



GENETICS IN PRIMARY CARE

The Mill medical practice & Fairlands medical practice



CONTENTS

- 1) Introduction
- 2) Inheritance patterns
- 3) Cystic Fibrosis
- 4) Mock CSA consultation
- 5) AKT questions



IMPORTANCE

- **1 in 10** patients seen in primary care have a disorder with a genetic component
- Three main themes: identification, clinical management, communication
- Taking and considering a genetic family history is a key skill
- GPs have a key role in referral to specialist genetic services

In the News.....

- <https://www.bbc.co.uk/news/health-50425039>





VIDEO: GENOMICS IN PRIMARY CARE





















- <https://www.genomicseducation.hee.nhs.uk/genomics-in-healthcare/genomics-in-primary-care/>




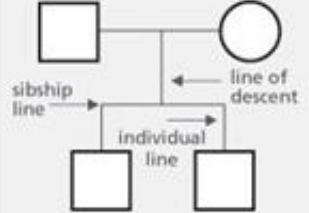




MODES OF INHERITANCE

- Autosomal dominant
- Autosomal recessive
- X linked recessive
- X linked dominant
- Mitochondrial

DRAWING A PEDIGREE

	Male	Female	Sex Unknown
Individual			
Affected individual (symbol coloured in)			
Multiple individuals			
Deceased			
Pregnancy			
Miscarriage	 male	 female	
Person providing pedigree information			

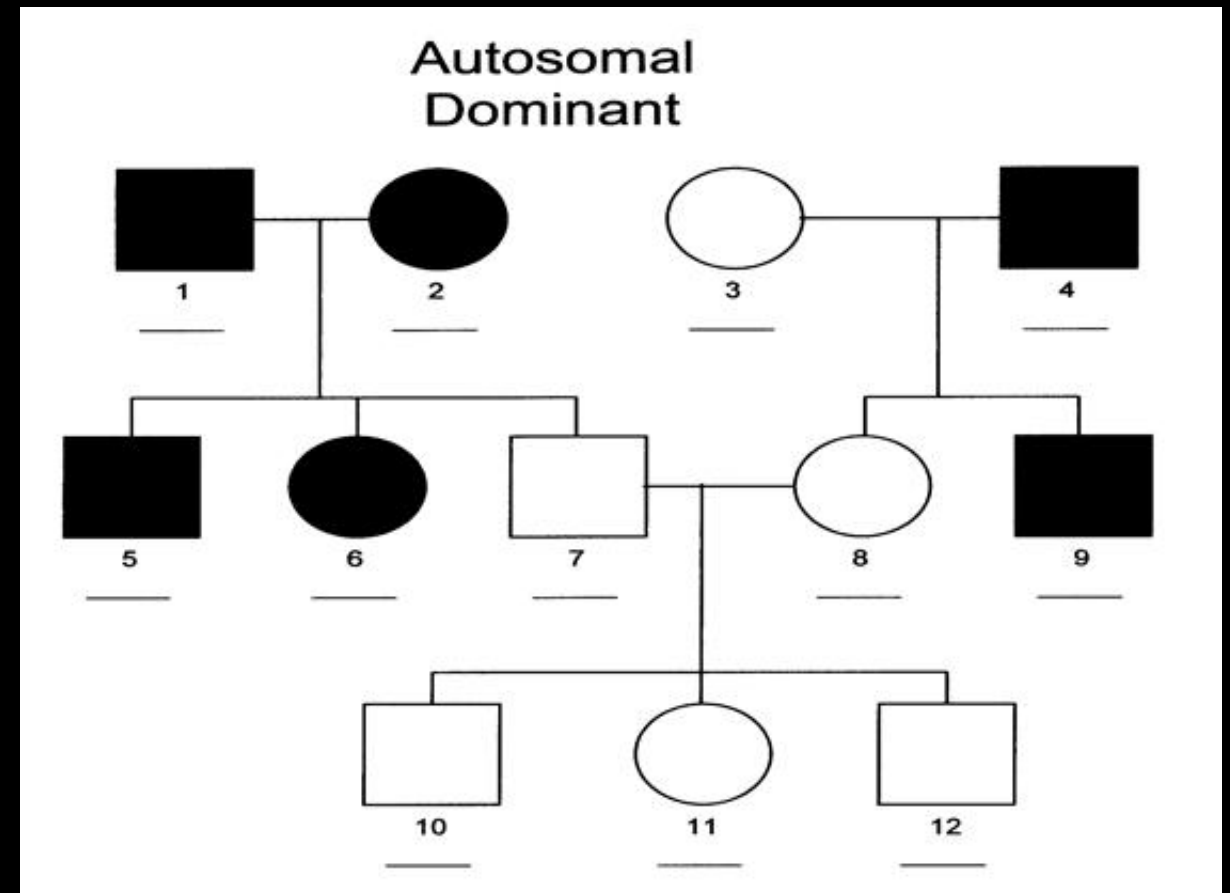
Marriage/partnership	
Divorce/separation	
Where the partners are blood relatives (consanguineous relationship)	
Children/siblings	
Identical twins (monozygotic)	
Non-identical twins (dizygotic)	

AUTOSOMAL DOMINANT

- 1 gene enough to develop condition
- No gender discrepancy
- Exhibits non penetrance – may not manifest clinically
- Expressed as homozygous and heterozygous states
- E.g. Huntingtons disease [anticipation], Marfan's, Ehlers-Danlos, Adult PKD, von Willebrands, familial hypercholesterolaemia

AUTOSOMAL DOMINANT SCENARIOS

- 1 parent has the gene
 - 50% chance child will have the condition
 - 50% chance child will not have the condition
- 2 parents have the gene
 - 75% chance the child will have the condition
 - 25% chance child will not have the condition



HUNTINGTON'S DISEASE

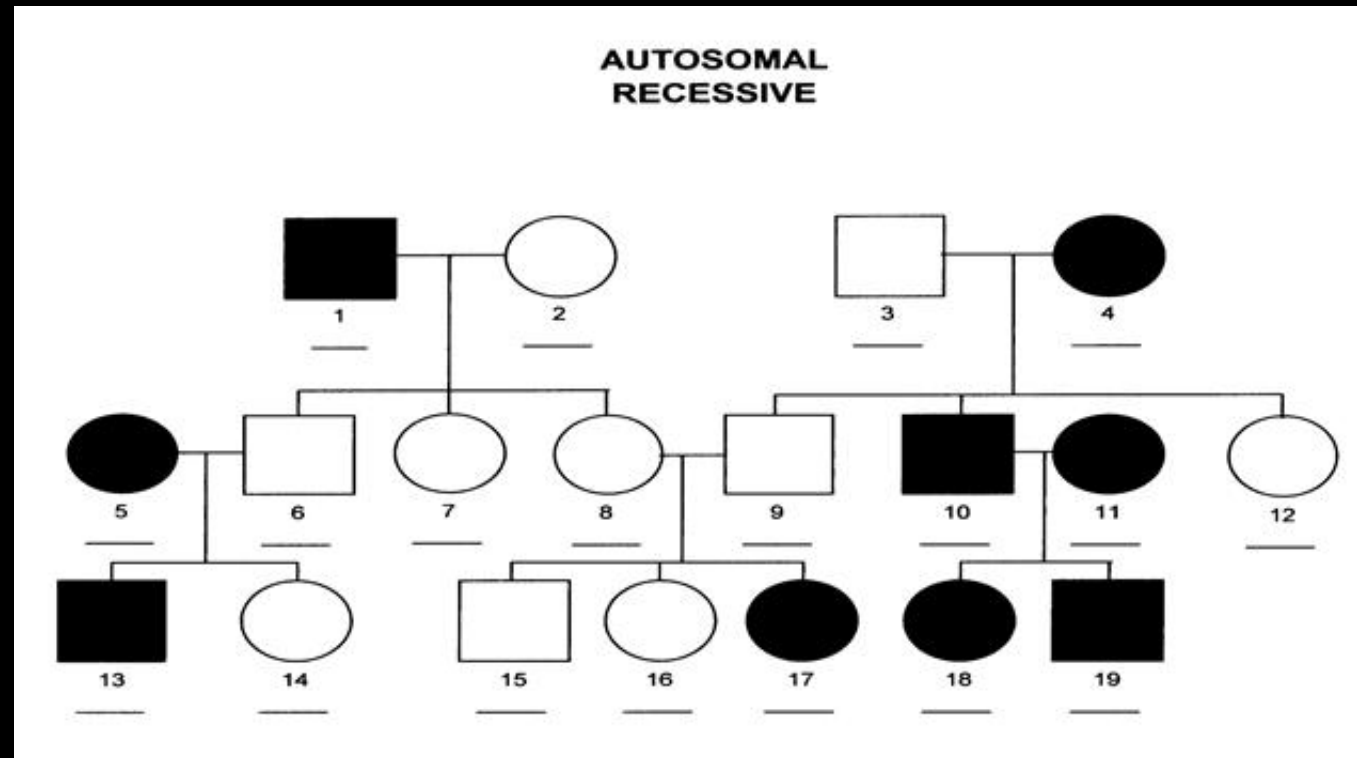
- Progressive neurodegenerative disorder
- Genetic anticipation (CAG trinucleotide repeat)
- Between 1 in 10,000 and 1 in 20,000
- Mean age of onset: 30 – 50
- Early signs may be personality change, self-neglect, apathy with clumsiness, fidgeting with fleeting facial grimaces.
- Chorea, dystonia, incoordination, cognitive decline, behavioural difficulties
- Genetics testing
- Management: symptomatic and supportive
- Poor prognosis.

AUTOSOMAL RECESSIVE

- 2 genes needed to develop the condition
- Homozygous
- 1 gene leads to carrier status
- No gender discrepancy
- Little variability of expression
- E.g. Thalassaemia, Sickle cell disease, haemochromatosis, cystic fibrosis, Wilsons disease, PKU

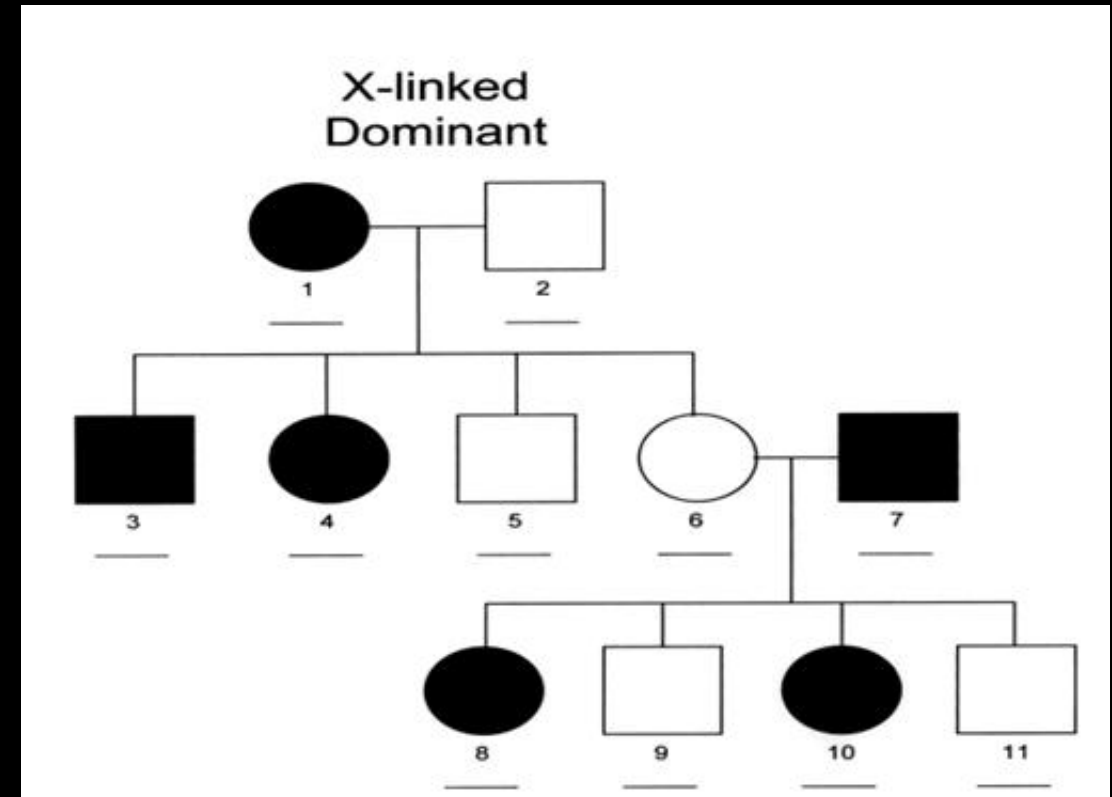
AUTOSOMAL RECESSIVE SCENARIOS

- 1 parent has one gene
 - 0% chance child will have condition
 - 50% chance child will be a carrier
 - 50% chance child will neither be carrier or have the condition
- 2 parents have a gene
 - 25% chance child will have the condition
 - 50% chance child will be a carrier
 - 25% chance child will neither be carrier or have the condition



X LINKED DOMINANT

- Normally female has two copies of X gene – XX
- Normally male has one copy of X gene – XY
- X linked dominant: e.g. Fragile X, Rett's. Both males and females affected. Female affected if heterozygous or homozygous.
- Positive father will give the condition to ALL daughters but NO sons.



FRAGILE X

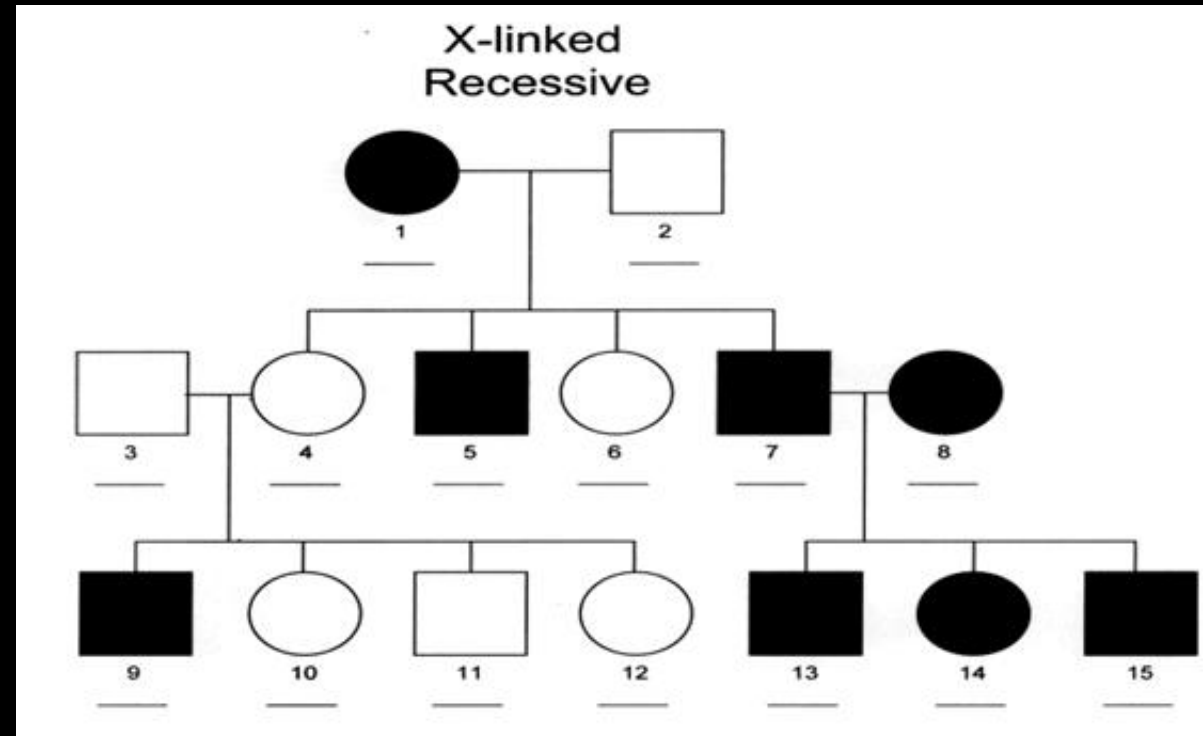
- Most common cause of sex linked, general learning disability
- Repeat expansion disorder
- 2.3 in 10,000
- Learning difficulties, delayed milestones, typical physical features
- Diagnosis usually made by age 3
- Supportive management
- No affect on life expectancy

X LINKED RECESSIVE

- X linked recessive: e.g. haemophilia A/B, Duchennes, red/green colour blindness.
- Males affected as the one affected X will overshadow the Y

Rare in females as need two affected Xs to cause the condition

A normal X will override the affected X



DUCHENNES MUSCULAR DYSTROPHY

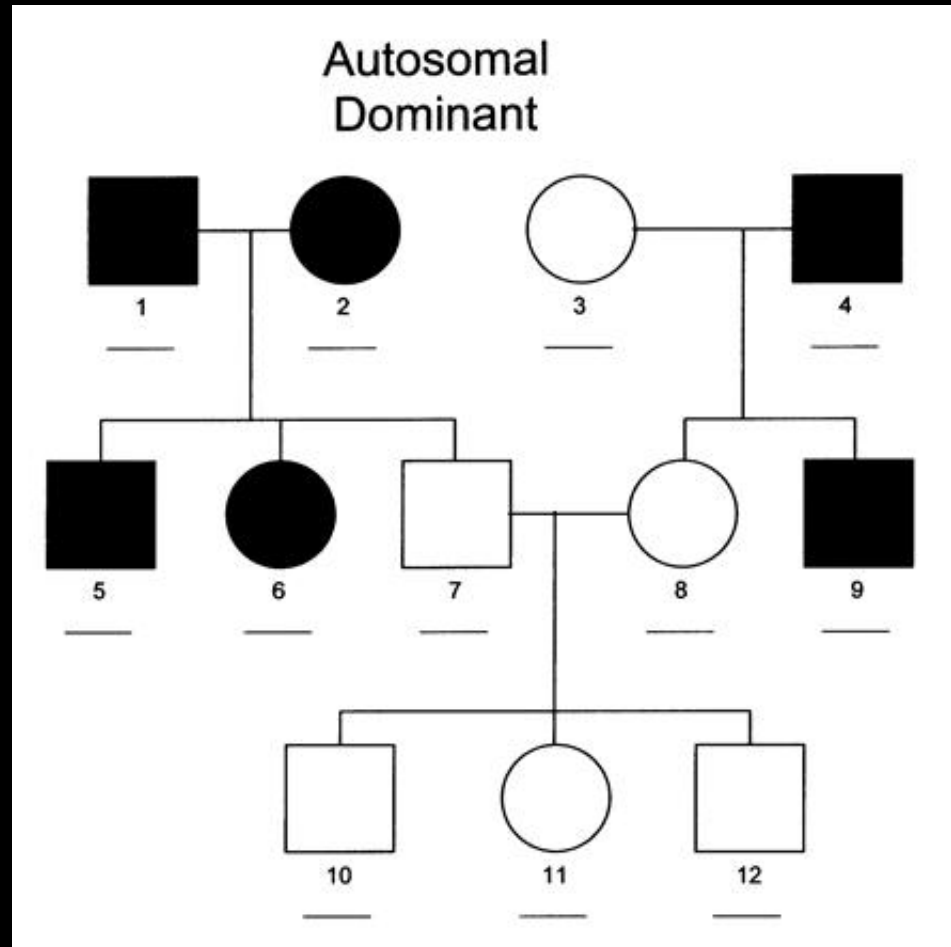
- Muscular dystrophies: progressive muscle wasting and weakness
- Most common inherited muscular dystrophy
- Mutation in dystrophin gene
- Presents in early childhood
- Some carriers have symptoms
- 1/3500 newborn males
- Progressive proximal muscular dystrophy + characteristic calf pseudohypertrophy
- Consider if: motor milestones delayed, inability to run, Gower's sign, FTT, fatigue
- Raised CK, genetic analysis, muscle biopsy
- Affected boys are normally confined to a wheelchair by 12 years of age and die from respiratory or cardiac complications in their 20s or 30



PEDIGREE ACTIVITY 1

- Clara marries Jed. Neither of them have the condition.
- Clara's Dad John has the condition but mother Sarah doesn't. Clara's sister Nora does have the condition.
- Jed's sister Brenda has the condition, as does his brother Edward. Jed's parents (Nellie and Edgar) both have the condition.
- Clara and Jed have three children: Angus, Rachel and Jacqui, none of whom have the condition.
- *What is the mode of inheritance?*

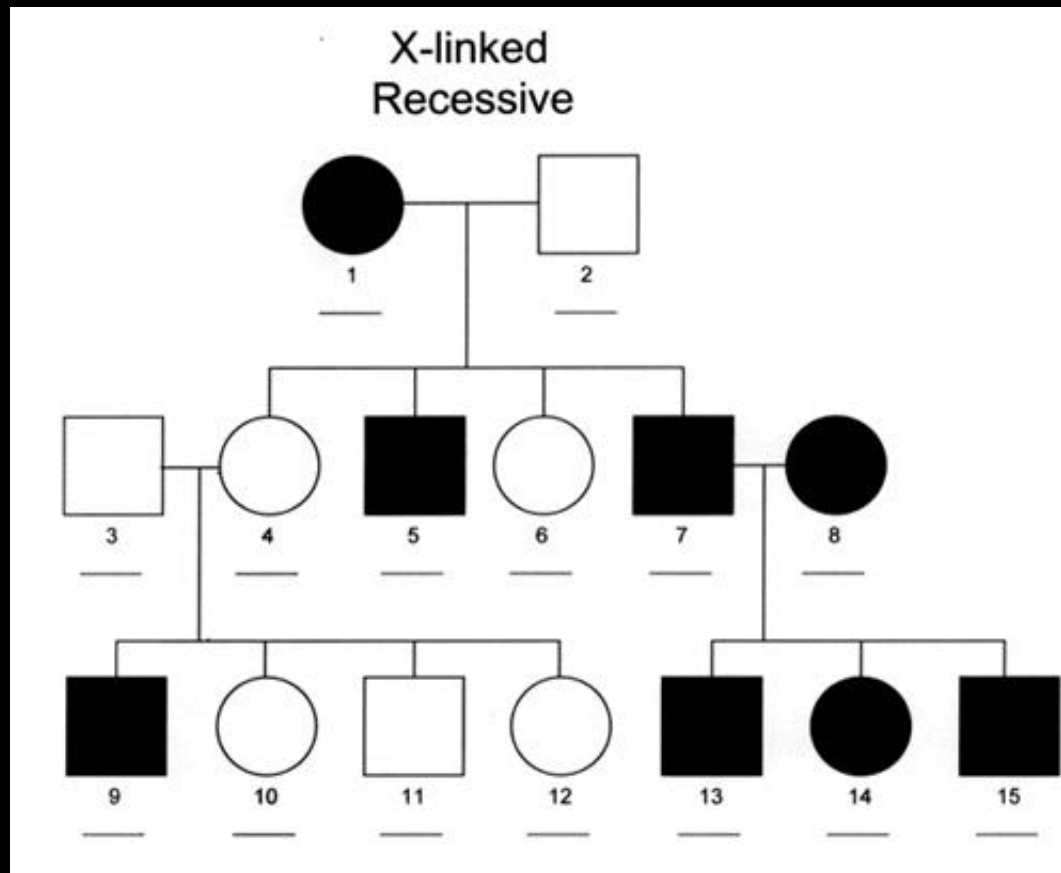
AUTOSOMAL DOMINANT



PEDIGREE ACTIVITY 2

- John has condition Z. He is married to Susan who does not.
- They have four children. Luke and Zak both have the condition. Anne and Zoe do not.
- Anne marries James. They have four children. Tom has the condition, Dan, Rebecca and Paula don't.
- Zak marries Carla. Carla has the condition. Their three children: Ben, Matthew and Amy all have the condition.
- *What is the mode of inheritance?*

X LINKED RECESSIVE





Cystic Fibrosis



What is it?

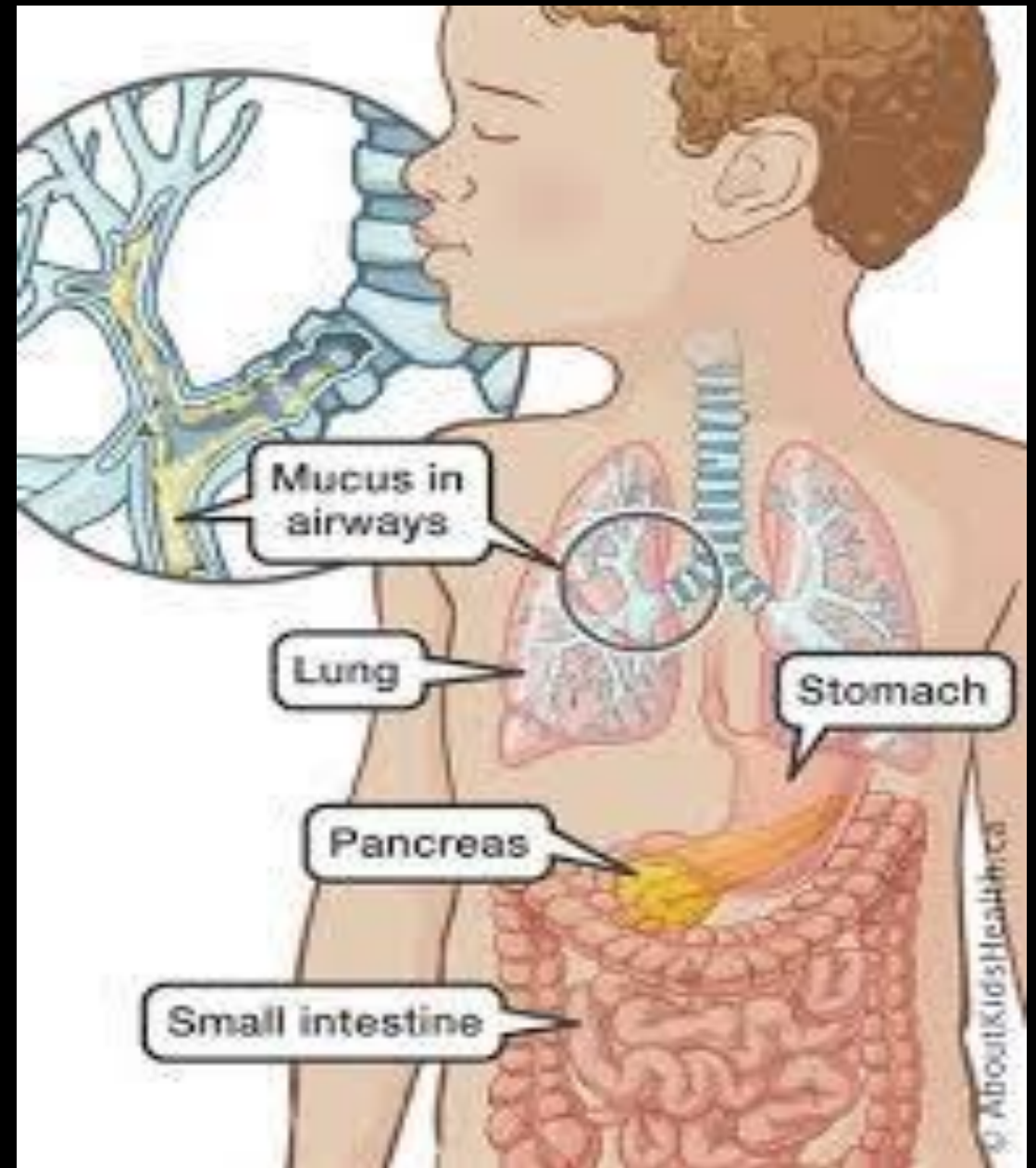
- Genetic disorder
- Most common autosomal recessive disorder
- Potentially lethal
- Chronic
- Multi-system affecting the lungs, pancreas, liver and intestine.
- Significant impact on life expectancy and quality of life

Who, where, when?

- Caucasian population
- 1 in 2500 infants in UK
- Frequency of carrier heterozygotes is estimated to be 5%
- Median age at diagnosis is 2 months
- 60% on the UK cystic fibrosis registry are over 16 years

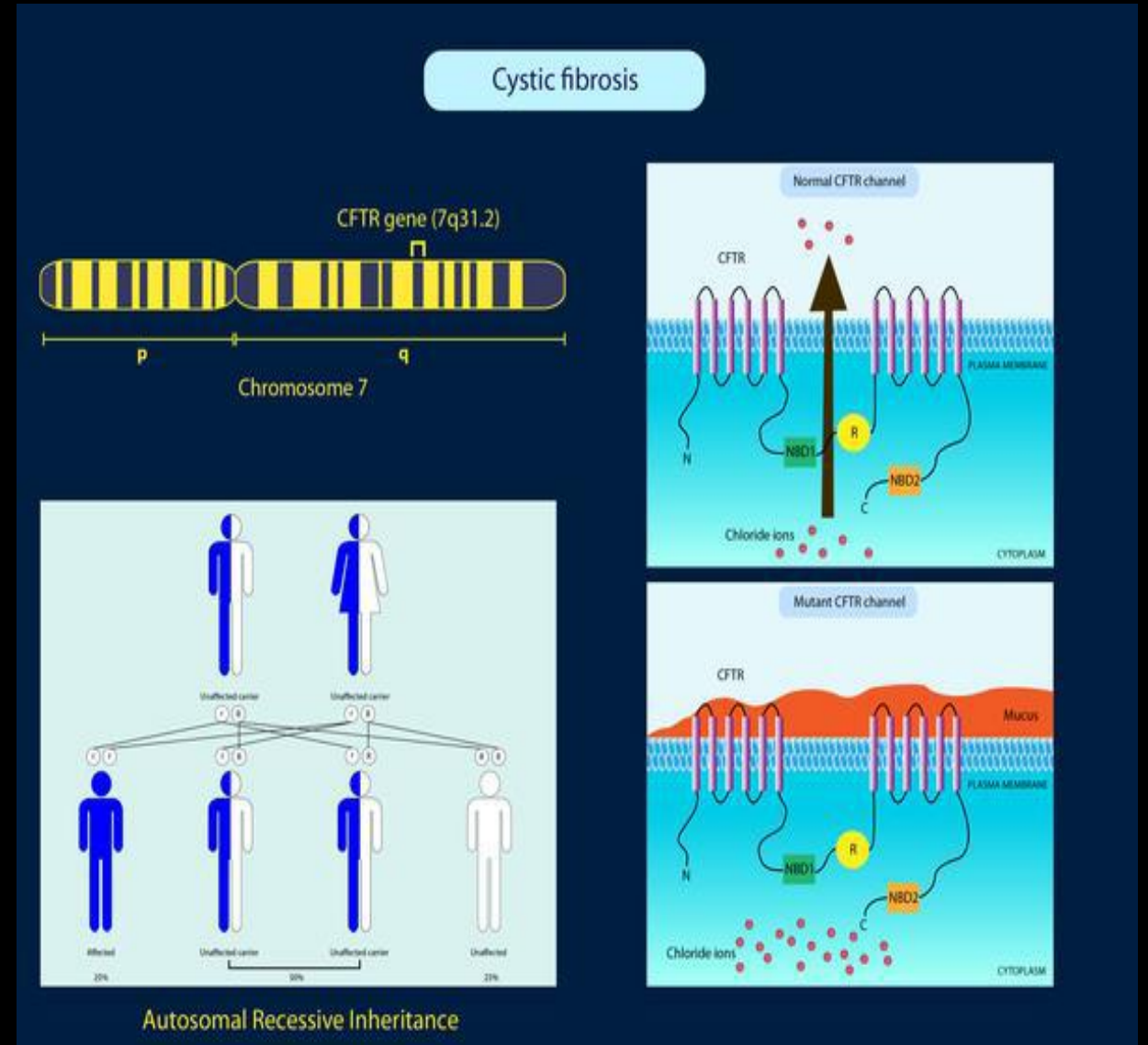
How?

- Symptoms are attributed to epithelial abnormalities in the respiratory, digestive and reproductive tracts



Let's talk Gene

- Different mutations responsible for cystic fibrosis





How to spot?

- meconium ileus (10% of newborns- presenting as intestinal obstruction; equivalent may occur in later life)
- respiratory features (recurrent respiratory infections)
- failure to thrive affects 50% of CF patients-often as a result of pancreatic insufficiency)

How to diagnose?

- immunoreactive trypsin in neonates
- sweat test
- nasal potential difference testing
- genotype is for diagnosis of children of known carrier parents
- NICE (October 2017) Cystic Fibrosis.



Do differentiate with:

- hypogammaglobulinaemia
- immotile cilia syndromes
- asthma
- coeliac disease
- Shwachmann-Diamond syndrome



Can I treat?

- optimisation of growth
 - delaying the progress of the lung disorder
 - life quality of the patient and their family
-
- heart-lung transplant operation
 - MDT management of complications



**THANKS FOR
LISTENING**

ANY QUESTIONS?

NO? SUPER!

BYE!



LET'S TALK EXAMS



CONTENTS

- CSA Case
- AKT questions

CSA CASE – DOCTORS NOTES

- Shane Dickens, 23years old
- PMHx – Hayfever, hand injury aged 11 years old
- Meds – No current medications
- Allergies – no allergies
- Consultations – no recent consultations
- Investigations – no recent investigations
- Household – no household members registered

OPENING/INFORMATION GATEHRING

- Open question – why is he here?
- *'My brother said I need a colonoscopy for familial adenomatous polyposis.'*
- What would you ask next?
- What information do you need?
- After history of presenting complaint is there anything else you want to know?
- Think about social history!

ICE/INTERPERSONAL SKILLS

- The non hidden 'hidden' agenda
- Shane is worried about Darren's prognosis as you were told the *'surgeons may not have got it all'*
- *'Mum is worried it'll affect me too'* She is wondering whether it affected grandmother and father ?affected his suicide.
- Shane feels anxious and is not sleeping well. He has started smoking more cannabis.

FAMILIAL ADENOMATOUS POLYPOSIS/MANAGEMENT

- How would you explain it to patients?
- Due to APC gene = tumour suppressor gene -> mutations cause a non functioning protein. Most common type is autosomal dominant.
- Development of benign adenomas throughout the colon -> risk of malignant transformation – 7% at age 21, 87% at age 45, 93% by age 50.
- Diagnosis by genetic testing or on colonoscopy.
- Management – often requires prophylactic colectomy +/- removal of rectum. This is indicated if >100 polyps, several dysplastic polyps, multiple polyps >1 cm. Often this is before 25 years.

CONSULTATION MODELS


- Neighbour (1987) – five part model:
 - Connecting = rapport building, data gathering
 - Summarising
 - Handing over = negotiate and agree management plan
 - Safety netting = this is what I expect, this is how you will know if I'm wrong and this is what you should do if so
 - Interpersonal skills = throughout consultation
- FOCUS model
 - Filter Opportunity Context Unite Safety net

MARKING SCHEME FOR CSA

- 3 domains for each station, 13 stations
- Each domain is equally weighted:
 - Data gathering
 - Clinical management
 - Interpersonal skills

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AKT QUESTIONS




A 25-year-old woman is consulting you for a repeat of her oral contraceptive. As she leaves, she mentions that she was watching a programme about bowel cancer and is concerned about her own risk. Her father died as a result of bowel cancer. On questioning, there is no other family history of colorectal cancer. However, she says that her paternal grandmother also died from some form of cancer.

- **Which type of cancer in her paternal grandmother would be of most significance in increasing her bowel cancer risk? Select ONE option only.**
- A. Endometrial cancer
- B. Cervical cancer
- C. Bronchial cancer
- D. Breast cancer
- E. Thyroid cancer

A: ENDOMETRIAL CANCER

- This link may be due to hereditary non-polyposis colorectal cancer (HNPCC) but in the majority of patients a genetic disorder is not found. HNPCC is estimated to be responsible for 2–5% of colorectal cancers.
- HNPCC (Lynch syndrome): early onset of bowel cancer Associated with non-colorectal cancers, including cancers of the endometrium, ovaries, stomach, pancreatobiliary system and urinary tract.
- Prophylactic surgery may be recommended.




Mohammad is a 35-year-old delivery van driver who presents with non-specific weakness. His past history is unremarkable. His father died in Iran in his 50s, after a long but obscure illness. His handshake feels unusual, and you are struck by his prematurely aged appearance with frontal baldness, ptosis and wasting of his shoulder muscles.

- **Which of the following is the SINGLE MOST likely diagnosis? Select ONE option only.**
- A. Becker muscular dystrophy
- B. Duchenne muscular dystrophy
- C. Facio-scapulo-humeral muscular dystrophy
- D. Limb girdle muscular dystrophy
- E. Myotonic dystrophy

E. MYOTONIC DYSTROPHY

- Myotonic dystrophy : the most common muscular dystrophy
Characterised by myotonia and muscular atrophy + cataract formation, hypogonadism, frontal balding, cardiac disorders.
Autosomal dominant, Onset between 15 and 40 years of age
- Duchenne and Becker's muscular dystrophy are X-linked.
Duchenne muscular dystrophy : aggressive, presents in the first five years of life and usually leads to death by the age of 20 years.
- Facio-scapulo-humeral muscular dystrophy: autosomal dominant. Weakness is predominantly facial, periscapular and humeral.
- Limb girdle dystrophy: autosomal recessive or polygenic mode of inheritance. Progressive symmetrical atrophy and weakness of muscles of proximal limbs, girdles and trunk, with sparing of facial muscles.



A woman of Cypriot origin is known to be a carrier of the variant gene for thalassaemia. Her future husband has been tested and is free of the variant. She wishes clarification on the various risks to a future child.

- **In each pregnancy, what is the probability of producing a healthy carrier offspring? Select ONE option only.**
- A. 0%
- B. 25%
- C. 50%
- D. 75%
- E. 100%



C: 50%

- The thalassemias are autosomal recessive conditions.
- When only one partner carries a gene variant, he or she can pass on to a child either the normal gene or the gene variant.
- Each child, therefore, has a 1:2 (50%) chance of inheriting the variant and being a healthy carrier. None of the children can have a serious haemoglobin disorder.
- Each child will also have a 50% chance of carrying the normal gene.



In which ONE of the following relatives is a history of breast cancer LEAST likely to predict a woman's risk of breast cancer? Select ONE option only.

- A. Aunt
- B. First cousin
- C. Half-sister
- D. Mother
- E. Niece



B: Cousin

- A cousin is a third degree relative whereas the others are first or second degree

A 22-year-old woman comes to see you for a routine review of her depression. She usually wears make up but today she has not got any make up on and you notice some odd freckling of her lips. On further questioning, her brother apparently has similar signs. Their father died from bowel cancer several years ago but she knows very little more about him or his family as her parents separated when she was very young.

• **What is the SINGLE MOST likely cause of this patient's signs? Select ONE option only.**

- A. Malignant melanoma
- B. Amalgum tattoo
- C. Peutz–Jeghers syndrome
- D. Kaposi's sarcoma
- E. Addison's disease



C. PEUTZ–JEGHERS SYNDROME

- Rare autosomal dominant inherited disease
- Characterised by gastrointestinal polyps in association with pigmentation affecting skin and mucous membranes.
- Specialist referral is required to ensure appropriate bowel screening is in place and for genetic counselling.



A 42-year-old man with Huntington's disease attends for advice. He has one 14-year-old son and wants to know the chance that his son has inherited the disease.

- **What is the chance that his son will be affected? Select ONE option only.**
- A. 0%
- B. 25%
- C. 75%
- D. 50%
- E. 100%



D: 50%

- Huntington's disease has an autosomal dominant pattern of inheritance, with each child having a 50% chance of inheriting the gene and subsequently the disease.



A 24-year-old woman who had done an early pregnancy test, has recently suffered a miscarriage at six-weeks gestation. She wishes to discuss why this might have happened.

- **What percentage of early spontaneous abortions are caused by chromosomal abnormalities? Select ONE option only.**
- A. 10%
- B. 20%
- C. 40%
- D. 60%
- E. 80%



D: 60%

- Chromosomal abnormalities account for 60% of spontaneous abortions occurring in the first seven weeks.
- The proportion decreases as pregnancy progresses



A 30-year-old man has a total cholesterol of 7.6 mmol/L and a low-density lipoprotein cholesterol (LDL-C) of 5 mmol/L.

- **According to the Simon Broome diagnostic criteria for definite familial hypercholesterolaemia, what additional feature is required? Select ONE option only.**
- A. Arcus senilis
- B. Diffuse plane xanthomatosis
- C. Eruptive xanthoma
- D. Palpebral xanthelasma
- E. Tendinous xanthoma



E. TENDINOUS XANTHOMA

- The Simon Broome criteria, which include a combination of family history, clinical signs (specifically tendon xanthomata), cholesterol concentration and DNA testing.
- Healthcare professionals should offer all people with FH a referral to a specialist with expertise in FH, for confirmation of the diagnosis and the initiation of cascade testing.



Following routine neonatal screening and mutation analysis, a 28-day-old baby has been diagnosed with suspected cystic fibrosis (CF). He has been referred to a specialist unit for clinical assessment.

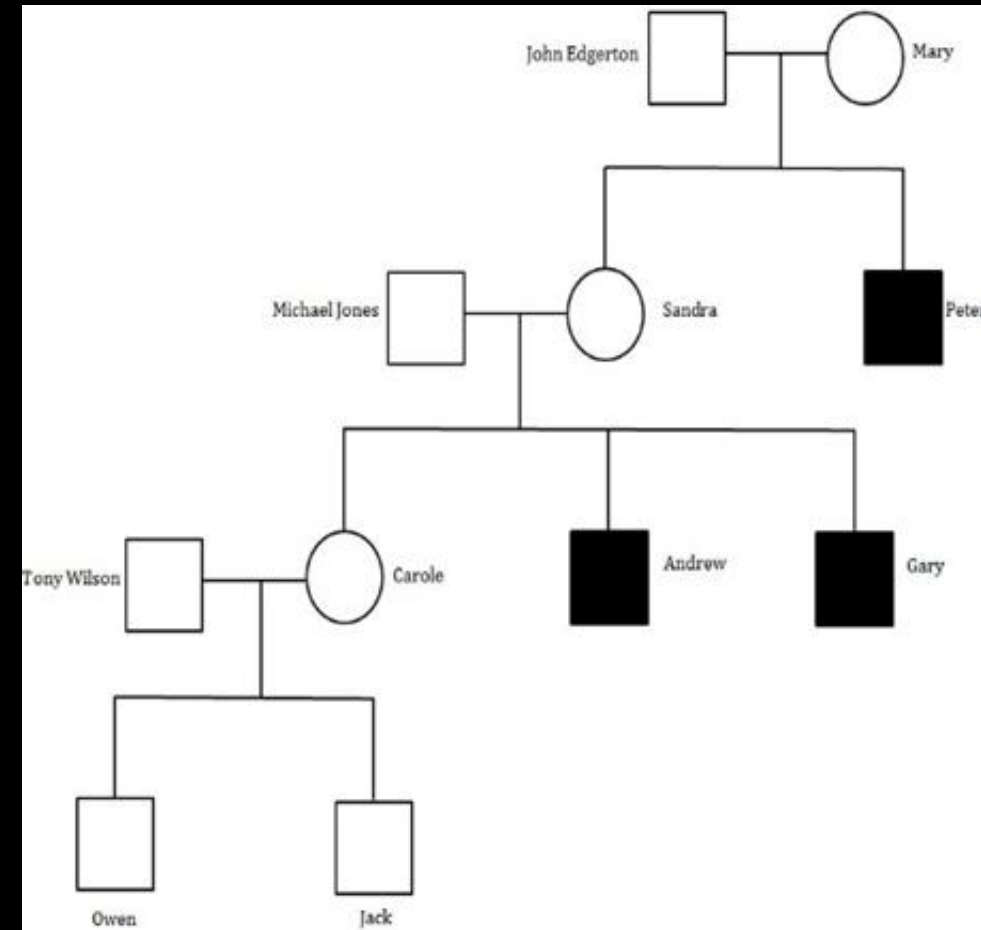
- **Which one of the following additional tests is recommended to confirm the diagnosis of cystic fibrosis? Select ONE option only.**
- A. Chest X-ray
- B. Faecal elastase
- C. Liver function tests (LFTs)
- D. Nasal transepithelial potential difference
- E. Sweat test

E. SWEAT TEST

- The neonatal bloodspot screening programme, performed within the first 10 days of life, allows for early diagnosis and treatment of CF.
- The neonatal bloodspot is tested using the immunoreactive trypsin (IRT) assay. A positive IRT test is not diagnostic; it only identifies infants at risk and requires further specialist confirmatory testing. This includes a positive sweat test and two-stage mutation analysis of the CFTR gene.

The following statements may or may not be correct:

- A. Mary Edgerton is a carrier of haemophilia
 - B. Carole Wilson (nee Jones) cannot be a carrier
 - C. John Edgerton is a carrier of haemophilia
 - D. Sandra Jones (nee Edgerton) must be a heterozygote
 - E. Andrew Jones is not a carrier of the haemophilia gene
- **Which one of the below answers is TRUE? Select ONE option only.**
-
- A. Statements A, C and D are all true – all the other statements are false
 - B. Statements A, D and E are all true – both the other statements are false
 - C. Statement A is false – all the other statements are true
 - D. Statements A, C and D are all false – all the other statements are true
 - E. Statement A is true – all the other statements are false



D. APOLIPOPROTEIN E (APO E4)

- BRCA1: increases the risk of breast cancer
- APC: codes for adenomatous polyposis
- Dystrophin gene: can cause Duchenne's muscular dystrophy.
- HFE gene: can cause haemochromatosis.



USEFUL RESOURCES

- The NHS national genetics and genomics education centre
- - Genetics conditions factsheets
- Contact a Family
- Unique
- E-GP course on Genetics in Primary Care
- UK National Screening committee

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THANK YOU



PHENYLKETONURIA

- Error of amino acid metabolism
- High plasma concentrations of phenylalanine = formation of neurotoxic byproducts
- If untreated: general learning disability and progressive developmental delay
- Generally treatable via dietary manipulation
- Part of heel prick blood test for newborns
- Marked variation between ethnic groups
- Excellent long term outlook



A 70-year-old man attends to discuss his wife's Alzheimer's disease.

Which GENE has been shown to influence the development of Alzheimer's disease? Select ONE option only.

- A. Dystrophin
- B. Adenomatous polyposis coli (APC)
- C. Breast cancer susceptibility gene (BRCA1)
- D. Apolipoprotein E (APO E4)
- E. Human factors engineering (HFE)

- John has a three-year-old son, Ben, and his partner, Julia, is pregnant with their second child. John's mother has Huntington's disease (HD) but John has had genetic counselling and opted not to be tested to see if he too is likely to develop HD. Julia comes to a routine appointment with you and asks if Ben can be referred for testing for HD and also whether her unborn child could have antenatal testing for the condition as well.

- **In this situation, what is the SINGLE MOST appropriate advice to give to Julia? Select ONE option only.**
- A. Both Ben and the unborn child can be tested for HD but only with both parents' permission
- B. Both Ben and the unborn child can be tested for HD without their father's permission
- C. Ben alone can be tested for HD but only with both parents' permission
- D. The unborn child alone can be tested for HD without its father's permission
- E. Ben alone can be tested for HD without his father's permission

D. The unborn child alone can be tested for HD without its father's permission

- Parents are decision makers for their children's therapeutic treatment
- But they do not have authority over nontherapeutic interventions, including genetic testing.
- There is currently no cure or intervention that will alter HD's development or progress. Therefore, testing Ben now will not alter whether or not he develops the disease or its severity.
- But it will remove his autonomy to make his own decision about whether or not he wishes to be tested when he is old enough to make that decision for himself.
- The decision to test should be deferred until children are competent to weigh up the pros and cons of testing for themselves.
- Paradoxically, the situation is different for the unborn child. The fetus is considered to be part of its mother and therefore she has the right to choose to test without the father's permission. Furthermore, testing might influence her antenatal choices as she might choose to have a termination if the fetus carried the gene for HD.

- Which ONE of the following statements is true?

- A. For a given autosomal dominant condition the chances of an offspring inheriting the condition is 75%
- B. For a given autosomal recessive condition the chances of unaffected offspring being a carrier is 25%
- C. Female carriers of X-linked disorders sometimes exhibit symptoms of that disorder
- D. Conditions which are lethal in early childhood are most commonly autosomal dominant
- E. X-linked dominant conditions are more common than X-linked recessives

C: FEMALE CARRIERS OF X-LINKED DISORDERS SOMETIMES EXHIBIT SYMPTOMS OF THAT DISORDER

- X-linked dominant conditions are less common than X linked recessive
- Autosomal recessive: 25% chance child developing the disease. There is a 50% chance of a child inheriting only one abnormal gene and of being a carrier
- Autosomal dominant: 50% chance of offspring inheriting the condition.
- Autosomal dominant traits generally tend to be less severe than autosomal recessive traits
- Female carriers of X-linked conditions are not typically affected by the condition, however they can have a normal X chromosome that is abnormally inactivated. They may have symptoms similar or milder to those of affected males.