GENETICS OF AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Dr Joanna Jarvis
Outline of talk:

- Role of Clinical Geneticist
- Genes and genetic mutations
- Autosomal recessive inheritance: implications for the family
- ARPKD: making the diagnosis
- Discovery of the gene (PKHD1)
- Genetic testing for ARPKD
- ARPKD families
- Reproductive options
- Future approaches
Role of Clinical Geneticist

- Detailed family history
- Confirm diagnosis
- Establish risk to family members
- Discuss reproductive options including prenatal diagnosis
Autosomal recessive inheritance
Chromosomes, DNA, and Genes

Cell → Nucleus → Chromosomes → Gene → Protein

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One gene - many mutations

- Some changes are clearly pathological mutations
- Mutations may be unique, not previously recorded
- Some changes are more difficult to interpret
  - Are they at a functionally critical position in the protein?
  - Are they polymorphisms, i.e., harmless gene changes seen in the general population that don’t change gene function
SEGREGATION OF AUTOSOMAL RECESSIVE TRAIT
(both parents carriers)

Carrier Father

Carrier Mother

R  r
R  r
R  r
r  r

Normal  Carrier  Carrier  Affected
PEDIGREE OF AUTOSOMAL RECESSIVE INHERITANCE

- **Affected Individual**
- **Normal Individual**
- **Non-Affected Carrier**
ARPKD families
Family 2

PKHD1 mutation
Diagnosis of ARPKD
Diagnosis of ARPKD

- Family history consistent with autosomal recessive inheritance
- Typical findings on imaging of the kidneys
- Absence of cysts on kidneys in both parents
- Liver fibrosis
- 'Ductal plate' abnormality
- Diagnosis of ARPKD in a brother/sister
- Genetic testing
Diagnosis of ARPKD: considering other causes of polycystic kidneys

- Autosomal dominant polycystic kidney disease (ADPKD)
- Glomerulocystic kidney disease;
- Syndrome conditions: eg nephronophthisis, Joubert syndrome, Meckel-Gruber syndrome
ADPKD v ARPKD

- ADPKD:
  - is dominantly inherited, passed from one generation to the next
  - More common
  - Linked with different genes (PKD1 and PKD2)
  - Age of end stage renal failure: commonly middle age
  - Liver and pancreatic cysts
  - Liver fibrosis very rare
Discovery of the ARPKD gene (PKHD1 gene)

- ARPKD first linked to Chromosome 6 in 1994
- PKHD1 (polycystic kidney and hepatic disease 1) gene identified and cloned: 2002
- Genetic code for a protein: fibrocytstin function
- The only gene linked with ARPKD
Discovery of the ARPKD gene (PKHD1 gene)

- Mutations in this gene shown to cause cystic kidney disease in mice and rats
- Mutations in this gene identified in families with ARPKD
PKHD1 mutations

- Pick-up rate 75-85%
- 1 in 70 people are carriers
- Type of mutation in the PKHD1 gene may cause more severe disease; others a more mild disease with later onset
- Variability in severity between families
- Severity of disease more consistent within a family
When to do genetic testing for ARPKD

- Uncertainty of diagnosis
- Prenatal diagnosis
- Preimplantation diagnosis
- Screening other family members
Reproductive options

- Antenatal scanning
- Prenatal diagnosis
- Preimplantation diagnosis
Antenatal ultrasound

- Fetal kidneys: large, bright; cysts may be visible
- Usually present in 2\textsuperscript{nd} trimester; may be visible earlier
Prenatal diagnosis

- Diagnosis needs to have been confirmed in affected relative by genetic testing
- Reasons:
  - Couple/doctors can prepare
  - Couple would opt for Termination of pregnancy
- Techniques:
  - Chorionic villus sampling
  - Amniocentesis
Chorionic villus sampling (CVS)

- Carried out at 11-12 weeks
- Placental tissue is used for genetic testing
- Miscarriage risk 1%
Amniocentesis (amnio)

- Carried out at 15 weeks + gestation
- Amniotic fluid is used for analysis
- Miscarriage risk 1%
Birth of a healthy infant following preimplantation PKHD1 haplotyping for autosomal recessive polycystic kidney disease using multiple displacement amplification

Eduardo C. Lau • Marleen M. Janson •
Mark R. Roesler • Ellis D. Avner • Estil Y. Strawn •
David P. Bick
Primplantation diagnosis (PGD)

- Uses In vitro Fertilisation (IVF) technology
- Allows detection of affected and unaffected embryos in the laboratory
- Unaffected embryos implanted to avoid affected pregnancy
**Primplantation diagnosis (PGD)**

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<th>Step</th>
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<tr>
<td>1</td>
<td>Embryos grown to 4 cell stage</td>
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<td>2</td>
<td>Laser to make hole in embryo wall</td>
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<td>Glass needle inserted in hole</td>
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Primplantation diagnosis (PGD)

- PGD successful for ARPKD families in UK
- Ongoing pregnancy rate:
  - 36% per cycle started or
  - 50% per embryo transferred
PGD: pros and cons

- **Pros**
  - Offers alternative to prenatal diagnosis, removes uncertainty of affected pregnancy
  - Consideration for couples already opting for IVF

- **Cons**
  - Cost
  - Time to treatment (usually around 9 months)
  - Poor response to IVF/side effects of IVF
  - No eggs available at egg collection
  - No eggs are fertilised to create an embryo
  - No unaffected embryos are available
  - Failure to get genetic result (less than 2% cases)
  - The diagnostic result may not be representative of the embryo
  - Emotional burden with failure of treatment
Future approaches

- Genes that are linked with cystic kidney conditions will be tested simultaneously including the ARPKD gene.
- Genetics may be used to tailor treatment and provide more accurate prognosis.
- Further integration of genetic service with other specialities eg paediatrics, nephrology.
Questions

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