The Royal College of Pathologists

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 under pining 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

The Royal College of Pathologists

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.

The Royal College of Pathologists

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.

The Royal College of Pathologists

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?

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 14 March 2006

MOLECULAR GENETICS

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1 Define imprinting and describe what is understood about the underlying molecular mechanisms regulating imprinting. Give examples of how imprinting can result in genetic disease.

2 Write short notes on 4 out of 5 of the following:

a) Define the term "oncogene" and give examples of their role in genetic disease

b) Define the term "tumour suppressor gene". Explain the method by which many have been identified and give examples in genetic disease

c) Draw a diagram of the cell cycle explaining the key events. Briefly describe how the cell cycle is thought to be regulated

d) What clinical features in a cancer patient would make you think that he/she had a familial cancer?

e) Define microsatellite instability in the context of cancers. What does this phenotype tell us about the genes that are dysfunctional and about the resulting molecular consequences?

Please turn over for Questions 3, 4 and 5

3 Define gain-of-function, loss-of-function and dominant-negative mutations. Give examples and describe how you would devise experiments to test a new disease caused by autosomal dominant missense mutations to discriminate between these possibilities. Why is this important?

4 Write short notes on 4 out of 5 of the following:

a) the Hardy-Weinberg equilibrium

b) lod score

c) the International HapMap Project

d) linkage analysis with affected sib pairs

e) heterozygote advantage

5 Describe the variable clinical phenotypes that arise due to mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR). What are the molecular determinants of phenotypic variability due to these mutations?

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 14 March 2006

MOLECULAR GENETICS

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1 What are the key managerial, certification and scientific requirements for maintaining a robust diagnostic service for cytogenetics and molecular genetics?

2 What functional and genetic experiments would you do to show that the following are real mutations that change the function of a gene?

a) stop codon

b) missense mutation

c) mutation in a consensus splice site

d) mutation in the 5' region upstream of a transcription start site

e) copy number change

Please turn over for Questions 3, 4 and 5

3 Discuss the current areas in which neonatal screening is being used. Describe new developments in neonatal screening in the 21st century and how they should be prioritised.

4 Discuss technologies that may impact on genetic diagnosis in the near future by becoming largely automated. What are the challenges of such methods for diagnostic laboratories and how may they effect clinical medicine and its services?

5 In the latest issue of an eminent journal there is a report showing a convincing association between the number of copies of the serum rhubarb gene (as assessed by quantitative PCR) and the risk of influenza (flu). The gene is present in 0-7 copies in the Japanese sample studied in the paper.

Discuss the steps that should be considered as a prelude to offering a genetic diagnostic test for this gene in order to prioritise whether people receive flu vaccination in the UK. Your answer should consider all aspects (genetic, clinical, scientific and costs).

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 15 March 2005

Molecular Genetics

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Explain the meaning of FIVE of the following terms, illustrating your answer with examples of human genetic disorders and explaining the underlying mechanisms:

   a) Anticipation
   b) Penetrance
   c) X inactivation
   d) Mitochondrial inheritance
   e) Uniparental disomy
   f) Tertiary trisomy

2. Discuss the relationship between phenotype and genotype in Fragile X syndrome.

3. Describe the mechanism of RNA processing including reference to the utility of RNA analysis within a diagnostic genetics laboratory and implications for future potential therapy.

Please turn over for Questions 4 and 5

4. Compare and contrast, with examples, the features of polyglutamine and polyalanine repeat disorders in humans.

5. One gene can cause several syndromes and several syndromes can be caused by more than one gene. Discuss with examples.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 15 March 2005

Molecular Genetics

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Describe causes of potential technical error within either a diagnostic molecular genetics or cytogenetics laboratory and the measures you would put into place to avoid them.

2. You have been asked to establish a service for rapid prenatal detection of the common trisomies. Describe how you would go about this and what mechanisms you would put into place to provide a rapid but accurate service.

3. Compare the advantages and disadvantages of direct sequence analysis with mutation scanning for analysis of multi-exon genes with reference to familial breast cancer and familial colon cancer.

4. Discuss the management of health and safety in the diagnostic molecular genetics laboratory. What are the key causes of non-compliances?

5. Population screening presents challenges to the diagnostic service. Discuss the criteria and conditions for which this may be appropriate with reference to service implications and ethical issues.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 16 March 2004

MOLECULAR GENETICS

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Describe what methods are available to investigate copy number changes of genes and chromosomes, citing examples. What are the relative advantages and disadvantages of the methods?

2. Describe briefly the technique of linkage analysis. What are its advantages and disadvantages? In what circumstances might linkage analysis be performed as an alternative to mutation detection for diagnostic purposes?

3. Discuss the relationship between genotype and phenotype with reference to the dystrophin gene and the Factor VIII gene.

4. Discuss the genetics of colorectal cancer. Include information on the functions of the genes involved and details of the disease phenotypes.

Please turn over for Question 5

5. EITHER

Write short notes on 3 of the following with respect to gene expression:

a) Nonsense mediated RNA decay
b) Position effect
c) CpG methylation
d) Small interfering RNA (siRNA)

OR

Write an essay on non-mendelian genetics.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 16 March 2004

MOLECULAR GENETICS

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. What are the principles and practice of internal laboratory audit for a diagnostic genetics laboratory? Describe in detail how you would set up and carry out a laboratory audit?

2. What are the ethical issues that should be considered when offering genetic testing?

3. You are asked to set up a diagnostic service for a specific genetic disease in your laboratory. Describe the processes you would go through to do this for either Rett syndrome or Duchenne muscular dystrophy (DMD).

4. Describe the principles of reverse transcription PCR (RT-PCR) and the protein truncation test (PTT). Give examples of their use in the diagnostic laboratory.

5. What are the errors that can occur in the analysis of prenatal samples in the DNA diagnostic laboratory? How would you minimise such errors?

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 18 March 2003

MOLECULAR GENETICS

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Indicate how Clinical Cytogenetics (including Molecular Cytogenetics) has been used as a key technique to identify disease gene loci, illustrating your answer with relevant clinical examples.

2. A family has been diagnosed with a fully penetrant inherited disease caused by an unidentified gene. What steps would you go through to identify the causative gene?

3. Outline five mutational mechanisms causative of genetic disease with examples.

4. What are the possible origins of uniparental disomy? Give examples of its role in human genetic disease.

5. **EITHER**
   Briefly describe the roles that CpG methylation has in gene expression. Give examples of the analysis of CpG methylation sites in diagnostic genetics.

   OR
   Write brief notes on the following:
   (a) A possible origin of pseudogenes and their role in inherited disease, citing two examples.
   (b) the observation of anticipation in inherited conditions, using two examples.
   (c) Mosaicism, giving one example of how mosaicism can be demonstrated in a genetic condition.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 18 March 2003

MOLECULAR GENETICS

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. In laboratory diagnostic genetics relate the roles; of internal quality control, external quality assessment and accreditation by external agencies.

2. In the context of diagnostic services discuss the arguments for and against the use of a direct sequence analysis approach to search for unknown mutations in multi-exonic genes. Contrast this approach with alternative mutation scanning technologies.

3. Give the different common indications for referral for molecular genetic testing for cystic fibrosis including both neonates and adults. Outline the differences in approach to genetic testing required for the different categories of referral.

4. Summarise a proposal for a service for fragile X testing in a new centre. With reference to the clinical and genetic features of the condition discuss the advised indications for referral. Describe the technology to be used and any limitations to the technology

5. Using examples from retinoblastoma, hereditary nonpolyposis colon cancer and breast ovarian cancer show how mutations in tumour suppressor genes can lead to the development of a cancer.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 2002

MOLECULAR GENETICS

First Paper

Candidates must answer FOUR questions ONLY

Time allowed – THREE HOURS

1. Write short notes on the cytogenetic (including molecular cytogenetic) and molecular genetic approaches to the investigation of:
   (a) Fragile X syndrome,
   (b) Prader-Willi and Angelman syndromes,
   (c) Type 1A Charcot-Marie-Tooth Disease/Hereditary Neuropathy with Liability to Pressure Palsies.

2. **EITHER**
   Discuss, using examples, the principles of mapping and identification of genes involved in inherited disease. Explain how gene mapping has been aided in some cases by linkage analysis in consanguineous pedigrees.

   OR
   Write brief notes on <u>three</u> of the following:
   (a) Linkage disequilibrium,
   (b) Identity by descent,
   (c) Online Mendelian Inheritance in Man,
   (d) Locus heterogeneity.

3. Discuss the contribution of nuclear and mitochondrial genes to the pathogenesis of hereditary mitochondrial disease.

[Turn over

4. Genomic deletions and duplications can give rise to monogenic disease. Give examples and describe appropriate laboratory diagnostic methods that can be applied for their identification.

5. Discuss the relationship between genotype and phenotype in monogenic diseases using the examples of cystic fibrosis and fragile X syndrome.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 2002

MOLECULAR GENETICS

Second Paper

Candidates must answer FOUR questions ONLY

Time allowed – THREE HOURS

1. Write short notes on the various cytogenetic (including molecular cytogenetic) and molecular genetic approaches to assessing genomic copy number.

2. Discuss the current and emerging technologies available for high throughput genotyping in a diagnostic genetics service setting and explain their roles and limitations.

3. Summarise the types of adverse events that can happen in a diagnostic genetics laboratory. Outline the policy and procedures required for the management of adverse events once they have happened.

4. In the course of testing the hMSH2 gene in an individual at risk of hereditary non polyposis colorectal cancer, you identify a missense mutation that has not been reported previously. How would you attempt to determine the pathogenic significance of your finding?

[Turn over

5. Your laboratory has a testing protocol for familial breast cancer that involves three stages:

   (i) A multiplex ARMS assay that detects mutations seen in 10% of an initial high risk series of 300 unrelated cases.

   (ii) A series of protein truncation assays that can identify a further 5% of mutations in the same series of cases.

   (iii) Complete sequence analysis of BRCA1 and BRCA2 gene coding regions from amplified genomic DNA.

   Outline the steps needed to establish and carry out a presymptomatic genetic test for a woman at high risk of inheriting a familial breast cancer gene mutation based on pedigree information. Describe the controls and precautions that are needed to assure the quality of this particular test at each stage.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 2001

MOLECULAR GENETICS

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Discuss, giving specific examples, how animal models have been useful in the study of human genetic disorders. Why might there be differences between humans and other animals that harbour mutations in homologous genes?

2. Discuss the biological significance of 5-methylcytosine in the mammalian genome. Give examples of particular disorders that are associated with defects in the establishment, maintenance or interpretation of genomic methylation.

3. Write notes on TWO of the following:
   (iii) denaturing high performance liquid chromatography
   (iv) the structure and function of telomeres
   (v) RNAase protection assays.

4. Describe how you would approach:
   (vi) the identification of monogenic causes of diabetes?
   (vii) the mapping of susceptibility genes for diabetes?
   What are the difficulties and potential pitfalls? How might the identification of a pathogenic mutation or susceptibility alleles(s) benefit diabetic patients and their relatives?

5. Explain how the sequence of the human genome was determined, describing the difference between draft and finished sequence. What risks and benefits will the availability of this sequence present to clinical genetics?

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 2001

MOLECULAR GENETICS

Second Paper

Candidates MUST answer the first question in the separate answer book provided and any THREE of the remaining FOUR questions

Time allowed - THREE HOURS

1. You have been invited to contribute to a regional Specialist Commissioning review. How would you justify the service that a diagnostic genetic laboratory provides? In light of the publication of the human genome sequence data, what improvements and developments of the service over the next 5 years would you request and why?

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2. Hereditary non-polyposis colorectal cancer accounts for only a proportion of familial bowel cancer, and is genetically heterogeneous. How might a diagnostic service for HNPCC, including germline mutation detection, be organised?

a. A clinician, investigating a severely ill neonate with encephalomyopathy and lactic acidosis asks your genetics laboratory to organise the investigation of oxidative phosphorylation defects. In addition to mutations in the mitochondrial genome, discuss other proteins, and the pattern of inheritance of their respective loci, that should be considered.

[Turn over

1. Discuss the genetic basis of Friedreich Ataxia. What is the current understanding of the biological function of frataxin? The genetic analyses of several loci are often requested in the investigation of patients presenting with 'ataxia'. What are these? Why is requesting for multiple loci sometimes appropriate given that some of these follow different pattern of inheritance?

5. Fragile X is clinically a highly heterogeneous disorder. What is the genetic basis of some of this heterogeneity? What is known of the biological function of FMRP? Briefly describe a practical diagnostic strategy for a molecular diagnostic laboratory.