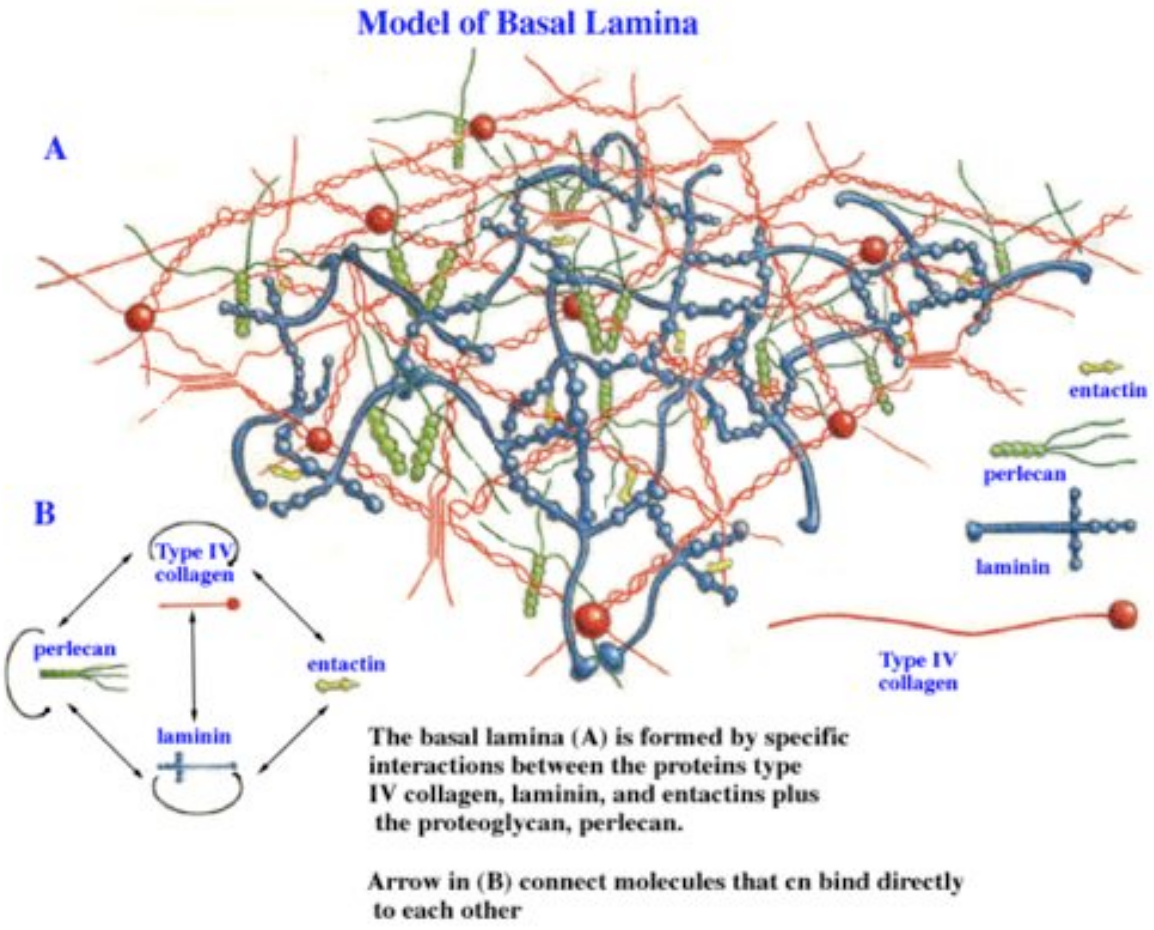
Inherited Basement Membrane Disorders

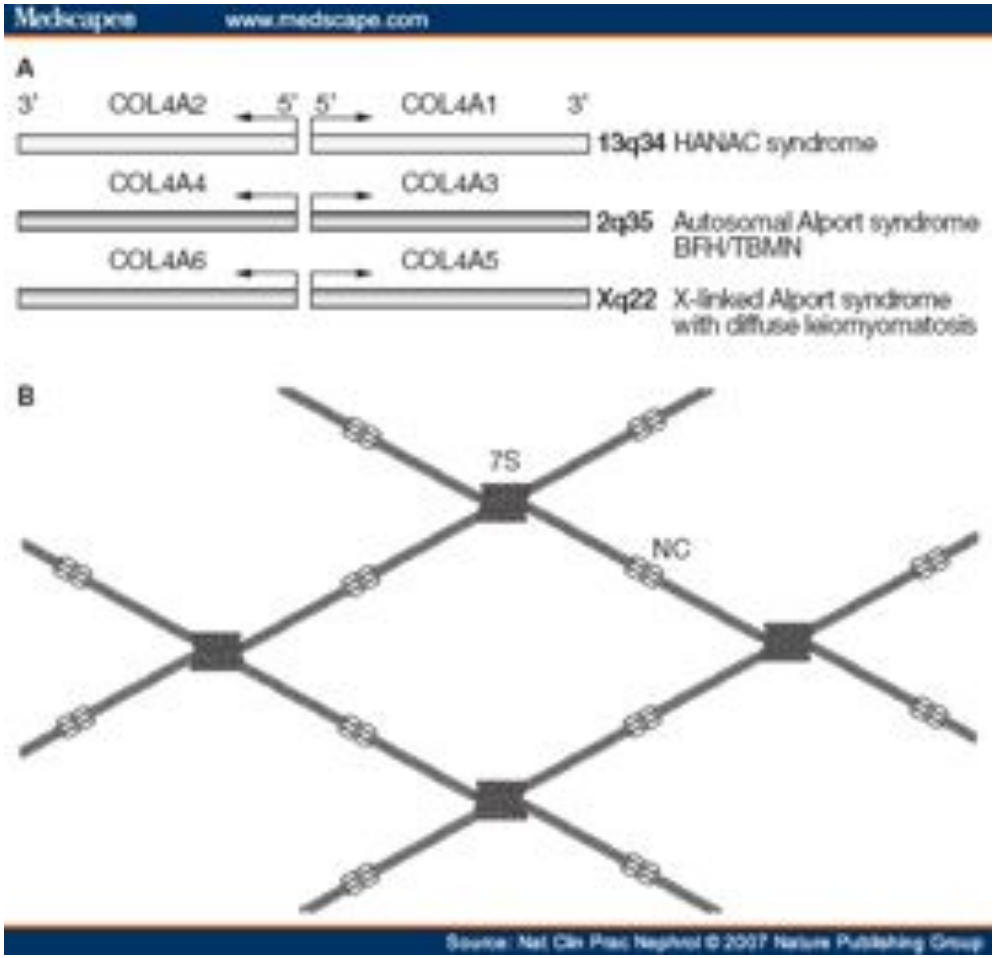
Dr Jackie Cook

Consultant in Clinical Genetics

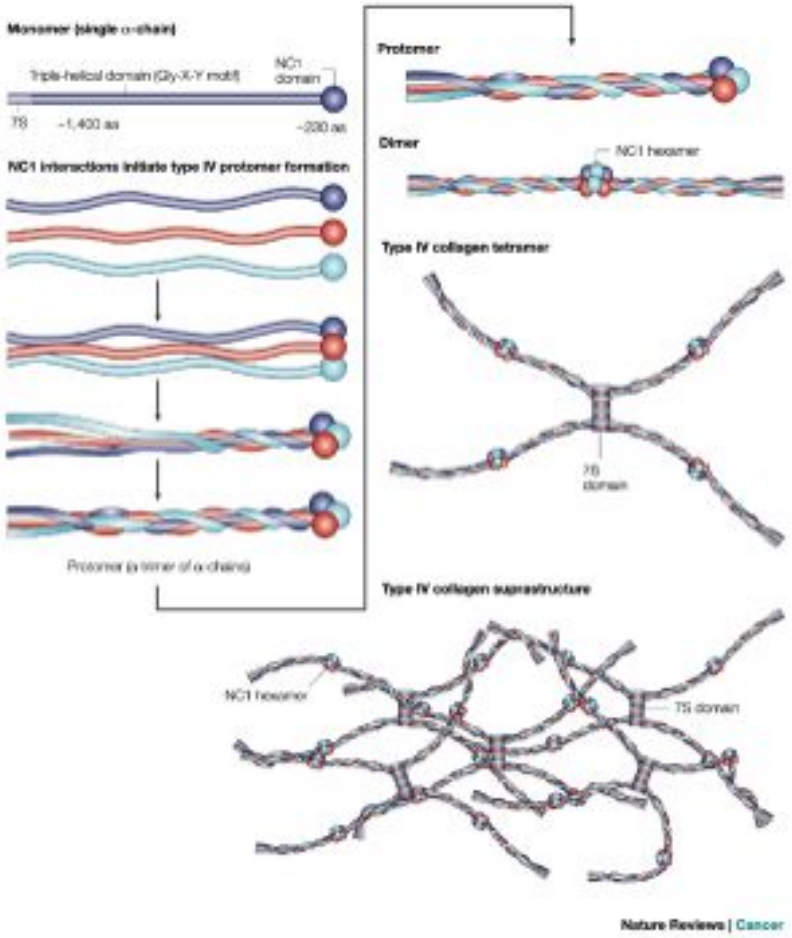
Glomerular Basement Membrane



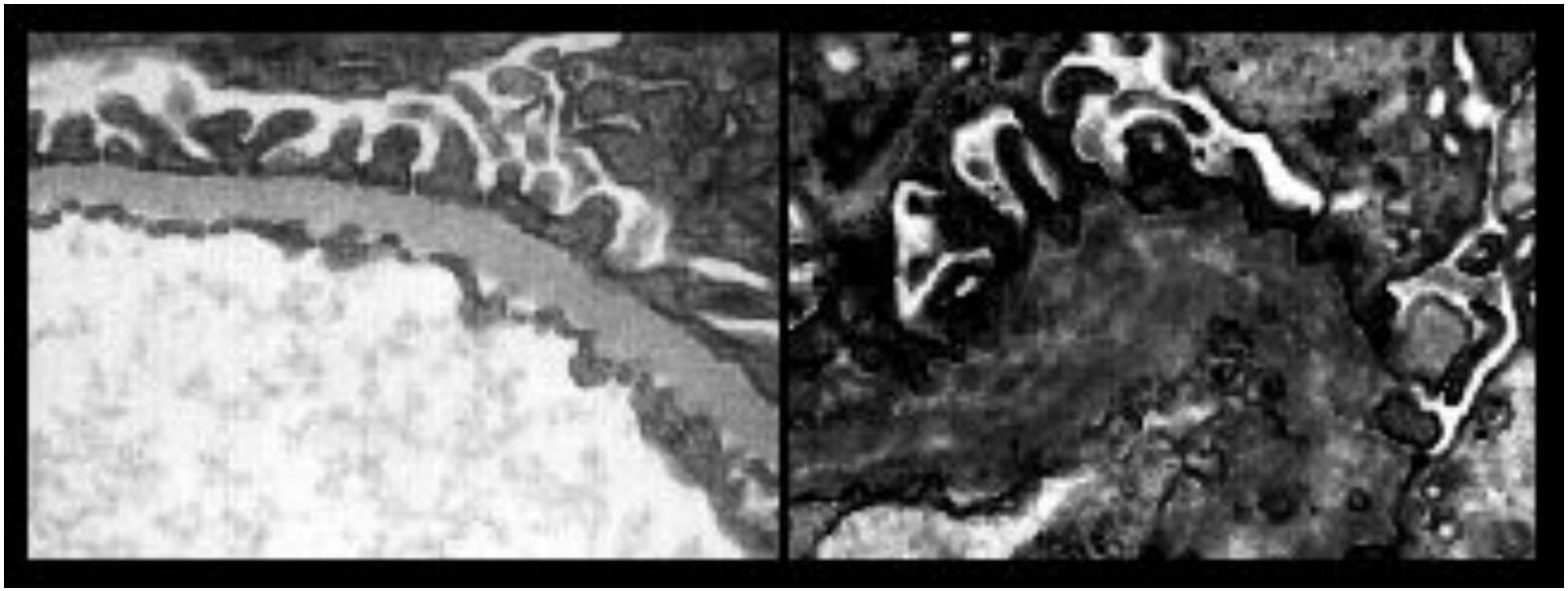
Type 4 collagen



Type 4 Collagen



COL4A5 X-linked Alport Syndrome



Normal

Alport Syndrome

COL4A5 – X-linked Alport Syndrome 85%

	Males	Females
haematuria	100%	95%
proteinuria	100%	75%
Hearing loss	90%	10% by 40, 28% by 60
Keratoconus, retinal flecks	40%	15%
ESRD	70% by 30, 90% by 40	12% by 40, 30-40% over 60
Oesophageal leiomyomatosis	rare	

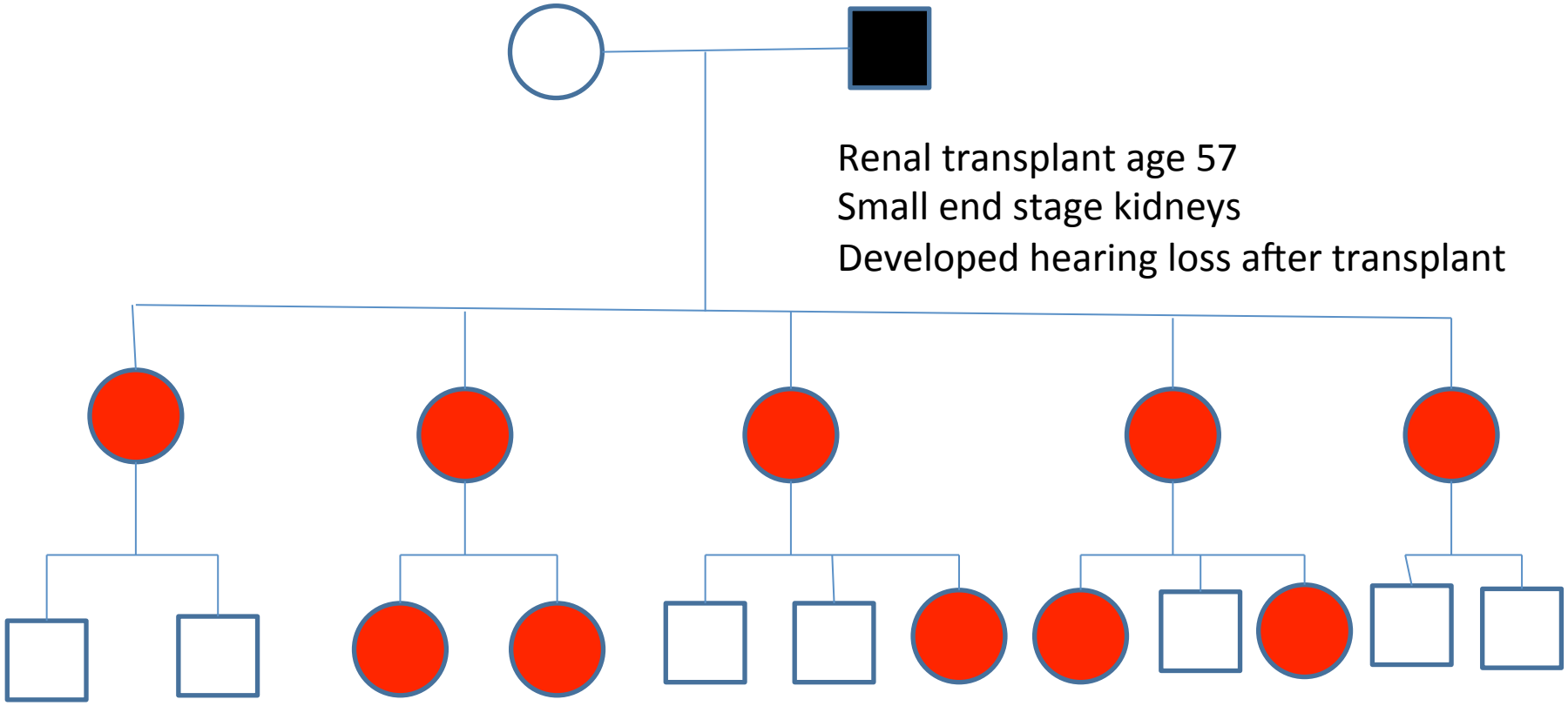
COL4A5 genotype / phenotype correlations

- In males protein truncating mutations confer a 90% chance of ESRD by 30
- With splice site mutations 70% chance of ESRD by 30
- With missense mutations 50% chance of ESRD by 30
- Lenticonus associated with large deletions and nonsense mutations
- Oesophageal leiomyomatosis only seen in deletions involving both COL4A5 and COL4A6

Ultrastructural findings of GBM in females

- Thin
- Thick / thin
- Thick / split

Sheffield Case 1 – COL4A5 missense mutation



COL4A3 & COL4A4 Autosomal Recessive Alport Syndrome 15%

- Same clinical features as X-linked recessive
- Males and females affected with equal severity at young age
- ESRD often between 5 -15
- Parents often have isolated haematuria
- Family may be consanguinous
- Have mutations in both copies of COL4A3 or COL4A4

Digenic Inheritance

- Individuals identified with one COL4A3 mutation and one COL4A4 mutation
- If mutations are in trans – AR Alport but milder
- If mutations in cis – AD inheritance pattern

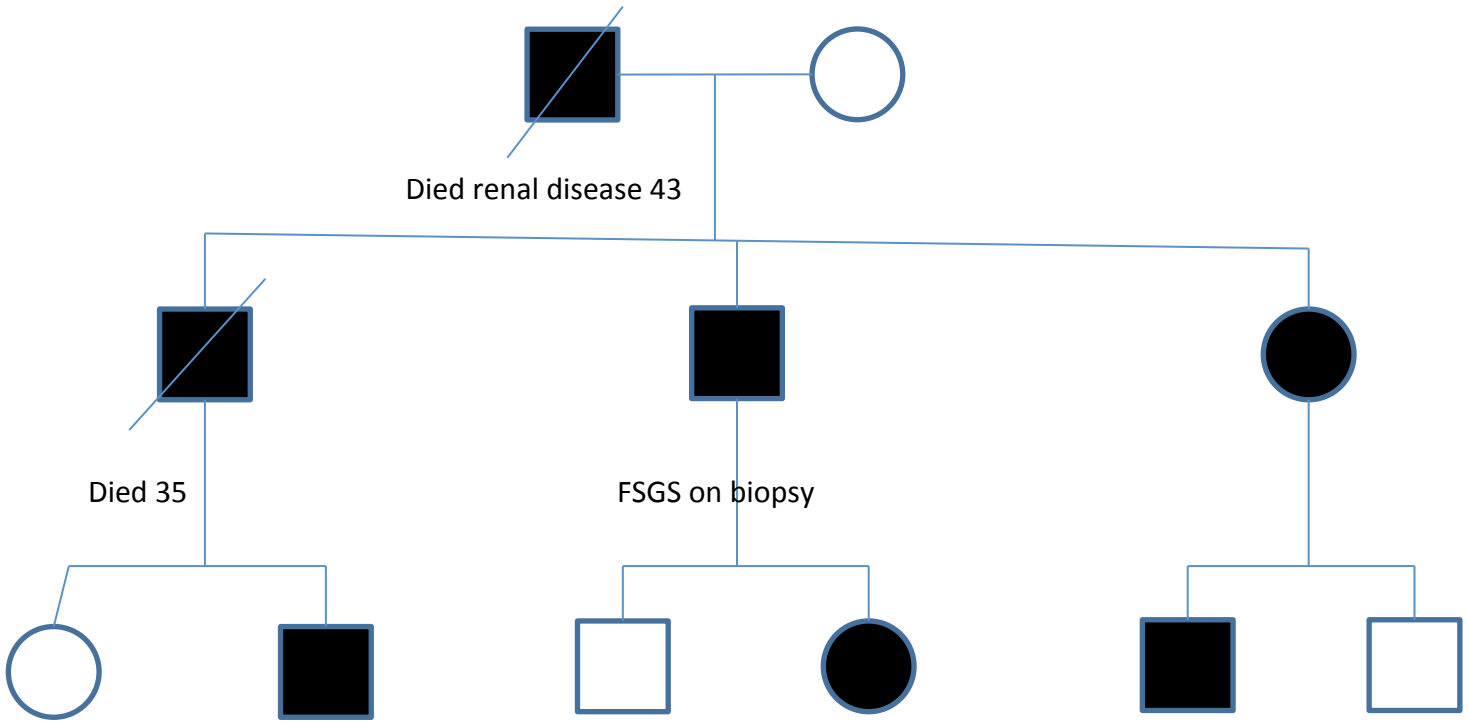
Thin Membrane Disease

- Autosomal dominant inheritance
- May affect up to 1% of the population
- Persistent haematuria
- Thin GBM on EM
- Proteinuria < 200 mg/l
- Usually carrier for a single recessive COL4A4 or COL4A3 mutation
- Increased risk to develop hypertension
- Increased risk to develop renal failure, particularly if there is co-existent renal disease e.g. diabetes

COL4A4 & COL4A3 Autosomal Dominant Alport Syndrome

- Considered to be very rare
- But, this belief is being challenged
- May not be presenting with the classical Alport symptoms
- Can present as familial segmental glomerulosclerosis

Sheffield Case 2 – heterozygous COL4A4 missense mutation, altered a.a. is in the NC1 domain responsible for correct heterotrimer assembly



Type 4 Collagen