The Royal College of Pathologists

Part 1 examination

Clinical Cytogenetics: First paper

Tuesday 27 March 2007

Candidates must answer FOUR questions ONLY

Time allowed: 3 hours

1. Explain the principles underlying the following techniques, illustrate with examples of application in a clinical cytogenetics service:

    a. C-banding
    b. Multiplex ligation dependent probe amplification
    c. Sister chromatid exchanges
    d. Fluorescence in situ hybridisation using unique sequence probes

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. Explain the relationship between particular types of DNA repeat sequences and recurrent structural chromosome abnormalities. Illustrate with examples of constitutional abnormalities.

Please turn over for Questions 4 and 5

4. Describe the clinical features and genetic causes associated with the following karyotypic findings. What are the main differential diagnoses?

    a. 46,XX karyotype in a phenotypic male
    b. 46,XY karyotype in a phenotypic female

5. Describe the disease and cytogenetic/molecular defects in the following:

    a. Burkitt's lymphoma
    b. Infant leukaemia
    c. Multiple myeloma

The Royal College of Pathologists

Part 1 examination

Clinical Cytogenetics: Second paper

Tuesday 27 March 2007

Candidates must answer FOUR questions ONLY

Time allowed: 3 hours

1. 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.

2. Describe the screening options available to achieve a detection rate for Down Syndrome greater than 75% with a false positive rate of 3%. How would the choice of these options by obstetricians affect prenatal diagnoses referrals to a cytogenetics laboratory?

3. Discuss the diagnostic and prognostic value of identifying acquired cytogenetic abnormalities in acute leukaemias.

Please turn over for Questions 4 and 5

4. Write fully interpreted reports for the following findings:

    a. A mosaic supernumerary bisatellited marker chromosome in a PHA stimulated culture of a blood sample from a child with developmental delay, which is shown by fluorescence in situ studies to be derived from chromosome 22

    b. Mosaicism for chromosome 14 in a cultured chorionic villus sample referred with a positive first trimester Down screening result

    c. 10% of metaphases from a blood sample from an infant with unexplained neurological problems show rearrangements involving 7, 14 and X

    d. A 46,XY karyotype in a cultured postnatal fetal skin tissue sample which was referred for confirmation following a rapid prenatal test result (for copy number of chromosomes 13, 18 and 21) on uncultured chorionic villi which indicated trisomy 18.

    Supplement your answer with any additional aspects you may have taken into consideration but which you have not included in your report.

5. Your service commissioners are undertaking a review of cytogenetic services and have invited you to write a report detailing what changes/developments in services and workforce can be expected in 5 years time. What developments and improvements would you put into your report and why?

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 14 March 2006

CLINICAL CYTOGENETICS

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

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

2 Explain the molecular genetics of fragile X syndrome and describe the cytogenetic (including molecular cytogenetic) and molecular genetic approaches to the investigation of the syndrome.

3 Write short notes on three of the following.

a) Retinoblastoma

b) Mantle cell lymphoma

c) Smith-Magenis syndrome

d) Williams syndrome

Please turn over for Questions 4 and 5

4 Describe how you would interpret the following scenarios:

a) 45,X/46,XX in a cultured blood sample in a female with a history of recurrent miscarriage

b) Mosaicism for chromosome 16 in a cultured amniotic fluid referral for positive maternal serum screen test

c) Random aneuploidy in a cultured blood sample from a child with growth retardation

5 Discuss, with examples, how genetic testing can contribute to the investigation of acute myeloid leukaemia (AML). Discuss the diagnostic and prognostic importance of the results of the tests carried out.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 14 March 2006

CLINICAL CYTOGENETICS

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 Discuss recent advances in technology that have been made in screening for cryptic chromosome rearrangements in patients with idiopathic learning disability.

3 Discuss the current options available for the screening of Down syndrome. What impact will or could they have on the service provided by a cytogenetics laboratory?

4 Automated techniques are being increasingly introduced into cytogenetic laboratories. Discuss what processes are amenable to automation and the advantages and disadvantages of introducing doing this.

5 Write an essay on the genetics of Fanconi's anaemia and describe the diagnostic testing strategy.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 15 March 2005

Clinical Cytogenetics

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. Describe a strategy for the genetic testing of Acute Lymphoblastic Leukaemia. Discuss the diagnostic and prognostic importance of the results of the tests carried out.

Please turn over for Questions 3, 4 and 5

3. Describe the reported cytogenetic abnormalities involving chromosome 22 and discuss their clinical significance, giving a range of examples from constitutional and malignancy related investigations.

4. Give an account of normal variation in the human genome.

5. Give an account of the genetic and cytogenetic causes of complete and partial sex reversal including sexual ambiguity.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 15 March 2005

Clinical Cytogenetics

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. Describe the main health and safety issues in the design and operation of a Clinical Cytogenetics laboratory.

3. You have been asked to produce a development plan for your service for the next five years. With reference to either constitutional or haematological cytogenetics, discuss the changes in the service that you predict and provide justification for any proposed developments.

4. You have been asked to give a presentation to the staff of your local miscarriage clinic covering the chromosomal contribution to miscarriage and the likelihood of the same abnormalities resulting in a live birth. Write out a draft of your presentation.

Please turn over for Question 5

5. The detection of mosaicism in prenatal diagnostic testing can give rise to difficulties in interpretation. In the cases of mosaic trisomy at CVS and amniocentesis discuss the different types of mosaicism that can occur, the follow up tests that would be appropriate and the implications of the possible findings.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 16 March 2004

CLINICAL CYTOGENETICS

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. Discuss the relative advantages and disadvantages of the methods.

2. Describe the different types of genetic mosaicism and discuss the aetiology for each type.

3. Describe reported cytogenetic abnormalities involving chromosome 8 and discuss their clinical significance, giving a range of examples from constitutional and acquired investigations.

4. Describe all the factors you would consider when evaluating and interpreting the following scenarios:

    a) Reciprocal translocation in a recurrent miscarriage referral

    b) Marker chromosome in a maternal age amniotic fluid referral

    c) Chromosome 2 mosaicism in a long term CVS culture, with no direct culture processed.

Please turn over for Question 5

5. **EITHER**

Write short notes on the clinical phenotype, chromosome abnormality and method of diagnosis in 4 of the following:

a) Beckwith-Wiedemann syndrome
b) Roberts syndrome
c) Cat eye syndrome
d) Pallister-Killian syndrome
e) Ring X chromosome

OR

Write short notes on the disease and the cytogenetic/ molecular genetic abnormality in 4 of the following:

a) follicular lymphoma
b) Ewing's sarcoma
c) Philadelphia positive acute lymphoblastic leukaemia
d) Secondary (therapy related) leukaemia
e) Infant leukaemia

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 16 March 2004

CLINICAL CYTOGENETICS

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. Discuss the ethical issues that should be considered when offering genetic testing.

3. All diagnostic laboratories aspire to operate with minimal risk (to the patient or within the laboratory). Discuss the minimisation of risk, considering risk in the broadest sense.

4. Your laboratory currently performs prenatal diagnosis using closed suspension cultures and turnaround times are approximately 14 days. Your clinicians are requesting a faster service. You have been asked to compare the relative merits of investing in:

a) change of practice to reduce full karyotyping turnaround times
b) developing a rapid aneuploidy screening service eg by FISH or molecular genetics

Present your appraisal of these options, describing the advantages and disadvantages of each approach.

Please turn over for Question 5

5. Your laboratory success rates and turnaround times have been declining over recent months in both your prenatal and haematological malignancy sections. Select either the prenatal or haematological malignancy section and describe how you would tackle the problem.

Part 1 Examination

Tuesday 18 March 2003

CLINICAL CYTOGENETICS

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. Write an essay on chromosome instability ("breakage") syndromes.

3. Describe the phenomenon of "X inactivation". How do you account for the fact that females with a 45,X karyotype have a clinical phenotype?

4. Describe the aetiology of Uniparental Disomy, and give examples of its role in human genetic disease.

5. **EITHER**

   A recent textbook about Human Chromosomes includes the statement "Given the frequencies of nondisjunction and chromosome loss throughout life, we are all mosaics to some degree". Discuss the cytogenetic evidence for and against this statement.

   OR

   Write short notes on the mechanisms and cytogenetic applications of any <u>three</u> of the following:

   (a) Whole Chromosome FISH ("Chromosome Painting")
   (b) Replication Banding
   (c) C-Banding
   (d) Comparative Genomic Hybridisation

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

Tuesday 18 March 2003

CLINICAL CYTOGENETICS

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. Discuss which diagnostic techniques could be improved or introduced by automation in a Clinical Cytogenetics Laboratory. What advantages and disadvantages does automation provide?

3. How would you evaluate the clinical effectiveness of different approaches to prenatal cytogenetic diagnosis?

4. Write an essay on the prognostic value of acquired structural cytogenetic abnormalities in acute leukaemias and solid tumours.

5. Discuss the relative advantages and disadvantages of (i) G-band analysis, (ii) M-FISH or SKY, and (iii) FISH with a set of sub-telomeric probes, as alternative methods to investigate couples with recurrent miscarriage or infertility.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 2002

CLINICAL CYTOGENETICS

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. Write an essay on the numerical and structural chromosome abnormalities associated with complete or partial sex reversal.

3. Discuss, with examples, how molecular cytogenetic techniques can contribute to the investigation of leukaemia and solid tumours.

4. Describe the composition, behaviour, and function of the chromatin associated with the bands revealed by C, G and R banding.

[Turn over

5. **EITHER**

Write short notes on any three of the following:

(a) Deletion 1p36.3 syndrome

(b) Euchromatic variants of 16p11.2

(c) ICF syndrome

(d) Reciprocal translocation t(11;22)(q23:q11).

OR

Write short notes on the type and prognostic significance of the cytogenetic rearrangements associated with any three of the following:

(a) Philadelphia chromosome negative chronic myeloid leukaemia

(b) Neuroblastoma

(c) Multiple myeloma

(d) Chronic lymphocytic leukaemia.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 2002

CLINICAL CYTOGENETICS

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 observation that the majority of constitutional chromosome abnormalities are numerical, whilst many of the key oncogenetic acquired chromosome rearrangements in leukaemia and lymphoma are structural.

3. Describe, with specific examples, the processes that contribute to quality assurance in a diagnostic clinical cytogenetics laboratory.

4. You have been asked to show a group of undergraduate genetics science students around your cytogenetics laboratory. How would you describe the benefits that your laboratory service provides to patients? One of the undergraduates asks a question about the applications of microarray technology. How would you explain the possible advantages and disadvantages of conventional G-band analysis versus microarray approaches?

[Turn over

5. Describe the structure of the human sub-telomeric region and the methods by which sub-telomeric rearrangements may be detected. How would you apply sub-telomeric testing to your local population? How do you account of the fact that the frequency of sub-telomeric rearrangements found in different published series varies from 0% to 23.5% of patients investigated?

Part 1 Examination

March 2001

CLINICAL CYTOGENETICS

First Paper

Candidates must answer FOUR questions ONLY

Time allowed - THREE HOURS

1. Discuss the roles of the following in human cancer and/or leukaemogenesis:
   (ii) p53 (Tumour Protein 53)
   (iii) MLL (Myeloid/Lymphoid Leukaemia gene)
   (iv) bcr.abl (breakpoint cluster region/Abelson leukaemia.

2. With reference to specific examples explain how low copy repeats or duplicons give rise to structural abnormalities and indicate their pathological consequences.

3. How can uniparental disomy arise? In what circumstances would you test for this phenomenon?

4. Write an essay on genetic recombination and the origin of the extra chromosome in human trisomies.

5. Write an essay on the mechanism and consequences of X chromosome inactivation in humans.

THE ROYAL COLLEGE OF PATHOLOGISTS

Part 1 Examination

March 2001

CLINICAL CYTOGENETICS

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. Explain what is meant by clinical audit. Describe, with specific examples, how it could be applied to diagnostic clinical cytogenetic laboratory services.

3. Indicate which categories of pregnancy might be regarded as of high risk for a chromosome abnormality? What diagnostic procedures would you recommend for these pregnancies? Discuss the problems that might be associated with the different procedures recommended.

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. Discuss appropriate strategies for following up the detection of a supernumary marker chromosome. What factors influence the final decision on whether the marker is of clinical significance?