Genetics Questions:
Answers
Discussion
Key Learning Points
Question One

Cystic fibrosis: Sibling carrier risk.

Carol and Frank present to you at 10 weeks gestation. Carol's brother has cystic fibrosis and the couple have come to you as they are concerned that their baby may inherit the disease.

What mode of inheritance does CF have?

What is the risk of Carol being a carrier?

What is the risk of Frank being a carrier?

What is the risk of the baby being affected by the condition?

What proportion of genes do we share with our first cousin?

What is the risk of a recessive condition in first cousin marriages?
Question One Model Answers

Cystic fibrosis: Sibling carrier risk.
Carol and Frank present to you at 10 weeks gestation. Carol’s brother has cystic fibrosis and the couple have come to you as they are concerned that their baby may inherit the disease.

What mode of inheritance does CF have?
Autosomal recessive

What is the risk of Carol being a carrier?
2/3 (67%) - as she is unaffected and her parents are both carriers

What is the risk of Frank being a carrier?
¼ - one of the partner’s grandparents must have been a mutation carrier as his aunt is a carrier. This means the partner’s father has a 50% chance of being a carrier. If the partner’s father does carry the gene he will only pass this on to half of his children. The chance of the partner himself being a carrier is ½ (the risk of his father being a carrier) x ½ (the risk of the gene being passed on) = ¼ (25%)

What is the risk of the baby being affected by the condition?
1/24 – the risk of the mother being a carrier as above is 2/3, the risk of the father being a carrier as above is ¼, if both parents happen to be carriers the risk of the baby getting both defective genes is ¼. Therefore the risk of the baby actually getting the condition is 2/3 x ¼ x ¼ = 1/24.

What proportion of genes do we share with our first cousin?
1/8 (12.5%) – siblings share half (50%) of their genes, each sibling will pass down half of these genes to their children (1/4, 25% of the original set), therefore children who are cousins share 1/8 of their genes.

What is the risk of a recessive condition in first cousin marriages?
3%, 3 in 100. When added to the baseline risk of a congenital defect in the general population of 2-3% the overall risk of a congenital defect with first cousins is around 6% - this is still a 94% chance of a normal baby. The risk of a baby having a recessive condition is higher than this when the parents of the couple and grandparents are also blood relatives and when there is a family history of a recessive condition.

Key learning points

First cousins share 1/8 of alleles in common on average so there is an increased risk of autosomal recessive conditions.

Cystic fibrosis is a common autosomal recessive condition with a carrier frequency of around 5%.

If both parents are carriers of an autosomal recessive condition an unaffected child has a 2 in 3 chance of being a carrier.

If both parents are carriers of an autosomal recessive condition there is a 1 in 4 chance of them having an affected child.

Virtual Genetics Education Centre: http://www.le.ac.uk/ge/genie/vgec/index.html
Question One Medical Discussion

A  Where these patients might be seen
   General practice, obstetrics, fetal medicine, paediatrics.

B  Patient outcome in this case
   Both parents were tested and were found to be carriers. An amniocentesis was carried out and no mutation was identified in the fetus. The parents were reassured that the fetus was at low risk of developing cystic fibrosis.

C  Red flags
   Common presentations of children with cystic fibrosis include:
   - Meconium ileus (about 10% of CF cases).
   - Recurrent chest infections.
   - Chronic cough.
   - Failure to thrive.
   - Gastrointestinal problems including constipation, diarrhoea, steatorrhoea.
   - Prenatal diagnosis.

D  Differential diagnosis
   - Hypogammaglobulinaemia which may present with recurrent infection.
   - Immotile cilia syndromes associated with situs inversus and/or sinusitis.
   - Asthma.
   - Coeliac disease presenting with diarrhoea, steatorrhoea and failure to thrive.
   - Schwachmann-Diamond syndrome. A rare (1 in 200,000) autosomal recessive disorder which can present with gastrointestinal symptoms due to pancreatic insufficiency, failure to thrive and immunodeficiency.
Question Two

Breast Lump

Barbara is a 36 year old lady who presents with a breast lump. Her mother had ovarian cancer at the age of 43 and a maternal aunt had breast cancer at the age of 40. Barbara has heard that some breast cancer can run in families and as she has Jewish ancestry, she was wondering if this might be the case in her family.

Is there likely to be a genetic inherited component to this pedigree?

Which genes could be involved / responsible?

Is the Jewish ancestry likely to be relevant?

What is the likelihood of this lady being a mutation carrier?

What factors need to be taken into consideration to calculate the risk of this lady developing breast cancer?
Question Two Model Answers

Breast Lump
Barbara is a 36 year old lady who presents with a breast lump. Her mother had ovarian cancer at the age of 43 and a maternal aunt had breast cancer at the age of 40. Barbara has heard that some breast cancer can run in families and as she has Jewish ancestry she was wondering if this might be the case in her family.

Is there likely to be a genetic inherited component to this pedigree?
Yes: things which point towards an inherited component are –
- Relative with breast cancer before the age of 45
- Relative with ovarian cancer
- Affecting multiple relatives possibly in more than one generation if Barbara is found to have breast cancer.

Which genes could be involved / responsible?
Only 5% of breast cancer can be attributed to known highly penetrant dominant genes. The most important and most well known are the BRCA genes: BRCA1 on chromosome 17q and BRCA2 on chromosome 13q. BRCA1 gives a lifetime risk of breast cancer of around 80% with a lifetime risk of ovarian cancer of between 40-60%. BRCA2 is associated with a lower risk than that of BRCA1 but has also been associated with an increased risk of other cancers. Mutations in the TP53 gene on chromosome17p also increase risk. Mutations in CHEK2 may double the risk. There are other genes which can be involved and many more which have not yet been discovered.

Is the Jewish ancestry likely to be relevant?
Yes – 1 in 40 Ashkenazi Jews carry a founder mutation in either BRCA1 or BRCA2

What is the likelihood of this lady being a mutation carrier?
Given one case of breast cancer and one case of ovarian in the family there is a 30% chance that a BRCA gene mutation may be responsible. Using the BRCA risk calculator http://www.myriadtests.com/provider/brca-risk-calculator.htm, if her family are Ashkenazi Jewish the risks are 27% and 51% with or without a personal diagnosis of breast cancer respectively.

What factors need to be taken into consideration to calculate the risk of this lady developing breast cancer?
This woman is at high risk based on family history alone and needs referral to a genetics clinic. The fact that she has a history of breast and ovarian cancer along with her Jewish ancestry suggests that she should be referred to a Clinical Genetics Unit.

Key learning points
It is important to take a detailed family history in women presenting with breast lumps. This should include first, second and third degree relatives and involve inquiry into ALL types of cancer in the family, not just breast.

BRCA1 gives a lifetime risk of breast cancer of 80% and a lifetime risk of ovarian cancer of 40-60%.
| Prophylactic surgery can be offered to women with known BRCA mutations. This dramatically reduces their chance of breast or ovarian cancer. However the risks and benefits of this need to be looked into on an individual basis for each woman. |
Question Two Medical Discussion

A  Where these patients might be seen

Oncology, general practice, gynaecology, breast surgery, palliative care.

B  Patient outcome in this case

The histology report came back as benign, however a BRCA 1 mutation was identified. Barbara then came back to discuss the pros and cons of preventative breast and ovarian surgery. At this point she has decided to continue with her normal screening.

C  Red flags

It is good practice to follow the NICE guidelines: http://www.nice.org.uk/Guidance/CSG
Question Three

Joint Pain

Harry is a 43 year old man who presents with joint pains. He is a diabetic and was treated for erectile dysfunction last year. He appears tanned. His sister is currently being investigated for cirrhosis.

What are the secondary causes of osteoarthritis?

What are the secondary causes of diabetes?

What are the secondary causes of cirrhosis?

What are the causes of tanned skin without sun exposure?

What is the most likely underlying diagnosis given his sister’s cirrhosis?

Which chemical pathology tests would you recommend?

What is the most likely gene mutation associated with this condition?

What is the mode of inheritance in this condition?
Question Three Model Answers

Joint Pain

A 43 year old man presents with joint pains. He is a diabetic and was treated for erectile dysfunction last year. He appears tanned. His sister is currently being investigated for cirrhosis.

What are the secondary causes of osteoarthritis?
- Infection, RA, gout, alkaptonuria
- Previous fracture, Paget’s disease and aseptic necrosis
- Acromegaly, haemochromatosis

What are the secondary causes of diabetes?
- Gestational (not in this case)
- Pancreatic: pancreatitis, cystic fibrosis and haemochromatosis
- Endocrine: acromegaly, cushing’s syndrome, glucagonoma and phaeochromocytoma
- Steroids, thiazides and phenytoin
- Huntingtons, DIDMOAD/ Wolfram syndrome, Prader-Willi syndrome and Laurence-Moon-Biedl syndrome

What are the secondary causes of cirrhosis?
- Alcohol
- Hepatitis
- Haemochromatosis, wilsons disease and alpha-1-antitrypsin deficiency
- Biliary cirrhosis
- Hepatic venous outflow obstruction
- Methotrexate and amiodarone

What are the causes of skin hyperpigmentation?
- Familial / racial
- Irradiation / sun exposure
- Endocrine: hypoadrenalism, cushing’s syndrome with high ACTH, acromegaly and high oestrogen levels
- Systemic disease: chronic renal failure, primary biliary cirrhosis and haemochromatosis
- Cytotoxics, phenothiazines and arsenic

What is the most likely underlying diagnosis given his sister’s cirrhosis?  
Haemochromatosis

Which chemical pathology tests would you recommend?  
Ferritin, TIBC, Iron binding saturation, Blood film
What is the most likely gene mutation associated with this condition?
It is very common to carry these gene mutations. Up to 1 in 10 people carry them. Not everyone that is homozygous for the gene mutation will go on to develop haemochromatosis. HFE gene mutation, most common are C282Y and H63D, and these account for the most common mutations in haemochromatosis. HFE gene is on 6p31.3

What is the mode of inheritance in this condition?
Autosomal recessive

Key learning points

Haemochromatosis is a common condition which may present as a number of other common conditions.

Haemochromatosis is relatively easy to treat and a missed diagnosis can have catastrophic consequences for the health of that individual.
Question Three Medical Discussion

A  Where these patients might be seen
Rheumatology, haematology, hepatology and general practice.

B  Patient outcome in this case
Harry and his sister both went on to have testing for haemochromatosis, they were both found to have the disease. Their diagnosis allowed other family members to be tested too. Both Harry and his sister are now having regular phlebotomy to reduce iron stores.

C  Red flags
- **Cirrhosis:** 30% of patients with cirrhosis develop hepatomas with a 200 times increased risk of hepatocellular carcinoma.
- **Bronzed appearance:** Due to melanin.
- **Impaired glucose tolerance:** 80% of symptomatic patients.
- **Diabetes mellitus:** 50% of symptomatic patients.
- **Degenerative arthritis:** Usually MCP and PIP, large joints such as knees.
- **Cardiac involvement:** 10% of symptomatic patients - arrythmias or progressive cardiomyopathy.
- **Hypogonadotrophic hypogonadism:** Causing loss of libido and impotence.

D  Differential diagnosis
This may be a series of unrelated conditions.
Question Four

Recurrent Miscarriage

A 32 year old woman and her partner present with recurrent miscarriages. She has had four confirmed pregnancies with miscarriages between 6-10 weeks. Her mother also had two miscarriages. The maternal sister has profound learning difficulties.

What is the definition of recurrent miscarriage?

What are the causes of recurrent miscarriages?

Given the maternal sisters learning difficulties what is the most likely underlying diagnosis?

What investigations would you recommend?

What can be done to reduce the risk of further miscarriages or birth of a child with learning difficulties?
Question Four Model Answers

Recurrent Miscarriage
A 32 year old woman and her partner present with recurrent miscarriages. She has had four confirmed pregnancies with miscarriages between 6-10 weeks. Her mother also had two miscarriages. The maternal sister has profound learning difficulties.

**What is the definition of recurrent miscarriage?**
*Three or more consecutive miscarriages occurring at less than 20 weeks gestation.*

**What are the causes of recurrent miscarriages?**
- Chromosomal translocations in parents
- Uterine abnormalities, cervical incompetence
- Severe chronic disease
- Thrombophilia, e.g. antiphospholipid syndrome
- PCOS, hypo or hyperthyroidism, hyperprolactinaemia

**Given the maternal sisters learning difficulties what is the most likely underlying diagnosis?**
*Parental chromosomal abnormality, namely a balanced translocation in the woman. This is most likely given her mother also had miscarriages and her sister has learning difficulties which may well be symptomatic of an unbalanced translocation.*

**What investigations would you recommend?**
- Karyotype of both parents and miscarriage products if available
- Pelvic ultrasound scan to exclude abnormal uterine anatomy.
- Bloods: full blood count, thyroid function tests, prolactin, anticardiolipin antibodies and lupus anticoagulant +/- thrombophilia screen.

**What can be done to reduce the risk of further miscarriages or birth of a child with learning difficulties?**
*If a balanced translocation is identified in either of the parents then they can be offered prenatal testing – usually chorionic villus sampling. This would enable detection of the translocation in current pregnancy so that the risk to the fetus is known. If this test reveals an unbalanced translocation in the fetus the parents are then able to make the decision to end the pregnancy if they want. Sometimes preimplantation genetic diagnosis may be offered especially in women who have not been able to have any unaffected children. Aspirin taken during pregnancy has also been suggested to reduce the risk of recurrent miscarriage.*

**Key learning points**
*It is important to ask about a family history of miscarriage or learning disability in women presenting with recurrent miscarriages.*

*Around 1 in 10 cases of recurrent miscarriage will be due to a balanced translocation.*

Virtual Genetics Education Centre: [http://www.le.ac.uk/ge/genie/vgec/index.html](http://www.le.ac.uk/ge/genie/vgec/index.html)
Question Four Medical Discussion

A Where these patients might be seen

Obstetrics, gynaecology, general practice and paediatrics.

B Patient outcome in this case

The mother was found to carry a balanced chromosomal translocations between chromosomes 3 and 8. The parents opted for prenatal testing and amniocentesis was carried out at 16 weeks gestation. An unbalanced rearrangement was detected and the couple decided to terminate the pregnancy.

C Red flags

Signs of a translocation:

- Recurrent miscarriage
- Family history of learning difficulties
- Family history of miscarriage

D Differential diagnosis

Inherited unbalanced chromosomal translocation
Antiphospholipid syndrome
Polycystic ovarian syndrome
Maternal severe chronic disease
Uterine abnormalities.
Cervical incompetence
Question Five

Collapse

A 25 year old man presents to accident and emergency on a Saturday afternoon after collapsing while playing basketball. He has sharp central chest pain, a weak left radial pulse and a mild pectus excavatum. His grandfather died from a suspected heart attack while pushing his car in Africa last year.

What other examination points might help to confirm a genetic cause for his current problem?

What is the cause of the weak left radial pulse?

What is the pattern of inheritance for this condition?

Which gene is affected and on which chromosome is it?

What is the main differential for this condition and how might you distinguish the two conditions?
Question Five Model Answers

Collapse

A 25 year old man presents to accident and emergency on a Saturday afternoon after collapsing while playing basketball. He has sharp central chest pain, a weak left radial pulse and a mild pectus excavatum. His grandfather died from a suspected heart attack while pushing his car in Africa last year.

What other examination points might help to confirm a genetic cause for his current problem?
- **Musculoskeletal:** arm span more than height, scoliosis, joint laxity, high arched palate.
- **Cardiovascular:** mitral valve prolapse, aortic regurgitation, signs of aortic rupture or dissection.
- **Lens subluxation.**

What is the cause of the weak left radial pulse?
*Aortic dissection.*

What is the pattern of inheritance for this condition?
*Autosomal dominant*

Which gene is affected and on which chromosome is it?
*Fibrillin (FBN1) gene on chromosome 15*

What are the main differentials for this condition and how might you distinguish them?
*Marfans: Examination points as above. Homocystinuria. Downward dislocation of the lens rather than sideways as seen in Marfans. Joint abnormalities are similar to Marfans. Homocystinuria is less likely to show heart disease but more likely to show learning difficulties, thrombophilia and osteoporosis. There should be a positive urine cyanide-nitroprusside test.*

*Ehlers Danlos syndrome: Joint laxity and aortic dissection or rupture can occur. These patients can have abnormal papyrus scarring and may have orthopaedic deformity including scoliosis. They are less likely to present with lens dislocation.*

**Key learning points**

- Marfan syndrome can present with severe cardiac problems.
- Marfan syndrome can present in a very similar way to Homocystinuria and Ehler Danlos syndrome.
- Young people can present with life-threatening cardiac problems.
Question Five Medical Discussion

A  Where these patients might be seen
   A & E, General practice, cardiology, rheumatology, physiotherapy.

B  Patient outcome in this case
   Aortic dissection was identified on ECHO. He went on to have an emergency graft
   and aortic valve replacement. A mutation in the fibrillin gene was later detected.

C  Signs and symptoms of an aortic dissection:
   Chest pain:
   Sudden, severe, tearing or pulsating pain.
   Radiates to back or left shoulder.
   Greater than 20mmHg difference in blood pressure between arms.
   Sweating and pallor.
   Prominent arterial pulsation in the neck.
   Aortic regurgitation.
   Sometimes neurological signs – e.g. stroke, horners.

D  Differential diagnosis

   Differential diagnosis of Marfans: homocystinuria, Ehlers Danlos syndrome.

   Differential diagnosis of aortic dissection: acute coronary syndrome, myocarditis,
   pulmonary embolism, pericarditis, pancreatitis, oesophageal problems.
Question Six

Acne

A 22 year old woman makes an appointment at the GPs to discuss her acne. She has also noticed that light patches have appeared on her arm after a recent holiday in Spain. She has a history of epilepsy. Her mother has recently been diagnosed with a renal cell carcinoma.

What is the underlying diagnosis?

What is the cause of her facial rash?

How would you examine her skin more closely?

What screening would you recommend?
Question Six Model Answers

Acne

A 22 year old woman makes an appointment with her GP to discuss her acne. She has a history of epilepsy. She has noticed that light patches have appeared on her arm after a recent holiday in Spain. Her mother has recently been diagnosed with a renal cell carcinoma.

What is the underlying diagnosis?
_Tuberous sclerosis_

What is the cause of her facial rash?
_Adenoma sebaceum_

How would you examine her skin more closely?
_Examine with a Woods lamp to identify oval hypopigmented areas (ash leaf macules. A shagreen patch may be seen over the sacrum and there may be periungual fibromas. Café au lait spots can be seen but are less specific to this condition._

What screening would you recommend?
- _Brain imaging to detect tubers or calcification_.
- _Renal ultrasound to detect any renal lesions_.
- _Echocardiogram if there is clinical suspicion of a cardiac rhabdomyoma which occur in up to 50% of cases_.
- _Ophthalmology review_.

**Key learning points**

Tuberous sclerosis can present with a variety of signs and symptoms ranging from mild to severe.

The phenotype can be extremely variable even in the same family so a Woods light and an understanding of the dermatological lesions found in this condition are needed.

The variable phenotype makes counselling about the pros and cons of prenatal testing extremely challenging.
Question Six Medical Discussion

A  Where these patients might be seen
   Neurology, endocrinology, paediatrics, general practice.

B  Red flags
   Signs and symptoms suggesting tuberous sclerosis:
   A triad of:
   a. Epilepsy – especially infantile spasms.
   b. Learning difficulties in approximately 50%.
   c. Adenoma sebaceum – pink to red-brown papules, normally found on the
      nose and nasolabial folds.
   Cortical tubers.
   Cutaneous lesions:
   a. Ash leaf macules in 85% - hypopigmented macules.
   b. Shagreen patch – irregularly coarsened skin over the sacrum.
   c. Periungal fibromas.
   d. Gingival fibromas and café au lait spots – uncommon.
   e. Port wine haemangiomas – uncommon.
   Tumours:
   a. Retinal hamartomas in 50%.
   b. Cardiac rhabdomyoma in 50%.
   c. Pulmonary and renal hamartomas.
   d. Periventricular hamartomas and/or intracranial calcification.
   e. Astrocytomas or other malignant brain tumours.
   Cysts in pleura, lungs and peripheral bones.

C  Differential diagnosis
   Epilepsy syndromes
   Brain tumours
   Hydrocephalus
Question Seven

A 12 year old boy

A 12 year old boy is taken to see the paediatric endocrinologist because of obesity, abdominal discomfort and poor behaviour. His father previously had kidney stones and his older sister is being investigated for galactorrhoea.

What are the causes of galactorrhoea in a women with no history of previous pregnancy?

What are the causes of kidney stones?

Which abdominal tumour can cause increased appetite and poor behaviour?

Which syndrome can link all of these things?
Question Seven  Model Answers

A 12 year old boy

A 12 year old boy is taken to see the paediatric endocrinologist because of obesity, abdominal discomfort and poor behaviour. His father previously had kidney stones and his older sister is being investigated for galactorrhoea.

What are the causes of galactorrhoea in a woman with no history of previous pregnancy?

- **Hyperprolactinaemia**
  - Prolactin secreting tumour.
  - Pituitary stalk compression reducing dopaminergic inhibition of prolactin release.
  - Pregnancy.
- **Medications**
  - Antidepressants.
  - COCP, neuroleptics and anti-emetics.

What are the causes of kidney stones?

- **Hypercalciuria**: renal tubular acidosis, acromegaly, cushing’s syndrome and paget’s disease.
- **Hyperoxaluria**: Inherited susceptibility, high oxalate diet, terminal ileal disease and pyridoxine deficiency.
- **Hyperuricaemia**
- **Cystinuria**
- **Schistosomiasis in tropical regions**

Which abdominal tumour can cause increased appetite and poor behaviour?

- **Insulinoma**
- **Cortisol producing adrenal tumours**

Which syndrome can link all of these things?

*Multiple Endocrine Neoplasia type 1*

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**Key learning points**

MEN type 1 causes tumours in the ‘three P’s’: parathyroid, pancreas and anterior pituitary.

Hypercalcaemia, hyperparathyroidism and renal stones may be found in MEN type 1 and 2.

It is important to ask about any medical problems in first degree relatives and to ask about timing of poor behaviour in relation to eating.

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Virtual Genetics Education Centre: [http://www.le.ac.uk/ge/genie/vgec/index.html](http://www.le.ac.uk/ge/genie/vgec/index.html)
Question Seven Medical Discussion

A Where these patients might be seen

Neurology, endocrinology, paediatrics, urology.

B Red flags

Signs and symptoms of MEN1

Parathyroid tumours in 90% leading in some to hyperparathyroidism. Pancreatic tumours in up to 75%.

a. Gastrinoma / Zollinger-ellison syndrome
   i. Abdominal pain
   ii. Diarrhoea
   iii. Ulcer or oesophagitis

b. Insulinomas cause hypoglycaemia.

c. Glucagonoma cause hyperglycaemia.

Pituitary tumours can cause headaches and visual problems.


b. Prolactin secreting – causing amenorrhoea or galactorrhoea.

c. Growth hormone secreting – leading to acromegaly.

d. ACTH secreting – leading to Cushing’s disease.

C Differential diagnosis

Gastroesophageal reflux

Hypercalcaemia from other sources

Isolated endocrine tumours: VIPoma, carcinoid tumour, phaeochromocytoma, parathyroid, pancreatic or pituitary tumours.
Question Eight

Drink driving?

A 42 year old man is brought into accident and emergency by the police after being arrested for drink driving. No alcohol was detected on a breath test. He has slurred speech and appears uncoordinated. His wife had left him after he was diagnosed with depression. His father died from dementia at the age of 53.

What are the causes of chorea?
What are the organic causes of depression?
What are the causes of pre-senile dementia?
What are the autosomal dominant causes of chorea and dementia?
What is the likely diagnosis?
Question Eight Model Answers

Drink driving?
A 42 year old man is brought into accident and emergency by the police after being arrested for drink driving. No alcohol was detected on a breath test. He has slurred speech and appears uncoordinated. His wife had left him after he was diagnosed with depression. His father died from dementia at the age of 53.

What are the possible causes of chorea?
- Huntington disease
- Sydenham’s chorea
- Trauma
- SLE
- Wilson’s disease
- Kernicterus
- Brain tumours
- Drug induced
- Benign hereditary chorea

What are the organic causes of depression?
- Endocrine: hypothyroidism, hyperparathyroidism, Cushing’s and Addison’s.
- Multiple sclerosis.
- Parkinson’s disease
- Alcoholism and substance abuse.

What are the causes of pre-senile dementia?
- Alzheimer’s disease
- Amyotrophic lateral sclerosis
- Lewy body dementia
- Pick disease
- Huntington disease

How could you link in his father’s dementia and what is the likely diagnosis?
Huntington disease

Key learning points
Huntington Disease is caused by an autosomal dominant trinucleotide repeat and is associated with depression and motor disorders.

Huntington Disease has 100% penetrance so if an individual has the gene they will develop the disease.

Huntington Disease shows paternal anticipation. This means that if an individual inherits the gene from their father they are likely to have an earlier onset more severe form than if they had inherited the same gene from their mother.
Question Eight Medical Discussion

A  Where these patients might be seen
  General practice, neurology, psychiatry, social work.

B  Patient outcome in this case
  A diagnosis of Huntington disease was made, confirmed with genetic testing. Two sons went on to have predictive testing.

C  Red flags
  Signs and symptoms suggesting Huntington Disease:
  Involuntary movements or rigidity.
  Choreoform movements: ‘piano-playing motion’ or facial grimaces.
  Off-balance gait but with relative preservation of patient’s ability to balance.
  Irritability or antisocial behaviour.
  Weight loss.
  Depression is often an early feature.
  Dementia.
  Rigidity and seizures in younger patients.

D  Differential diagnosis
  Other causes of chorea as above
  Other causes of depression as above
  Other causes of dementia as above
Question Nine

Hypocalcaemia

A baby in the neonatal ward with a cleft palate starts to fit. The calcium is noted to be low. The father has recently been discharged from a psychiatric hospital with schizophrenia.

What are the causes of neonatal hypocalcaemia?

What are the syndromic causes of a cleft palate?

Which cytogenetic abnormality may be found in bipolar disorders and schizophrenia?

What is the most likely diagnosis?
Question Nine Model Answers

Hypocalcaemia

A baby in the neonatal ward with a cleft palate starts to fit. The calcium is noted to be low. The father has recently been discharged from a psychiatric hospital with schizophrenia.

What are the causes of neonatal hypocalcaemia?
- Sepsis
- Infant of a diabetic mother
- Exchange transfusion
- Preterm delivery, birth asphyxia and respiratory distress syndrome
- Maternal hyperparathyroidism, cow’s milk
- DiGeorge syndrome

What are the syndromic causes of a cleft palate?
- Trisomy 13 or 18
- Pierre-Robin Sequence
- Goldenhar sequence
- EEC syndrome
- Di George syndrome

Which cytogenetic abnormality is linked to bipolar disorder and schizophrenia?
22q11.2 microdeletions

What is the most likely diagnosis?
Di George Syndrome / 22q11 deletion

Key learning points

The majority of the sequelae of 22q11 deletion are treatable in their own right.

Patients with a 22q11 deletion have an increased risk of learning difficulties and mental health issues. A significant proportion of patients develop schizophrenia in late adolescence or adulthood.

22q11 deletion is also referred to as Di George Syndrome and Velocardiofacial Syndrome.
Question Nine Medical Discussion

A  Where these patients might be seen
   Paediatrics, obstetrics.

B  Patient outcome in this case
   The baby was shown to have a 22q11 deletion. The father was later tested and
   was shown to have the same deletion.

C  Red flags
   Signs and symptoms of 22q11 deletion
   Dyssorphic facial features: Long bulbar nose, short philtrum and bifid uvula.
   Thymic hypoplasia with increased susceptibility to infections.
   Congenital heart disease, e.g. truncus arteriosus, septal defects and abnormal
   aortic arch.
   Absent / reduced parathyroid glands.
   Neonatal hypocalcaemia.
   Basal ganglia calcification
   Intellectual impairment.
   Congenital pulmonary abnormalities: e.g. tracheoesophageal fistula and laryngo-
   tracheomalacia or bronchomalacia.

D  Differential diagnosis
   See above
Question Ten

Cataracts

A 36 year old diabetic is seen in the ophthalmology clinic with cataracts. He complains that he finds it difficult moving his hands after carrying bags in cold weather. His mother is in a wheelchair with a muscular dystrophy.

Which disease links cataracts, diabetes and autosomal dominant muscular dystrophy?

Why might this patient be presenting with symptoms earlier than his father?

What should this patient be told about any hospital admissions?
Question Ten Model Answers

Cataracts

A 36 year old diabetic is seen in the ophthalmology clinic with cataracts. He complains that he finds it difficult moving his hands after carrying bags in cold weather. His mother is in a wheelchair with a muscular dystrophy.

Which disease links cataracts, diabetes and autosomal dominant muscular dystrophy?

Myotonic Dystrophy

Why might this patient be presenting with symptoms earlier than his father?

Myotonic Dystrophy is a classic example of maternal anticipation of a tri-nucleotide repeat expansion disorder. This means that progressive generations will have a more severe and earlier onset disease, especially down the maternal line. Very large expansions can result in congenital myotonic dystrophy.

What should this patient be told about any hospital admissions?

There is an increased risk of arrhythmias with anaesthetic and he may have problems with reversal of muscle relaxants. Anaesthetist needs to be informed of diagnosis.

Key learning points

These patients have an increased risk of arrhythmia with anaesthetic and may have problems recovering from muscle relaxants.

Myotonic Dystrophy is a classic example of maternal anticipation of a tri-nucleotide repeat expansion disorder. This means that progressive generations will have a more severe and earlier onset disease, especially down the maternal line. Very large expansions can result in congenital myotonic dystrophy.
Question Ten Medical Discussion

A  Where these patients might be seen  
General practice, neurology, endocrinology, ophthalmology.

B  Red flags  
*Signs and symptoms of myotonic dystrophy:*  
Myotonia  
Facial features:  
  a. Frontal baldness  
  b. Wasting of facial and sternocleidomastoid muscles  
  c. Cataracts  
Limb features:  
  a. Patient is unable to release examiners hand after gripping.  
Intellectual impairment  
Cardiac arrhythmias which may very rarely cause sudden death.  
Diabetes mellitus.  
Infertility and recurrent miscarriages.

C  Differential diagnosis  
*Differentials for cataracts in a young adult:*  
Trauma, infection or surgery  
Excess UV light exposure  
Diabetes  
Medications: e.g. steroids, statins, phenothiazines

*Differentials for muscle weakness in a young adult:*  
Myotonic dystrophy  
Beckers  
Emery-Dreifuss  
Limb girdle muscular dystrophy  
Spinal muscular atrophy  
Myasthenia gravis
Question Eleven

Multiple fractures

A two year old child is brought into the fracture clinic with a fracture of the right radius and ulna. Other older fractures have also been observed. The mother claims she had numerous fractures due to horse riding as a teenager. On examination her sclerae are blue and teeth enamel is poor.

What are the causes of multiple fractures of different ages?

What conditions can cause blue sclera?

What makes the sclera blue?

Is the poor enamel linked to the other signs?

How is this condition inherited?

What tests could help make a diagnosis?
Question Eleven Model Answers

Multiple fractures

A two year old child is brought into the fracture clinic with a fracture of the right radius and ulna. Other older fractures have also been observed. The mother claims she had numerous fractures due to horse riding as a teenager. On examination her sclerae are blue and teeth enamel is poor.

What are the causes of multiple fractures of different ages?
- Non-accidental injuries
- Osteogenesis imperfecta

What conditions can cause blue sclera?
- Osteogenesis imperfecta
- Ehlers Danlos syndrome
- Pseudoxanthoma elasticum
- Marfans syndrome
- Corticosteroids

What makes the sclera blue?
Sclerae are thinner than normal allowing the underlying epithelium to show through.

Is the poor enamel linked to the other signs?
Yes, dentinogenesis imperfecta can occur with patients having small blue-yellow, misshapen teeth, presence of this determines the subtype of osteogenesis imperfecta.

How is this condition inherited?
Autosomal dominant

What tests could help make a diagnosis?
Skeletal survey may show thinning of the cortices of long bones with wormian bones in mild cases. Moderate cases may show cysts or a popcorn appearance of the growth cartilage. Severe cases may show beaded ribs, broad bones, fractures and bone deformities.
DEXA scan usually shows low bone mineral density.

Key learning points
Non-accidental injury MUST be considered when a child presents with multiple fractures of different ages.
Question Eleven Medical Discussion

A  Where these patients might be seen
   A & E, paediatrics, orthopaedics, dentistry, social work.

B  Patient outcome in this case
   Skeletal survey was performed and showed characteristic changes of osteogenesis imperfecta.

C  Red flags
   Signs and symptoms of mild osteogenesis imperfecta.
   Multiple fractures after minor trauma.
   Blue sclera
   Easy bruising.
   Deafness – 50% by age 40
   Poor dental enamel.
   Kyphoscoliosis.

   Signs and symptoms of non-accidental injury
   Abnormal bruising, burns or scalds, fractures or bites.
   Inconsistent history with a delayed presentation - e.g. 4 week old rolled off the bed.
   Abnormal interaction between child and caregivers.

D  Differential diagnosis
   Differentials for multiple fracture:
     o  Non-accidental injury is an important diagnosis to rule out
Question Twelve

Prenatal diagnosis

A 24 year old woman is eight weeks pregnant. Her maternal uncle died of a ‘progressive muscle wasting disease’ in his twenties. She brings a death certificate stating her uncle died of Duchenne Muscular Dystrophy (DMD). Her mother has a cardiomyopathy and does not want to know if she is a carrier.

What features in the history suggest that DMD is the correct diagnosis?

Give three investigations which can help confirm a diagnosis of DMD?

What is the risk of the baby developing this condition?
Question Twelve Model Answers

Prenatal diagnosis

A 24 year old woman, Mrs F is eight weeks pregnant. Her maternal uncle died of a ‘progressive muscle wasting disease’ in his twenties. She brings a death certificate stating her uncle died of Duchenne Muscular Dystrophy (DMD). Her mother has a cardiomyopathy and does not want to know if she is a carrier.

Is this likely to be Duchenne muscular dystrophy?
The history of a progressive muscle wasting disease in a boy and the fact that the mother has a cardiomyopathy suggest that an X-linked muscular dystrophy is possible.

Give three investigations which can help confirm a diagnosis of DMD.
- Molecular analysis of the DMD gene
- Serum creatinine kinase
- Muscle biopsy

Assuming that the diagnosis of DMD is correct, what is the risk if the baby developing the condition?
Mrs F’s mother has a cardiomyopathy and therefore is almost certainly an obligate carrier of the DMD mutation in the family. Therefore, Mrs F is at 1 in 2 risk of being a carrier. The risk that the baby is affected with DMD is the risk that the mother is a carrier x the risk that the baby inherits the gene change x the likelihood it is male.

Key learning points

DMD is an X-linked condition and can be passed down through female carriers. There is no male to male transmission.

Female carriers are at moderate risk of cardiac abnormalities (up to 36%) which include cardiomyopathy and can lead to overt cardiac failure.

Non-disclosure can be a serious issue particularly for the release of molecular diagnostic test results and emotional support.

Feelings of guilt discussing bad news and grief reactions associated with incurable conditions can be barriers to effective communication in families. Ensuring informed consent and family relations and lines of communication are assisted is key to effective counselling.
Question Twelve Medical Discussion

A Where these patients might be seen
Neurology, paediatrics, general practice.

B Patient outcome in this case
Mrs F was keen to know if she was carrying a male pregnancy and was offered maternal free plasma DNA analysis, which is highly sensitive for detecting Y-chromosomal material.

C Red flags
Signs and symptoms of DMD:
Delayed walking usually – greater than 18 months
Frequent falls and abnormal gait.
Gower’s sign
Symmetrical weakness usually affecting the hips first.
Muscle wasting with pseudohypertrophy of the calves.
Later onset of cardiac abnormalities.

D Differential diagnosis
Differential for history of muscle weakness and early death
Duchenne muscular dystrophy
Emery-Dreifuss muscular dystrophy
Limb girdle muscular dystrophy
Facioscapulohumeral dystrophy
Spinal muscular atrophy
Endocrine or metabolic myopathy
Question Thirteen

A visit to the neonatal ward

You go to see a baby on the neonatal ward with seizures. The baby has macroglossia and asymmetry and weighs 4.5kg.

What are the causes of increased birth weight?

What are the causes of macroglossia?

What are the causes of asymmetry?

What quick bedside test would aid diagnosis and treatment?

What is the genetic differential for asymmetry?

What other features can be associated with body asymmetry?

Which screening tests should be offered?
**Question Thirteen Model Answers**

**A visit to the neonatal ward**

You go to see a baby on the neonatal ward with seizures. The baby has macroglossia and asymmetry and weighs 4.5kg.

**What are the causes of increased birth weight?**
- Diabetic mother
- Beckwith Wiedemann syndrome
- Sotos syndrome

**What are the causes of macroglossia?**
- Downs syndrome
- Beckwith Wiedemann syndrome
- Hurlers syndrome
- Congenital hypothyroidism / Acromegaly
- Tumour Infiltration or deposition

**What are the causes of asymmetry?**
- Mosaic chromosomal cell lines
- Beckwith Wiedemann syndrome
- Russell-Silver Syndrome
- Neurofibromatosis type 1

**What quick bedside test would aid diagnosis and treatment?**
*Blood glucose as hypoglycaemia is associated with Beckwith-Wiedemann Syndrome*

**What other features can be associated with body asymmetry?**
- Wilms’ tumour
- Hepatoblastoma
- Adenocortical carcinoma

**Which screening tests should be offered?**
*Blood glucose
Regular abdominal / renal ultrasound scan
Consider alpha fetoprotein.*

**Key learning points**

Macrosomnic infants may be syndromic, especially if there is another feature such as macroglossia.
Question Thirteen Medical Discussion

A  Where these patients might be seen
   Paediatrics, obstetrics.

B  Patient outcome in this case
   The baby was found to be severely hypoglycaemia. Close control of blood glucose
gave good seizure control. He was discharged home after a month in NNU.

C  Red flags for Beckwith Wiedemann Syndrome
   Classic triad:
   a. Exomphalos or other abdominal wall defects.
   b. MacroGLOSSIA.
   c. Prenatal and postnatal overgrowth.
   Other features:
   a. Organomegaly particularly of the liver and kidneys.
   Forehead naevus flammeus, ear lobe grooves or pits.
   Hemihypertrophy
   Neonatal hypoglycaemia.
   Tumours: Wilms' tumour, hepatoblastoma and adenocortical carcinoma.
   Intellectual impairment may be due to neonatal hypoglycaemia.

D  Differential diagnosis
   o  WAGR syndrome: Wilms tumour, aniridia, genitourinary abnormalities and
     learning difficulties, detected by 11p13 deletion.
   o  11p trisomy: Dysmorphic facies and severely impaired.
   o  Simpson-Golabi-Behmel syndrome causes syndactyly, extra ribs, cataracts,
     retinal detachment, pectus excavatum, intestinal malrotation and
     hydronephrosis.
   o  Sotos syndrome causes macrosomia with advanced bone age, hypotonia
     and generalized neonatal oedema.
   o  Weaver syndrome associated with camptodactyly and cryptorchidism.
   o  Klippel-Trenaunay-Weber syndrome can cause hemihypertrophy with port-
     wine staining.
Question Fourteen

Polyuria, Polydipsia and Tiredness

Mary, a 43 year old woman presents with polyuria, polydipsia and constant tiredness. Her sister, Anne, has hearing loss of unknown type and her mother, Iris, died from a diabetic coma at the age of 50.

What is the possible unifying diagnosis?

What is the inheritance pattern of this condition?

What chemicopathological test would aid the diagnosis?

Name at least three causes of pancreatitis other than alcohol.
Question Fourteen Model Answers

Polyuria, Polydipsia and Tiredness

Mary, a 43 year old woman presents with polyuria, polydipsia and constant tiredness. Her sister Anne, has hearing loss of unknown type and her mother, Iris, died from a diabetic coma at the age of 50.

What is the possible unifying diagnosis?
MIDD – maternally inherited diabetes and deafness. Sensorineural hearing loss develops following the onset of diabetes mellitus. Link with other syndromes such as Kearns_Sayre.

What is the inheritance pattern of this condition?
Mitochondrial – maternal inheritance (can put a link here to mitochondrial inheritance). Base pair substitution for tRNA.

What chemicopathological test would aid the diagnosis?
Blood glucose followed by an oral glucose tolerance test if required. Patient fasts overnight (at least 8 hours). Drinks 75g of glucose and has their blood taken 2 hours later. Should the BM level exceed 7 mmol/L then the individual is likely to have diabetes. The glucose has not been taken up by the cells due to insulin not being present (produced in too low a quantity / or the insulin activity is impaired).

During Mary’s first pregnancy, she developed the symptoms mentioned above.

Explain the role of progesterone in this process.
Progesterone is produced by the placenta. During the 2nd trimester, insulin resistance begins to emerge. Progesterone increases insulin resistance of cells. β-cells (of the pancreas) are unable to increase production to overcome this resistance, hence symptoms of diabetes emerge. This occurs in approximately 2-5% of all pregnancies. The patient is at risk of developing cardiovascular complications.

Name at least three causes of pancreatitis other than alcohol.
- Gallstones
- Trauma
- Steroids
- Mumps
- Autoimmune – SLE
- Scorpion venom
- Hyperlipidaemia
- ERCP
Mary’s urine underwent urinalysis: if the result had show low osmolarity and electrolyte levels, what might this have suggested?

Diabetes Insipidus. The symptoms are relatively similar to those of untreated diabetes mellitus. One exception is that the urine does not contain glucose. In DI, there is an inability to concentrate the urine due to a deficiency of (ADH) or due to renal resistance to ADH.

### Key Learning Points

Mitochondrial inheritance is exclusively maternally. Diabetes Mellitus has two forms and must be differentiated from Diabetes Insipidus and psychogenic polydipsia. It can present at childhood, with age, or during pregnancy.

Management of DM is important as it is relevant in numerous fields of medicine. It needs to be managed well to reduce future complications.

Emergency presentation of DM involves immediate rehydration.
Question Fourteen Medical Discussion

A Where might these patients be seen?
Endocrinology, ophthalmology, ENT, general practice, obstetrics

B Patient outcome in this case
The patient is managed as non-insulin dependent diabetes mellitus. Conservative management involves lifestyle factors (exercise, diet, stop smoking). They may also use oral hypoglycaemics, metformin and, eventually, they may require insulin.

C Red flags
Signs & symptoms:
- Hypoglycaemia – most patients will have an aura before this occurs and need to be trained on how to recognise when one may arise.
- Diabetic ketoacidosis (DKA) – Type 1 DM – requires immediate rehydration.
- Hyperosmolar non-ketotic hyperglycemia (HONK) – Type 2 DM – urgent rehydration.

D Differential diagnosis
- Diabetes Mellitus
- Diabetes Insipidus
- Psychogenic polydipsia – compulsion to drink.

If excessive and unable to excrete sufficient water, this can lead to hyponatraemia and subsequent seizures, cardiac arrest and death.

Can perform a water deprivation test: measure weight, urine volume and osmolarity and also serum osmolarity 8-hourly. Need to check plasma and urine osmolarity. If there is a high concentration, consider diabetes mellitus, with a low concentration suggesting diabetes insipidus. If urine osmolarity is very high, then consider psychogenic polydipsia.
Question Fifteen

Alpha 1 antitrypsin deficiency

A 45 year old man visits his GP. His newborn daughter has been diagnosed with alpha 1 antitrypsin deficiency after developing severe neonatal jaundice and breathing difficulties. He wants to continue smoking and has been advised by the respiratory physicians that he should have a carrier test.

Is the risk of emphysema increased in mutation carriers of the MZ alpha-1-antitrypsin mutation?

Is the risk altered by smoking?

If carrier testing shows this man to be normal MM what are the possible reasons for this? How would you broach these possibilities?
Question Fifteen Model Answers

Alpha 1 antitrypsin deficiency

A 45 year old man visits his GP. His newborn daughter has been diagnosed with alpha 1 antitrypsin deficiency (ZZ genotype) after developing severe neonatal jaundice and breathing difficulties. He wants to continue smoking and has been advised by the respiratory physicians that he should have a carrier test.

How is the alpha-1-antitrypsin deficiency inherited?
There are a number of different alpha-1-antitrypsin alleles with different levels of function. The ZZ phenotype is usually the most severe and leads to an inability to cope with airborne pathogens.

Is the risk altered by smoking?
There is good evidence that ZZ homozygous alpha-1-antitrypsin mutation carriers have a far higher risk of emphysema if they smoke. There is some evidence that MZ carriers may be at an additional increased risk if they smoke.

If carrier testing shows this man to be normal MM what are the possible reasons for this? How would you broach these possibilities?
If the baby has severe alpha-1-antitrypsin deficiency and the ZZ genotype, she would have inherited a Z allele from each parent. Therefore, if confirmed on repeat testing, this man has a normal MM genotype he is not likely to be the father of this child. This possibility would preferably have been broached before testing was on the consent form.

Key learning points

There are a number of different alleles with variable phenotypes.

Homozygous mutation carriers are at a higher risk of neonatal jaundice and emphysema.

There is a possible increased risk of emphysema in heterozygous mutation carriers.

Confirmation of parental heterozygous mutation carrier status should be discussed with Clinical Genetics.
Question Fifteen Medical Discussion

A  Where these patients might be seen
    Hepatology, neonatology, respiratory medicine, general practice, gastroenterology.

B  Patient outcome in this case
    This man was tested and was found to be a carrier of the mutation. He has decided to cut down on the amount he smokes for the sake of his daughter.

C  Red flags
    - Signs and symptoms of alpha-1-antitrypsin deficiency
    - Intermittent cough, sputum production and wheezing, often mistaken for asthma.
    - Shortness of breath.
    - Classical features of COPD.

D  Differential diagnosis
    Causes of neonatal hyperbilirubinaemia:
    - Sepsis or congenital infection
    - Haemolytic disease of the newborn.
    - Breast milk jaundice or parenteral nutrition
    Respiratory:
    - Cystic fibrosis
    - Alpha-1 antitrypsin deficiency
    Metabolic/ endocrine:
    - Galactosaemia.
    - Aminoacidurias or organoacidaemias.
    - Hypothyroidism
    Gastrointestinal:
    - Biliary atresia
    - Neonatal hepatitis
    Syndromic:
    - Dubin-Johnson syndrome
    - Crigler-Najjar syndrome
    - Gilbert syndrome