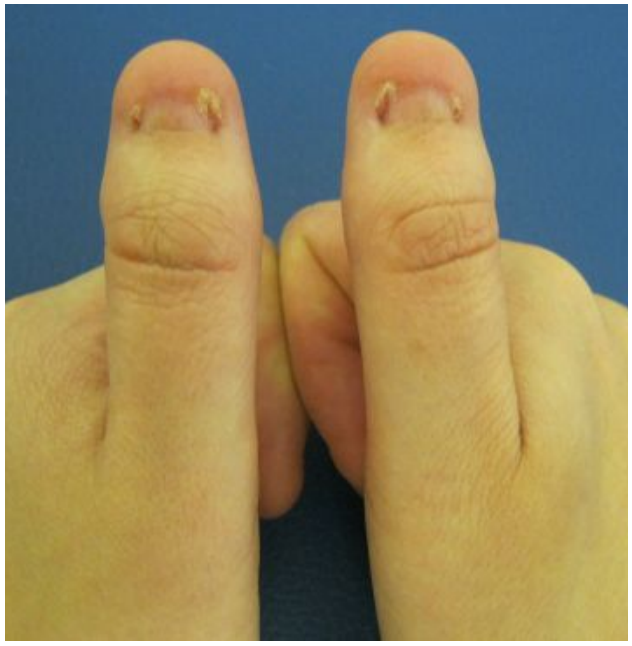
- SRNS panel
- ***WT1* mutation**
  - **c.1228+5G>A**

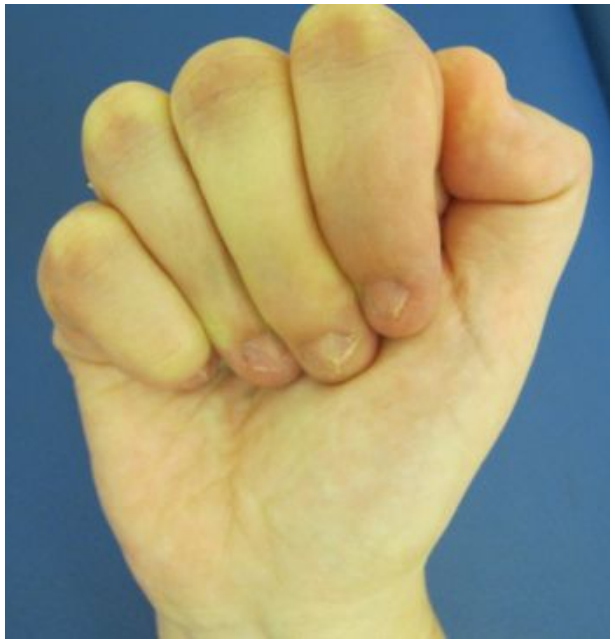
- **Frasier syndrome**

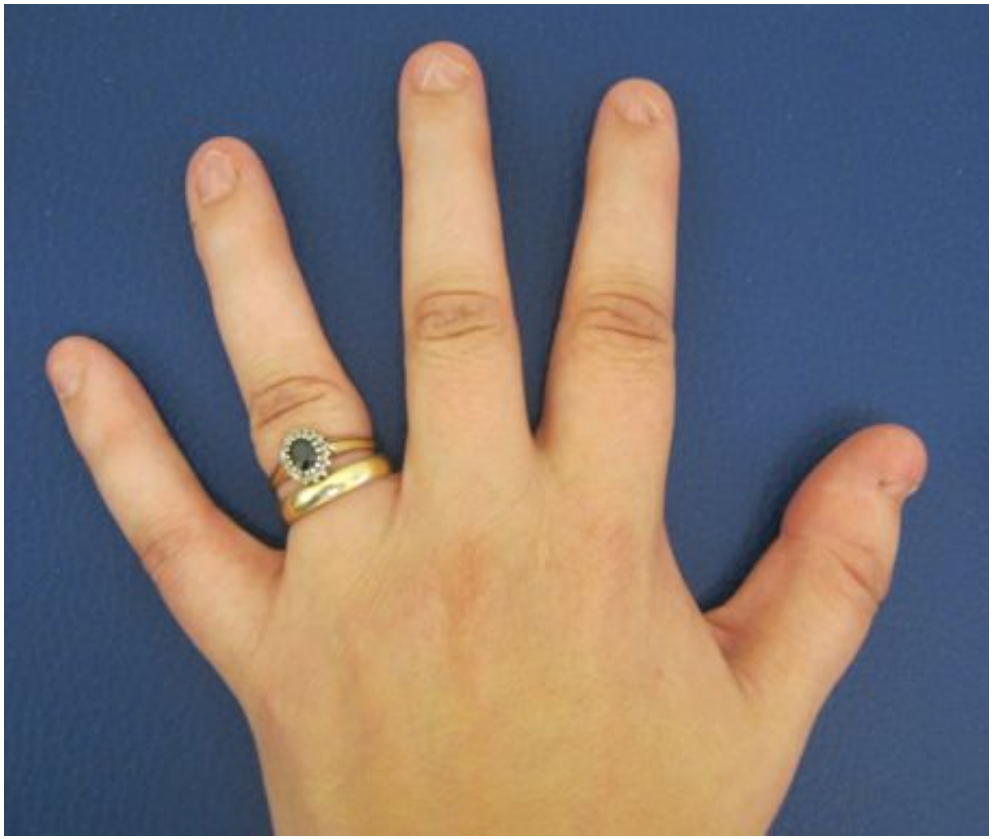
- **Implications**
  - Progressive decline in renal function
  - Immunosuppression will not help

  - Sex reversal
  - Karyotype 46,XY
  - Risk of gonadoblastoma
  - Infertility
  - Puberty induction









Nail-patella syndrome
Heterozygous *LMX1B* mutation

Summary

- Timely identification of genetic forms of SRNS changes management
- Age at presentation, history and physical examination can provide clues to syndromic diagnosis

- Cause of non-genetic FSGS remains a mystery but insights into podocyte biology might provide an answer?