



The Royal College of Pathologists

Pathology: the science behind the cure

**Part 1 Examination**

**Molecular Genetics First Paper**

**Tuesday March 23<sup>rd</sup> 2010**

***Candidates must answer FOUR questions only***

**Time allowed THREE HOURS**

- 1 Write brief notes on the cytogenetic and molecular genetic techniques used in the investigation of:
  - a) DiGeorge syndrome
  - b) Fragile X syndrome
  - c) Chronic myeloid leukaemia
  
- 2 Briefly describe the DNA repair pathways involved in the repair of damaged bases, mismatched bases and double strand breaks. Explain, with examples, how mutations in components of these pathways can lead to disease.
  
- 3 The first example of the use of exomic sequencing to identify a single gene responsible for a genetic disorder was published recently. Describe the principle of exomic sequencing and the recent developments in technology that enabled this strategy to be used. Are the authors correct in stating that this development will 'likely transform the genetic analysis of monogenic traits'?

**Please turn over for Questions 4 & 5**

4 Briefly explain the meaning of FOUR out of five of the following terms, giving examples drawn from human molecular pathology:

- a) haploinsufficiency
- b) retrotransposition
- c) dominant-negative mutations
- d) position effect
- e) inversion

5 What is a pseudogene and how do pseudogenes originate? Illustrate your answer with examples from the human genome, indicating how pseudogenes can be involved in human disease.



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**Part 1 Examination**

**Molecular Genetics – Second Paper**

**Tuesday March 23<sup>rd</sup> 2010**

***Candidates must answer FOUR questions only***

**Time allowed THREE HOURS**

- 1 What is mosaicism? Describe how mosaicism can be detected by both cytogenetic and molecular genetic techniques and discuss the limitations of different methods, with reference to clinically relevant situations.
  
- 2 How will the introduction of routine use of array CGH and next generation sequencing change diagnostic genetics? Briefly discuss how laboratories should deal with results of uncertain status (use as examples a copy number variant and a deep intronic single base change).
  
- 3 How does molecular pathology relate to phenotypic variability in *FMR1*-related disorders?

**Please turn over for Questions 4 & 5**

- 4 Make brief notes on the uses and limitations of FOUR of the five following techniques in diagnostic genetic testing:
- a) Pyrosequencing
  - b) MALDI-TOF mass spectrometry
  - c) Oligonucleotide ligation assay
  - d) Immunohistochemistry
  - e) High-resolution melt curve analysis
- 5 What are the clinical, ethical and scientific issues that should be taken into account when deciding whether population screening is appropriate for an inherited single gene condition?



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## **Part 1 examination**

### **Molecular Genetics: First paper**

**Tuesday 24 March 2009**

*Candidates must answer FOUR questions ONLY*

**Time allowed: 3 hours**

- 1 What are genomic disorders? Describe the mechanism that generates them, any predisposing features and the copy number changes they give rise to. Illustrate your answer with the key points using **THREE** specific examples.
  
- 2 Describe the principles of next generation sequencing. Outline the possible applications of this technology and the current limitations for use in a clinical diagnostic laboratory.
  
- 3 Write short notes on **EACH** of the following:
  - a) Pathogenic effects of gene variants in 5' or 3' untranslated regions
  - b) Dominant negative mutations
  - c) Autozygosity mapping

**Please turn over for Questions 4 & 5**

- 4 Using the example of **EITHER** familial adenomatous polyposis **OR** chronic myeloid leukaemia, describe the genetic mechanisms underlying development of the disease and how molecular genetic testing can be used to assist with clinical management.
  
- 5 Describe the **FIVE** different molecular classes of human *CFTR* gene mutations with reference to genotype-phenotype correlation



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## **Part 1 examination**

### **Molecular Genetics: Second paper**

**Tuesday 24 March 2009**

*Candidates must answer FOUR questions ONLY*

**Time allowed: 3 hours**

- 1 Outline the factors that should be taken into account when deciding whether, and how, new diagnostic tests should be introduced into the laboratory repertoire. |
- 2 Outline the current methods available to analyse free fetal DNA in the maternal circulation. What are the possible applications of these techniques in the diagnosis of genetic disease?
- 3 Genetic testing for risk factors for common disorders is becoming widely available to the public. Discuss the scientific and ethical issues raised by this practice.

**Please turn over for Questions 4 & 5**

- 4 Describe examples of pharmacogenetic tests used to:
  - a) reduce adverse drug reactions
  - b) determine drug dosage
  - c) identify patients likely to respond to specific pharmacological therapies
  
- 5 Critically evaluate the use and limitations of bioinformatic tools for determining the pathogenicity of novel variants.



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**Part 1 examination**

**Molecular Genetics: First paper**

**Tuesday 18 March 2008**

*Candidates must answer FOUR questions ONLY*

**Time allowed: 3 hours**

- 1
  - a) Explain the term 'contiguous gene deletion syndrome'.
  - b) Use examples to describe the phenotypic effects of such deletions (excluding imprinted genes).
  - c) Outline the methods available for identifying contiguous gene deletions.
  
- 2 Define mosaicism. Explain the underlying mechanisms with reference to the following diseases:
  - a) Either Achondroplasia or Apert syndrome
  - b) Either Tuberous sclerosis or Neurofibromatosis type 2
  - c) Beckwith Wiedemann syndrome

**Please turn over for Questions 3, 4 & 5**

- 3 Discuss genotype/phenotype relationships for males and females with the following disorders:
  - a) X-linked lethal
  - b) X-linked dominant
  - c) X-linked recessive
  
- 4 Biochemical tests can assist with the diagnosis of many molecular genetics disorders. Write short notes on such tests and their underpinning scientific basis, currently in use in the routine diagnosis of disease for clinical genetics, clinical biochemistry and haematology. Give IFVE examples to illustrate your answer
  
- 5 Using examples from retinoblastoma, hereditary non-polyposis colon cancer and breast ovarian cancer show how mutations in tumour suppressor genes can lead to the development of a cancer



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**Part 1 examination**

**Molecular Genetics: Second paper**

**Tuesday 18 March 2008**

*Candidates must answer FOUR questions ONLY*

**Time allowed: 3 hours**

- 1 Describe the role of external agencies in ensuring the quality of service delivery provided by Genetics Laboratories.
  
- 2 Explain the principles underlying the following techniques, illustrate with examples of application in clinical molecular genetics:
  - a) High resolution melt analysis
  - b) In-silico tools for predicting pathogenicity of novel missense variants
  - c) Pre-implantation genetic diagnosis
  - d) Fetal sexing from maternal plasma
  
- 3 You are asked to respond to a proposal for the inclusion of Fragile X testing in the national newborn screening programme. What are the potential limitations and associated risks?

**Please turn over for Questions 4 & 5**

4 Define, with examples, the following:

- a) Exon Splicing Enhancer
- b) Nonsense Mediated Decay
- c) Cryptic Splice Site

How would you investigate the effect of a potential splicing mutation?

5 Whole genome association studies have led to the identification of new susceptibility genes involved in the aetiology of obesity, diabetes, cancer and inflammatory bowel disease, amongst others.

Describe the methodologies utilised in these studies and comment on how this knowledge might be used in future clinical practice.



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**Part 1 examination**

**Molecular Genetics: First paper**

**Tuesday 27 March 2007**

*Candidates must answer FOUR questions ONLY*

**Time allowed: 3 hours**

1. Explain the principles underlying following techniques, illustrate with examples of application in clinical molecular genetics
  - a. Di-deoxy DNA sequencing
  - b. western blotting
  - c. Multiplex ligase-dependent probe amplification (MLPA)
  - d. Immunocytochemistry/immunohistochemistry
  
2. What is X-inactivation, how is it mediated, and for what purpose? How using cytogenetic and molecular genetics methods can X-inactivation status be assessed in a female? How can skewed X inactivation lead to disease?
  
3. Describe how different types of repeat sequences in the genome (other than trinucleotide repeats and other microsatellites) can contribute to disease. Give examples. Describe possible mechanisms.

**Please turn over for Questions 4 and 5**

- 4 Define, with examples, the following:
- a. Random genetic drift
  - b. Founder effect
  - c. X-linked dominant disease

How you would test if a common mutation was due to a Founder effect rather than recurrent mutation at a hot spot.

- 5 Describe how abnormalities in protein folding can cause diseases with gain-of-function, loss-of-function or dominant-negative mutational mechanisms. Give examples of diseases to illustrate the relevant principles.



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## Part 1 examination

### Molecular Genetics: Second paper

Tuesday 27 March 2007

*Candidates must answer FOUR questions ONLY*

**Time allowed: 3 hours**

1. The 2006 Nobel Prize in Physiology or Medicine was awarded to Andrew Fire and Craig Mello. It honours a discovery that has transformed biological research and may, in the future, prove useful in treating human disease. The discovery is called RNA interference, or RNAi.

Describe the basic principles of how siRNA (small interfering RNA) and miRNA (microRNA) regulate gene expression. Describe the possible physiological roles of this process, how this discovery has provided critical biological reagents for functional genomics (give examples) and describe how it may be useful for therapy of certain diseases (give examples and describe possible risks of the methodology).

2. A recent report evaluating the use of array comparative genomic hybridisation (aCGH) in the investigation for idiopathic learning disabilities suggests it should be considered as a first line investigation.

Describe the issues, (biological, scientific, and technical) which would need to be taken into consideration prior to a CGH as a first line investigation being introduced for these patients into a diagnostic genetics laboratory.

**Please turn over for Questions 3, 4 and 5**

3. Define:

- a. Lod score; and the principles of genetic linkage analysis (Parametric linkage)
- b. Transmission disequilibrium test
- c. Population stratification

Give examples of methods that can be used to limit risk of false positive results due to population stratification in genetic association studies.

4. What types of mutations give rise to the absence of a protein product of the expected correct size on a denaturing SDS gel? Describe why the protein is absent or has abnormal gel mobility and describe the experimental methods that you would use to define the relevant mechanisms.

5. Answer the following questions in relation to Huntington's disease (HD):

- a. What is anticipation and what is the molecular basis for this phenomenon in HD?
- b. What is a prenatal exclusion test? Describe the principles used with a hypothetical example?
- c. What is the evidence supporting the argument that HD is caused by a mutation that confers a toxic gain-of-function on the mutant gene product?