

Mock ECMGG exam 1/2:

1. A 4-month-old boy has hypotonia and tongue fasciculation. Spinal muscular atrophy (SMA) is suspected.

Investigations:

Child: 0 copies of *SMN1* exon 7.

Mother: 1 copy of *SMN1* exon 7.

Father: 2 copies of *SMN1* exon 7.

What is the most likely explanation for these results in the father?

- A Both copies of *SMN1* are *in cis* in the father
- B Conversion of *SMN1* to *SMN2* locus in the father
- C Laboratory error
- D Non-paternity
- E The father has a point mutation in *SMN1*

2. A 23-year-old woman has familial gastric cancer.

Investigations

DNA sequencing detects a heterozygous nonsense *CDH1* variant. The gene contains 16 exons, all coding.

Nonsense-mediated decay is most likely to occur if the variant is located in which position?

- A Third codon in exon 1
- B Middle of exon 6
- C End of exon 15
- D Start of exon 16
- E End of exon 16

3. A 31-year-old woman has autosomal dominant familial hypertrophic cardiomyopathy (HCM).

Investigations

Next-generation sequencing: A missense variant in *MYBPC3* is identified.

Which single finding would be sufficient to classify the variant as benign?

- A Allele frequency of 5.2% in gnomAD
- B Benign prediction by Polyphen-2 and SIFT scores
- C Lack of splicing interference shown by minigene assay
- D Low inter-species protein sequence conservation
- E Low missense-constraint Z score for *MYBPC3* in gnomAD

4. A 54-year-old man has had multiple spontaneous pneumothoraces. His mother had a similar history and died of bilateral renal cancer.

What is the suspected diagnosis?

- A Alpha-1 Antitrypsin deficiency
- B Birt-Hogg-Dubé syndrome
- C Fumarase deficiency
- D Marfan syndrome
- E Multiple endocrine neoplasia type I

5. A 38-year-old man has colon cancer. Next generation sequencing of a panel of cancer genes identifies a number of variants.

Investigations:

	Gene	Variant	No. Cases in gnomAD	
A	<i>BRCA2</i>	p.Ile3418Ser	0	Heterozygous
B	<i>MLH1</i>	p.Val194Ile	1	Heterozygous
C	<i>MSH2</i>	p.Arg711Ter	1	Heterozygous
D	<i>MUTYH</i>	p.Gln335Ter	37	Heterozygous
E	<i>SMAD4</i>	c.516+6T>A	0	Heterozygous

Which variant is most likely to be causal?

- A A
- B B
- C C
- D D
- E E

6. A 35-year-old man has Leber hereditary optic neuropathy (LHON).

Which inheritance pattern is most likely?

- A Autosomal dominant
- B Autosomal recessive
- C Mitochondrial
- D X-linked dominant
- E X-linked recessive

7. A 48-year-old woman has 40 colonic adenomas and 5 duodenal adenomas. Her brother died of a colonic adenocarcinoma at 49 years. Her parents are first cousins.

Investigations:

APC mutation analysis: no pathogenic variant and no exonic deletion or duplication.

What is the most likely diagnosis?

- A Juvenile polyposis syndrome
- B *MLH1*-associated Lynch syndrome
- C *MUTYH*-associated polyposis
- D Peutz-Jeghers syndrome
- E Polymerase proofreading-associated polyposis

8. A 32-year-old woman has myotonic dystrophy type 1 (DM1).

Investigations:

DMPK analysis: Heterozygous CTG-repeat expansion >200.

What cardiac complication is most likely to affect her?

- A Aortic dilatation
- B Atrioventricular septal defect
- C Conduction defects
- D Dilated cardiomyopathy
- E Peripheral pulmonary stenosis

9. A 40-year-old man has progressive muscle weakness affecting the shoulder and pelvic girdles.

Investigations:

Echocardiogram and cardiac MRI: Dilated cardiomyopathy.

ECG: first degree A-V block

A pathogenic variant in which gene is most likely to explain the phenotype?

- A *KCNQ1*
- B *LMNA*
- C *MYBPC3*
- D *MYH7*
- E *SCN5A*

10. A 2-month-old boy with rhizomelic shortening also has punctate ossifications detected by X-rays.

Which group of disorders is most likely to cause this?

- A Ciliopathies
- B Golgi apparatus diseases
- C Peroxisomal disorders
- D RASopathies
- E Ribosomopathies

11. A 36-year-old woman is pregnant. Fetal growth was normal until 22 weeks, when femur length fell, crossing below the 1st centile at 27 weeks. Abdominal and head circumference remain in the normal range.

What is the most likely cause of the short limbs?

- A Achondroplasia
- B Campomelic dysplasia
- C Hypophosphatasia
- D Osteogenesis imperfecta type 1
- E Thanatophoric dysplasia

12. A 20-year-old woman has early onset bilateral cataracts and primary ovarian failure (POF).

What is the most likely diagnosis?

- A Alagille syndrome
- B Fragile X syndrome-associated POF
- C Galactosaemia
- D McCune-Albright syndrome
- E Turner syndrome

13. A 33-year-old man has azoospermia, small testes, and short stature. He underwent surgery for gynaecomastia when he was 14 years old.

Investigations:

Karyotype (blood): normal female: 46,XX

What is the most common genetic cause of the patient's disorder?

- A 5-alpha reductase deficiency
- B Androgen receptor deletion
- C FSH receptor duplication
- D *SHOX* deletion
- E *SRY* translocation

14. A 2-year-old boy has developmental delay and febrile seizures.

Investigations:

Chromosome microarray of the boy:

arr[GRCh37] 8p23.3p23.1(191530_6644251)x1, 8q24.3(142840194_146280020)x3

Karyotype of the mother: 46,XX

What is the most likely karyotype of the father?

- A 46,XY
- B 46,XY,del(8)(p23.3p23.1)
- C 46,XY,ins(8)(q24.3p23.1p23.3)
- D 46,XY,inv(8)(p23.1q24.3)
- E 46,XY,r(8)(p23.1q24.3)

15. A 6-month-old boy has Down syndrome, born to healthy parents both aged 25 years.

Investigations:

Karyotypes:

Boy: 46,XY,rob(14;21)(q10;q10),+21

Mother: 45,XX,rob(14;21)(q10;q10)

Father: 46,XY

What is the recurrence risk of Down syndrome for this couple?

- A <1%
- B 1-2%
- C 10-15%
- D 40-50%
- E 90-100%

Question	Correct answer
1	A
2	B
3	A
4	B
5	C
6	C
7	C
8	C
9	B
10	C
11	A
12	C
13	E
14	D
15	C