Genetics

Learning Objectives

- Modes of inheritance:
  - Draw family trees to illustrate dominant, recessive and X-linked inheritance (with examples)
  - Calculate recurrence risks
- Neonatal screening:
  - Rationale for screening
  - Which conditions are screened for and why
- Antenatal diagnosis:
  - Methods available (with pros and cons)
  - Examples of conditions that can be detected
- Dysmorphology:
  - Recognise + describe dysmorphic features
  - Basic knowledge of common syndromes (Down's, Turner's, William's, fragile X)

Autosomal Dominant

- Most common mode of inheritance
- Often structural proteins
- Variation in expression

Mnemonic	Condition
***Ac**tually*	*Achondroplasia*
My	Myotonic Dystrophy
Hunch	Huntington
Ech**o**es	Ehlers Danlos
***T**he*	*Tuberous Sclerosis*
Most	Marfan (1 in 5000)
Numerously	Neurofibromatosis 1 (NF1)
Occurring	Otosclerosis
Familial	Familial Hypercholesterolaemia
Ones	Osteogenesis Imperfecta

Autosomal Recessive

- Often affect metabolic pathways

Mnemonic	Condition
c.f.	Cystic Fibrosis
These	Thalassaemia
Specific	Sickle Cell
Genetic	Galactosaemia? Is it metabolic
Conditions	CAH
Frequently	Friedrich's Ataxia
Affect	Albinism
Metabolic	
Pathways	PKU
By	Biotinidase Deficiency
Hindrance	Hurler (MPS type 1) and Hunter (MPS type 2)

X-linked Recessive

Mnemonic	Condition
6 (**G**enetic)	G6PD (most common human enzyme defect)
Conditions	Colour blindness (red-green)
David	Duchenne's Muscular dystrophy
Beckham's	Becker's Muscular dystrophy
Football team	Fragile X
Has	Haemophilia A & B

X-linked Dominant

Mnemonic	Condition
Rare	Rett's syndrome
Infrequent	Incontinentia Pigmentosa

Recurrence Risk: the likelihood that a trait or disorder present in one family member will occur again in other family members in the same or subsequent generations. *This depends on the trait's penetrance and its inheritance pattern*

Penetrance: likelihood of a gene generating its associated phenotype: the proportion of people with the genotype who demonstrate the phenotype. This may be age dependent

Expressivity: measured only when there is 100% penetrance, it is the variation in a phenotype among individuals carrying a particular genotype. i.e. variable features, show features to differing degree. This may be affected by ageing, environmental factors

Prenatal Diagnosis for Congenital Abnormalities

Summary of Genetic screening

On booking visit (10wk pregnant)

- Counsel all regarding prenatal diagnosis options
- Arrange genetic counseling +/- later CVS/amniocentesis if risk of inherited disorder
- Advise regarding screening for trisomy e.g. combined test

18-21wk

- Routine anomaly USS for structural abnormalities
- Counsel and offer amnio if abnormalities found
- Offer cardiac scan if high risk

Later e.g. USS if polyhydramnios, breech, suspect IUGR

	Maternal Blood tests:	**Condition**	**Indications**
Screen	AFP (product of foetal liver)	Often raised maternal levels in: Neural tube defects (NTD), Gastroschises, 3rd trimester complications	Seldom used as USS more accurate
Screen	Beta-hCG (*beta subunit of human chorionic gonado-trophin),* PAPP-A (*pregnancy associated plasma protein A*), AFP, oestriol, inhibin A	Chromosomal abnormalities e.g. Down syndrome 21, Patau 13, Edward 18	Used integrated with other risk factors e.g. maternal age, USS nuchal translucency
Dx	Cff-DNA (free foetal DNA)	Gender	
	USS:	Gestation (dates), pregnancy site, exclude multiple pregnancy	
Screen	Nuchal translucency (space between skin and soft tissue overlying cervical spine) between 11-14wk	The larger it is, the higher the risk of Trisomy, also 25%+ of all structural abnormalities (cardiac in particular). NB 50% of trisomy have structural abnormalities such as exomphalos	Cornerstone of screening for trisomy
Dx aid	Amniocentesis and CVS are perfomed under USS guidance		
Dx	18-21 wk anomaly scan	Structural congenital malformations of all organs and systems are detectable, heart in particular may remain undiagnosed even at 20wk (operator experience-dependent)	Routine
	Subsequent scans	Some abnormalities do not show up until later – not visible or develop with gestation	^ Liquor volume (polyhydramnios) in later pregnancy warrants repeat
Dx	**Foetal MRI in utero**	Dx Intracranial lesions	
		Can distinguish between different types of soft tissue e.g. liver, lung	
		Alternative to post-mortem examination?	
	3D or real-time 3D (4D) USS uses computer reconstructed 3D US image	Better evaluation of certain abnormalities	Used largely in tertiary referral centres
Dx	**Amniocentesis** (US-guided removal of amniotic fluid with fine-gauge needle) NB 1% risk miscarriage	Chromosomal abnormalities Some infections e.g. CMV, toxoplasmosis Inherited e.g. sickle cell anaemia, thalassaemia, CF	Safest from 15wk
Dx	**Chorionic Villus Sampling** (biopsy of trophoblast – pass fine-gauge needle through abdominal wall/cervix into placenta) slightly higher risk of miscarriage: harder procedure + also slightly higher rate of spont. Miscarriage as earlier	Chromosomal problems AD and AR genetic conditions NB in both Amnio and CVS, FISH (fluorescent in situ hybridization) and PCR (polymerase chain reaction) can siagnose the most common abnormalities in <48h	After 11wk – faster result than amniocentesis; abnormal foetus can be identified when abortion (if requested) can be performed under GA
	Preimplantation genetic Dx	Select + implant embryos not affected by disorder for which it is being tested: sex-linked disorders, trisomy, AD, AR	In IVF, cell(s) from developing embryo can be removed for genetic analysis before transferring embryo to uterus. ££. Ethical dilemmas

Neonatal screening

Rational: Conditions suitable for screening must be

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

Guthrie Heel-Prick

Condition	Why Screen?	Method
Congenital Hypothyroidism	Growth failure + permanent intellectual disability if untreated	Heel prick (Guthrie): TSH +/- thyroid scan
Cystic Fibrosis	Early treatment increases survival (reduce multi-organ morbidity and mortality esp lung, pancreas)	Heel prick (Guthrie) for IRT (Immunoreactive trypsin) + Common CF mutations
PKU *Phenylketonuria*	Intellectual disability, seizures risk without special diet	Heel prick (Guthrie): Biochemical assay, or amino acid measurement (tandem mass spec)
MCADD *Medium-chain acyl-coenzyme A dehydrogenase deficiency*	Significant hypoglycaemia, sudden death	Heel prick (Guthrie) + Tandem mass spec
Sickle cell	Repeated sickle cell crises causes major multi-organ damage	Heel prick (Guthrie) + isoelectric focusing analysis. Linked antenatal and newborn programme (with thalassaemia)

NIPE (Newborn & Infant Physical Examination)

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

For Pedigree chart + Dysmorphology pictures, see slide show.
Good luck!