Welcome to

ERKNet/ESPN Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

WEBINAR

22/02/22

The genetics of human renal agenesis and renal dysplasia

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ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

Genetics of human renal agenesis and renal dysplasia

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University of Manchester
and
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Children's Hospital

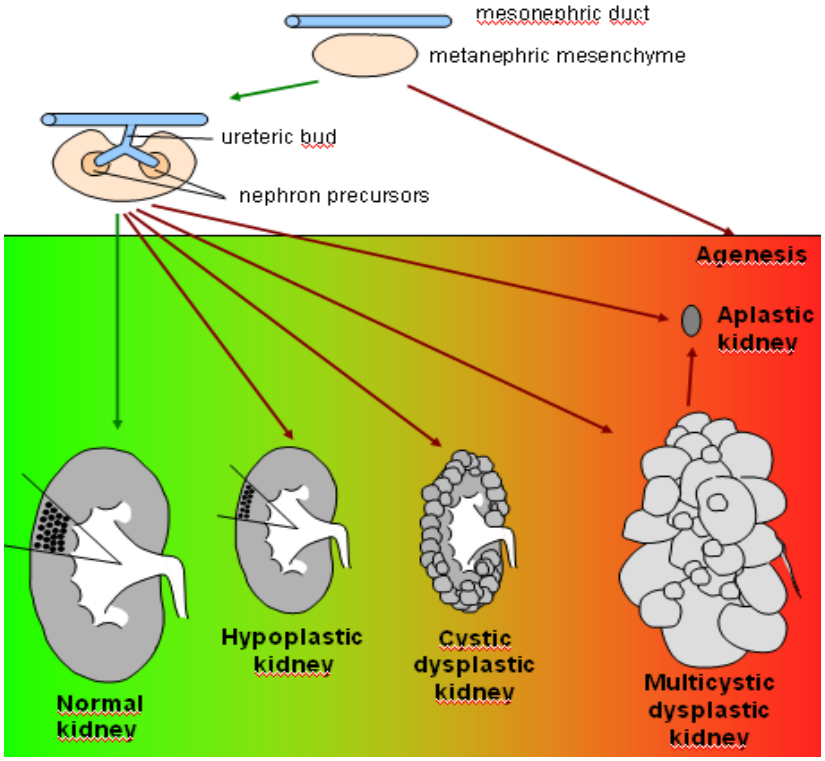
Manchester Regenerative Medicine Network

Overview

- **Some clinical aspects about human renal malformations**
- A genetic example of renal agenesis
- Two genetic examples of renal dysplasia:
- a. intrinsic to abnormal kidney development
- b. secondary to lower urinary tract obstruction

1. **Half of all children with end-stage kidney failure (ESKF) were born with malformed kidneys**

2. Worldwide, 20,000-90,000 children are estimated to have ESKF and malformed kidneys



Normal Worsening renal function

3. Around 1 in 5 young adults with ESKF were born with malformed kidneys

4. There is increasing evidence that such individuals carry mutations of genes that drive the growth of the renal tract.

Edith Potter's microdissection studies of human embryonic kidneys

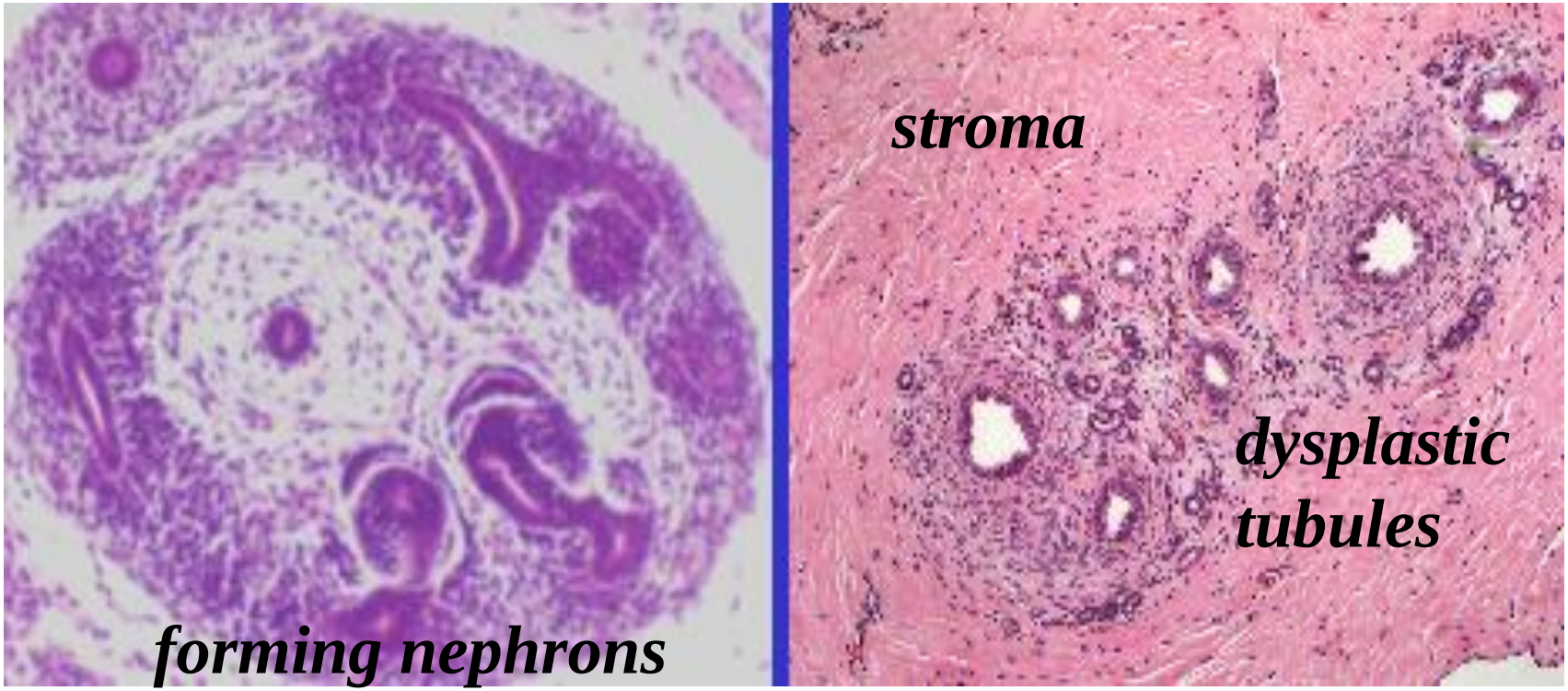
Normal branching

Dysplastic branching

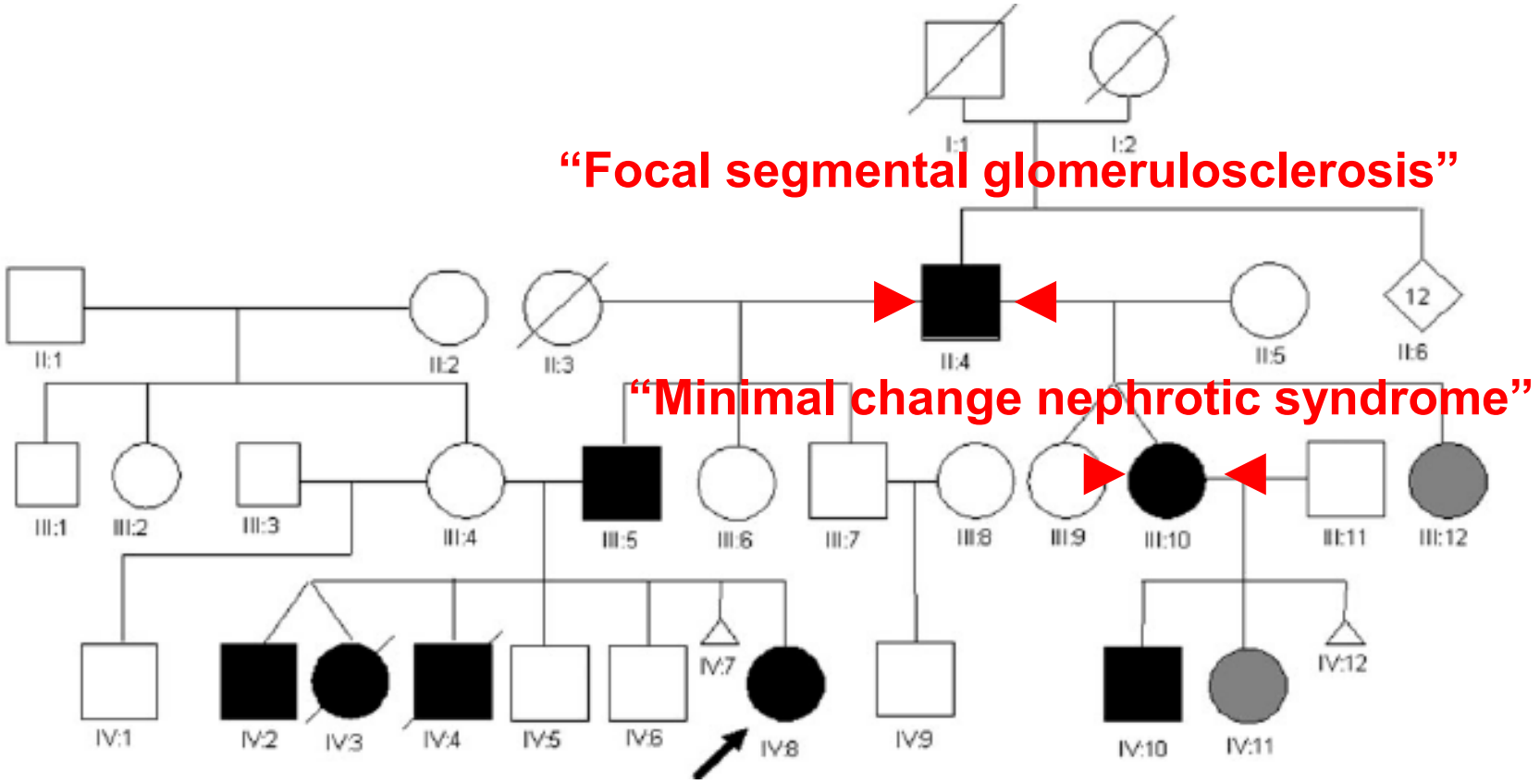
Osathanondh V and Potter EL *Arch Pathol* 1963
Potter EL *Normal and Abnormal Development of the Kidney* 1972

DYSPLASTIC KIDNEY SUPERFICILLY RESEMBLES AN EMBRYONIC KIDNEY FROZEN IN TIME

Normal metanephros ***Dysplastic kidney***



THREE GENERATIONS AFFECTED BY KIDNEY MALFORMATIONS: MIS-CLASSIFICATION OF TWO ADULTS



Kerecuk L *et al Nephrol Dial Transplant* 22:259-263, 2007

Overview

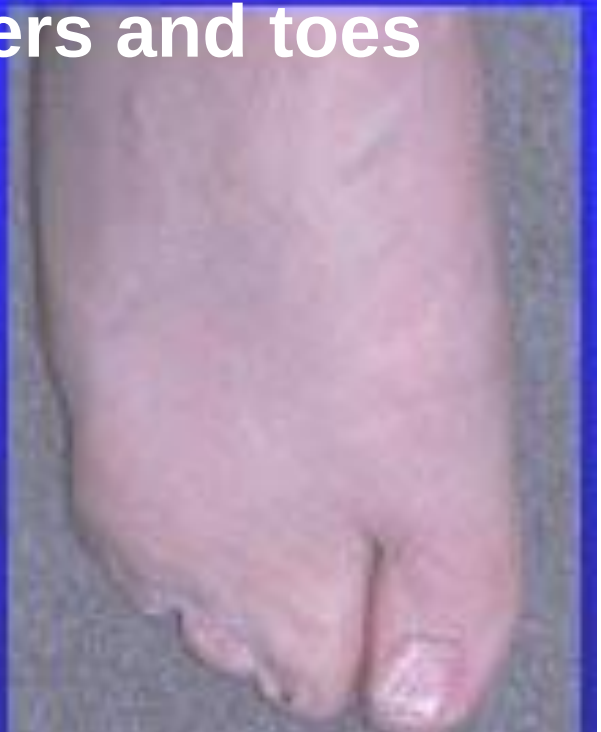
- Some clinical aspects about human renal malformations
- **A genetic example of renal agenesis**

  Fraser syndrome (*FRAS1* mutation)
- Two genetic examples of renal dysplasia:
- a. intrinsic to abnormal kidney development
- b. secondary to lower urinary tract obstruction

Fraser syndrome

Cryptophthalmos ‘hidden eyes’

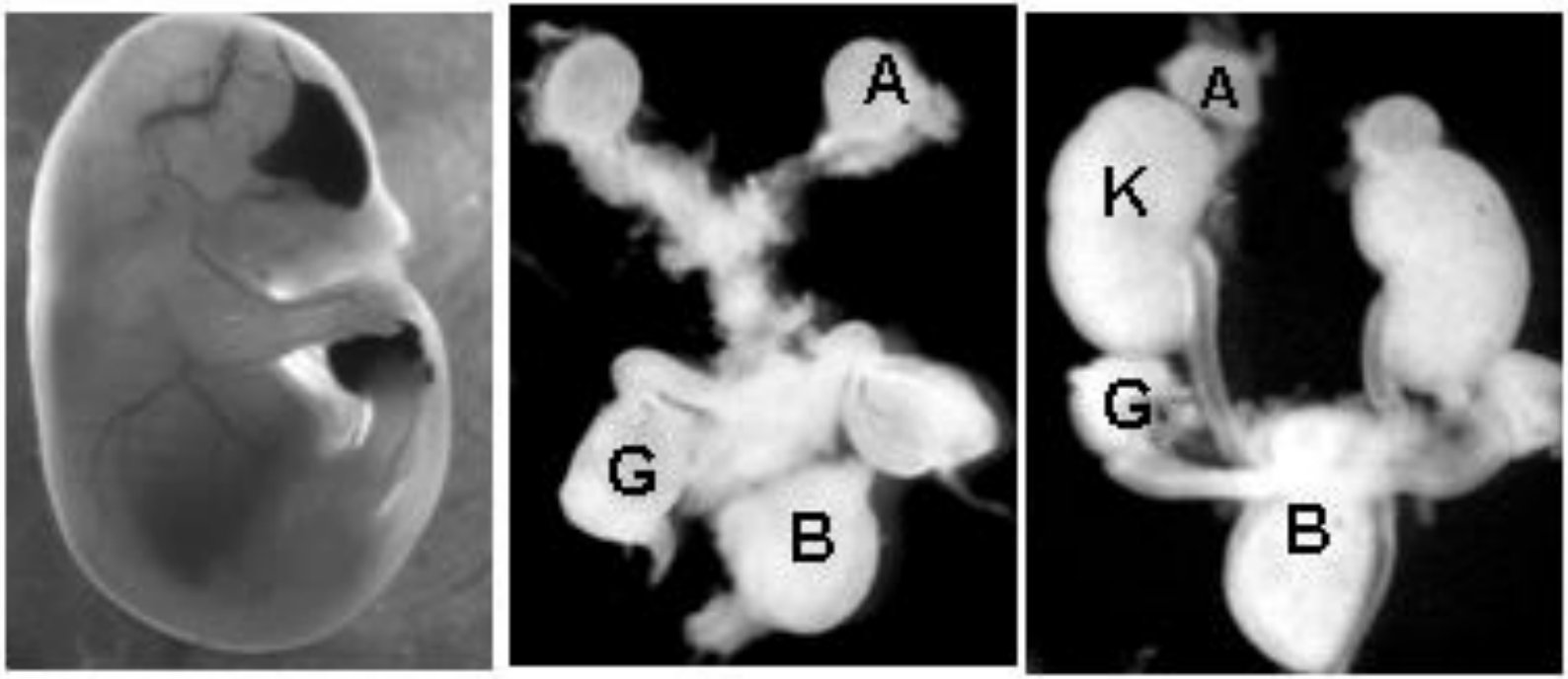
Short and fused fingers and toes



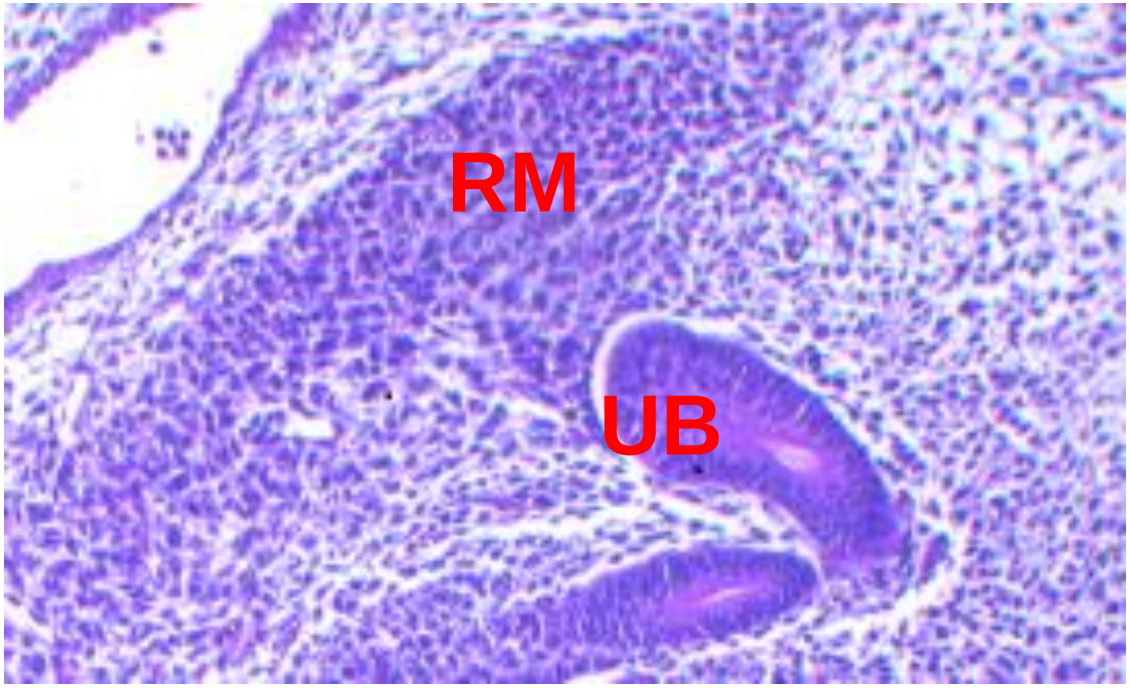
Mutant *bl/bl* mice with Fraser syndrome

Homozygous mutants have embryonic skin blisters and lack kidneys and ureters

Wild-type littermate



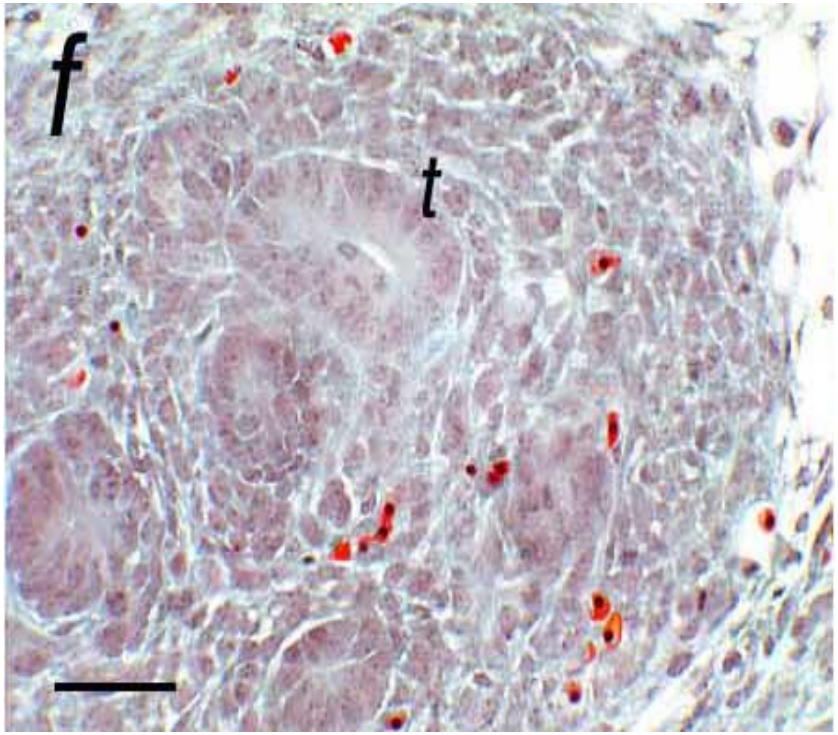
In Fraser syndrome the ureteric bud (UB) fails to penetrate the renal mesenchyme (RM), so a discrete kidney never forms



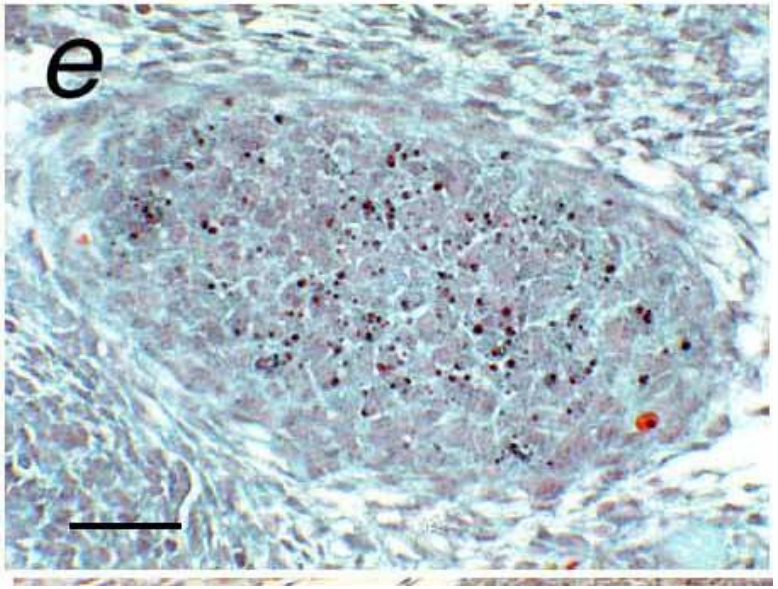
Pitera JE *et al Hum Mol Genet* 17:3953-3964, 2008

Precursor kidney cells self-destruct in Fraser syndrome mice

Wild type with tubules

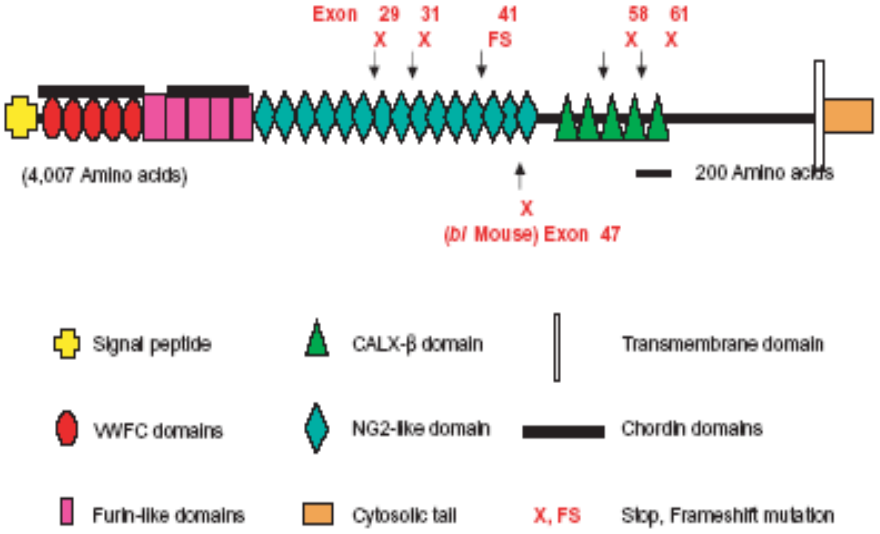


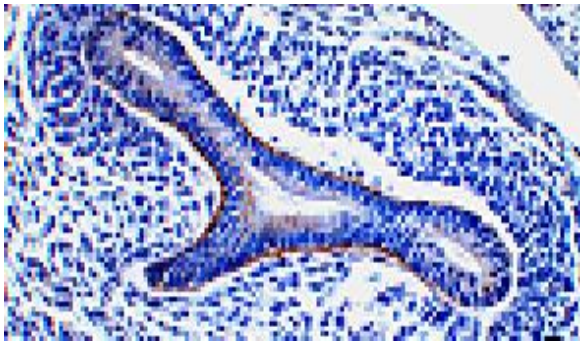
Mutant ++apoptosis



MacGregor L *et al Nature Genet* 34:203-208, 2003

FRAS1 protein is absent in Fraser syndrome

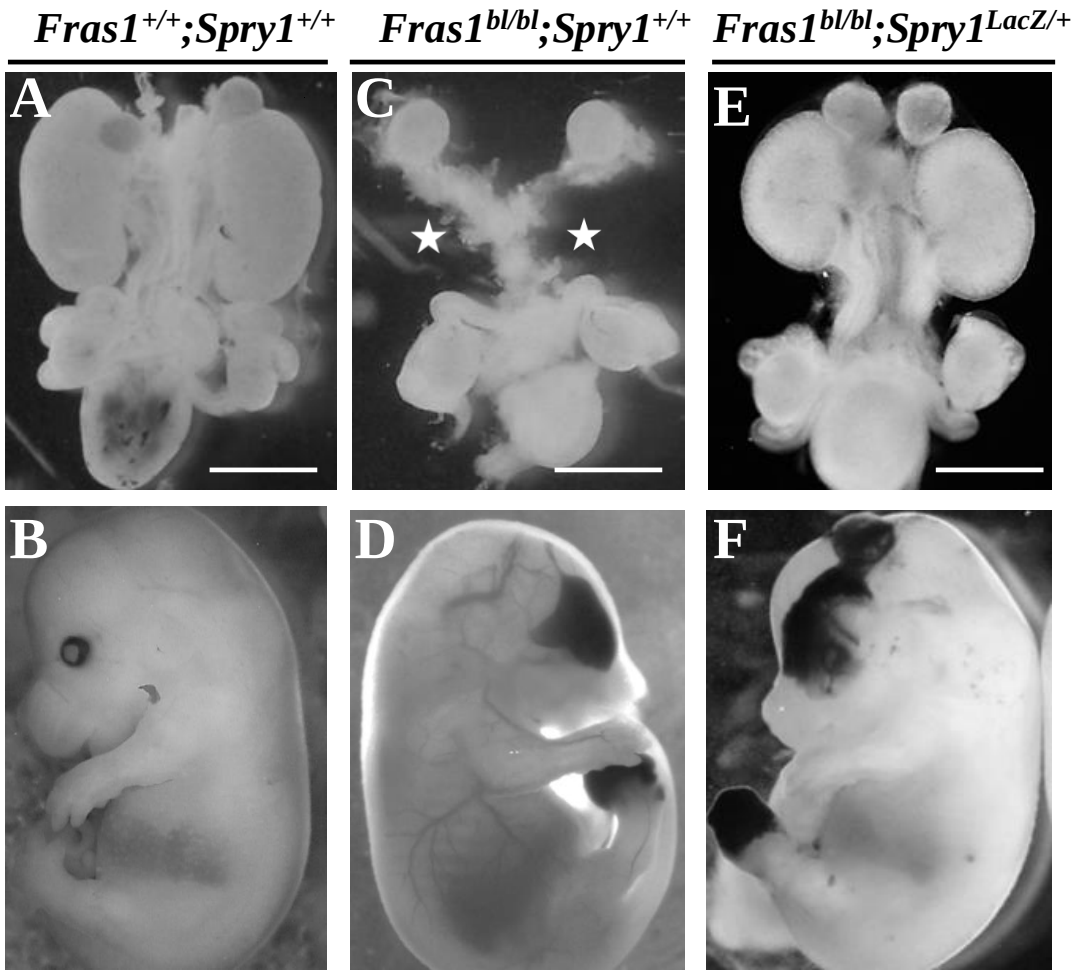




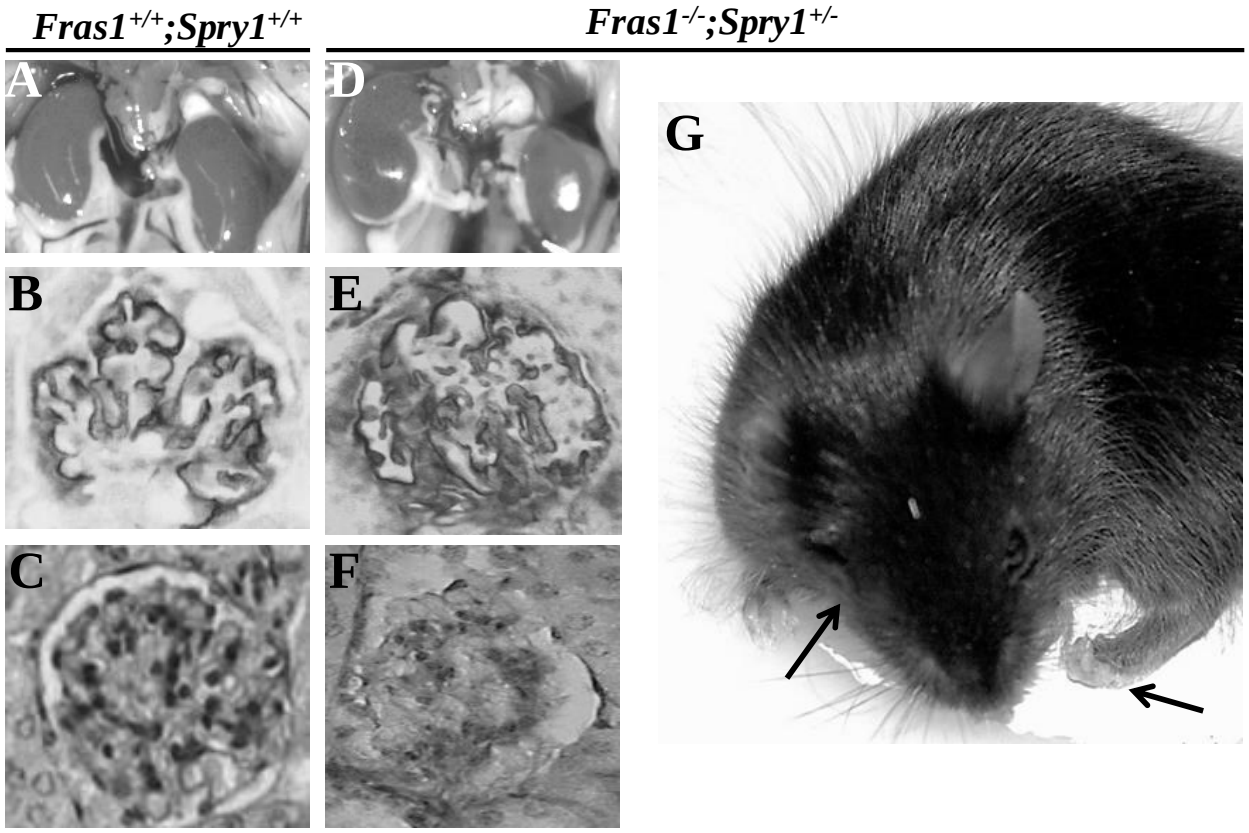
FRAS1 codes for a 4007 amino acid protein which coats the surface of the ureteric bud and mediates growth factor signalling

MacGregor L et al *Nature Genet* 34:203-208, 2003
Pitera JE *et al Hum Mol Genet* 17:3953-3964, 2008

Renal agenesis in Fraser syndrome mice is rescued by increase growth factor signalling in the metanephros



Fraser syndrome mice with genetically-rescued kidneys survive to adulthood but have sclerotic glomeruli



Pitera JE *et al J Am Soc Nephrol* 23:1790-1796, 2012

Overview

- Some clinical aspects about human renal malformations
- A genetic example of renal agenesis
- **Two genetic examples of renal dysplasia:**
- **a. intrinsic to abnormal kidney development *HNF1B* disease**
- b. secondary to lower urinary tract obstruction

RENAL CYSTS AND DIABETES SYNDROME (RCAD)

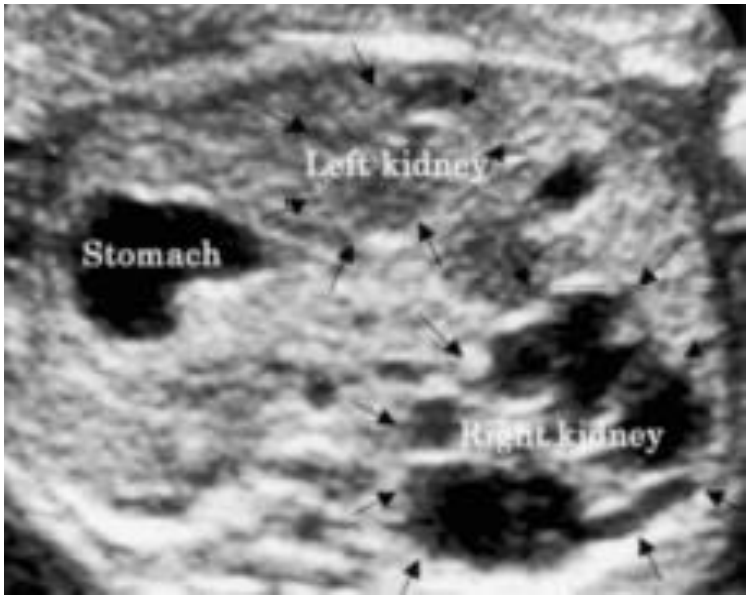
- RCAD was defined at the start of the 2000's
- Autosomal dominant or sporadic
- Diabetes mellitus (MODY5) and uterus malformations
- Renal disease resulting from abnormal development (but not classic 'diabetic nephropathy')
- Renal cysts on scans, with histology showing cystic dysplasia and sometimes glomerular cysts
- *Hepatocyte Nuclear Factor 1B* transcription factor mutations (chromosome 17cen-q21.3)

HNF1B example

- Antenatal diagnosis of right multicystic dysplastic kidney: this involuted (spontaneously disappeared) after birth.
- Left solitary functioning kidney was ‘normal size’ (but should have been larger than normal) and was echobright on ultrasound scan.
- At 12 years of age she developed overt diabetes mellitus (non ketotoic) with blood sugar of 30 mM.
- Then presented with acute abdominal pain due to retained blood in malformed uterus

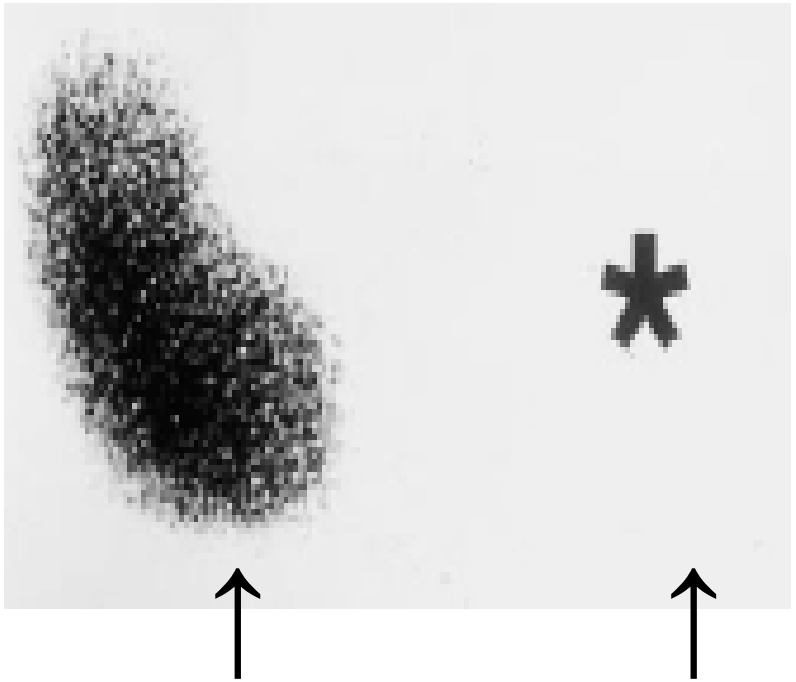
MULTICYSTIC DYSPLASTIC KIDNEY - RADIOLOGY

Ultrasound scan
32 weeks gestation



Shukunami K *et al*
J Obstet Gynaecol
24:458-459, 2004

Postnatal renal
DMSA isotope scan

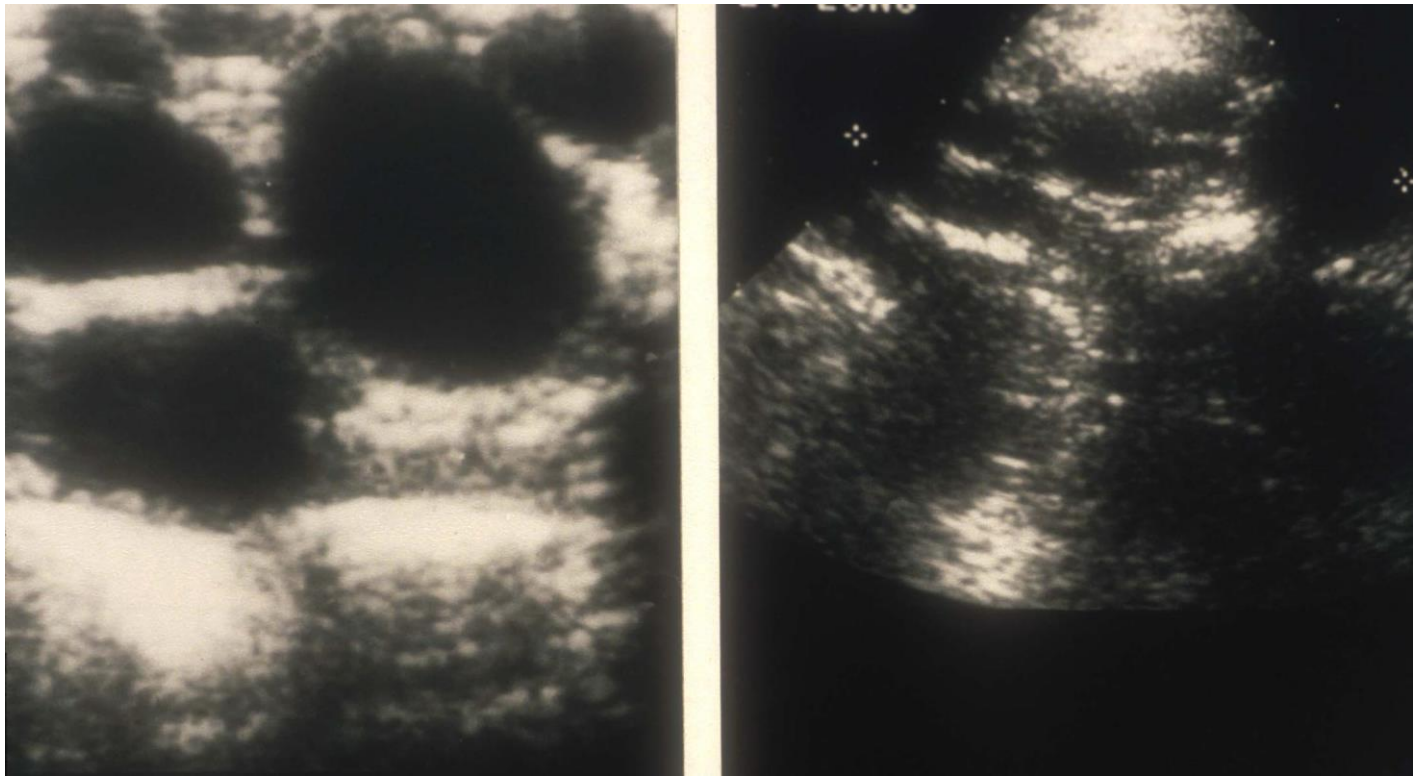


‘Normal’ kidney

MCDK (no uptake)

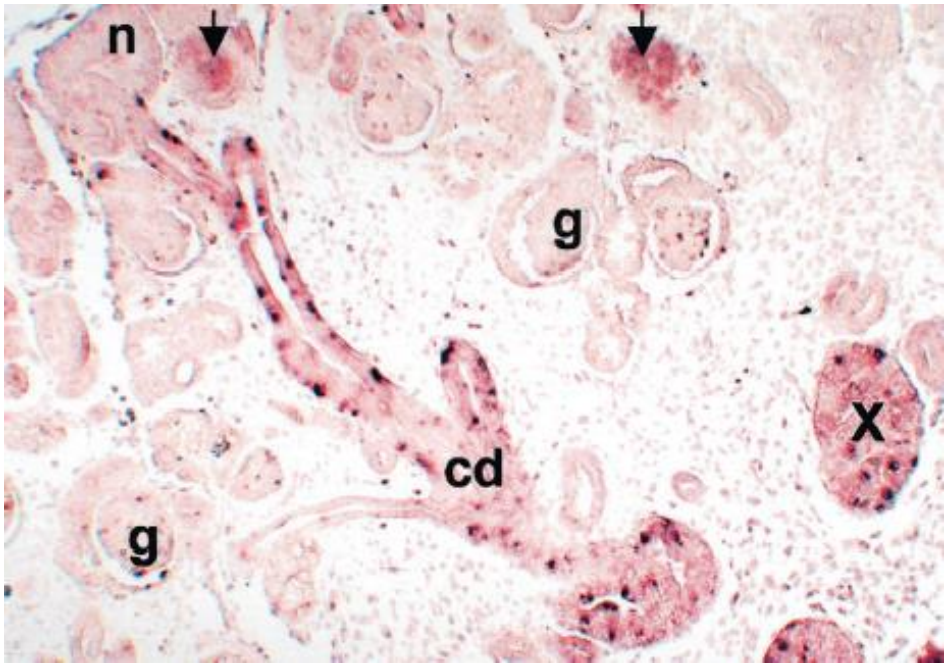
INVOLUTION OF MULTICYSTIC DYSPLASTIC KIDNEYS

Neonatal ultrasound…….and two years later

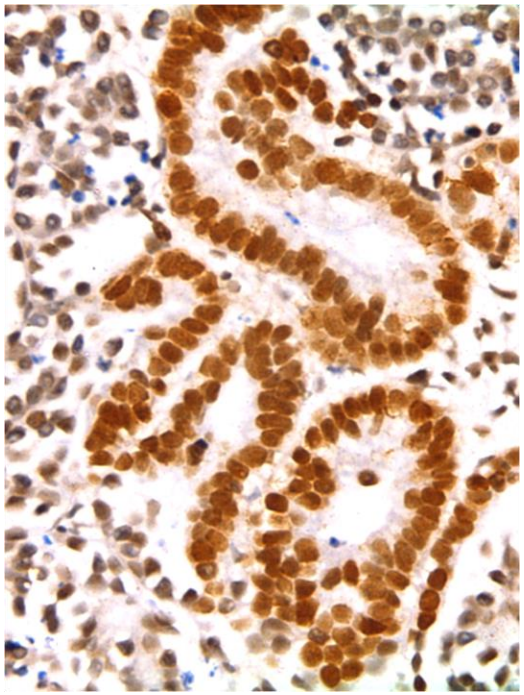


HNF1B GENE EXPRESSED IN HUMAN EMBRYONIC KIDNEY

RNA

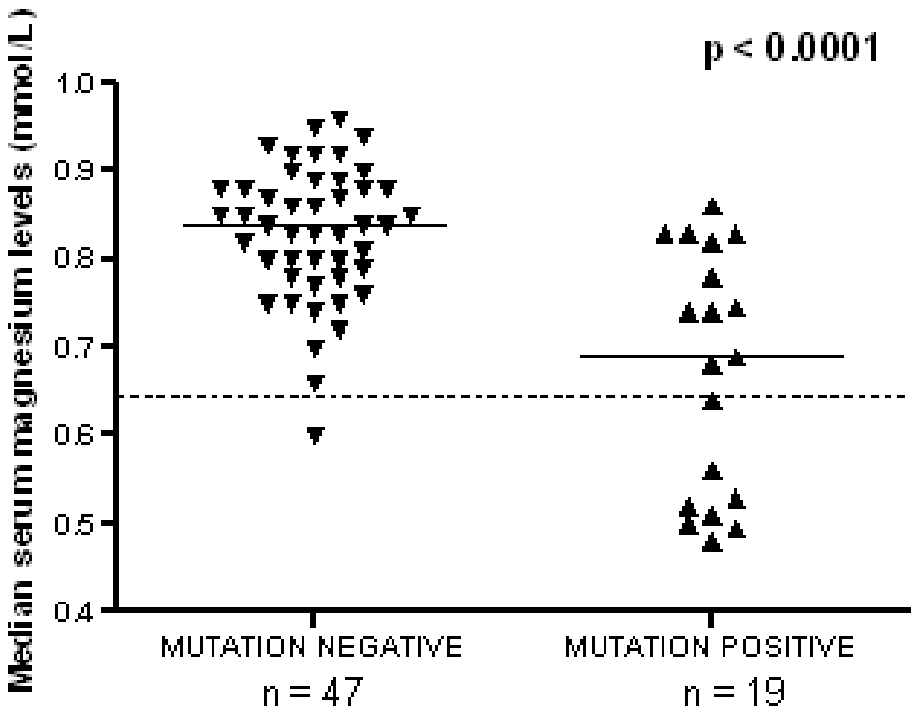


Protein



Kolatsi-Joannou M *et al* *J Am Soc Nephrol* 12:2175-2180, 2001
Tengku F *et al* unpublished data

HNF1B Mutations Cause Kidney Malformations and also Lead to Abnormal Kidney Physiology after Birth

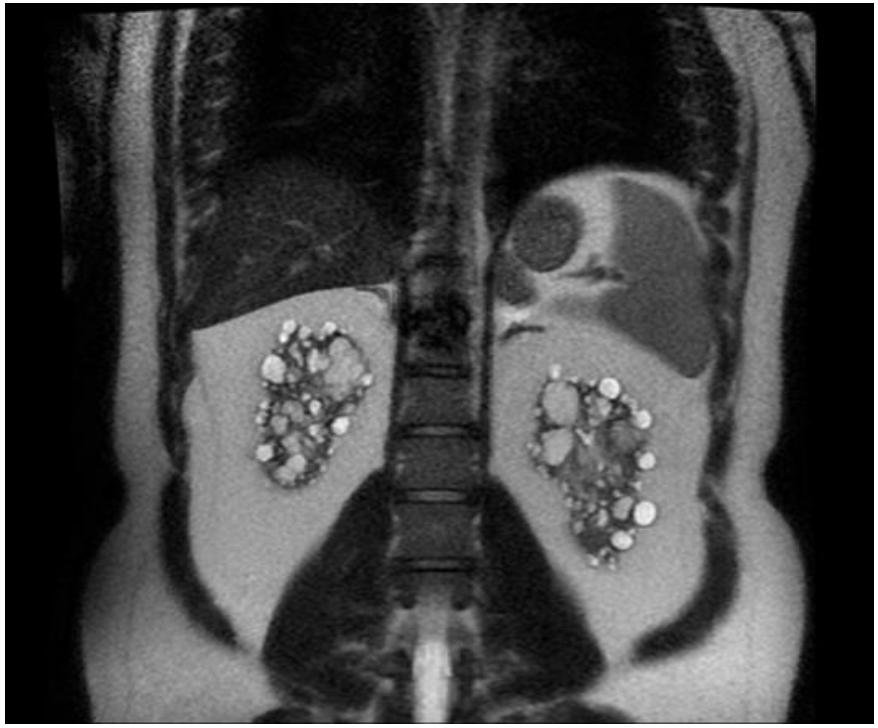


- Blood magnesium levels in children with renal malformations
- Those with *HNF1B* mutations can have low blood magnesium levels
- HNF1B transactivates *FXYD2*, a gene implicated in magnesium handling in the distal convoluted tubule

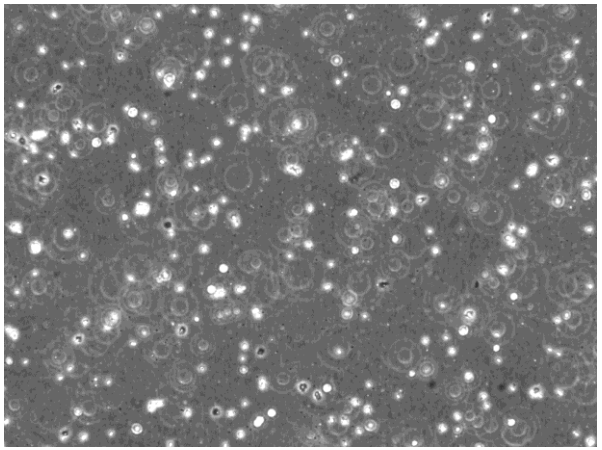
Adalat S *et al J Am Soc Nephrol* 20:1123-1131, 2009

Making pluripotent stem cells from people with *HNF1B* mutations and dysplastic kidneys

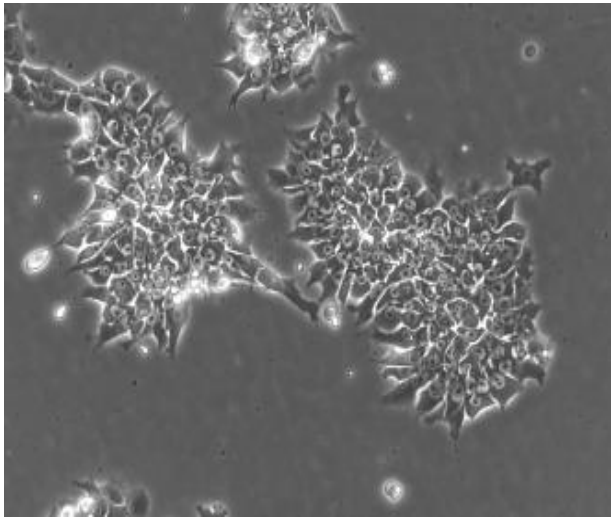
Cystic dysplastic kidneys a & end-stage kidney disease



Donated venous blood….

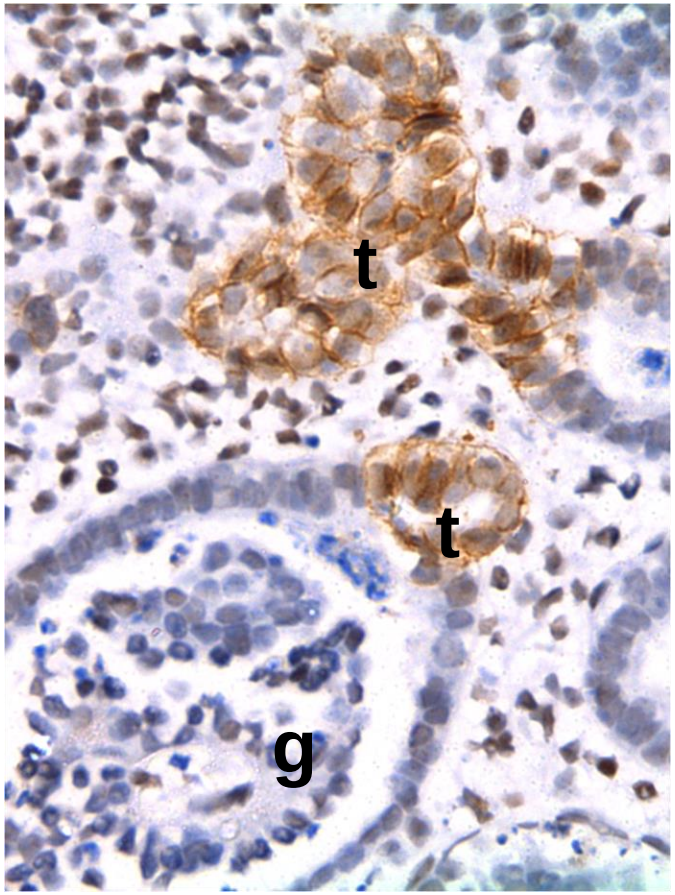


…to pluripotent stem cells

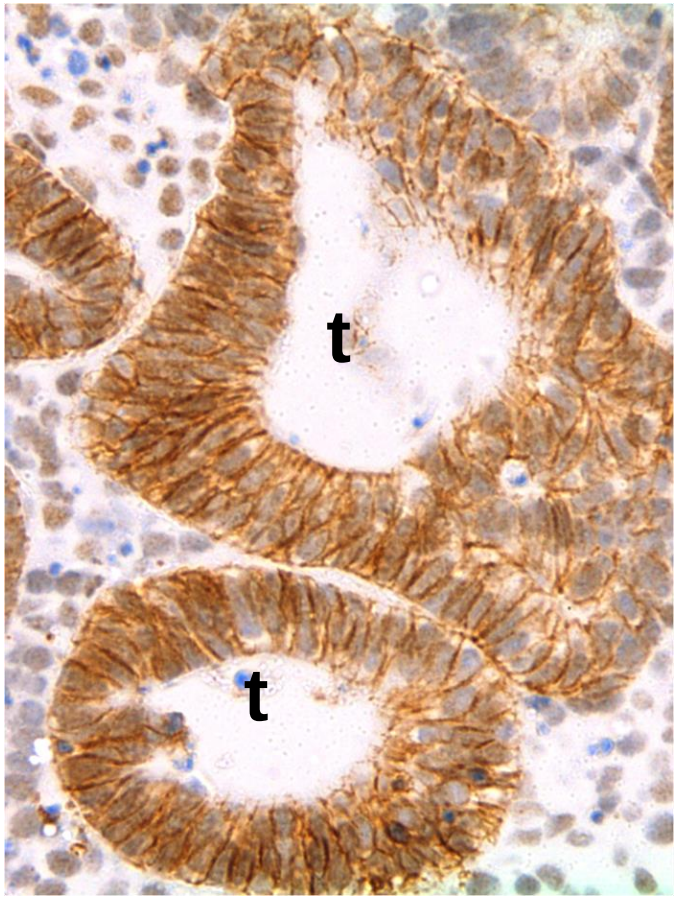


Histology of wildtype and *HNF1B* heterozygous mutant mini-kidneys we created from stem cells generated from blood samples donated by a family cared for by our Foundation Trust. Note the abnormal dilated tubules ('**t**' marked by brown E-cadherin immunostaining) but the lack of glomeruli ('**g**') in the mutant mini-kidney

Unaffected mother



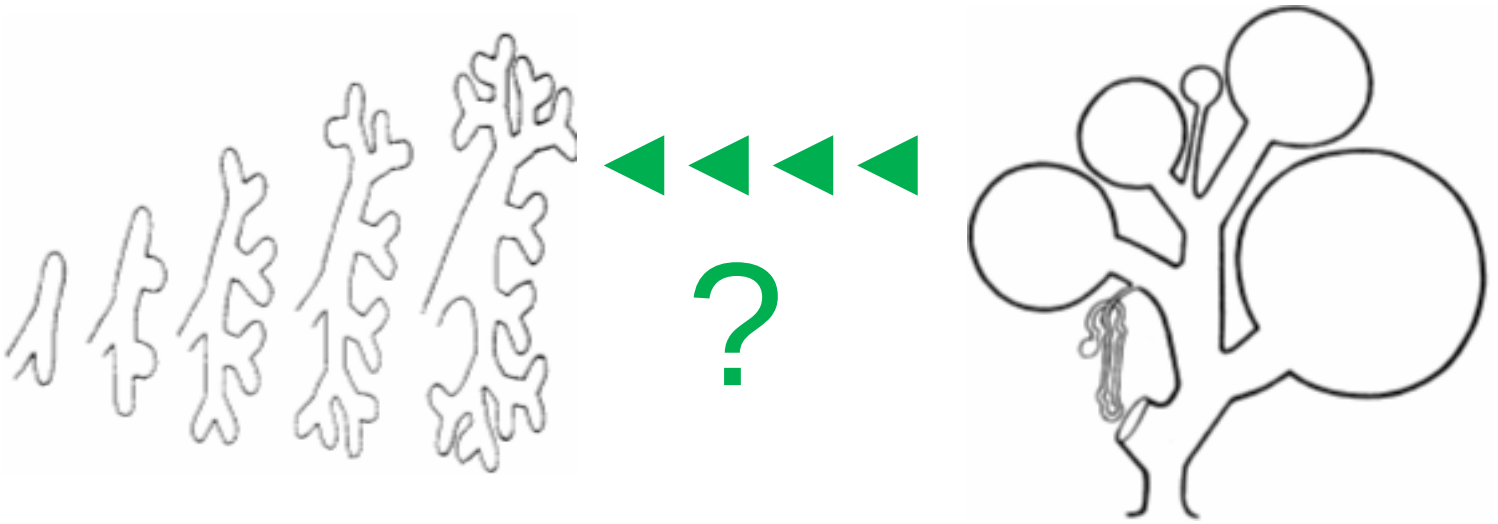
Mutant son



Kimber and Woolf laboratories, unpublished data

Our long term aim is to turn dysplastic human kidneys into more normal kidneys

Normal branching tubules ***Malformed kidney tubules***



…..ongoing work e.g. working out the molecular pathways that are going wrong and looking for druggable targets

Other dominant genetic disorders with kidney phenotypes that can mimic *HNF1B related disease*

- *PAX2* in the renal-coloboma syndrome (blindness)
- *EYA1* in the branchio-oto-renal syndrome (deafness)
- *GATA3* in the HDR syndrome (hypoparathyroidism and deafness)
- *UMOD and MUC1* in medullary cystic kidney disease (gout)

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- Some clinical aspects about human renal malformations
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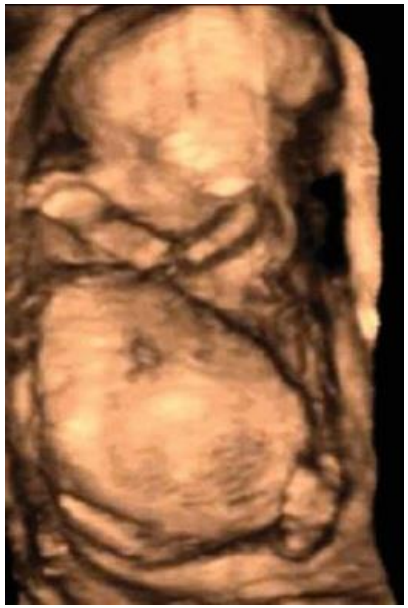
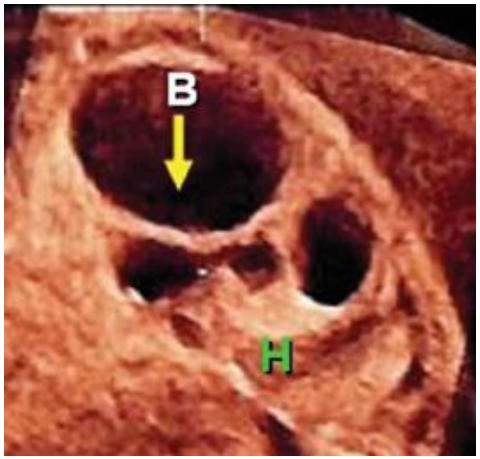
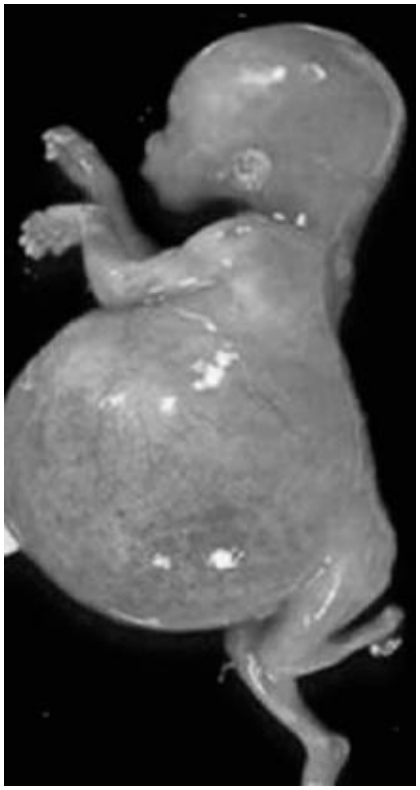
- **b. secondary to lower urinary tract obstruction *Myocardin***

Prune belly syndrome

‘functional bladder outflow obstruction’
(no anatomical obstruction of urethra)



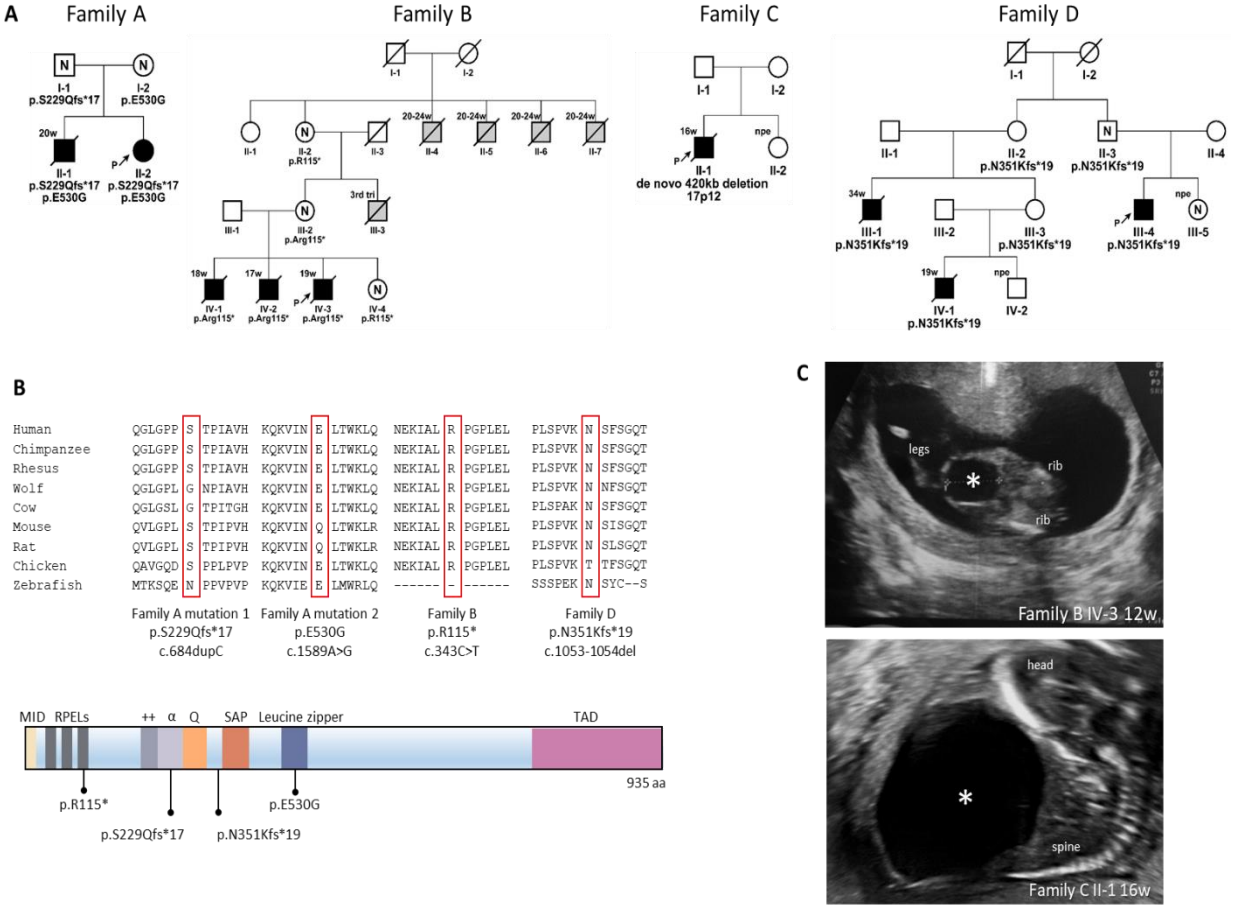




Osborne NG *et al J Ultrasound Med* 30:833-841, 2011

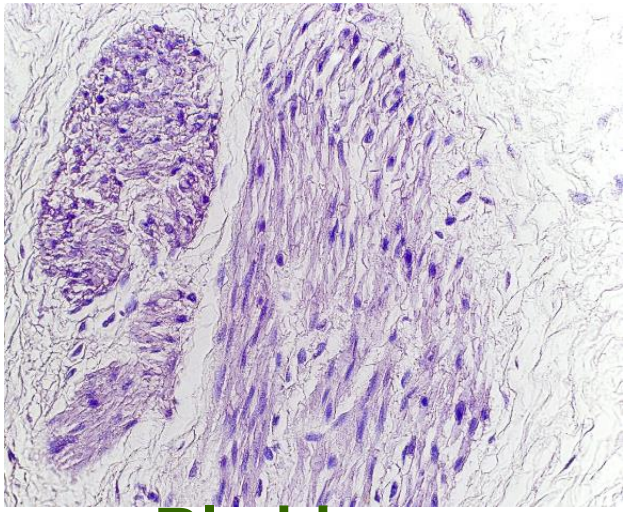
Myocardin variants in families with megabladder prune belly syndrome

- here it is a male-limited disease



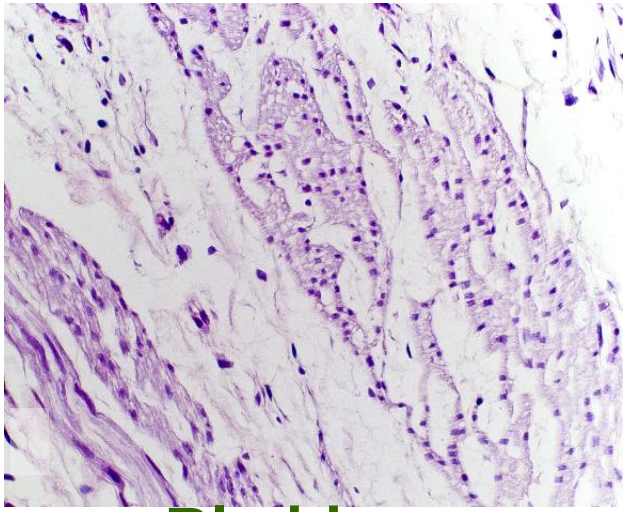
Houweling A *et al J Clin Invest* 2019*129:5374-5380, 2019.*

Normal fetus



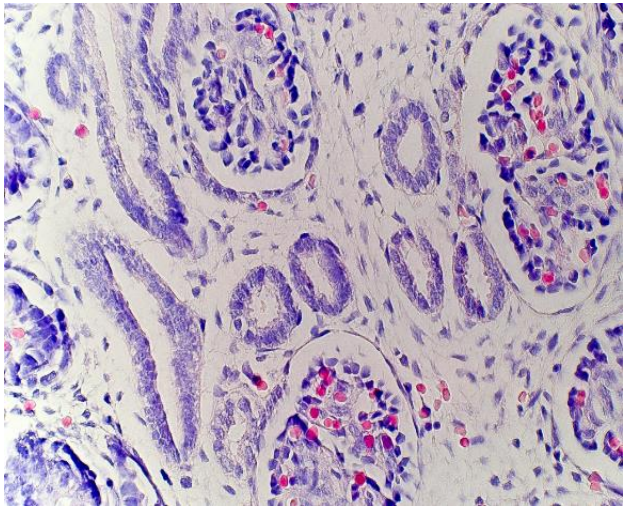
Bladder

Affected fetus

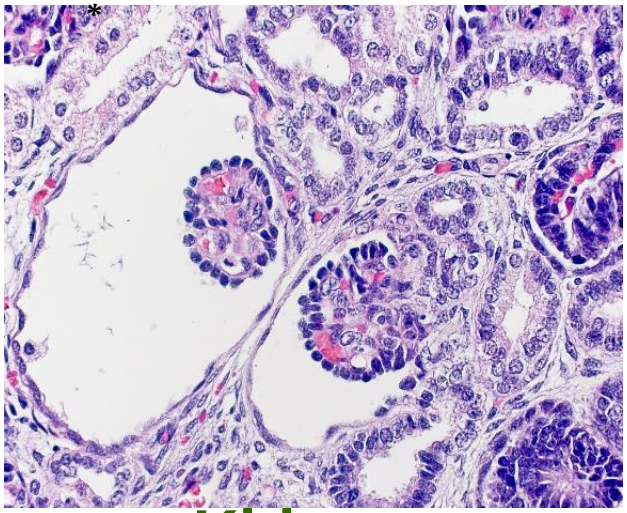


Bladder

Ragged muscle fibres

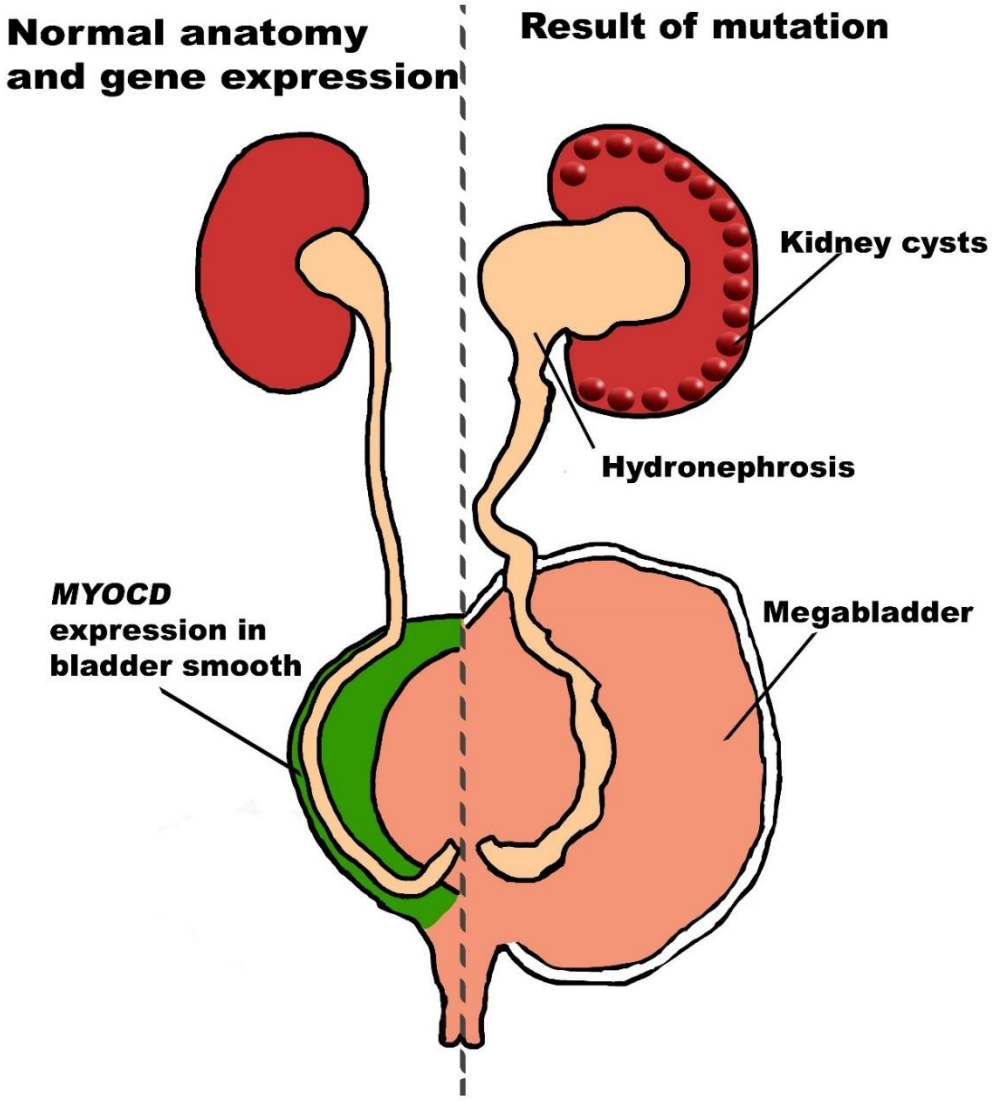


Kidney



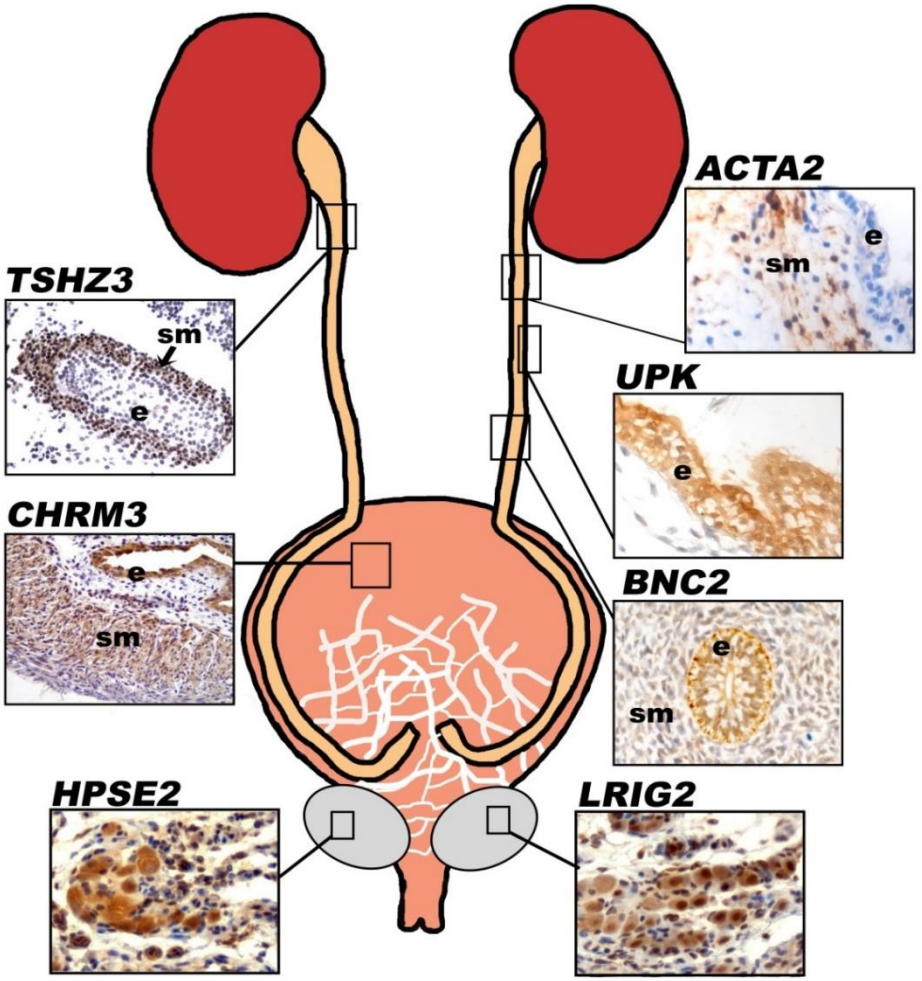
Kidney

Glomerular cysts



Lopes FM *et al J Pediatr Urol* 5:610-620, 2021

Summary of some of the other genes mutated in human lower urinary tract malformations



Summary – genetics of human renal agenesis and dysplasia

- A genetic example of renal agenesis *FRAS1*
- Two genetic examples of renal dysplasia:
- a. intrinsic to abnormal kidney development *HNF1B*
- b. secondary to lower urinary tract obstruction *Myocardin*

MANCHESTER

Human stem cells

Susan Kimber, Ioannis Bantounas, Parisa Ranjzad, Tengku Faris, Amir Salahi, Jason Wong, Sophie Ashley & many others

Murine models

Neil Roberts, Filipa Lopes, Subir Sigh, Karl Chopra, Sarah Laurie, Andy Thom, Corrine Anders, Nick Ashton, and Riccardo Coletta

Human Genomics

Bill Newman, Helen Stuart, Ryan Taylor, Gabriella Galata, Glenda Beaman, Sara Cuvertino, Siddarth Banka

Mesothelial Cells

Sarah Herrick and Sara Namvar

Protein Studies

Rachel Lennon, Mike Randles, Edward McKenzie

Renal Genetics Clinics

Bronwyn Kerr, Helen Stuart, Kate Hillman, David Keene & Max Cervellione

Xenopus

Emma Hilton, Karel Dorey, Raphael Thuret

Physiology

Natalie Gardiner, Emad Hindi and Alison Gurney

LONDON David Long, Karen Price, Daniyal Jafree, Peter Scambler, Paul Winyard, Jenny Papakrivopoulou

NOTTINGHAM Simon Welham

LIVERPOOL Bettina Wilm and Thomas Wilm

DUBLIN John Darlow and colleagues

YORK Jenny Southgate and her team

NEWCASTLE Health Lambert, Heather Cordell, John Sayer, Tim & Judith Goodship

ANKARA Berk Burgu

MARSEILLES Laurent Fasano and Xavier Caubit

MARBURG Stefanie Weber

BONN Alina Hilger and Benjamin Odermatt

HONG KONG Alisa Shum and her team

….and many other collaborators and families, UK & Worldwide!

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newlife
foundation for disabled children

wellcome

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registered charity no. 1091024

Kidney Research UK
Funding research to save live

Kids Kidney Research

KIDNEYS FOR LIFE

THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION
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