Paediatric Genetics

Katie Townsend
Learning Objectives

1. Modes of inheritance:
   – Draw family trees to illustrate dominant, recessive and X-linked inheritance (with examples)
   – Calculate recurrence risks

2. Dysmorphology:
   – Recognise + describe dysmorphic features
   – Basic knowledge of common syndromes (Down's, Turner's, William's, fragile X)

3. Neonatal screening:
   – Rationale for screening
   – Which conditions are screened for and why

4. Antenatal diagnosis:
   – Methods available (with pros and cons)
   – Examples of conditions that can be detected
1. Modes of Inheritance: Drawing Pedigrees

- Male
- Female
- Sex undesignated
- Adopted
- Pregnancy
- Deceased
- Affected with trait
- Carrier for trait
- Carrier for X-linked trait
- Mating
- Consanguineous mating
- Siblings
- Number of children
- Divorced or separated
- Miscarriage, SAB
- Dizygotic twins
- Monozygotic twins
- No offspring
- Patient initiating genetic workup (proband, index case, consultand)
- Two matings
1. Modes of Inheritance

Recurrence Risks

- **Recurrence Risk**: likelihood that a trait or disorder present in one family member will occur again in other family members in the same or subsequent generations

  \[
  \text{Recurrence Risk} = \text{Penetrance} \times \text{Probability}
  \]

- **Penetrance**: likelihood of a gene generating its associated p/t, i.e. proportion of people with g/t who demonstrate p/t.

- **Expressivity**: measured only when there is 100% penetrance, it is the variation in a p/t among individuals carrying a particular g/t. i.e. variable features, show features to differing degree. Can be affected by ageing, environmental factors.
Recurrence Risks
Inheritance Patterns: Recurrence Risks

AD
X-linked Recessive
(affected father)

AR
X-linked Recessive
(carrier mother)
Autosomal Dominant

- Most common mode of inheritance
- Often structural proteins
- Variation in expression
## Autosomal Dominant conditions

<table>
<thead>
<tr>
<th>Mnemonic</th>
<th>Condition</th>
<th>/10,000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Actually</strong></td>
<td>Achondroplasia <em>(BUT 80% are sporadic)</em></td>
<td></td>
</tr>
<tr>
<td><strong>My</strong></td>
<td>Myotonic Dystrophy</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hunch</strong></td>
<td>Huntington’s</td>
<td>5</td>
</tr>
<tr>
<td><strong>On</strong></td>
<td>Otosclerosis <em>(most cases are AD)</em></td>
<td>10</td>
</tr>
<tr>
<td><strong>Familial</strong></td>
<td>Familial Combined Hyperlipidaemia</td>
<td>50</td>
</tr>
<tr>
<td><strong>Heredity</strong></td>
<td>Familial Hypercholesterolaemia</td>
<td>20</td>
</tr>
<tr>
<td><strong>Patterns</strong></td>
<td>Adult AD Polycystic Kidneys <em>(most common type)</em></td>
<td>4-8</td>
</tr>
<tr>
<td><strong>Echoes</strong></td>
<td>Ehlers Danlos <em>(most forms are AD)</em></td>
<td>~1</td>
</tr>
<tr>
<td><strong>The</strong></td>
<td>Tuberous Sclerosis <em>(66.7% are sporadic)</em></td>
<td>~1</td>
</tr>
<tr>
<td><strong>Most</strong></td>
<td>Marfan</td>
<td>2-3</td>
</tr>
<tr>
<td><strong>Numerously</strong></td>
<td>Neurofibromatosis 1 <em>(NF1) (up to 50% are sporadic)</em></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Noonan syndrome</td>
<td>4-10</td>
</tr>
<tr>
<td><strong>Occurring</strong></td>
<td>Osteogenesis Imperfecta type I <em>(60% sporadic)</em></td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Pathologies</strong></td>
<td>Polyposis Coli <em>(APC)</em></td>
<td>1</td>
</tr>
</tbody>
</table>
# Autosomal Recessive

- Often affect metabolic pathways

<table>
<thead>
<tr>
<th>Mnemonic</th>
<th>Condition</th>
<th>/10,000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.f.</td>
<td>Cystic Fibrosis</td>
<td>4</td>
</tr>
<tr>
<td>Several</td>
<td>Spinal Muscular Atrophy</td>
<td>1</td>
</tr>
<tr>
<td>Conditions</td>
<td>CAH</td>
<td>1</td>
</tr>
<tr>
<td>Are</td>
<td>Alpha-1 Antitrypsin Deficiency</td>
<td>2</td>
</tr>
<tr>
<td>Frequently</td>
<td>Friedrich’s Ataxia</td>
<td>0.2</td>
</tr>
<tr>
<td>Associated</td>
<td>Albinism</td>
<td>0.5</td>
</tr>
<tr>
<td>To</td>
<td>Thalassaemia (beta)</td>
<td>0.5</td>
</tr>
<tr>
<td>Specific</td>
<td>Sickle Cell</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>MCADD</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Pathways</td>
<td>PKU</td>
<td>1</td>
</tr>
<tr>
<td>By</td>
<td>Biotinidase Deficiency</td>
<td>0.3</td>
</tr>
<tr>
<td>‘Hurting’</td>
<td>Hurler (MPS type 1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Genes</td>
<td>Galactosaemia</td>
<td>0.1-0.2</td>
</tr>
</tbody>
</table>
# X-linked Recessive

<table>
<thead>
<tr>
<th>Mnemonic</th>
<th>Condition</th>
<th>/10,000 male births</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6 (Genetic)</strong></td>
<td>G6PD (most common human enzyme defect, prevalence varies greatly with ethnicity as associated with malaria distribution)</td>
<td></td>
</tr>
<tr>
<td><strong>Conditions</strong></td>
<td>Colour blindness (red-green)</td>
<td>700-1000 (i.e. 7-10%)</td>
</tr>
<tr>
<td>David</td>
<td>Duchenne’s Muscular dystrophy</td>
<td>3</td>
</tr>
<tr>
<td>Beckham’s</td>
<td>Becker’s Muscular dystrophy</td>
<td>0.5</td>
</tr>
<tr>
<td>Football team</td>
<td>Fragile X</td>
<td>4</td>
</tr>
<tr>
<td><strong>Has (As Boys)</strong></td>
<td>Haemophilia A, &amp; B</td>
<td>1-2, &amp; 0.3</td>
</tr>
</tbody>
</table>
X-linked Dominant*

<table>
<thead>
<tr>
<th>Mnemonic</th>
<th>Condition</th>
<th>/10,000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very</td>
<td>Vitamin D resistant Rickets (X-linked Hypophosphataemia)</td>
<td>0.5</td>
</tr>
<tr>
<td>Rare</td>
<td>Rett syndrome</td>
<td>1/10,000 F births</td>
</tr>
<tr>
<td>And</td>
<td>Alport Syndrome (85% cases)</td>
<td></td>
</tr>
<tr>
<td>Infrequent</td>
<td>Incontinentia Pigmenti</td>
<td></td>
</tr>
</tbody>
</table>

*Labeling X-linked disorders as dominant or recessive is simplistic: multiple mechanisms can result in expression of X-linked traits in females, e.g. genetic anticipation, cell autonomous expression, skewed X-inactivation
Down Syndrome:
- Growth failure
- Mental retardation
- Flat back of head
- Abnormal ears
- Many "loops" on finger tips
- Palm crease
- Special skin ridge patterns
- Unilateral or bilateral absence of one rib
- Intestinal blockage
- Umbilical hernia
- Abnormal pelvis
- Diminished muscle tone
- Congenital heart disease
- Enlarged colon
- Big toes widely spaced

Turner Syndrome:
- Short stature
- Low hairline
- Shield-shaped thorax
- Widely spaced nipples
- Shortened metacarpal IV
- Small finger nails
- Brown spots (nevi)
- Characteristic facial features
- Fold of skin
- Constriction of aorta
- Poor breast development
- Elbow deformity
- Rudimentary ovaries
- Gonadal streak (underdeveloped gonadal structures)
- No menstruation
Williams Syndrome

- Star-like pattern in iris of eyes
- Short nose with broad nasal tip
- Small, widely spaced teeth
- Small chin
- Puffy Eyes
- Full cheeks
- Full Lips
- Wide Mouth

Fragile X Syndrome

- normal structure
- broad forehead
- elongated face
- large prominent ears
- strabismus (crossed eyes)
- highly arched palate
- hyperextensible joints
- hand calluses (from self-abuse)
- pectus excavatum (indentation of chest)
- mitral valve prolapse (benign heart condition)
- enlarged testicles
- hypotonia (low muscle tone)
- soft, fleshy skin
- flat feet
- seizures (in about 10 percent)
2. Dysmorphology

Chromosomal disorders:

– Down Syndrome
– Turner’s
– William Syndrome
– Fragile X
Down Trisomy 21 (47,XX,+21)

• Incidence of DS: 1/1000 babies born each year
• Most common Trisomy resulting in live birth
• Occurs due to abnormal meiosis + non-dysjunction (so no need to check parental chromosomes)
• Risk factor: Maternal age
  – aged 40, chance 1/100
  – aged 50, chance 1/50
• ~95% of Down syndrome is due to trisomy. Of remaining 5%:
  – ~3-4% caused by Robertsonian translocation
  – ~1-2% Mosaicism
Translocation Down Syndrome

• Robertsonian Translocation: two ‘acrocentric’ chromosomes break at the centromeres and fuse to form one single large chromosome (with a single centromere)

• Acrocentric chromosome: a chromosome with centromere near end; i.e. 13,14,15,12,22

• Check karyotype of mother, as may occur
  – *de novo* (i.e. at time of child’s conception, not inherited), or
  – inherited from a parent with a balanced translocation (1 in 1000 are carriers)
Mosaic Down Syndrome
(46,XX/47,XX,+21)

Either:

• Nondisjunction event occurs at later stage in embryonic development, i.e. during an early cell division, leading to a fraction of the cells with trisomy 21;

• Aneuploidy rescue: An anaphase lag of a chromosome 21 in a Down syndrome embryo leads to a fraction of euploid cells (2n cells)

May produce less developmental delay than full DS on average
Down syndrome: Physical Features

- Upslanting palpebral fissures
- Epicanthic folds
- Brushfield spots (iris)
- Small mouth, protruding tongue
- Small ears
- Flat facies, flat occiput, third fontanelle
- Short neck
- Single palmar crease (not specific)
- Hypotonia
- Associations:
  - Cardiac malformations, (40%) one of commonest AVSD (USS 20 week anomaly scan)
  - Duodenal atresia
  - Hirschprung’s disease
  - Congenital Cataracts
- Wide Sandal gap
flattened nose and face, upward slanting eyes,

single palmer crease, short fifth finger that curves inward

widely separated first and second toes and increased skin creases
Down Syndrome: later problems

- Delayed motor milestones
- Moderate to severe learning difficulties
- Small stature
- Infection susceptibility e.g. recurrent secretory otitis media
- Hearing impairment
- Visual impairment (strabismus, myopia + congenital cataracts)
- Juvenile/AI hypothyroidism
- Leukaemia ~2x increased risk
- Epilepsy increased risk
- Alzheimer’s risk, younger
Turner Syndrome (45,X)

• Incidence: 1 in 2500 live born females
• Genetics: karyotype XO
  – Spontaneous loss of foetus in ~>95%
• Diagnostics: abnormal USS e.g.
  – Cardiac defect
  – Kidney abnormality
  – Very large nuchal fold/high nuchal translucency implies cystic hygroma: high chance Turner
+ CVS/Amniocentesis, or Postnatal karyotyping
Turner’s syndrome

• Physical Phenotype:
  Girl with
  – Short stature (Wincy)
  – Webbed neck
  – Wide Broad chest
  – Widely spaced nipples
  – Wide carrying angle of arms (Cubitus Valgus)
  – Widespread Neonatal lymphoedema (most prominent in hands, feet, neck)

• Additional features:
  – Heart USS: e.g. coarctation aorta, bicuspid AV
  – Kidney USS: horseshoe kidney
  – GU: streak ovaries + infertility

• Rx symptoms
  – GH for height
  – Oestrogen replacement for puberty
Williams Syndrome (7q11)

- Incidence: 1 in 10,000-20,000 births
- Genetics: Submicroscopic deletion usually of >26 genes from long arm of chromosome 7
  - Elastin gene is central for dysmorphological features: pure gene deletion leads to physical dysmorphismology +/- some CT pathology
- Diagnostics: postnatal recognition of physical symptoms and markers, confirmatory genetic test: FISH or micro-array analysis
William Syndrome: Features

• Physical Features
  – Wide-set large blue eyes
  – Iris: star-like/lacy pattern
  – Long smooth philtrum
  – Larger lower lip, thin upper lip
  – Increased Interdental spacing
  – Absence of some teeth
  – Mouth wide, periorbital fullness
  – Short upturned nose
  – Saggy lower cheeks/jowelly
    —> full cheeks and lips
  – Short stature and sloping shoulders

• Associated features
  – Developmental milestones: mild-mod learning difficulties
  – Good verbal skills, friendly personality - ‘cocktail’ party manner
  – Supravalvular aortic stenosis in 50%
  – Hypercalcaemia
Fragile X

• Incidence: Very common, most common cause of severe LD after Down syndrome
  – 1 in every 3600 males and
  – 1 in 4000–6000 females

• Genetics: X-linked, >98% due to expansion of CGG repeat on *Fragile X mental retardation 1 (FMR1)* gene → Failure to express the fragile X mental retardation protein (FMRP), required for normal neural development

• Number of repeats affect allele & phenotype:
  – 5-44 repeats: Normal, unaffected by the syndrome
  – 45-54: Premutation, at risk of fragile X associated disorders, or
  – 55-200: usually affected by the syndrome
  – 200+: full mutation, usually with methylation + silencing of gene  
    – complete lack of expression
Fragile X

• Diagnostics: genetic testing to determine the number of CGG repeats
• Males affected more frequently and more severely than females (X-inactivation in females)
  – Male with full expansion always mod/severe LD
  – 50% females with full expansion have mild/mod learning difficulties
• Female premutation carriers can have premature ovarian failure: need to have kids earlier.
Fragile X: Presentation

Physical Phenotype
• Large, protruding ears
• Vertical maxillary excess (long face) + assoc. High-arched palate
• Hyperextensible finger + thumb joints
• Flat feet
• Soft skin
• Hypotonia

Associated Features

• Learning Difficulties
• Neuropsych: Autism (up to 50%), impaired social development, behavioural e.g. stereotyped movements (hand-flapping), ADHD, epilepsy
• Recurrent otitis media + sinusitis in early childhood
• Eyes: strabismus
• Postpubescent macro-orchidism
Screening

**Rationale:** Conditions suitable for screening must be

1. Identifiable at latent/early symptomatic stage
2. Treatable, and
3. Early treatment should alter the prognosis
## Antenatal Screening

<table>
<thead>
<tr>
<th>Condition</th>
<th>Indication &amp; Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down Syndrome</td>
<td>All women offered, particularly &gt;35yo</td>
</tr>
<tr>
<td></td>
<td>- USS nuchal skin fold</td>
</tr>
<tr>
<td></td>
<td>- Biochemistry: AFP, B-hCG</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Universal (Antenatal &amp; Newborn)</td>
</tr>
<tr>
<td></td>
<td>- HPLC to identify variants</td>
</tr>
<tr>
<td>Haemoglobinopathies including Thalassaemia</td>
<td>Universal</td>
</tr>
<tr>
<td>Congenital Abnormalities</td>
<td>Routine USS at 18-20 wk</td>
</tr>
</tbody>
</table>
# Antenatal Methods

<table>
<thead>
<tr>
<th>Method:</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal blood:</strong></td>
<td>• Safe</td>
<td>• Minimal information about foetus/indirect evidence</td>
</tr>
<tr>
<td>- Blood group &amp; Abs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Infection status of mother (Hep B Hep C, Syphilis, Rubella, HIV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MS AFP, ?B-hCG</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>USS</strong></td>
<td>• Safe</td>
<td>• User dependent</td>
</tr>
<tr>
<td>- Gestational age, multiple</td>
<td>• Non-invasive</td>
<td>• Cannot provide genetic level evidence for disorders</td>
</tr>
<tr>
<td>- Structural malformation</td>
<td>• Accurate if performed by skilled operator</td>
<td></td>
</tr>
<tr>
<td>- Foetal growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oligo-/poly- hydramnios</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amniocentesis</strong></td>
<td>• Allows screening for genetic disorders + inborn errors of metabolism</td>
<td>• Invasive</td>
</tr>
<tr>
<td>- Chromosome analysis</td>
<td></td>
<td>• Small chance of miscarriage</td>
</tr>
<tr>
<td>- DNA analysis</td>
<td></td>
<td>• Can only be carried out 15+ wk</td>
</tr>
<tr>
<td>- NTD (AFP, ACh)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bilirubin: rhesus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Enzyme analysis (inborn errors metabolism)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PCR: Foetal infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Antenatal Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foetal Tissue sampling:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Skin biopsy for severe congenital skin disorders</em></td>
<td>• Allows identification of rare skin disorders</td>
<td>• Invasive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Limited usefulness unless at risk</td>
</tr>
<tr>
<td>Foetal Blood sampling:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <em>Chromosome analysis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <em>DNA analysis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <em>Hb + Bilirubin: Rhesus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <em>Serology: Foetal congenital infection</em></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <em>Chromosome analysis</em></td>
<td>• Can be performed 9-12wk pregnancy (early)</td>
<td>• Invasive</td>
</tr>
<tr>
<td>- <em>DNA analysis</em></td>
<td></td>
<td>• Risk of miscarriage higher than amniocentesis</td>
</tr>
<tr>
<td>- <em>Enzyme analysis</em></td>
<td></td>
<td>• Infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bleeding</td>
</tr>
<tr>
<td>PGD:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Genetic analysis of cells from developing embryo prior to transfer into uterus</em></td>
<td>• Allows identification of genetic disorders prior to implantation</td>
<td>• Ethical implications of selecting embryo</td>
</tr>
</tbody>
</table>

The table above provides a summary of different antenatal methods, their pros, and cons. Each method is described with its specific advantages and disadvantages, allowing parents to make informed decisions.
# Neonatal Screening: Guthrie Heel-Prick

<table>
<thead>
<tr>
<th>Condition</th>
<th>Why Screen?</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Hypothyroidism</td>
<td>Growth failure + permanent intellectual disability if unRx</td>
<td>Heel prick (Guthrie): TSH +/- thyroid scan</td>
</tr>
<tr>
<td>CF</td>
<td>Early treatment increases survival (esp lung, pancreas)</td>
<td>Heel prick (Guthrie) for IRT (Immunoreactive trypsin) + Common CF mutations</td>
</tr>
<tr>
<td>PKU</td>
<td>Intellectual disability, seizures</td>
<td>Heel prick (Guthrie): Biochemical assay, or amino acid measurement (tandem mass spec)</td>
</tr>
<tr>
<td>MCADD</td>
<td>Significant hypoglycaemia, sudden death</td>
<td>Heel prick (Guthrie) + Tandem mass spec</td>
</tr>
<tr>
<td>Sickle cell</td>
<td>Repeated sickle cell crises causes major multi-organ damage</td>
<td>Heel prick (Guthrie) + isoelectric focusing analysis</td>
</tr>
</tbody>
</table>
### Neonatal Screening:
**NIPE (Newborn & Infant Physical Examination)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Why Screen?</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital cataract</td>
<td>If suspect, can consider surgery, reduce risk long-term impaired vision</td>
<td>Referral if suspect + clinical examination by ophthalmologist</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>If high risk infant, e.g. preterm Rx &lt;6mo: able to develop equiv. communication skills</td>
<td>OAE testing AABR</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>May be indication for surgical Rx, e.g. prevent HF, Eisenmenger’s</td>
<td>Clinical examination of neonate, repeated at 6wk</td>
</tr>
<tr>
<td>DDH</td>
<td>Early secondary OA, risk AVN of femoral head</td>
<td>Clinical examination of neonate, repeated at 6wk +/- USS for high risk</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>Orchidopexy can improve fertility, ability to spot testicular cancer/risk of cancer</td>
<td>Clinical examination of neonate, repeated at 6-8wk, and 3mo (undescended testes abnormal)</td>
</tr>
</tbody>
</table>
The End!

Any Questions?