

Polycystic kidney disease: recent advances

PKD Charity, Birmingham 2007
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wellcome trust



Sheffield Kidney Institute



Four areas of advance

- How do cysts form?
- Can we test for who will get the disease?
- Can we tell who will develop kidney failure?
- Can we do anything about it?

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The first descriptions of ADPKD



D.M.G. GALBRAZZI



Galbrazzi (1757)

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Fogazzi, NDT 1999



'The cystic degeneration of the kidneys, once it reaches the point where it can be recognised or suspected during life, is an illness without cure'

Rayer 1841

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Milestones in PKD

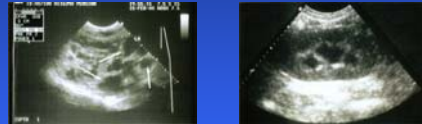
1757 – 3 cases described
 1841 – Cystic degeneration
 1888 – Polycystic kidneys
 1899 – Dominant transmission
 1934 – Recessive transmission



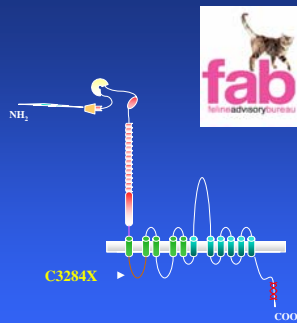
1957 – Incidence 1 in 1000
 1985 – Linkage of PKD1
 1993 – Linkage of PKD2
 1994 – Identification of PKD1
 1996 – Identification of PKD2
 2002 – Identification of PKHD1



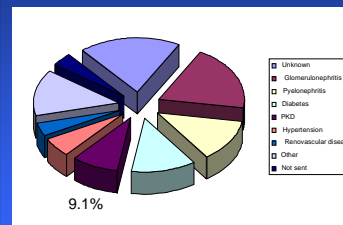
Whose scans are these?



38% of Persian cats
 6% of all cats



Primary diagnosis in prevalent RRT patients in E&W (2004)



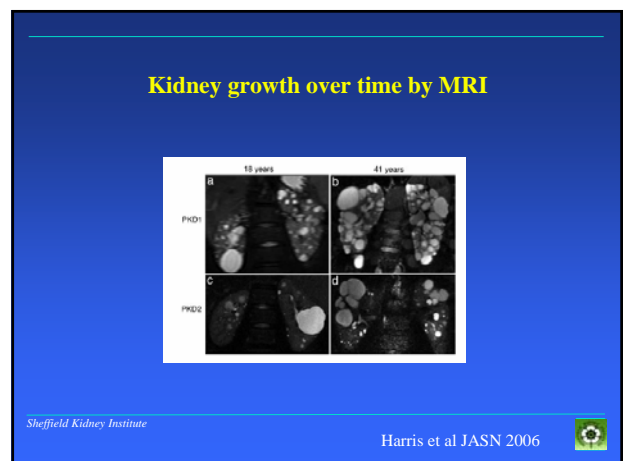
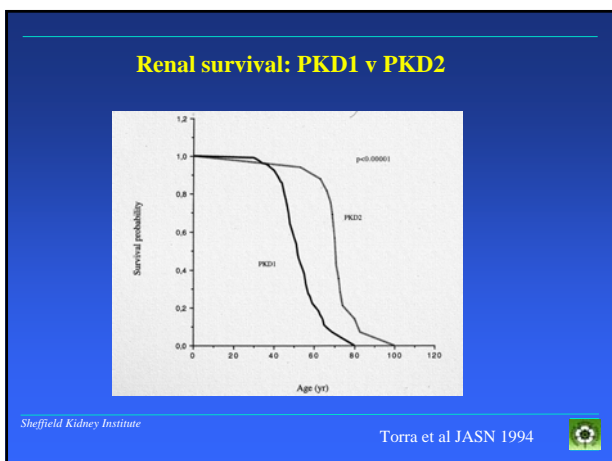
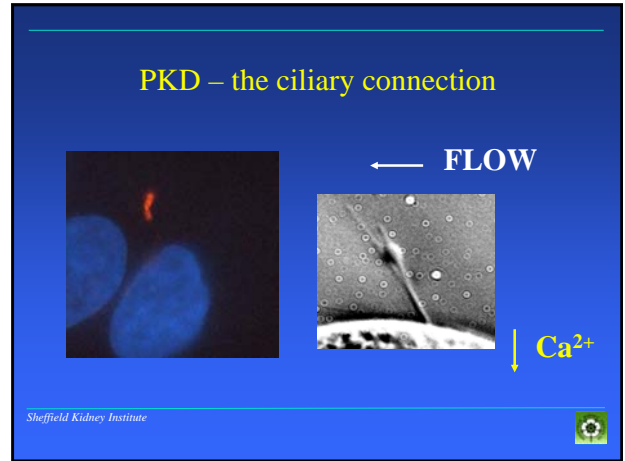
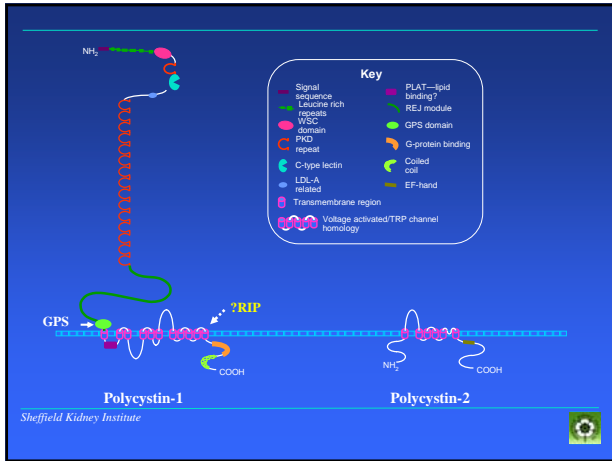
4th most common cause of ESRD

Incidence: 1 in 500-1000

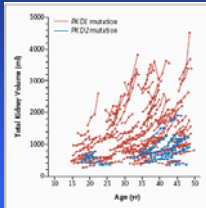
All ethnic groups

5-10 million world-wide





CRISP study



PKD1 n=153
PKD2 n=32

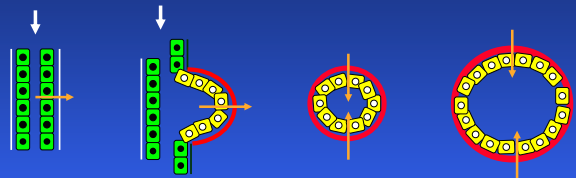
- Individual signature
- Big kidneys (>1.5L) deteriorate faster
- PKD1 kidneys are bigger than PKD2 and have more cysts
- The rate of cyst growth is the same (5% pa)
- Male kidneys grow faster than females

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Grantham et al, NEJM 2006
Harris et al, JASN 2006



The stages of cyst formation



Cyst initiation

Cyst expansion

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Mutation detection in ADPKD

CRISP study (n=239 in 202 pedigrees by MRI over 3 years)

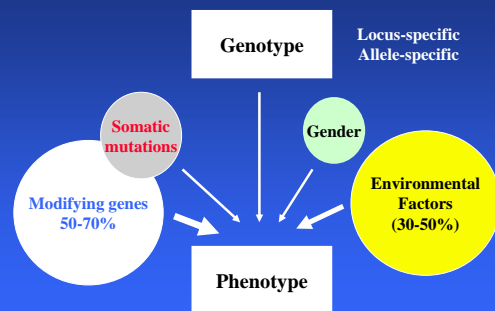
- Mutation detection rate is 90% by DHPLC and sequencing
- Frequency in cohort: PKD1 (85%) v PKD2 (15%)
- 63% are definite, 26% are probable
- No mutations found in 11%

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Harris et al JASN 2005
Rossetti et al JASN 2007



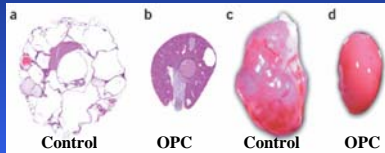
What determines phenotype?



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VP2R (OPC31260) in *pkd2^{ws25/-}* mice



Treatment from 3-16wks reduced %KW by 30-50%

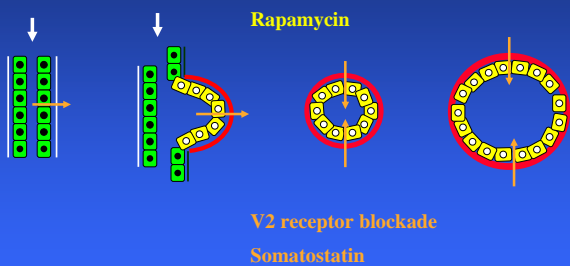


The Tolvaptan study

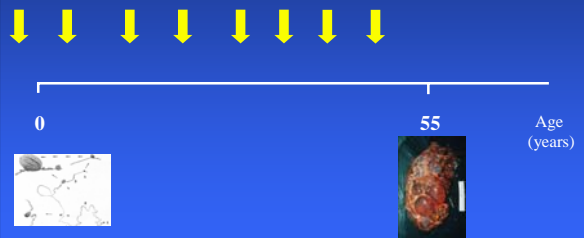
- Eligibility: 18-50 yrs, both sexes, eGFR >60, MRI kidney vol >750cc
- Numbers: 100 centres, 1500 patients
- Duration: 60 months (36 months treatment) – 2007-2011
- Treatment: Placebo ratio = 2:1
- Primary end-point: rate of kidney volume change (MRI)



Arresting cyst growth and expansion



When to intervene and for how long?





'...an illness without cure?....'

Rayer 1841

