Genetics in PID and practical applications

Helen Braggins
Clinical Nurse Specialist
Chronic Granulomatous Disorder

Jinhua Xu-Bayford
Clinical Nurse Specialist
Gene Therapy and Immunology
Primary immunodeficiency (PID)

• PID disorders are inherited conditions, which means the gene responsible for causing the disorder can be passed from parents to child
• Often caused by single -gene defect (mutation)
• Usually diagnosed during infancy or childhood
• Relatively rare but extremely diverse and serious
• Over 300 mutations have been identified so far
• PID diagnosis is life-changing in both the child affected and their families
Pattern of inheritance

• Autosomal recessive inheritance
• X-linked pattern of inheritance
• Autosomal dominant inheritance
• De Novo mutation:
  • New mutation that occurred and that was not present in either parents
Autosomal recessive inheritance

- An individual, affected child, has inherited two abnormal copies of a gene, one from each parent
- Both parents are carriers of the faulty gene (mutation), they are also called heterozygous
- Autosomal recessive pattern of inheritance means that the condition can be passed on to both boys and girls
- Often no family history
Autosomal recessive inheritance

- Unaffected "Carrier" Father
- Unaffected "Carrier" Mother
- Unaffected 1 in 4 chance
- Unaffected "Carrier" 2 in 4 chance
- Affected 1 in 4 chance
Autosomal recessive inheritance

Summary

• 1 in 4: 25% chance of having an unaffected and non carrier child
• 1 in 4: 25% chance of having an affected child
• 2 in 4 : 50% chance of having a carrier
Autosomal recessive immunodeficiencies

- Several forms of severe combined immunodeficiency, ADA, PNP, RAG, JAK3, IL7R
- Several forms of Chronic granulomatous disease (CGD), p22,p47,p67 and p40
- Cartilage hair hypoplasia (CHH)
- LRBA (lipopolysaccharide responsive beige-like anchor protein)
- Leucocyte adhesion deficiency (LAD)
- Familial forms of haemophagocytic lymphohistiocytosis (HLH)
- Ataxia-Telangiectasia
X-Linked inheritance

• Mutations are in a gene on the X chromosome
• Almost exclusively affect boys only, as males have only one X chromosome
• Females are unaffected carriers (with some exceptions like XCGD)
• Females are unaffected because their second X chromosome carries the normal gene and compensates for the affected gene
• No male-to-male transmission
X-linked inheritance

Unaffected father

Carrier mother

- XY
- XX
- XX
- XY
- XY

carrier daughter
unaffected daughter
unaffected son
affected son
X-linked inheritance

- Carrier female: 1 in 4 or 25% chance
- A non carrier or Normal female: 1 in 4 or 25% chance
- A heathy male 1 in 4 or 25% chance
- An affected boy: 1 in 4 or 25% chance
X-Linked Recessive

Parents

Father Affected  Mother Unaffected

Children

Son Unaffected  Daughter Carrier  Son Unaffected  Daughter Carrier

Father Unaffected  Mother Carrier

Son Affected  Daughter Carrier  Son Unaffected  Daughter Unaffected

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X-linked immunodeficiencies

- X-CGD
- X-SCID
- Wiskott-Aldrich syndrome (WAS)
- X-linked hyper IgM (CD40 ligand)
- X-linked inhibitor of apoptosis (XIAP) disease
- X-linked lymphoproliferative disease (XLP)
- X-linked agammaglobulinemia (XLA)
Autosomal dominant inheritance

- Rare
- One abnormal gene is sufficient to cause the disorder
- Both boys and girls are equally affected
- Variable penetrance
- Examples:
  - Hyper IgE syndrome due to STAT3 mutation,
  - Autoimmune lymphoproliferative syndrome (ALPS), FAS mutation
Carrier and Prenatal Testing

• Non-invasive testing
  – Ultrasound scanning
  – Free fetal DNA analysis

• Invasive testing
  – Chorionic villus sampling (CVS)
  – Amniocentesis
  – Fetal tissue biopsy e.g blood, skin muscle (these tests are uncommon)
Free fetal DNA analysis

- Non invasive
- Maternal blood can be taken as early as 8-9 weeks of gestation
- Usually performed in conjunction with ultrasound scan
- 99% reliability results
- Not widely available
- Benefit to carrier mothers for an X-linked disorder only
Chorionic villus sampling

- CVS is usually scheduled at 10-13 week of pregnancy, most centre perform this around just over 11 weeks.
- A small sample is taken from the developing placenta tissue which directly arises from the growing foetus.
- Transabdominal CVS,
- Transcervical CVS
- *Results usually are back within three days*
- Very accurate results
- Risk of miscarriage, 0.5%-1%
CVS testing
Amniocentesis

• It’s usually done in second trimester from 15 weeks and beyond
• A sample is taken from amniotic fluid which surrounds the growing foetus which contains foetal cells
• Results are very accurate,
• Amniocentesis also carries a risk of miscarriage, which estimated to be 0.5% to 1%
Amniocentesis testing

- Placenta
- Fetus
- Uterus (womb)
- Cervix
- Amniotic fluid
Prenatal testing

- Fetal Blood sampling
Preimplantation genetic diagnosis (PGD)

- Using IVF technique to create embryos and then be tested for the genetic disorder
- Only unaffected embryos are transferred back to the uterus
- The number of conditions can be tested using PGD in increasing and various from centre to centre
- Each condition needs to have a licence issued by the licensing body, the Human Fertilisation and Embryology Authority (HEFA)
PGD cont’d

• Usually up to 2 embryos are transferred back to the uterus

• *Embryos can also be tested to exclude the genetic disorder and selected to be the tissue typing match for an affected sibling*

• Funding is not available to all couples requesting PGD,

• Highly regulated by the HFEA

• Limited centres offer PGD treatment in the UK
Cord blood collection

- Diagnose at birth on cord blood
- Cord bloods collection and storage
Comparison of overall outcomes

Probands
n=45

- Death before HSCT
  n=14
  31% mortality

- Progress to HSCT
  n=31

  - Deaths after HSCT
    n=13
    41%

Overall mortality/survival:
27/45 (60%) (40%)

Siblings
n=55

- Death before HSCT
  n=1
  1.8% mortality

- Progress to HSCT/GT
  n=54

  - Deaths after HSCT/GT
    n=3
    5.5%

Overall mortality/survival:
4/55 (7.2%) (92.8%)

Any Questions?