Overview

• Chromosomes, genes & DNA

• Pattern of Inheritance
  – X-linked recessive

• The factor 8 & 9 genes
  – Mutation detection
  – Who gets tested?

• Reproductive options
The genetic recipe is present in the fertilised egg and then copied into every cell of the body.
DNA the molecule of life

Trillions of cells
Each cell:
- 46 human chromosomes
- 2 meters of DNA
- 3 billion DNA subunits (the bases: A, T, C, G)
- Approximately 30,000 genes code for proteins that perform most life functions
Standard chromosome set: 23 pairs
Normal Male 46XY

Normal male karyotype

F8 gene
faulty gene carrier mother

non carrier father

LEGEND: $X^r = \text{recessive faulty gene on X chromosome}$

X or Y = correct gene

eggs $X^r \times X$
sperm $X \times Y$

faulty gene carrier
non carrier
affected
non carrier

GIRLS

BOYS

1 out of 4 chance 25%
1 out of 4 chance 25%
1 out of 4 chance 25%
1 out of 4 chance 25%
non carrier mother

affected father

LEGEND: $X^r$ = recessive faulty gene on X chromosome

$X$ or $Y$ = correct gene

eggs $X$ $X$

sperm $X^r$ $Y$

faulty gene carrier GIRLS

non-carrier BOYS
Pedigree of X-Linked Recessive Inheritance

- Affected man
- Generally unaffected woman
- Woman who is a genetic carrier of the condition

Counselling Aids for Geneticists, 3rd edition, 1995, Greenwood Genetic Center
X-LINKED RECESSIVE INHERITANCE

- Males will show the condition more severely than females
- Females may show no or only mild effects
- All daughters of affected males will be genetic carriers
- Condition never transmitted from father to son
Genetic testing in Haemophilia

- Close co-operation between haematology and local genetic service
- Confirmatory diagnostic testing
- Carrier testing
- Discussion re reproductive options
- Prenatal and Preimplantation Genetic Diagnosis
• Factor 8 levels unreliable to exclude carrier status in females

• F8 gene test on male with Haemophilia A

• 98% chance of identifying mutation

• Carrier testing can then be done

? carrier
## F8 gene testing - Cost $1,000

<table>
<thead>
<tr>
<th>MUTATION</th>
<th>F8 &lt; 1% (severe)</th>
<th>F8 &gt; 1% (mild)</th>
</tr>
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<tbody>
<tr>
<td>Intron 22 or 1 inversion</td>
<td>48%</td>
<td>0%</td>
</tr>
<tr>
<td>Various</td>
<td>40%</td>
<td>1%</td>
</tr>
<tr>
<td>Missense</td>
<td>10%</td>
<td>97%</td>
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</tbody>
</table>
• People have different experiences of haemophilia that may impact on their decision about having a child with haemophilia or having more children when they have an affected child already
3 Main Components of Genetic Counselling

• 1. Diagnosis
  – Usually straight forward
  – Discuss implications for immediate and more distant family
  – Arrange gene testing if indicated

• 2. Risk estimation
  – 80% chance mother is a carrier if only one male affected

• 3. Supportive role
Reproductive Options

- Take the chance (50% chance of another affected boy if mother is a carrier)
- No further children
- Contraception
- Sterilisation
  - Must be viewed as not reversible and possibility of divorce considered
- Adoption
- Donor egg
- Prenatal diagnosis
  - Determine sex
  - Mutation analysis*
- Pre-implantation diagnosis*

* Gene mutation must be known prior to conception
Invasive Prenatal Testing

Chorion Villus sample

Amniocentesis

11 weeks

15 weeks
PREIMPLANTATION GENETIC DIAGNOSIS (PGD)

1. Egg + Sperm
2. Using IVF techniques
3. Blastomere
4. Remove one or two cells for testing
5. Test DNA or chromosomes
6. Test result
   - Genetic disorder excluded
     - Embryo implanted
   - Genetic disorder detected
     - Embryo discarded
ISSUES WITH PGD

• Success rates similar to IVF ie around 20% chance of successful pregnancy per cycle
• Stressful process
• Cost (> $5,000 per cycle after rebate)
• Safety
Embryo biopsy
To help the message to “get across”

- Multiple consultations with counsellors and geneticists may be required
- Information recorded in letters
  - for the GP & other professionals
  - for the family/patient specifically written for them
- Use of counselling diagrams and fact sheets
- Summary for the record
Genetics Services