Genetic inheritance

Autosomal recessive	Autosomal dominant	X-linked dominant	X-linked recessive
• 25% chance of inheritance if BOTH parents are carriers *Unaffected → 1:4* *Affected → 1:4* *Carrier → 1:2*	• 50% chance of inheritance if ONE parent is a carrier *Unaffected → 1:2* *Affected → 1:2* *25% chance to pass to a grandson* *If the affected parent is Homozygous → 4:4* *If Heterozygous → 1:2*	• 50% chance of inheritance if MOTHER has the disorder • If FATHER has the mutation, a female child has a 100% chance while a male child has 0% *In X-linked diseases, sexes of offspring are usually mentioned*	• Male child has a 50% of inheritance if MOTHER is a carrier • Female child has 50% chance to be a carrier if MOTHER is a carrier • X-linked recessive conditions don't affect females to a significant degree as the other X-chromosome is likely to be normal and can compensate • Infected males don't live long enough to be fathers → Mom is the culprit
• Cystic fibrosis • Sickle cell anemia • Thalassemia • Congenital adrenal hyperplasia • Infantile PCKD	• Huntington • Neurofibromatosis • PCKD • OI	• Fragile X syndrome	• Hemophilia • Duchenne muscular atrophy

Approach

➢ Firstly, find out what is the disease? Then figure out its type

1. **Autosomal recessive**
   - Usually both parents will have the faulty gene → *Unaffected 1:4, Affected 1:4, Carrier 1:2*
2. **Autosomal dominant**
   - There's no need to know the other partner genotype, as it's enough to have one parent with the faulty gene to have the disease → Unaffected 1:2

In X-linked → we need to know if the mother and the father are affected or not, also the effect on the offspring

3. **X-linked dominant**
   a) MOTHER affected, FATHER affected → *Unaffected 1:2, Affected 1:2*
   b) MOTHER unaffected, FATHER affected → *100% girls Affected, 0% boys Affected*

Because the boy will always take his Y gene from his father, leaving the faulty X gene of the father behind and he'll receive his X gene from his mother who's free of the disease
Girls will get one X gene from the father which is faulty, so all girls XX will have one gene X damaged

4. **X-linked recessive**
   - Carrier MOTHER and unaffected father
     - *Affected boys 1:2, Unaffected boys 1:2*
     - *Girls who become carrier 1:2*

Duchenne muscular dystrophy (DMD)

- A boy comes to the clinic by age **4-8 years**
- **Delayed motor milestones**: walking at >18 months, can't hold objects
- **Inability to run** – *waddling gait*
- **Gower's sign**, proximal muscle weakness (rising from a sitting position)
- **Pseudohypertrophy of calf muscles**
- There may be **respiratory** or **cardiac** symptoms
- Elevated CK, AST, ALT

Diagnosis

- Initial → ***CK*** (extremely high since birth)
- **Blood sample** and **muscle biopsy** → genetic testing for **dystrophin** mutations → **PCR**
- **Neuromuscular assessment** → diagnose severity and determine management
- **Genetic testing** after a positive biopsy diagnosis of DMD is mandatory

***B**ecker's muscular dystrophy (BMD) → **B**ig boys*

- *Less common than DMD, clinical course is milder*
- *Walking difficulties begin <u>after the age of 16</u>*

***My**otonic muscular dystrophy*

- ***My** testis (Testicular atrophy)*
- ***My** Ticker (Arrythmias)*
- ***My** Toupee (Frontal balding)*

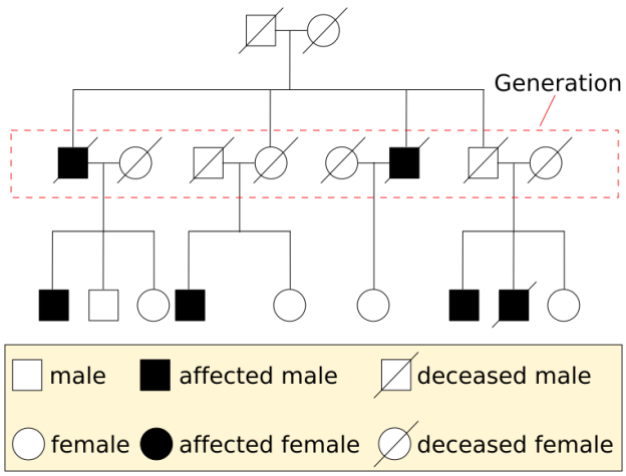
Huntington's disease

- **Autosomal-dominant inheritance <u>with anticipation</u>**, progressive neurodegenerative disorder with a distinct phenotype → enlargement of the **frontal horns** of the lateral ventricles

Presentation

- Typically, onset of symptoms at **middle age**
- Early signs may be **personality change**, **self-neglect** and **clumsiness**
- **Incoordination**
- **Cognitive decline**
- **Behavioral difficulties**
- Later → **Chorea (dancing movements)**, **dystonia**, **rigidity**, **dementia** and **athetosis (involuntary writing movements)**

Pedigree charts



Klinefelter's syndrome (XXY)

- **Mental retardation** (average IQ 85-90)
- **Behavioral problems**
- **Long limbs** (decreased upper: lower segment ratio)
- **Tall** and slim
- **Hypogonadism**
- **Infertility**
- **Gynecomastia**

*Diagnosed by **Chromosomal analysis***

The most common indications for karyotyping → *hypogonadism* *and* *infertility*

Turner syndrome

[45**XO**]

- ***X**tra skin folds*
- ***O**varian failure*

- Some turner syndrome patients can conceive with assisted reproductive techniques

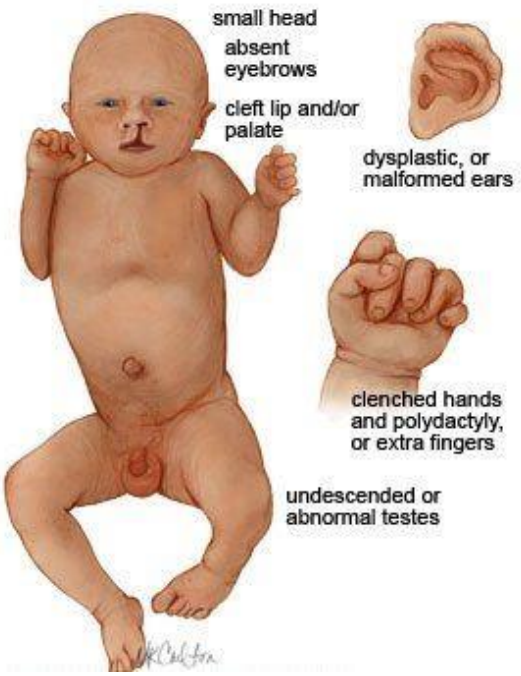
Other features

- Low set of ears
- Broad chest with widely spaced nipples and Webbed neck
- Peripheral edema, horseshoe shaped kidneys, aorta bicuspid
- No Barr body

Comparing the trisomies

	Features
Patau syndrome (Trisomy 13)	Microcephalic Microphthalmia Cleft lip and palate Polydactyly Scalp defects (cutis aplasia: skin missing from the scalp)
Edward syndrome (Trisomy 18)	Microcephaly Micrognathia Prominent occiput Rocker bottom feet Clenched hand-index over third; fifth over fourth
Down syndrome (Trisomy 21)	Flat occiput Round/flat face Epicanthal folds Single palmar crease Protruding tongue Duodenal atresia

Patau's



Edward's

Down's

Ovarian cancer

- If high risk with no symptoms of ovarian cancer, next step is → ***Genetic counseling***

Criteria of increased risk of ovarian cancer

- BRCA1 or BRCA2 mutations
- 1st degree relative who carries a gene mutation
- Two family members who are 1st degree relatives of each other have ovarian cancer
- One family member has both breast and ovarian cancer

High risk women should be offered ***genetic screening and counselling***

Steps to investigate a patient with suspected ovarian cancer

1. CA 125
2. US pelvis and abdomen
3. CT pelvis and abdomen
4. MRI for pre-operative staging
5. Prophylactic salpingo-oophorectomy may be offered

Chorionic Villus Sampling vs Non-invasive Prenatal Testing

INVASIVE PRENATAL TESTING	
Amniocentesis	**Chorionic Villus Sampling (CVS)**
• Samples amniotic fluid using an ultrasound-guided transabdominal needle • Usually performed between 15 and 18 weeks of gestation • The karyotype results typically take 3 weeks	• Samples placenta using an ultrasound-guided transabdominal needle or ultrasound-guided transcervical cannula aspiration • Cannot be used to screen for neural tube defects (unlike amniocentesis) • Usually performed between 11 and 14 weeks (11+0 to 13+6) • Results are obtained within 1 to 2 weeks • Because CVS allows diagnosis earlier in pregnancy compared to amniocentesis, there is an earlier opportunity to consider termination of pregnancy in the event of a fetal abnormality

CVS is done in late 1st trimester as the baby is still small and a placental sampling can be obtained
Amniocentesis is done in early 2nd trimester
Risk of fetal loss is 0.5-1%
Conditions which can be diagnosed with Amniocentesis

- *NTD (raised AFP)*
- *Chromosomal disorders*
- *Inborn errors of metabolism*

NON INVASIVE PRENATAL TESTING (NIPT)
• NIPT looks at fetal cells and fetal DNA circulating in maternal blood • It is non-invasive because the test only involves taking a sample of the mother's blood • It is now possible to use NIPT to detect chromosomal abnormalities such as Down syndrome and three of the other common aneuploidies: Edwards syndrome, Patau syndrome and Turner syndrome • Certain NIPT tests have a detection rate of around 99.9% for Down's syndrome and result only take a few days • Unfortunately, NIPT is not available on the NHS and is only available privately in the UK at present • Like the combined test, NIPT is a screening test, and a diagnostic test like a CVS or amniocentesis will still be needed to confirm a positive result

Notes

- Diagnostic test to help diagnose genetic defects (e.g. Cystic fibrosis) prior to conception → ***Pre-implantation genetic diagnosis (PGD)***
- Chromosomal karyotyping can only be performed after conception
- Most enzymatic/metabolic diseases → ***Autosomal recessive***
- Most structural diseases → ***Autosomal dominant***
- Paternal inheritance by deletion of chromosome 15 → ***Prader Willi $***
- Maternal inheritance of deletion of chromosome 15 → ***Angelman's $ (happy puppet $)***
- **D**ouble bubble sign = **D**uodenal atresia = **D**own's syndrome
- Cardiac complications of Down's syndrome → ***ASD, VSD***
- Late complications of Down's syndrome → *Subfertility, learning difficulties, short stature,* ***ALL, Alzheimer's***
- **Microphthalmia** → one eye or both are abnormally small
- **Micrognathia** → undersized jaw
- Edward $ → ROME
  - *Rocker bottom feet*
  - *Overlapping fingers*
  - *Micrognathia*
  - *Ear (low set)*
- Flat occiput → ***Down's***
- Prominent occiput → ***Edward's***
- Scalp defects → ***Patau***
- Bloods in Down's → ***low alpha-feto protein, hCG high, estriol low***
- Most common US finding in Edward's → ***Nuchal translucency thickness*** and ***absence or hypoplasia of the nasal bone***
- Infants with Edward's don't survive the first week of life, majority don't survive longer than a year
- In chromosomal inheritance, each pregnancy is considered a new event so the probability is always the same
- **Alport's syndrome** → X-linked mode of inheritance
- **Familial hypercholesterolemia** → Autosomal dominant
- **VWD** → Autosomal dominant
- **Hereditary spherocytosis** → Autosomal dominant