Medical Genetics Specialty Knowledge Assessment

Questions (with model answers)

1) Topic Area: Campomelic dysplasia

This is a photograph and X-ray obtained at PM in a 22 week fetus; Ultrasound scanning showed short limbs and the Fetal Medicine Team suggested a differential diagnosis of osteogenesis imperfecta or campomelic dysplasia.

a) What key feature is present in the image and X-ray of the limbs to suggest the diagnosis? (2)

Marked symmetrical angulation of the legs and femoral bowing on the x-ray.

b) Why is campomelic dysplasia a more likely diagnosis in this case? Name three X ray features (6)

Normal calvarial ossification and no fractures or beading of ribs to suggest osteogenesis imperfecta. Severe scapular hypoplasia, 11 pairs of ribs, poorly ossified pedicles of thoracic vertebral bodies and tall and narrow iliac bones in keeping with a diagnosis of campomelic dysplasia.

c) List two additional clinical features that may be observed on examination of a fetus with campomelic dysplasia. (4)

Micrognathia
Cleft palate
Ambiguous genitalia
Talipes

d) What are the likely outcomes for a baby born with campomelic dysplasia? Name two possible outcomes. (4)

Most die in infancy. Survivors have short stature, dysmorphic features (hypertelorism, depressed nasal bridge, long philtrum, and micrognathia) progressive kyphoscoliosis, recurrent apnoea, recurrent chest infections, stridor, conductive hearing loss, dental caries, and learning difficulties.

e) What is the genetic link between campomelic dysplasia and ambiguous genitalia? (2)

Campomelic dysplasia is caused by mutations in the SOX9 gene. SOX9 has a key role in male sex determination and around 75% of 46,XY male fetuses with campomelic dysplasia have female or ambiguous external genitalia.

f) What is the recurrence risk in a future pregnancy for a couple with a pregnancy affected by campomelic dysplasia? (2)

Most patients with campomelic dysplasia have a heterozygous de novo mutation in the SOX9 gene. The recurrence risk in a future pregnancy for the parents of these patients is very small.

A few patients with campomelic dysplasia have been reported with balanced or unbalanced chromosomal rearrangements involving 17q24-q25 that do not disrupt the SOX9 gene at 17q24.3. Most of these rearrangements can be shown to have arisen de novo and therefore the recurrence risk in a future pregnancy for the parents of these patients is also very small.

2) Topic Area: Chromosome Anomalies (1)

Reciprocal translocations are characterized by exchange of genomic material between at least two chromosomes.

a) What is the genomic imbalance in a pregnancy with 46,XX, -7, der(7), t(7,9)(q31;p22)mat? (4)

Partial monosomy (1) of maternally inherited distal 7q (2)
Partial trisomy (1) of maternally inherited distal 9p (1)

b) List four genomic or genetic mechanisms by which constitutional reciprocal translocations can result in disease. (4)

Unbalanced segregation
Cryptic deletions at breakpoint
Direct interruption of coding region of gene,
Loss of cis-regulatory elements,
Abnormal meiotic pairing
UPD
Change of gene expression in case of translocation

c) Give two techniques that can be used to map translocation breakpoints. (2)

Fluorescent in situ hybridization (FISH) to metaphase chromosomes
Array CGH
Massively parallel (Next Generation) sequencing

d) How might a somatic translocation cause cancer? (2)

Gene fusion
Abnormal activation
Gene disruption

e) What are the possible karyotypes in a baby born to a mother carrying a balanced translocation 46,XX,t(1;8)(p36.1;q22)? (4)

Normal (1)
Balanced translocation carrier (1)
Partial monosomy of 1p & partial trisomy of 8q (1p36 deletion syndrome acceptable) (1)
Partial monosomy of 8q & partial trisomy of 1p (1)

f) Give two clinical situations by which reciprocal translocations can cause infertility or apparent infertilty.
(4)

Oligospermia (1) associated with impaired meiotic cell divisions (1)
Very early pregnancy loss (1) of embryos with severe genomic imbalance (1)

3) Topic Area: Chromosome Anomalies (2)

A paediatrician refers a child to you querying whether chromosomal mosaicism might be the cause of their problems.

a) Name two clinical features that are suggestive of chromosomal mosaicism. (2)

Asymmetry
Pigmentary mosaicism or patches of hypo-/ hper-pigmentation

b) Each of these clinically recognisable syndromes is commonly associated with one of the listed features. Indicate which. (4)

Cat-eye syndrome	deep creases
Diploid/triploid mosaicism	diaphragmatic hernia
Mosaic trisomy 8	iris colobomata
Pallister Killian syndrome	syndactyly

Cat-eye syndrome	*iris colobomata* (1)
Diploid/triploid mosaicism	*syndactyly* (1)
Mosaic trisomy 8	*deep creases* (1)
Pallister Killian syndrome	*diaphragmatic hernia* (1)

c) Array CGH analysis did not detect any significant abnormalities. What further samples would you suggest and what analysis would you request on each?
(4)

Skin biopsy (1) *for fibroblast karyotype* (1)

Buccal mucosal (1) *swab for FISH* (1)

d) Give two mechanism by which chromosomal mosaicism can arise? (2)

Trisomic rescue
Mitotic non-disjuction

e) What is the difference between mosaicism and chimerism? (4)

Mosaicism is derived from a single parental cell (2)
Chimerism is mixture of cells of different parental origin (2)

f) Suggest two approaches which would differentiate somatic mosaicism from cell-culure artefact in prenatal karyotyping. (4)

Presence in direct and indirect culture
QFPCR of original material
Array CGH of original material
Second amnio/CVS

4) Topic Area: Ocular Genetics

Eye malformations are common causes of visual impairment in childhood.

a) Name a congenital eye anomaly caused by congenital infection and name the pathogen. (2)

Cataract
Rubella

b) What is aniridia and what is the most common genetic cause? (4)

Absence of iris

PAX6 mutation or deletion

c) What serious complication in childhood may be associated with aniridia and why?
(4)

Wilms tumour
WT1 and PAX6 closely located on 11p – deletion

d) Name two monogenic or chromosomal disorders associated with iris coloboma. (4)

CHARGE, Wolf Hirschorn 4p-, cat-eye etc

e) Why do children with neurofibromatosis Type 1 require opthalmological assessment? name two reasons (4)

Optic glioma, Lisch nodules, Strabismus, retinal vasoproliferative tumors, neovascular glaucoma

f) Name an autosomal trisomy syndrome that is commonly associated with microphthalmia. (2)

t13; Patau syndrome

5) Topic Area: renal cancer

A 43-year-old woman presents with haematuria. On investigation, she is shown to have a mass in the lower pole of her left kidney. She undergoes nephrectomy and histology reveals clear cell carcinoma. There is no family history of renal cancer.

a) Why is a mutation in the MET gene unlikely to be the underlying cause? (2)

MET mutations usually associated with papillary renal cell carcinoma.

b) If her mother has had a hysterectomy aged 45, name one condition this might suggest. (2)

HLRCC or HNPCC

c) If examination of the patient reveals fibrofolliculomas, what condition might be suggested? Name one pulmonary manifestation of this disorder. (4)

BHD, pneumothorax

d) If her father had a hemicolectomy aged 49, name one condition this might suggest. (2)

HNPCC

e) The eye examination in the 14 year old son confirms a retinal angioma. Name two other investigations, other than genetic testing, that are needed and explain why. (4)

24 hour urine for catecholamines, MRI abdomen to image kidneys and adrenals, MRI brain and spinal cord,

f) Describe the mode of action of the gene causing VHL. What is the normal physiological function of the gene product? (6)

tumour suppressor mechanism; oxygen sensing pathway, ubiquitination and degradation of a hypoxia-inducible factor

6) Topic Area: phaeochromocytoma

Over the course of the previous three years, a 39-year-old office worker had experienced episodes of a feeling of impending doom, panic and rapid pulse. These occasions were associated with sweating, headache and high blood pressure. After investigation, she was found to have a phaeochromocytoma.

a) What proportion of isolated cases of phaeochromocytoma are genetic?

(2)

25 – 30%

b) Name one biochemical test and one diagnostic imaging investigation that might establish the diagnosis. (4)

24 hour urine for catecholamines; Abdominal MRI or CT scans or MIBG scan

c) Name two clinical complications of this condition if left untreated. (4)

malignant phaeochromocytoma; chronic hypertension; CVA; renal failure

d) Patients with Neurofibromatosis type 1 have an increased risk to develop phaeochromocytoma. Name two other inherited disorders that can confer an increased risk of this condition.

(4)

von Hippel-Lindau disease, Multiple endocrine neoplasia type 2, etc.

e) Specify another cancer associated with neurofibromatosis type 1.

(2)

malignant peripheral nerve sheath tumors, pilocytic astrocytoma of the optic nerve, rhabdomyosarcoma, breast cancer

f) Mutations in SDHD can be associated with this condition. What additional considerations are important in genetic counselling when undertaking any analysis of this gene? (4)

imprinted disease usually only causes disease if paternally inherited

7) Topic Area: Paraganglioma

A 29-year-old male with an isolated paraganglioma has been referred to the genetics laboratory for analysis of the SDHB and SDHD genes. The report back from the laboratory is as follows.

The coding exons of SDHB and SDHD have been sequenced and the missense variant p.Ala98Glu in the last codon of the penultimate exon of SDHD has been identified. This variant has not previously been described in the literature or on any mutation database so its significance is uncertain at present. No other variants were seen in either SDHB or SDHD. In order to clarify the significance of the variant in SDHD samples from other family members and if possible a tumour block from this patient's tumour are requested.

a) What is the general definition of a missense variant? (4)

A nucleotide substitution that predicts an amino acid change in a protein. Non-synonymous change. These may or may not affect the function of the protein. May be conservative (i.e. the amino acids are of similar chemical composition) or non conservative (amino acids are not similar based on polarity, size etc).

b) What effect do you think this variant may have on the gene and how would you prove this?

(4)

Could just result in an amino acid change. Need software programmes to clarify any effect. Position of the change in last codon of the exon may affect the normal splicing of the gene as sequences either side of the consensus splice sites also important. Can confirm with RNA studies.

c) Why has the laboratory asked for samples from other family members?

(2)

Segregation studies

d) What information can be gained by studying tumour material? (2)

Look for LOH – if present may increase the likelihood of causality

e) Are there any types of mutation which would not be detected by direct sequencing? How would you test for them? (4)

Deletions or duplications. MLPA or another form of dosage assay

f) What are the additional considerations that are important for genetic counselling when interpreting the results of any analysis of the SDHD gene? (4)

Imprinted gene. Only causes disease if paternally inherited.

8) Topic Area: FRAX (1)

A 60-year-old male with a history of gait ataxia and intention tremor has been referred for Fragile X gene testing following a negative result from testing the SCA1,2,3 and 6 genes. PCR analysis shows the presence of a 75 repeat allele, suggesting a diagnosis of FXTAS.

a) What is the mechanism to explain the pathogenesis of FXTAS? (2)

RNA mediated toxicity

b) What is the implication for the patient in finding 75 repeats? (2)

Consistent with a diagnosis of FXTAS. Patient also a carrier of a premutation so implications for family members

c) What is the phenotype seen in males with the full Fragile X mutation,

and why is this milder in females ? (5)

Full repeat expansion mutation is associated with moderate to severe intellectual disability, long face, prominent jaw, large ears, macroorchidism. Milder features due to X-inactivation in females.

d) What is the most common mechanism for inactivation of the FMR1 gene ? (3)

Methylation of full CGG repeat expansion leads to suppression of transcription

e) What tests other than PCR are available for the analysis of the FMR1 gene? (4)

Methylation PCR, Southern blotting, sequencing for the <1% with no expansion, cytogenetics..

f) What are the clinical implications of this result for the patient's 26-year-old daughter? (4)

obligate carrier of premutation with risk of affected children, risk of premature ovarian failure

9) Topic Area: Beckwith-Wiedemann syndrome

Baby Jones was born with an exomphalos and macroglossia. She was diagnosed with Beckwith Wiedemann syndrome

a) What is the main complication for baby Jones to look out for in the neonatal period? What is the recurrence risk for her parents?

(4)

hypoglycaemia.
Very low recurrence risk.

b) What is the chromosomal region associated with Beckwith Wiedemann syndrome? (2)

11p15 containing two imprinted domains.

c) Give two alternative mechanisms which can result in Beckwith Wiedemann syndrome.

(4)

Gain of methylation at H19 differentially-methylated region (DMR)
Mosaic segmental paternal uniparental disomy (UPD)
Chromosomal copy number change (microdeletion) affecting H19DMR or KvDMR1
Loss of function mutation in maternally-inherited CDKN1C gene
Cytogenetic abnormality (maternally-inherited translocation/inversion at 11p15 or paternally-inherited duplication of this region)

d) Give two genetic testing strategies which can be used to diagnose Beckwith Wiedemann syndrome .

(4)

Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA)
Microsatellite marker analysis for mosaic segmental paternal UPD,
Standard karyotype to look for 11p15 rearrangements (translocation, inversion, or duplication)
CDKN1C mutation analysis

e) Apart from exomphalos and Macroglossia name two other clinical features associated with Beckwith Wiedemann syndrome. (4)

Overgrowth
Hemihypertrophy/hemihyperplasia
Ear lobe creases/posterior helical pits
Embryonal tumours or Wilms tumour
Renal abnormalities (enlarged kidneys, medullary sponge kidney)

Hepatomegaly

f) Name one other condition that is associated with abnormalities in the same chromosome region as Beckwith Wiedemann syndrome? (2)

Silver-Russell syndrome
Isolated hemihypertrophy/hemihyperplasia

10) Topic Area: Foetal sexing on free foetal DNA

A known carrier of DMD requests information on a non invasive prenatal diagnosis by fetal sexing.

a) What is the basis of the test? (4)

Isolation of fetal DNA from the maternal blood. Detection of Y specific sequences to enable sex determination.

b) Why is the timing of the test procedure important? (4)

Need to wait until at least 7 weeks (often 9) to ensure the levels of fetal DNA are high enough for detection. Needs to be before an invasive test would be carried out

c) What is the source of the fetal DNA and what is the mechanism through which it is released into the maternal circulation? (2)

placenta and apoptosis

d) Give two significant limitations in diagnosis using free fetal DNA. (4)

Present in low levels, not currently clinically available for maternal mutations.

e) In what non X linked disorder can sex determination by free fetal DNA testing be helpful ? (2)

Congenital adrenal hyperplasia, to identify female fetus at risk of virilisation.

f) Give 2 further examples of the current use of free fetal DNA. (4)

Prenatal detection of fetal trisomies within antenatal screening programme, diagnosis of achondroplasia/thanatophoric dysplasia when short limbs detected on antenatal scan.

11) Topic Area: Apert

Apert syndrome is due to mutation in the *FGFR2* gene.

a) Name the two cardinal features of Apert syndrome. (2)

Craniosynostosis (coronal)
Significant / total syndactyly of fingers and toes

b) Name a structural abnormality that might give rise to respiratory problems in infancy. (2)

Choanal atresia / midface hypoplasia / depressed nasal bridge
Cleft palate

c) What parental factor might be important in an apparently isolated case (2)

Increased paternal age

d) Neither parent has features of Apert syndrome. What is the recurrence risk in another pregnancy and why? (4)

Very low, <1%
Although there is a paternal age effect the proportion of affected sperm is small enough to advise a low risk of recurrence for this couple.
[Recurrence risk potentially associated with parental gonadal mosaicism]
[Only one case of affected sibs to normal parents reported]

e) Mutations in the FGFR2 gene can cause several distinct craniosynostosis syndromes. Give two general explanations for why different mutations in the same gene can lead to different phenotypes. (4)

Mutations in different functional domains of the gene may have different phenotypic effects.
There may be different classes of mutation leading to gain of function or loss of function, with different phenotypic consequences

f) Match each of the following conditions with the most appropriate clinical feature. (6)

a. Saethre-Chotzen syndrome . cutis gyrate (c)

b. Antley-Bixler syndrome facial asymmetry/ prominent nasal crus (a)
c. Beare-Stevenson syndrome femoral/ulnar bowing (b)

12) Topic Area: OI

A 2-months old baby presents to A & E with fractures. The mother questions whether her child has brittle bone disease. Most types of osteogenesis imperfecta (OI, brittle bone disease) are caused by mutations in *COL1A1* and *COL1A2.*

a) Name the main differential diagnosis. (2)

Non-accidental injury

b) List two clinical features that the geneticist would look for on clinical examination that would make a diagnosis of OI more likely. (4)

Triangular facies
Blue sclerae
Bony deformity
Joint laxity
Soft skull bones
Wide fontanelles

c) Name one feature, apart from fractures, that you would look for on a skeletal survey. (2)

Wormian bones
Reduced ossification (skull and elsewhere)

d) What two other systems might be affected by someone with a diagnosis of OI? (4)

Hearing
Teeth/dental

e) A diagnosis of OI type III/IV is confirmed. You are asked to see the parents to discuss recurrence risks. They do not have OI. Discuss the risk to their next pregnancy. (4)

Most cases arise due to new AD mutations but the recurrence risk is ~7-8% based on empiric data. This is based on the possibility of parental gonadal or low-level somatic mosaicism for AD COL1A1/ COL1A2 mutations and the possibility of some AR causes of OI due to genetic heterogeneity (other genes involved).

Alternative answer that is also correct: Test affected infant for mutations in a panel of genes causing AD and AR forms of OI by

next-generation sequencing. Recurrence risk would depend on the identification of a specific heterozygous mutation in COL1A1 or COL1A2 or biallelic mutations in one of several different genes known to cause AR OI (e.g. CRTAP, LEPRE1, etc) followed by the results of parent's tests for the identified mutation(s).

f) Explain how the mutations in *COL1A1* and *COL1A2* lead to bone fragility. (4)

Type I collagen is a heterotrimer made up of two procollagen α1(I) and one procollagen α2(I) polypeptide chains (2 marks). Loss of function (null) mutations in COL1A1 or COL1A2 result in a 50% reduction of the protein products of these genes resulting in reduced Type I collagen (1 mark). Glycine substitutions in the helical domain of COL1A1 or COL1A2 alter the cross linking of the collagen helix exerting a dominant-negative effect causing a more a serious phenotype than loss-of-function mutations (1 mark).

13) Topic Area: array CGH

Array comparative genomic hybridisation (aCGH) is a technique that reveals copy number variation in an individual compared to a control sample. It is sometimes called a molecular karyotype.

a) What is copy number variation? (2)

A copy number variant is a segment of DNA in which copy-number differences have been found by comparison of two or more genomes. CNV is variation from this.

b) A patient has been tested with a 180k oligoarray. Explain the principle of the test and what '180k' means. (4)

It is a genome wide analysis that compares the ratio of patient DNA with a reference DNA sample to detect CNV. 180k refers to the use of 180,000 oligonucleotide probes.

c) Give two reasons why aCGH is a more sensitive method of chromosome analysis than a G-banded karyotype. (4)

Better resolution
Smaller chromosome deletions and duplications can be identified.
Size of deletion/duplication more accurately determined
Breakpoint mapping and determination of genes involved
Not dependent on human visual interpretation

d) Give a difference between a SNP (single nucleotype polymorphism) array and an oligoarray. (2)

A SNP is a polymorphic probe. It can detect:

- *Uniparental disomy (UPD)*
- *Homozygosity*
- *Non-paternity*

e) A previously unreported deletion of 1Mb has been detected in your patient using the 180k oligoarray. Explain two ways in which you would ascertain if this was the cause of the phenotype observed in your patient. (4)

Test both parents to check if de-novo (essential)
Search databases – are gene(s) in the deleted region associated with any features (phenotype) found in the patient
Consider if any of deleted genes act by haploinsufficiency

f) A deleted gene can lead to a phenotype by haploinsufficiency. What do you understand by the term haploinsufficiency? (4)

In haploinsufficiency, a single copy of the gene does not produce enough product (protein) and this 50% reduction compared to normal gives rise to the phenotype. In haploinsufficiency the mutations are dominant loss-of-function mutations (hypomorph).

14) Topic Area: Hemihypertrophy

An infant is referred to the genetics clinic by his general paediatrician with hemihypertrophy affecting the right arm and leg.

a) Apart from Beckwith Wiedemann syndrome, name three conditions that manifest with hemihypertrophy. (6)

Isolated hemihypertrophy
Beckwith-Wiedemann syndrome
Silver-Russell syndrome
Mosaic chromosome abnormalities
Neurofibromatosis type 1
Klippel-Trenaunay syndrome
Maffucci syndrome
Hemihyperplasia-multiple lipomatosis

No marks for Proteus syndrome or PIK3CA-related overgrowth spectrum disorders (PROS), e.g. CLOVES syndrome, macrocephaly-capillary malformation, as these cause segmental overgrowth rather than hemihypertrophy. The exception to this is hemihyperplasia-multiple lipomatosis syndrome (see list above)

b) In addition to hemihypertrophy the infant had a birth weight of 5kg and a history of neonatal hypoglycaemia and had Beckwith Wiedemann syndrome. State two other clinical features that you would look for on clinical examination. (4)

Overgrowth
Macroglossia
Coarse facial features
Ear pits/Ear lobe creases
Umbilical hernia or diastasis recti or scar of exompholos repair

*c) W*hat molecular test would you request for a child with Beckwith Wiedemann syndrome and what types of molecular defect does this test detect? (4)

11p15 methylation and dosage analysis/11p15 MS-MLPA/ MS-MLPA test for Beckwith-Wiedemann syndrome

One mark only for UPD 11p1511p15 MS-MLPA test detects all epigenetic abnormalities and copy number changes in this region: These include gain of methylation at H19 differentially methylated region (1 mark), loss of methylation at KvDMR1 (1 mark), uniparental disomy (1 mark), and copy number changes involving 11p15 (1 mark)

d) For a child who fulfils clinical diagnostic criteria for Beckwith Wiedemann syndrome give your advice regarding Wilms tumour surveillance if molecular testing gave a negative result. (2)

20% of those with clinical BWS have negative 11p15 MS-MLPA results. I would therefore advise Wilms tumour surveillance by renal ultrasound scans every 3-4 months) until the age of 7 years

e) What would be your advice be if a child with clinical features of Beckwith Wiedemann syndrome had loss of methylation at KvDMR1? (2)

In this case I would advise that Wilms tumour surveillance is not necessary

f) what other tumour surveillance might you consider recommending for a child with Beckwith Wiedemann syndrome?

AFP for hepatoblastoma (2)

15) Topic Area: Polyposis Coli

A surgeon refers a 37-year-old woman to you. She has undergone a total colectomy and an ileo-rectal anastomosis for an adenocarcinoma and 'multiple polyps' in the large bowel. A diagnosis of Polyposis Coli has been suggested. The woman's parents have both had negative colonoscopies.

a) Name two extra-colonic features of familial adenomatous polyposis (FAP). (4)

Osteomas
Desmoid
Dental anomalies
CHRPE
Duodenal adenomas/carcinoma
Thyroid cancer
Hepatoblastoma

b) Describe the underlying mechanism of polyp formation in carriers of an *APC* gene mutation. (4)

APC is a tumour suppressor gene. (2)

A second hit/loss of function mutation in the normal APC allele abrogates APC *protein function such that it no longer facilitates destruction of free beta-catenin. Free beta-catenin is thus able to bind to transcription factors activating various genes causing cellular dysplasia and thus polyp formation.(1)*

Loss of APC function also causes abnormal spindle formation thus predisposing to aneuploidy. (1)

(c) On colonoscopic screening, the brother was found to have less than 100 adenomas. What other diagnoses should you consider? (2)

Attenuated FAP (1)

MUTYH-associated polyposis (MAP) (1)

d) What other clinical investigation would be warranted in this woman? (2)

Upper GI endoscopy (for Spigelman staging)

e) The patient is concerned about whether her diagnosis has implications for her children's health. (6)

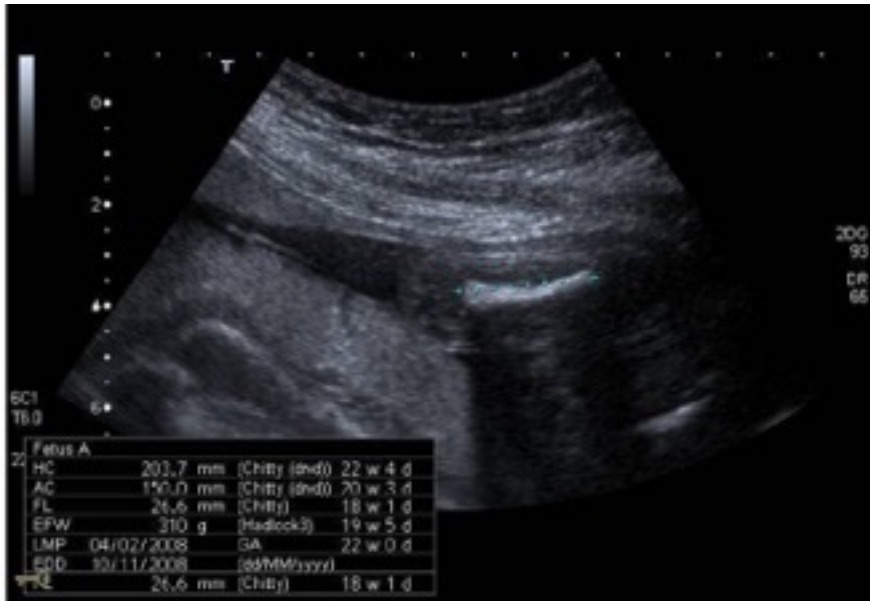
APC – dominantly inherited; risk to children; consider early colonoscopic screening and presymptomatic genetic testing
MUTYH – recessive inheritance; lower risk to children. Might consider screening of partner for common MUTYH mutations appropriate to their ethnic group.

f) If the patient has learning disability what further investigation would you request? (2)

Array CGH to identify 5q microdeletion. (or other appropriate dosage test

16) Topic Area: Jeune Syndrome

This is an image of an ultrasound scan taken at 21 weeks gestation.



The image shows a short femur. Based on other associated abnormalities the fetal medicine team has suggested a diagnosis of Jeune syndrome.

a) Name three abnormalities other than short long bones that might be visible on scan to suggest this diagnosis? (3)

Short ribs
Polydactyly
Large echogenic kidneys

b) The parents ask what this diagnosis means for their baby. Give three key clinical features of the condition post-natally. (3)

Respiratory distress / Increased risk of neonatal death
Cirrhosis
Retinitis
Renal failure in childhood

c) Name four features you would look for on a postnatal skeletal survey to confirm the diagnosis of Jeune syndrome? (4)

Bell-shaped thorax
Short ribs
Iliac hypoplasia
Trident acetabulum
Acetabular spurs
Premature ossification of capital femoral epiphyses

Metaphyseal irregularity/ spurs
Platyspondyly

d) The molecular genetic report confirms the diagnosis, showing:
DYNC2H1 c.6161G>C c.9353+1G>A
Explain what this means with regards to each of the mutations. (3)

c.6161G>C: *Guanine at position 6161 changed to cytosine* (1)
c.9353+1G>A: *Guanine in the intron changed to adenine* (1 for intron; 1 for rest)

e) Jeune syndrome is a "ciliopathy", as is Primary ciliary dyskinesia (PCD).
What are the three common respiratory presentations of PCD? (3)

Neonatal respiratory distress
Chronic/ repeated respiratory/ ENT infections
Bronchiectasis

f) Name two other clinical features/ problems frequently seen in PCD? (4)

Infertility (2)
Dextrocardia/ situs inversus (2)

17) Topic Area: COL2A1

The COL2A1 gene encodes collagen type II, a major component of cartilage. Mutation of this gene has been linked with a wide spectrum of phenotypes including Stickler syndrome.

a) Name three other conditions associated with mutations in this gene. (6)

Anchondrogenesis type 2
Hypochondrogenesis
Torrance dysplasia (also called platyspondylic lethal dysplasia)
Autosomal dominant rhegmatogenous retinal detachment (ARDD)
SEDC or Spondyloepiphyseal dysplasia congenita
Strudwick dysplasia or Spondyloepimetaphyseal dysplasia
Kniest syndrome
Spondyloperipheral dysplasia
Bilateral Perthes (also called avascular necrosis of femoral head)

b) Name two ocular problems linked with collagen II disorders. (4)

Abnormal vitreous
Myopia
Retinal detachment

c) Give two features of Stickler syndrome that may affect language development. (2)

Cleft palate
Hearing difficulties

d) Mutations in which gene cause autosomal dominant non-ocular Stickler syndrome? (2)

COL11A2

e) What orthopaedic complicati

on ma y ne ce ssit ate sur gic al int erv ent ion for pat ien ts wit h Sti ckl er sy ndr om e?

(2)

Hip / knee replacement for osteoarthritis

f) Mutations in collagen genes causing a severe phenotype are often dominant negative. Why? (4)

Type 1 collagen is a triple helix formed from 3 alpha chains. Abnormal chain interferes with function disrupting entire molecule. More severe effect than under-production of normal Type 1 collagen.

18) Topic Area: Cleft lip and palate

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palate (CP) may be associated with a small lower jaw (micrognathia).

a) What name is given to this association? (2)

Pierre Robin sequence or Robin sequence

b) When micrognathia and CP co-exist what complication can arise in pregnancy and why? (4)

Polyhydramnios
Fetus may have difficulty in swallowing amniotic fluid

c) Discuss two complications of CP and micrognathia at birth. (4)

Upper airway obstruction may require insertion of an oropharyngeal airway or tracheostomy
Feeding difficulties

d) What syndrome associated with mutations in *COL2A1* can present like this and what key clinical feature should be screened for in infancy? (4)

Stickler syndrome Myopia

e) What recurrence risk can be given to parents after the birth of one child with isolated CP? (2)

About 2%

f) A woman with two brothers affected by cleft palate has an affected boy. What is the recurrence in a future male pregnancy and which gene is implicated? (4)

1 in 2
TBX22

19) Topic Area: Imprinting

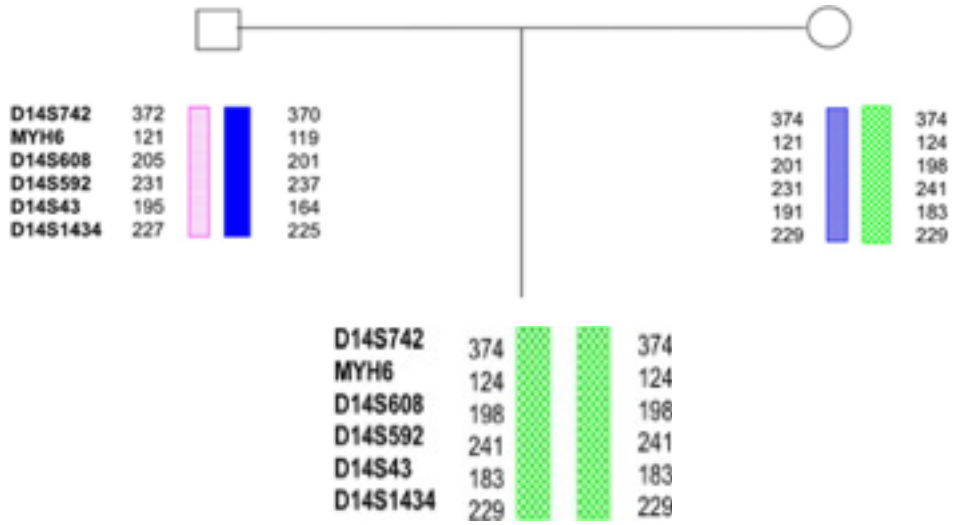
A baby born to non-consanguineous Caucasian parents presents with hypotonia and poor feeding. She is non-dysmorphic and Array CGH has not detected any abnormalities.

a) List two likely differential diagnoses. (2)

SMA (1)

Prader-Willi (1)

b) Further testing produces the following results on chromosome 14. What is the specific genetic finding? (3)

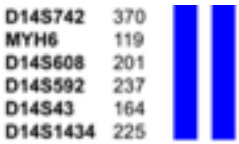


Maternal (1) *isodisomy* (2) (*Only 1 mark if indicates Uniparental disomy/ UPD but not isodisomy)*

c) Why might you expect these results to be associated with a phenotypic effect? How may paternal and maternal alleles differ biochemically? (4)

Because there are imprinted gene(s) (1) *on chromosome 14 so the infant needs both maternal and paternal alleles* (1)
Different methylation patterns (2)

d) Suggest a mechanism that might affect the early embryo to give rise to these results with normal parental karyotypes and a parental karyotypical abnormality that could predispose to this disorder. (6)



Non-dysjunction (2) *then trisomic rescue* (2)
Robertsonian translocation involving chromosome 14 (2)

e) Another, dysmorphic, baby has slightly different results, as shown below. What phenotypic features (not the dysmorphology) would you expect with these results? (3)

Developmental delay
Short stature
Abdominal wall defects

f) Which radiological feature can give a very good clue to this diagnosis? (2)

'Coat hanger' ribs

20) Topic Area: Gene structure

The first exon of the CF gene CFTR is shown below. The exon is highlighted in pink. Flanking nucleotides which are not highlighted are intronic. The blue dots are placed over the first nucleotide of a codon. The amino acid code is also provided below.

CFTR Exon 1

AAAGCCGCTAGAGCAAATTTGGGGCCGGACCAGGCAGCACTCGGCTTTTAACCTGGGCAG

TGAAGGCGGGGGAAAGAGCAAAAGGAAGGGGTGGTGTGCGGAGTAGGGGTGGGTGGGGGG

a

AATTGGAAGCAAATGACATCACAGCAGGTCAGAGAAAAAGGGTTGAGCGGCAGGCACCCA

GAGTAGTAGGTCTTTGGCATTAGGAGCTTGAGCCCAGACGGCCCTAGCAGGGACCCCAGC

b

. . . . . .

GCCCGAGAGACCATGCAGAGGTCGCCTCTGGAAAAGGCCAGCGTTGTCTCCAAACTTTTT

c d e

. .

TTCAGGTGAGAAGGTGGCCAACCGAGCTTCGGAAAGACACGTGCCCACGAAAGAGGAGGG

f g

CGTGTGTATGGGTTGGGTTTGGGGTAAAGGAATAAGCAGTTTTTAAAAAGATGCGCTATC

Which underlined regions (labelled a-g) correspond to

a) The initiation codon?[2]

c

b) The splice donor site. What is the term used for the other splice site? [4]

f ; splice acceptor site

c) The 9th codon?. Which amino acid does it encode? [4]

Answer: d ; Alanine (or Ala)

d) Part of intron 1? [2]

g

e) Is it possible to translate the complete amino acid code for exon 1 from the sequence given? Explain your answer [4]

no as the last nucleotide of the final codon is missing and the last two nucleotides AG can be followed by either T or C to encode serine or A or G to encode arginine

f) In a patient with cystic fibrosis the second and third nucleotides are found to be deleted at codon 17 of the *CFTR* gene. What type of mutation is this and what are the consequences for translation? [4]

frameshift mutation and leads to introduction of a stop codon

Amino Acid	SL	DNA codons
Isoleucine	I	ATT, ATC, ATA
Leucine	L	CTT, CTC, CTA, CTG, TTA, TTG
Valine	V	GTT, GTC, GTA, GTG
Phenylalanine	F	TTT, TTC
Methionine	M	ATG
Cysteine	C	TGT, TGC
Alanine	A	GCT, GCC, GCA, GCG
Glycine	G	GGT, GGC, GGA, GGG
Proline	P	CCT, CCC, CCA, CCG
Threonine	T	ACT, ACC, ACA, ACG
Serine	S	TCT, TCC, TCA, TCG, AGT, AGC
Tyrosine	Y	TAT, TAC
Tryptophan	W	TGG
Glutamine	Q	CAA, CAG
Asparagine	N	AAT, AAC
Histidine	H	CAT, CAC
Glutamic acid	E	GAA, GAG
Aspartic acid	D	GAT, GAC
Lysine	K	AAA, AAG
Arginine	R	CGT, CGC, CGA, CGG, AGA, AGG
Stop codons	St	TAA, TAG, TGA

In this table, the twenty amino acids found in proteins are listed, along with the single-letter code used to represent these amino acids in protein data bases. The DNA codons representing each amino acid are also listed. All 64 possible 3-letter combinations of the DNA coding units T, C, A and G are used either to encode one of these amino acids or as one of the three stop codons that signals the end of a sequence. While DNA can be decoded unambiguously, it is not possible to predict a DNA sequence from its protein sequence. Because most amino acids have multiple codons, a number of possible DNA sequences might

21) Topic area: Neuromuscular Disorders (1)

A child is referred with a suspected clinical diagnosis of Friedreich Ataxia (FA)

a) Name two neurological signs associated with FA, apart from ataxia, nystagmus and dysarthria (2)

Absent reflexes
Loss of position sense
Loss of vibration sense
Pyramidal weakness
Extensor plantar responses
Pes cavus

b) Name two complications of FA outside the nervous system. (4)

Hypertrophic cardiomyopathy
Scoliosis
Diabetes
Deafness
Optic atrophy

c) Give two characteristics of the underlying mutation. (4)

Autosomal recessive
Fully penetrant
GAA repeat
Intron 1 frataxin (FXN) gene
Pathological expansion >65 repeats
Premutation 34-65 repeats
Severity correlates with expansion size
2% alleles have inactivating point mutations

d) If the unaffected sibling of a person with FA marries an unrelated person without a family history of FA, what is the risk of their first child being affected? [population carrier frequency 1 in 80] Show calculation

(2)

2/3 x 1/80 x 1/4 = 1/480

e) If an unaffected sibling of a person with FA marries an unaffected first cousin (in a family with no other consanguineous marriages), what is the risk of their first child being affected? (2)

2/3 x1/4 x1/4 = 1/24

f) Match the conditions below with the most appropriate clinical feature (6)

a. *Ataxia telangiectasia*
b. *Vitamin E deficiency*
c. *Marinesco Sjogren syndrome*
d. *Cerebrotendinous xanthomatosis*
e. *Oculomotor apraxia type 1*
f. *Behr syndrome*

1. *Defective liver tocopherol binding protein (b)*
2. *Infantile diarrhea and failure to thrive (d)*
3. *Breast cancer risk in mutation carriers (a)*
4. *Hypoalbuminaemia (e)*
5. *Hypergonadotrophic hypogonadism (c)*
6. *Early onset optic atrophy (f)*

22) Topic area: Neuromuscular Disorders (2)

A couple whose first child died with SMA1, present with dizygous twins in their second pregnancy. Both parents have been confirmed to be carriers.

a) What is the chance that at least one of the twins will be affected by SMA1? Show workings (4)

7/16 working: [(1/4x1/4) + (1/4x3/4) + (3/4x1/4)]

b) If the mother's brother and his unrelated partner are also found to be SMN gene deletion carriers, explain why they might have a child with SMA type II rather than type I. (4)

Multiple copies of SMN2 may be present
This can increase the level of full length SMN protein sufficiently to allow improved function of motor neurones.
(Most SMN2 RNA transcripts lack exon 7 and the protein produced is unstable. However, a small amount of full length protein is produced. 25% protein levels allow normal motor neurone function)

c) Give two reasons why the recurrence risk may not be 1 in 4 for a couple who have had one affected child. (4)

Non-paternity
New mutation
UPD

d) What is the main clinical distinction between SMA type I and type II (3)

Babies with type II are able to sit unsupported, babies with type I do not

e) Why does the presence of two copies of the SMN1 gene not always exclude carrier status? (3)

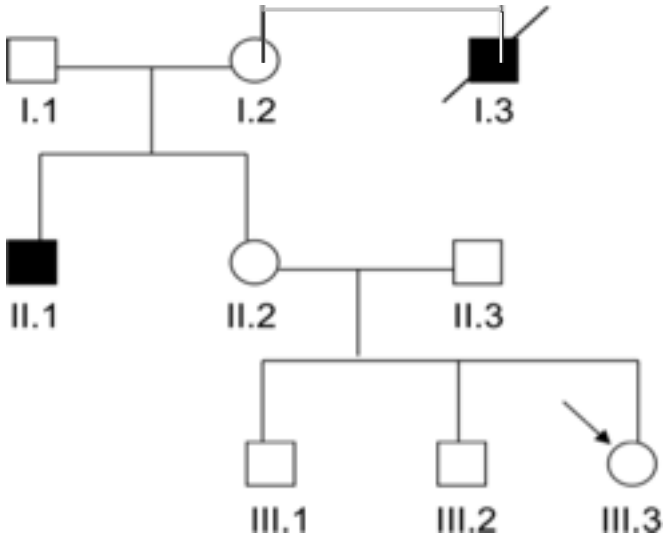
4% of chromosomes carry 2 copies of the SMNI gene

f) What is the main additional clinical feature in babies who have SMARD1 due to an IGHMBP2 gene mutation? (2)

Early onset respiratory failure / respiratory distress / diaphragmatic paralysis

23) Topic area: Bayes calculation (1)

The affected males in this pedigree have/had a diagnosis of Duchenne Muscular Dystrophy (DMD) and the arrowed individual is the consultand.



a) What is the chance that I.2 would have had another child with DMD if she became pregnant again? [2]

1/4

b) Name two ways in which manifesting carriers can be affected. [4]

Proximal muscle weakness
Cardiomyopathy

c) What is the prior risk of II.2 being a carrier of DMD? [2]

1/2

d) If II.2 is a carrier of DMD, what is the chance of having two unaffected sons (as in the pedigree)? [2]

1/4

e) On the basis of the pedigree complete a Bayes' calculation to determine the chance of the consultand being a carrier of DMD [8]

Probability	*II.2 is a carrier*	*II.2 is not a carrier*
Prior	*1/2*	*1/2*
Conditional	*1/2 x ½*	*1*
Joint	**1/8**	**4/8**

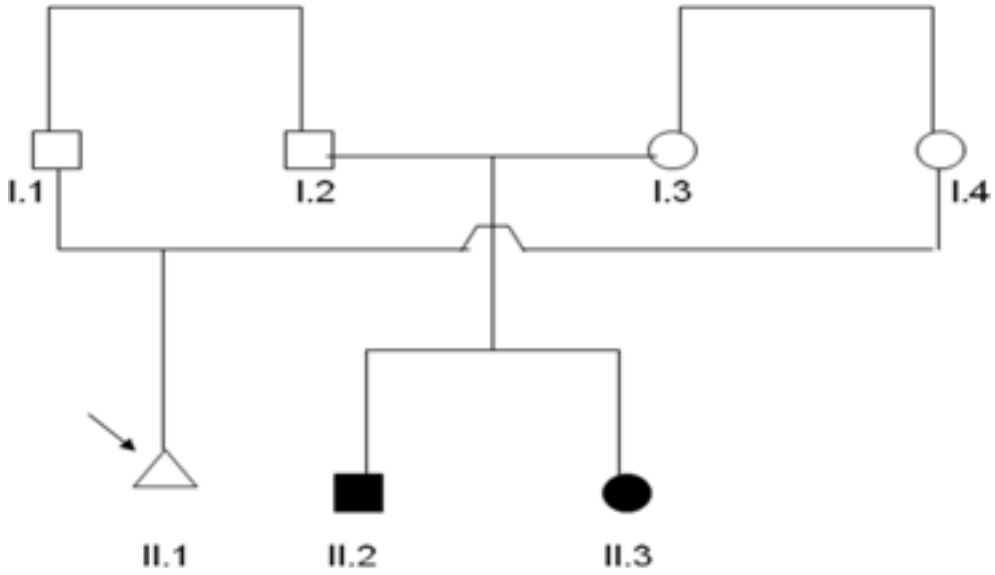
Posterior 1 / 1 + 4 = 1/5

Probability that III.3 is a carrier = 1/10

f) Name one reason why this condition is associated with a high new mutation rate. [2]

Large gene
Mutational hot spots

24) Topic area: Bayes calculation (2)



couple, I.2 and I.3, have two children with an autosomal recessive disorder.

a) I.1 and I.4 are married and expecting their first baby. What is the chance that this child will be affected with the same condition as II.2 and II.3? [2]

1/ x **1/** = 1/16

b) If I.1 and I.4 are both carriers of the condition, what is the chance that they will have two children who are both unaffected? [2]

$^{3}/_{4}$ x $^{3}/_{4}$ = 9/16

c) If I.1 and I.4 have two healthy children and their carrier status is unknown, complete a Bayes' calculation to determine the chance that their next child will be affected by the same condition as II.2 and II.3 [8]

Probability parent, or carriers	Both parents are carriers	Only one neither, are
Prior	$^1/_4$	$^3/_4$
Conditional:		
2 normal children	$(^3/_4)^2$	1
Joint	9/64	48/64
Posterior	**9 / 57**	

Risk of next child being affected = 9/57 x $^1/_4$ = 9/228 = ~ 1/25

d) II.2 and II.3 have been diagnosed with metachromatic leukodystrophy (MLD), with the onset of signs between 15-18 months. Name the biochemical abnormality associated with MLD. [2]

Arylsulphatase A (ARSA) deficiency

e) Describe one pitfall in biochemical testing for MLD [2]

Enzyme assay cannot distinguish between MLD and ARSA pseudodeficiency, which is present in 5-20% of normal controls

f) Name one method of confirming a diagnosis of MLD [2]

Molecular testing of ARSA, urinary excretion of sulphatides, or the presence of metachromatic lipid deposits in nervous system tissue

25) Topic area: NF1

An 11-year-old boy is referred from the paediatrician with possible type 1 neurofibromatosis. He has two cafe au lait spots and has had five skin lesions removed since the age of 5. The histology report indicated that these were consistent with neurofibromas.

a) Why is this presentation not typical of NF1? [4]

Usually >6 CAL spots by the age of 2. Neurofibromas are not a typical feature of childhood NF1

b) Name one congenital anomaly that may complicate NF1 [2]

Pseudarthrosis of the tibia or Plexiform neurofibromas

c) Give two clinical features you could look for to confirm a diagnosis of NF1 [4]

Skin fold freckling (neck, axilla, groin); recount cafe au lait spots; other skin lesions;

d) Give two things you could ask about in the history or family history to confirm this or another likely diagnosis. [4]

FH of NF1 or NF2 features, eg: learning difficulties; hearing problems; visual problems; brain/spinal tumours

e) Why would you ask for the histology to be reviewed? [2]

Recheck re schwannomas

f) If the histology suggests a different diagnosis and this is confirmed by molecular testing, describe the management of two major complications of this other condition. [4]

Acoustic neuromas – scans; optic gliomas – ophthalmology; meningiomas – MRI brain scan. Surgery and prognosis for each.

26) Topic area: DiGeorge

A microdeletion at 22q11.2 is associated with the clinical phenotype known as DiGeorge syndrome or velocardiofacial syndrome.

a) Name three major congenital malformations apart from congenital heart disease. [3]

- *Cleft palate*
- *Renal tract anomalies*
- *Parathyroid hypoplasia/aplasia*
- *Thymic hypoplasia/aplasia*

b) Name three non-genetic laboratory investigations that should be requested. [3]

- *PTH and Calcium level*
- *Thyroid function test*
- *T, B, and NK(natural killer) lymphocyte subsets*
- *Serum immunoglobulins and tetanus, diphtheria, and Hib antibody titres (if older than 4 months)*

c) After prenatal detection of del 22q11 and a cardiac lesion, name two additional potential management issues and their reasons in the newborn period [4]

- *Feeding problems related to palatal abnormalities such as cleft palate, submucous cleft palate, or velopharyngeal insufficiency*
- *Management of seizures due to hypoparathyroidism and hypocalcaemia*
- *Renal ultrasound scan due to possible renal tract anomalies*
- *Need for CMV-negative and irradiated transfusion products due to variable defect in cell-mediated immunity*
- *Consider antibiotic prophylaxis pending results of immune function after discussing with an immunologist due to variable defect in cell-mediated immunity*

d) Describe how copy number variants in this region occur and what is the typical size of the deletion. [4]

- *There are several low-copy repeats (LCRs) on chromosome 22 and those flanking the 22q11.2 region facilitate homologous recombination. Misalignment between blocks of LCRs leads to non-homologous recombination and either a deletion or duplication.*
- *Most have a 3Mb deletion whereas a minority have a distal deletion of 1.5Mb.*

e) Name three differential diagnoses of 22q11.2 deletion syndrome [3]

- *CHARGE syndrome*
- *VATER/VACTERL association*
- *Oculo-auriculo vertebral (Goldenhar) syndrome*
- *Alagille syndrome*

f) Describe three of the well characterised behavioural and psychiatric features described in 22q11.2 deletion syndrome. [3]

- *Autism spectrum disorder*
- *Attention deficit*
- *Difficulty with social interactions*
- *Schizophrenia*
- *Bipolar disorders*
- *Anxiety and depression*

27) Topic area: Turner

Turner syndrome is most commonly due to loss of an X chromosome and a 45,X karyotype

a) Give three features in the newborn period that may suggest this diagnosis. [3]

- *Oedema of hands and feet*
- *Short, broad, webbed neck*
- *Low posterior hairline*
- *Congenital heart defect such as coarctation of aorta or ventricular septal defect (VSD)*
- *Renal anomalies including horseshoe kidney or unilateral renal agenesis*
- *Widely spaced nipples*

b) Name 2 potentially life threatening findings on prenatal ultrasound scan [2]

- *Cystic hygroma/very large nuchal translucency measurement*
- *Hydrops*
- *Severe cardiac defect*

c) Describe the possible aetiology of short stature and its treatment in 45,X Turner syndrome. [4]

- *Combination of SHOX deletion and absent pubertal growth spurt*
- *Growth hormone treatment and oestrogen replacement therapy*

d) Name four health problems that may occur in adults that require screening/treatment, apart from short stature. [4]

- *Primary ovarian insufficiency leading to osteoporosis and infertility*
- *Autoimmune disorders such as hypothyroidism, diabetes mellitus and inflammatory bowel disease*
- *Obesity*
- *Hypertension*
- *Dyslipidaemia and increased cardiovascular risk*
- *Hearing loss – conductive and sensorineural*

e) Name three reproductive options for women with 45,X who are infertile. [3]

- *Egg donation*

- *Adoption*
- *Surrogacy*

f) Describe two other structural abnormalities of the X chromosome found in Turner syndrome and a unique characteristic feature of each [4]

- *Mosaic 45,X/46,XX – milder features with increased chance of fertility*
- *Mosaic 45,X/46,XY – risk of gonadoblastoma, genital ambiguity*
- *Ring X – more severe phenotype with moderate/severe intellectual disability*
- *Deletion X variant Turner syndrome – milder features, increased chance of fertility, premature ovarian failure, compatible with liveborn males with developmental delay/intellectual disability and autism spectrum disorder*
- *And others! (duplication, inversions, isodicentric X)*

28) Topic area: Huntingtons Disease

A 45-year-old Japanese man presents with a history of deteriorating performance at work, poor concentration and abnormal movements. His mother had experienced similar problems some 25 years ago. You suspect the man to be affected by Huntington's disease (HD)

a) Why has HD a higher prevalence in some populations of Western European descent compared to Japan? [2]

distribution of specific predisposing alleles and haplotypes in the normal population of these ethnic groups; predisposition for CAG expansion of specific haplotypes

b) Name two alternative diagnoses that should be considered. [4]

Dentatorubropallidoluysian atrophy (DRLPA) (AD)
Benign familial chorea (AD)
Alternative acceptable answers Spinocerebellar ataxia (SCA3)
Neuroacanthosis (but AR, mostly described in Japanese)

c) What molecular genetic test result would provide unequivocal confirmation of your suggested diagnosis? [2]

expanded repeat = 1 mark. Either CAG or ≥40 repeats for 2nd mark

d) Give two possible molecular mechanisms for the pathogenesis of this man's symptoms. [4]

(i) Altered post---translational modification of mutant huntingtin (phosphorylation, acetylation, sumoylation)
(ii) Toxicity of the expanded polyglutamine tract in mutant huntingtin

e) Name a specific drug or class of drugs that may be used to manage his abnormal movements. [2]

either named drug (Amantadine, Remacemide, Levetiracetam,Tetrabenazine) or dopamine depleting drug

f) His asymptomatic daughter, aged 25, is pregnant. She is concerned to know whether her father's symptoms have implications for the health of her fetus. Describe two prenatal diagnostic strategies (not tissue sampling methods) that could be used to obtain information about the genetic status of the fetus, giving an advantage and disadvantage of each. [6]

1 mark for each of direct mutation testing and exclusion testing, plus one mark for an advantage and disadvantage for each.

	Direct testing of fetus	*Exclusion testing*
Advantages	*Fetal risk clearly defined.*	*Mother't status not revealed;*
Disadvantages	*Mother may be passively tested / mother may feel forced to undergo rapid predictive*	*Requires DNA samples from several family members; risk of terminating unaffected foetus*

29) Topic area: PTEN

A 47-year-old man presented with a neck lump. He underwent total thyroidectomy. Histology showed thyroiditis with no evidence of malignancy. On examination, he was macrocephalic, and was noted to have multiple small skin tags . He had previously been investigated in the ENT department where he had undergone removal of multiple buccal and pharyngeal polyps. Genetic testing revealed a mutation in the *PTEN* gene.

a) Name two other genes, mutations in which are associated with macrocephaly. [4]

FRAXA, NSD1, PTCH2, NSD1, NF1, RAS/MAPK pathway genes, ROR2, GFAP, GLI3, CXORF5, L1CAM, MLC1, BRWD3 etc

b) Name two syndromes associated with mutations in *PTEN* [4]

Bannayan-Riley-Ruvalcaba, Cowden, Mhyre-Smith, Proteus, Proteus-like, PTEN-related Hamartomatous Tumour Syndrome (PHTS)

c) Patients with *PTEN* mutations are at increased risk of thyroid cancer. What two additional types of screening do female gene mutation carriers warrant ? [4]

Breast cancer, endometrial cancer

d) What is the main function of the PTEN protein? [2]

Tyrosine phosphatase

e) To which functional class of genes does *PTEN* gene belong? [2]

Tumour suppressor

f) Name two other genes, mutations in which also predispose to hamartomatous tumours. [4]

TSC1, TSC2, STK11, SMAD4, BMPR1A