The Royal College of Pathologists
Pathology: the science behind the cure

Part 1 examination

Genetics: First Paper

Tuesday 24 September 2019

Candidates must answer FOUR questions ONLY

Time allowed: Three hours

1. For the molecular diagnosis of many genetic disorders there is a move towards using whole genome sequencing (WGS) rather than exome sequencing or large NGS gene panels.

   What additional insights has WGS provided for the aetiology of genetic disease in rare disease and cancer? Discuss the advantages of the different testing strategies that can be used for WGS.

2. After a successful business case, you have been provided funding to implement a new test into your laboratory. Using a defined example of a test, describe the quality management process that you would undertake to bring this test into a routine clinical service.

3. Abnormal fetal structural anomalies which are detected by ultrasonography have a range of genetic causes. Discuss how whole genome analysis for prenatally diagnosed structural congenital anomalies has evolved over the years. In particular, discuss

   (i) the advantages and disadvantages of the differing technologies

   (ii) the challenges we currently face to ensure appropriate reporting of genetic findings within a prenatal setting

4. Chromosome 11 is gene rich. Cytogenetic and molecular aberrations involving this chromosome have been observed in both constitutional and acquired disorders.

   Give examples of 2 constitutional and 2 acquired disorders involving chromosome 11. For each of your choices, briefly describe the disorder and the genetic mechanism/s involved.

5. Discuss the significance and implications of germline findings in the context of molecular genetic testing in somatic cancer. Using examples, consider both laboratory and clinical aspects.

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1.You have been contacted by a consultant clinical geneticist as she thought there was a discrepancy in results reported by your laboratory. Detail the investigations you would carry out and describe any changes you would put in place depending on the outcomes of your investigations.

The details of the case are as follows: Two years ago your laboratory performed a predictive test for breast cancer on a patient with a confirmed family history of cancer associated with a BRCA1 mutation (testing of several affected family members also carried out by your laboratory). There was no evidence of the mutation and a normal report was issued. The consultant has contacted you to say that the patient has now developed breast cancer.

2. Describe how and why the following are used in the management of disease. Provide an answer for **3** out of 5 only

- DPYD
- Imatinib
- Olaparib
- Dexamethasone
- Ivacaftor

3. Discuss the current technical and scientific limitations of whole genome sequencing analysis within the field of rare disease. Include examples of application into practice. Discuss the implications of a negative result on future testing for the patient.

4. Describe the mechanisms by which uniparental disomy can arise. Give two examples of when testing for this phenomenon would be carried out, including brief details of the methodologies used.

5. Genomic aberrations involving chromosome 22 have been observed in both constitutional and acquired disorders.
Give examples of two constitutional **and** two acquired disorders involving chromosome 22. For each of your choices, briefly describe the disorder and the genetic mechanisms involved.

FRCPath Part 1 Genetics Paper 1 Autumn 2021 – Essays

1. Non-invasive prenatal testing (NIPT) is currently being evaluated within different international Antenatal Screening Programmes for Down's syndrome, Edwards syndrome and Patau syndrome.

    a. Describe the difference between a screening test and a diagnostic test in relation to NIPT.

    b. What do you anticipate might be future applications of non-invasive prenatal testing in pregnancy, and how do existing technologies need to improve for these to be possible?

2. Cytogenetic and molecular aberrations involving chromosome 17 have been observed in both constitutional and acquired disorders.

    Give examples of two constitutional and two acquired disorders involving chromosome 17. For each of your choices, briefly describe the disorder and the genetic mechanisms involved.

3. Describe the role of external agencies in ensuring the quality of service delivery provided by Genetics Laboratories.

4. Describe the genetic tests that would be appropriate in the diagnosis of male infertility. How do the abnormalities found in these tests relate to the causes of infertility?

5. The introduction of whole genome/exome sequencing into routine clinical practice has the potential to identify clinically relevant incidental findings (also known as secondary findings or opportunistic findings) in both the germline and somatic setting. Similarly, clinically relevant germline variants may be identified when sequencing tumour tissue.

    a. What are the advantages and disadvantages of detecting and reporting incidental findings which are unrelated to the clinical indication under investigation?

    A number of genes found on somatic cancer panels for solid tumours and haematological malignancies may be associated with germline pre-disposition to cancer.

    b. Across a range of different cancers, name four such genes and describe the clinical features associated with each hereditary cancer syndrome. What might alert you to a suspicion of a germline predisposition?