



X

A 12-year-old boy is brought to the clinic for evaluation of muscle weakness. The patient has a history of seizures, and he has recently had several stroke-like episodes that resulted in muscle weakness. Examination shows decreased strength in the upper and lower extremities on the left compared to the right. Laboratory evaluation shows increased serum lactate levels both after exercise and at rest. Further work-up confirms that the patient has a genetic condition that is transmitted exclusively through the maternal line. His older sister is affected by the same disorder, but she displays very few symptoms. Which of the following is the most likely explanation for the variability in clinical presentation between this patient and his sister?

- A. Anticipation
- B. Genetic heterogeneity
- C. Genetic imprinting
- D. Heteroplasmy
- E. Pleiotropy

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X  
tion Id: 1788

A 14-year-old boy experiences severe, prolonged bleeding following a tooth extraction. He also has a history of multiple episodes of painful joint swelling following minor trauma. His parents have no bleeding problems. Evaluation shows that the patient has an inherited disorder and that one of his parents is a genetic carrier. His older sister, who does not have this condition, is pregnant. She does not know the sex of her child. She asks about the risk that her child will be affected. Which of the following is the best estimate that this child will have the disease?

- A. Near 0
- B. 1/2
- C. 1/4
- D. 1/8
- E. 1/16
- F. 1/32

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A 10-year-old boy is brought to the emergency department for new swelling in his right leg. He has a history of lens dislocation and intellectual disability. Physical examination demonstrates moderate, pitting edema from his right calf to his right thigh and a normal left lower extremity. In addition, the patient has a caved-in appearing chest wall. He has no family members with similar conditions. Ultrasound reveals a deep venous thrombosis in his right femoral vein. Further genetic testing reveals a single missense mutation in the gene coding for cystathione beta-synthase enzyme. Which of the following is the most likely explanation for this patient's genetic defect affecting multiple tissues?

- A. Dominant negative mutation
- B. Genetic linkage
- C. Incomplete penetrance
- D. Locus heterogeneity
- E. Pleiotropy
- F. Polyploidy
- G. Segregation

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A patient is suspected of having an inherited disorder. Pedigree analysis shows the following pattern:

This patient most likely has which of the following conditions?

- A. Classic galactosemia
- B. Hemophilia B
- C. Huntington disease
- D. Leber hereditary optic neuropathy
- E. Rett syndrome

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A 25-year-old nulligravid woman comes with her husband to the clinic for preconception genetic counseling. She has oculocutaneous albinism due to a homozygous *OCA2* gene mutation within the region of chromosome 15q12-q13. Examination shows pale hypopigmented skin with blonde hair. Eye examination shows faint brown irises. Her husband is 26 years old and has oculocutaneous albinism due to a biallelic *TYR* gene mutation at position 11q14.3. Examination of the husband shows complete absence of pigmentation in the skin, hair, and irises. The couple asks about their chance of having a child with oculocutaneous albinism and are told that the chance is 0%. Which of the following is the best explanation for this?

- A. Allelic heterogeneity
- B. Heteroplasm
- C. Incomplete penetrance
- D. Linkage disequilibrium
- E. Locus heterogeneity
- F. Pleiotropy

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A study is undertaken to map the HLA-DQ loci in a population with a high incidence of celiac sprue. High-resolution HLA typing of the DQA1 and DQB1 loci is performed using polymerase chain reaction sequencing. The frequency of the DQA1\*0501-DQB1\*0201 haplotype, strongly implicated in autoimmunity, is found to be 0.2. However, in the same population, the frequency of the DQA1\*0501 allele is 0.3 and the frequency of the DQB1\*0201 allele is 0.2. Which of the following best explains the observed DQA1\*0501-DQB1\*0201 haplotype frequency in this population?

- A. Heteroplasmy
- B. Increased penetrance
- C. Linkage disequilibrium
- D. Pleiotropy
- E. Segregation

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A 50-year-old previously healthy man is evaluated for progressive fatigue, weakness, and recurrent gingival bleeding. Laboratory studies reveal normocytic normochromic anemia, thrombocytopenia, and leukocytosis with circulating myeloblasts. Bone marrow biopsy establishes a diagnosis of acute myeloid leukemia. Induction chemotherapy followed by allogeneic hematopoietic cell transplantation (HCT) is planned. Molecular typing of human leukocyte antigen (HLA) -A, -B, -C, -DP, -DQ, and -DR is performed. The patient's biological sister, with whom he shares both parents, is eligible for stem cell donation and undergoes HLA typing. Which of the following is the most likely probability that the sibling will be an identical HLA match with this patient?

- A. 0
- B. 1/16
- C. 1/8
- D. 1/4
- E. 1/2

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A 19-year-old woman is evaluated for new onset generalized tonic-clonic seizures. For the past several years, she has also been having erratic jerks of her arms and legs, and intermittent muscle weakness. The girl has multiple family members with similar symptoms. Neurological examination reveals decreased sensation in the lower extremities and a broad-based gait. Skeletal muscle biopsy shows ragged, red-appearing muscle fibers. Further analysis reveals that the patient's symptoms are due to a mutation affecting extranuclear DNA. Which of the following pedigrees is most likely to represent this patient's family history? (The arrow points to the patient.)

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

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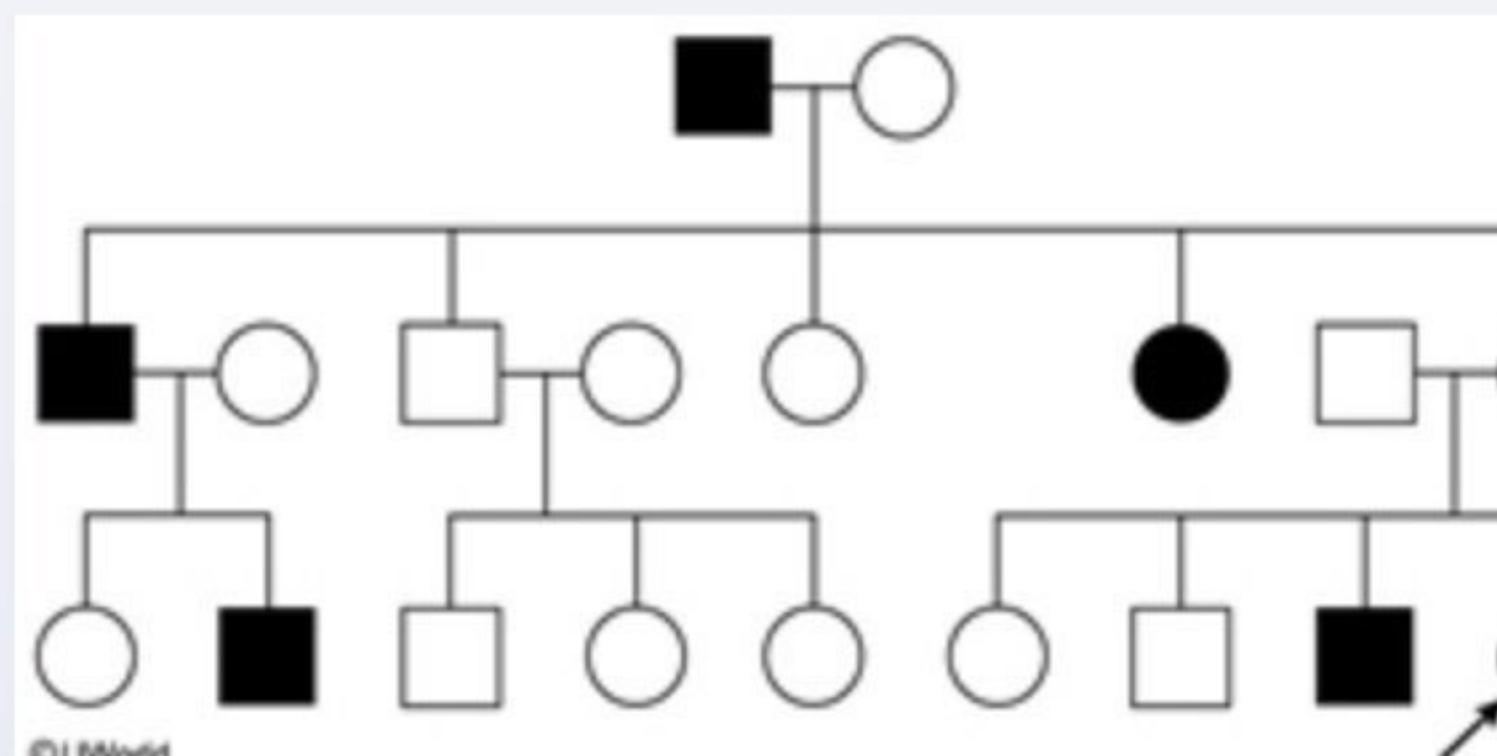
A healthy couple, who recently emigrated from Eastern Europe, brings their 3-year-old son to the office for evaluation of an eczematous rash. On examination, the child also shows signs of intellectual disability and gait abnormality and has a musty body odor. Which of the following is the likelihood that this couple's next child will be affected with the same disease?

- A. Same as the general population
- B. 1/32
- C. 1/16
- D. 1/8
- E. 1/4
- F. 1/2

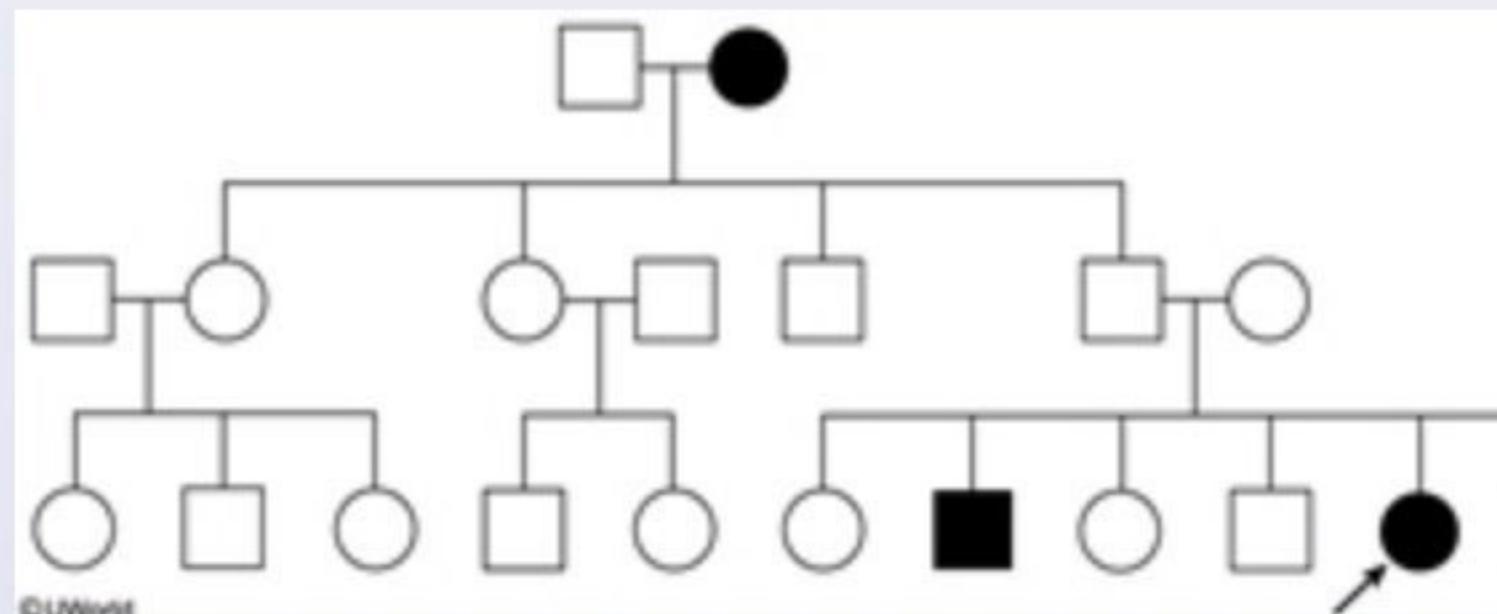
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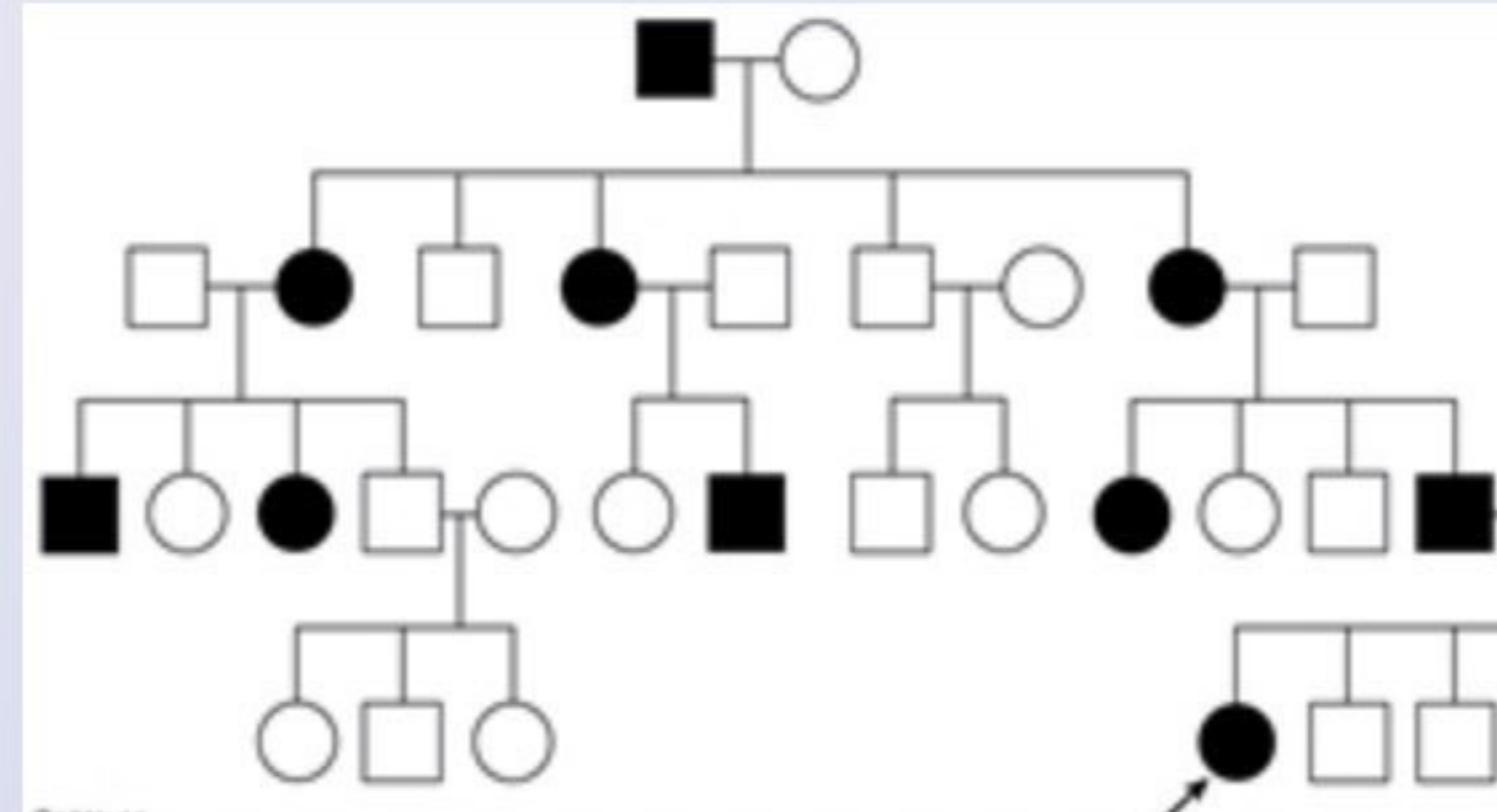
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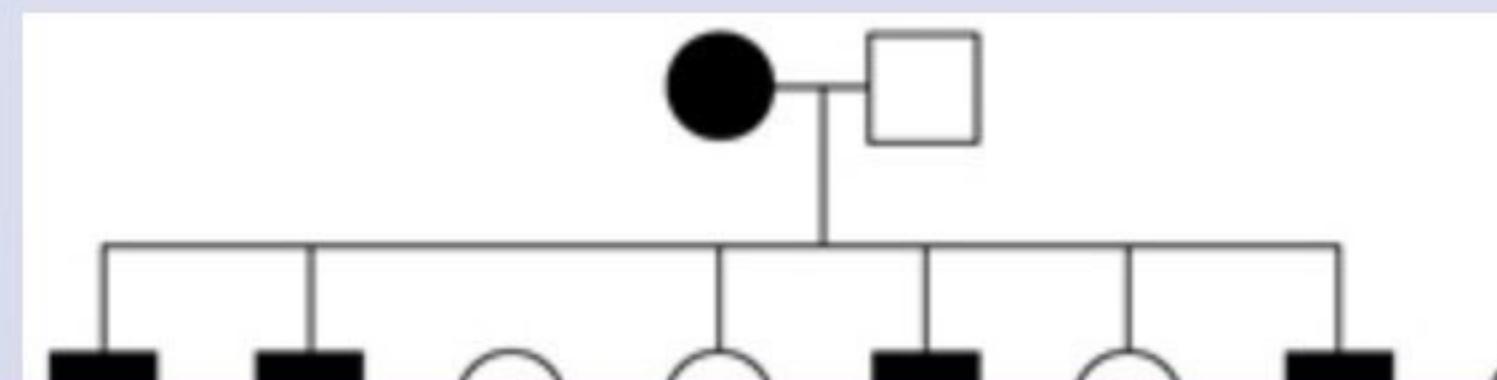
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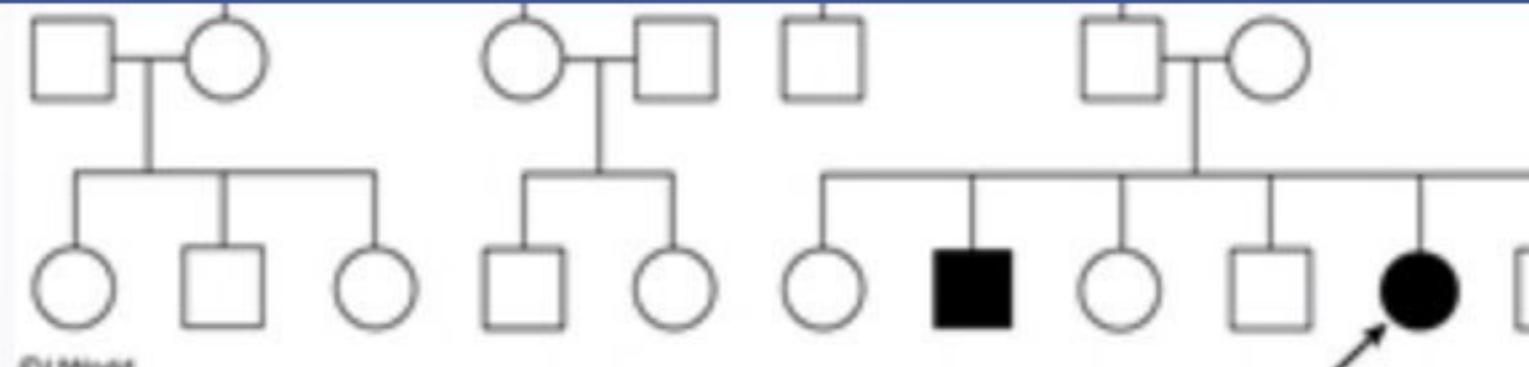
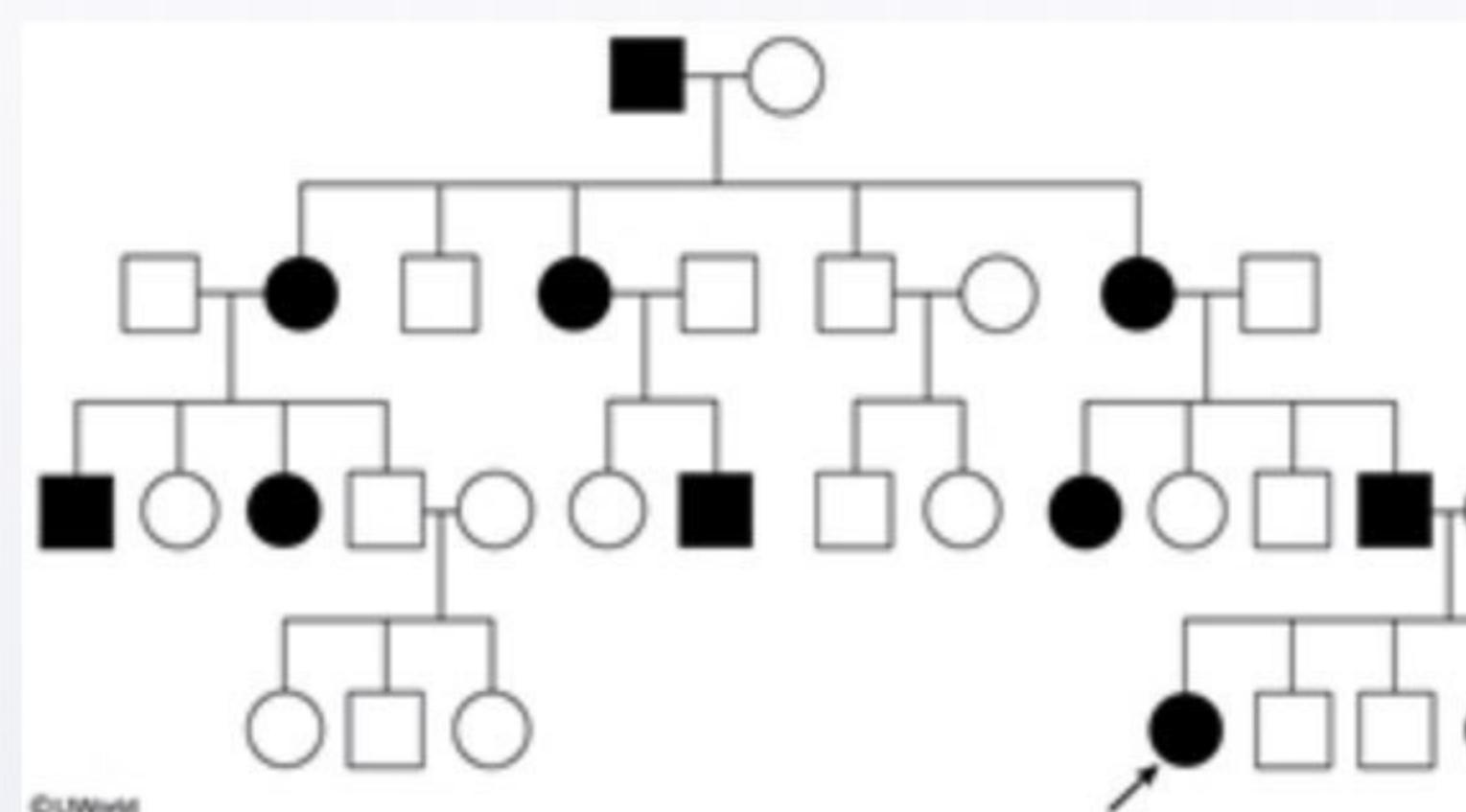
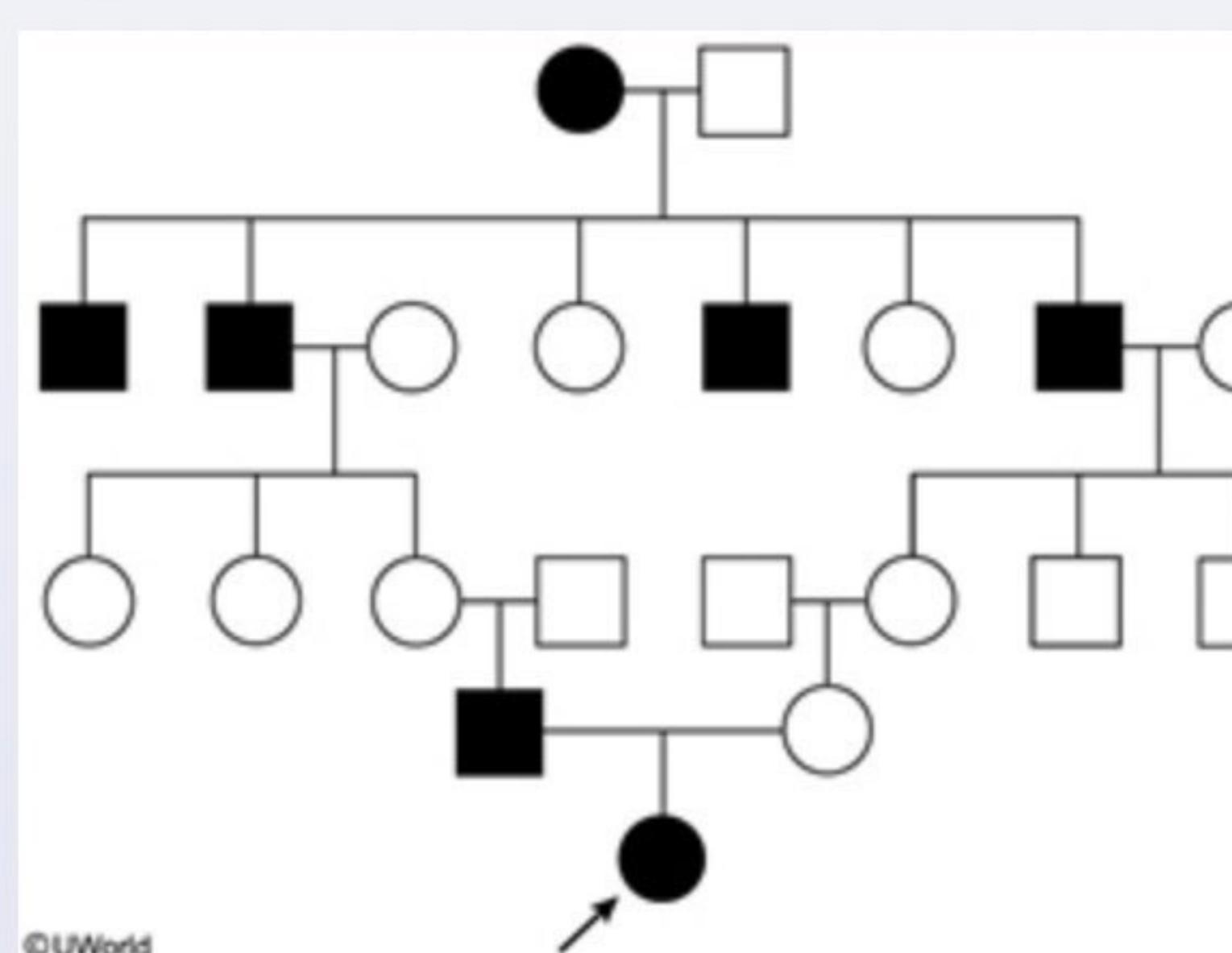
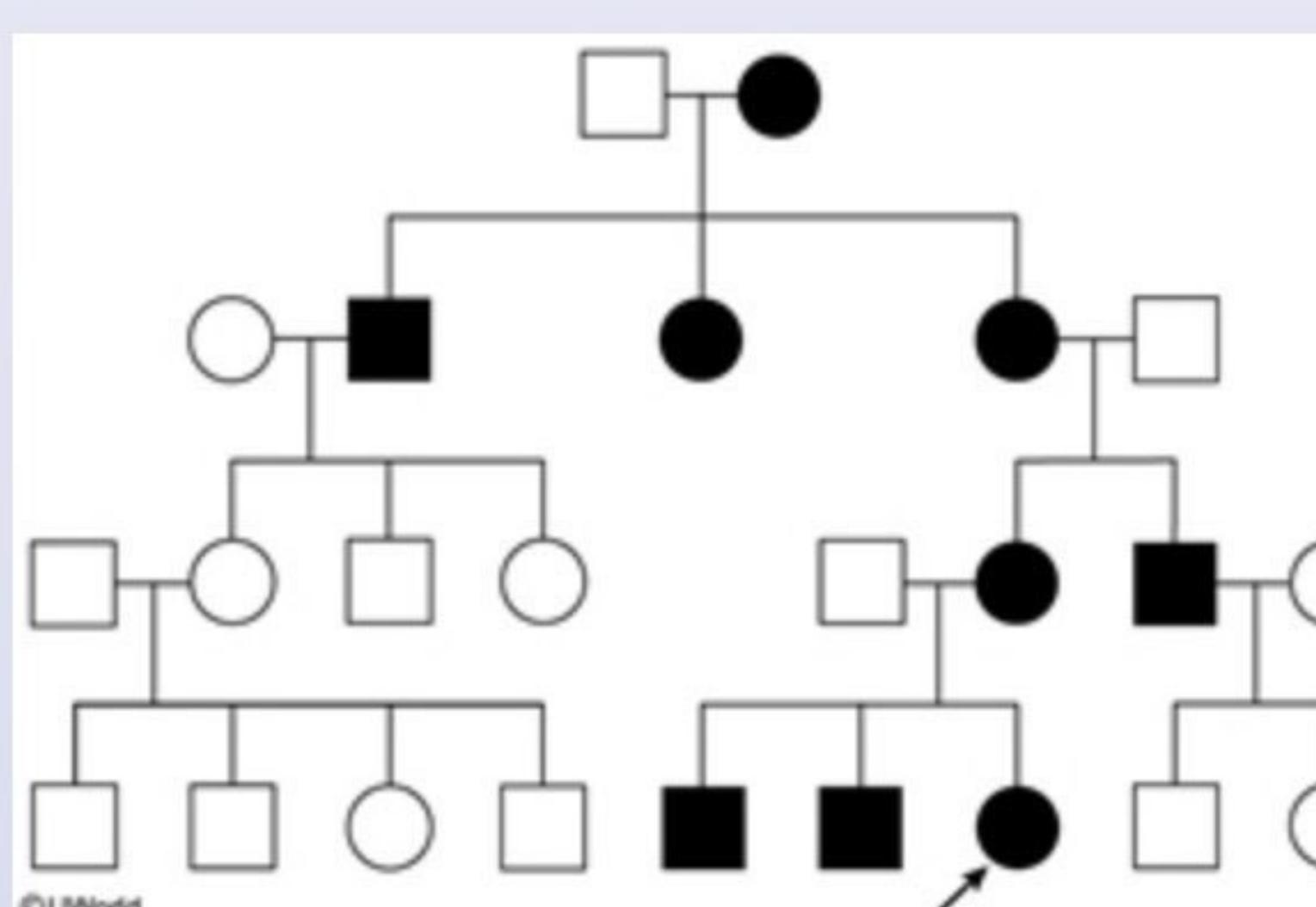


C.



D.



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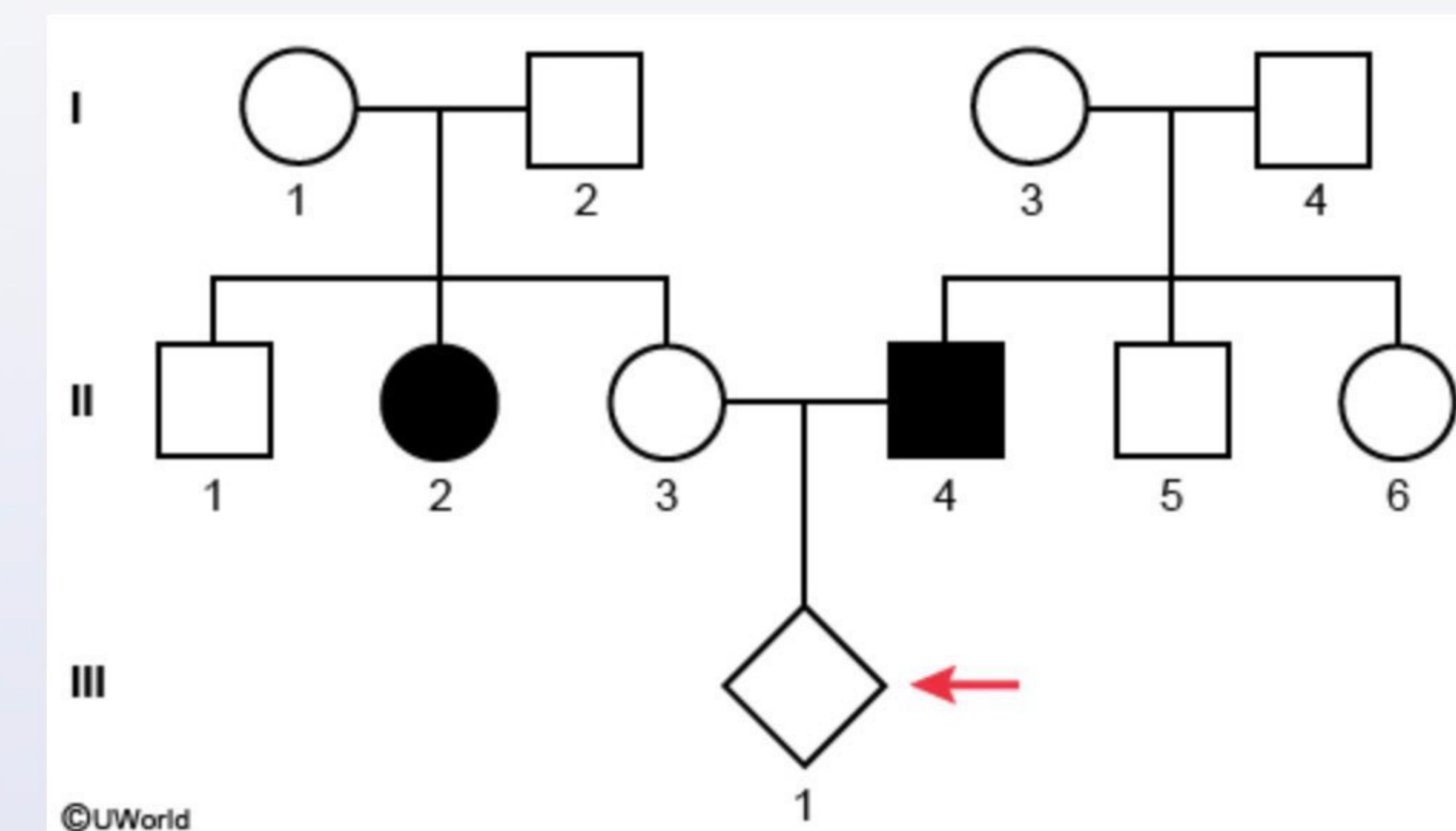


A 5-year-old boy is being evaluated for progressive muscle weakness that has resulted in numerous recent falls. There is no family history of muscle disorders. Physical examination reveals bilateral calf enlargement. When the patient is asked to stand, he uses his hands and arms to help push himself to an upright position. Serum creatine kinase is 12,600 U/L (normal: 30-170 U/L). Molecular tests reveal a large muscle protein that is defective due to the loss of 508 amino acid residues. Genetic analysis reveals a single base substitution within exon 48 of the gene encoding this muscle protein. This patient's gene mutation has most likely resulted in which of the following mRNA codon changes?

- A. CUU → AUU
- B. UAA → UAG
- C. UAC → CAC
- D. UCA → UGA
- E. UUU → UUC

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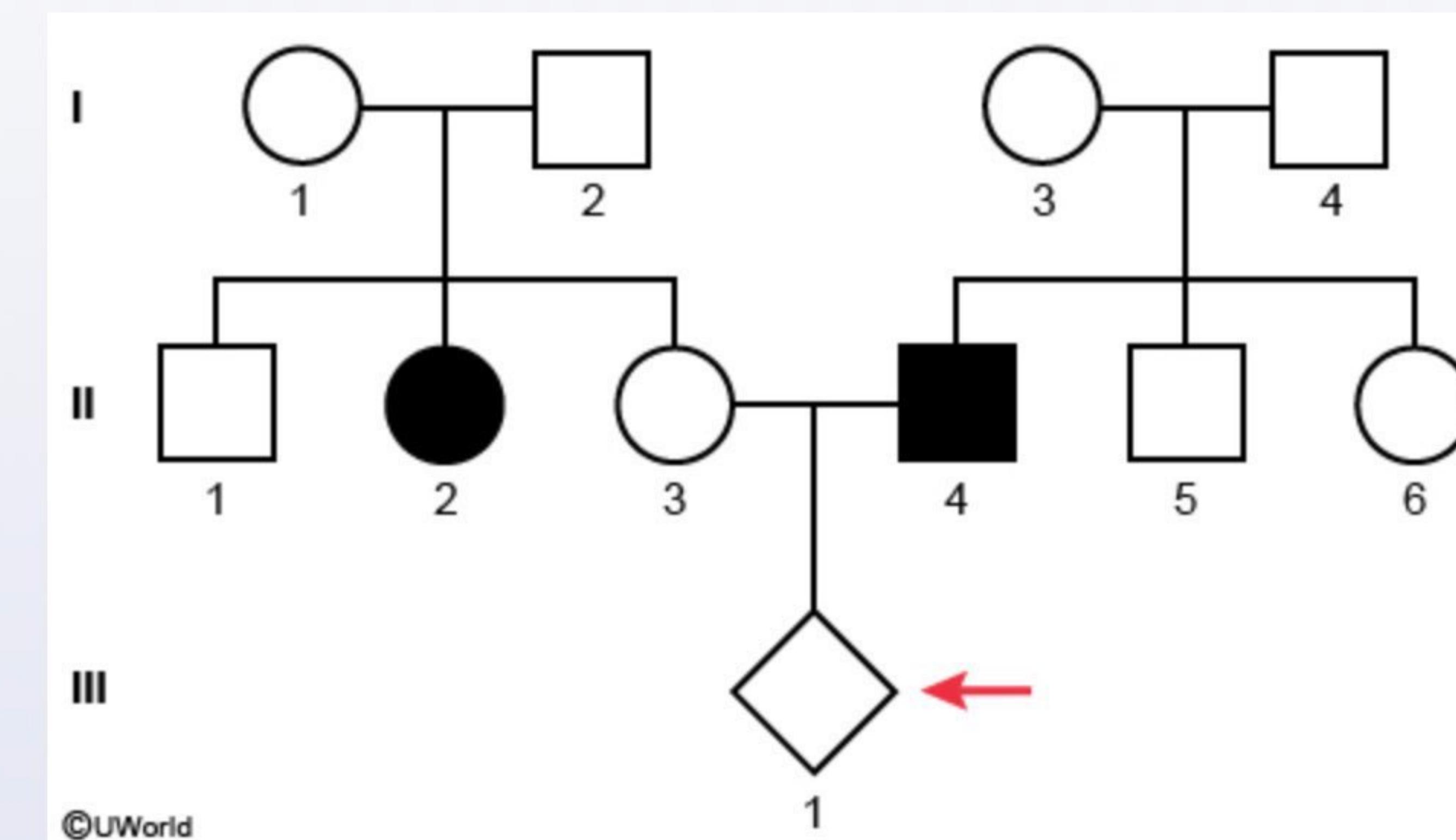
A young couple has undergone a successful in vitro fertilization procedure. The father has cystic fibrosis and the mother has a sister with cystic fibrosis. The father as well as the mother's sister are both known to have  $\Delta F508$  mutations, but the mother's carrier status is unknown. Before making the decision to conceive, the couple underwent extensive genetic counseling regarding the potential risks of having a child with cystic fibrosis. The family pedigree is diagrammed below with the unborn child marked by the red arrow.



What is the probability that the unborn child will have cystic fibrosis?

- A. 1/16
- B. 1/8
- C. 1/4
- D. 1/3
- E. 2/3
- F. 3/4

A young couple has undergone a successful in vitro fertilization procedure. The father has cystic fibrosis and the mother has a sister with cystic fibrosis. The father as well as the mother's sister are both known to have ΔF508 mutations, but the mother's carrier status is unknown. Before making the decision to conceive, the couple underwent extensive genetic counseling regarding the potential risks of having a child with cystic fibrosis. The family pedigree is diagrammed below with the unborn child marked by the red arrow.



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- C. 1/4
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- E. 2/3
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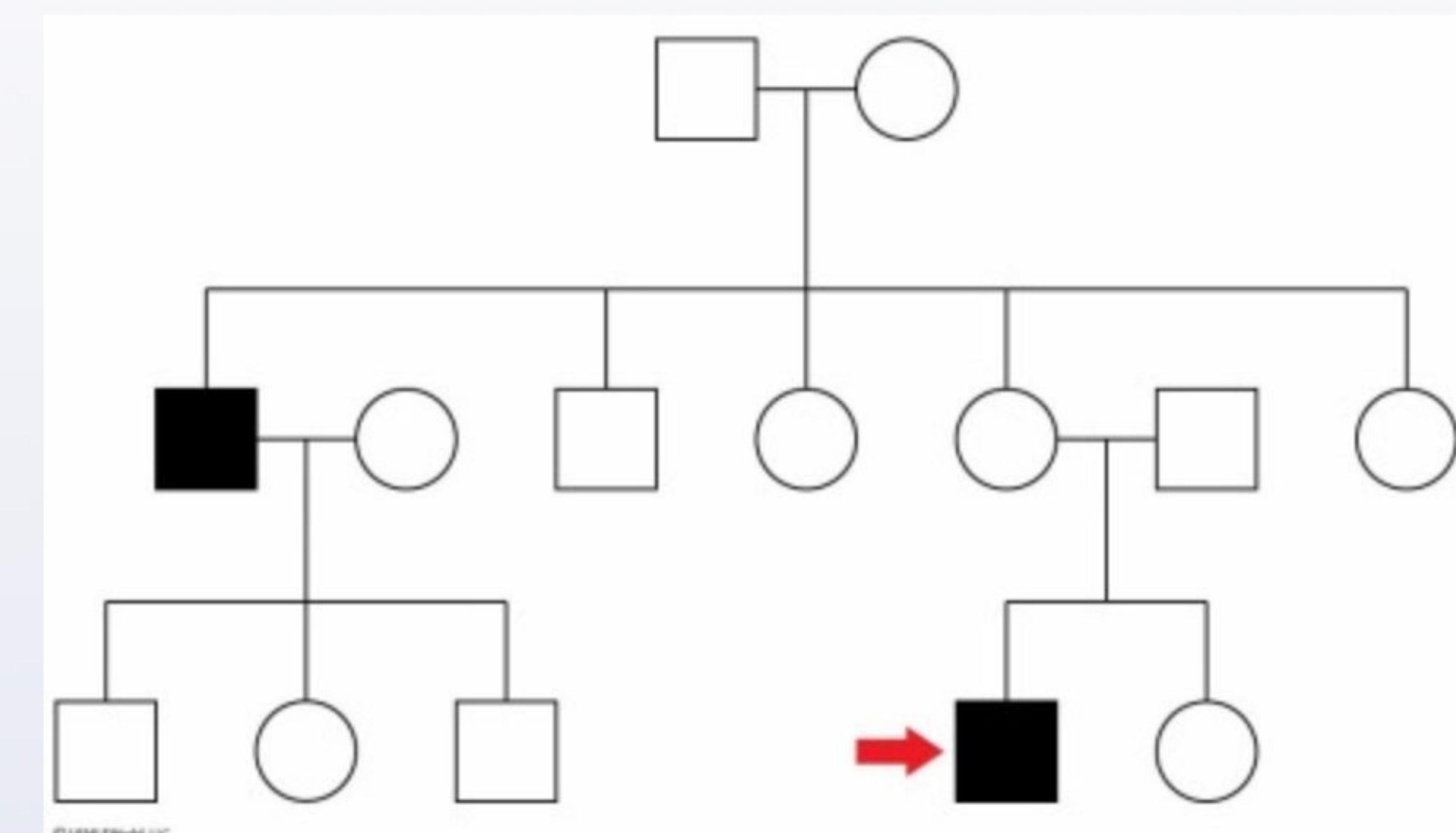


A married couple comes to the office for routine prenatal counseling. The husband is 120 cm (3 ft 11 in) tall with disproportionately short upper and lower extremities, a large head, and a prominent forehead. He cannot provide a biological family history because he was adopted. His spouse is average height with no dysmorphic features, and her family history is insignificant. They inquire about the likelihood that their offspring will have short stature due to the same condition as the father. Which of the following is the best response to their concerns?

- A. The condition is not hereditary
- B. The probability depends on the child's biological sex
- C. The probability depends on the mother's carrier status
- D. The probability is about 25%
- E. The probability is about 50%

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A 25-year-old man experiences severe intolerance to certain medications. On 2 occasions, his reactions to various drugs have necessitated hospital admission. His family pedigree with respect to this condition is shown below, with the red arrow indicating his position within the family.



Assuming that the genetic condition demonstrates complete penetrance and is rare in the general population, which of the following inheritance patterns is most likely?

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

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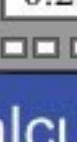
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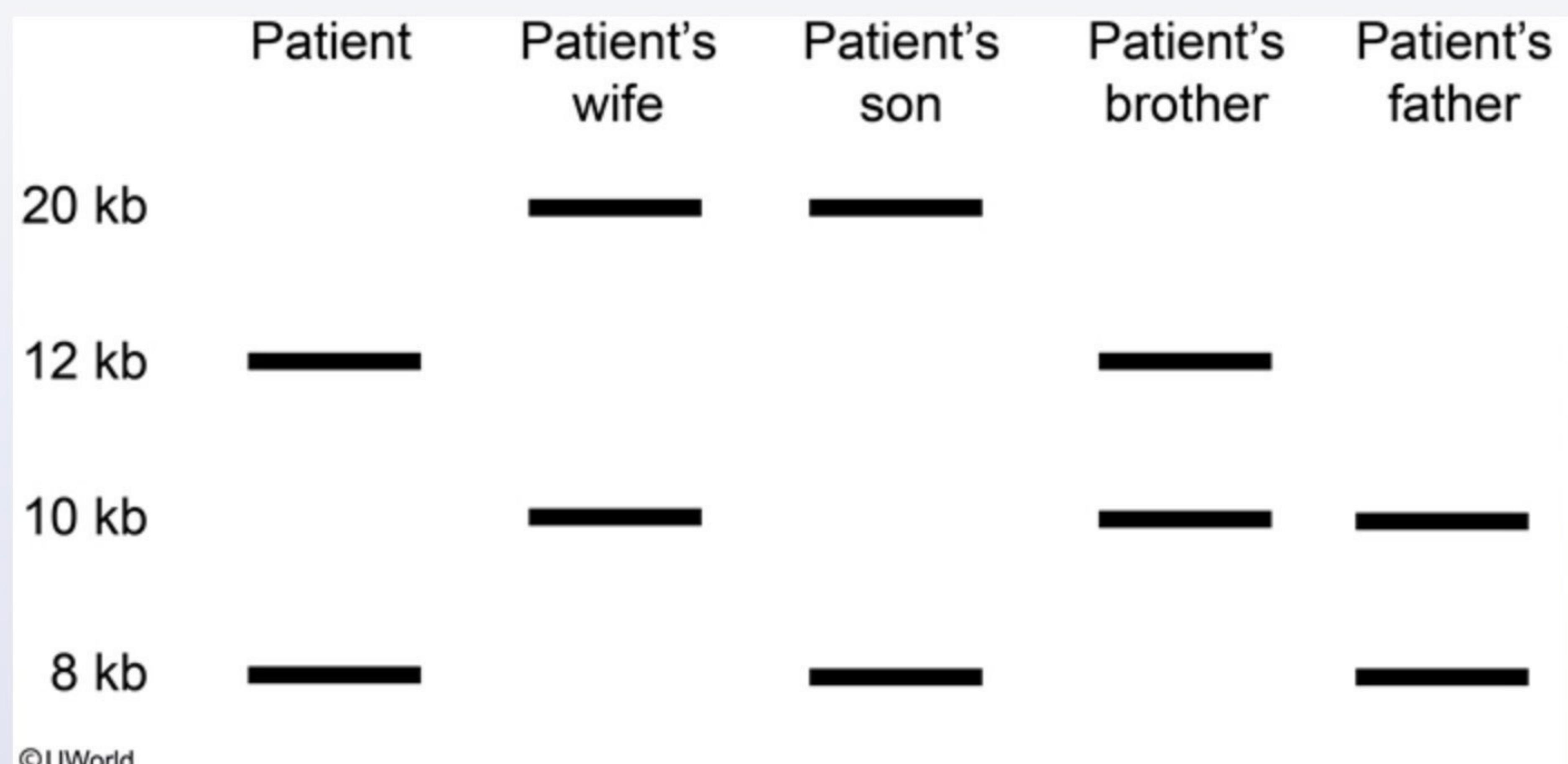


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A 34-year-old man is found to have an LDL level of 310 mg/dL and a normal serum triglyceride level. His father suffered a myocardial infarction at age 39, and his paternal grandfather died of a heart attack at age 40. The patient's wife has a normal lipid profile. DNA samples are obtained from several family members for genetic analysis. Southern blotting of restriction fragments from a region containing the LDL receptor gene shows the following pattern:



Which of the following statements best describes the DNA analysis results?

- A. The disease is transmitted in an X-linked recessive fashion (3%)
- B. The mutation is probably located in the 10 kb band (1%)
- C. The mutation is probably located in the 12 kb band (1%)
- D. The patient's brother most likely inherited the mutation (2%)

Which of the following statements best describes the DNA analysis results?

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- C. The mutation is probably located in the 12 kb band (1%)
- D. The patient's brother most likely inherited the mutation (2%)
- E. The patient's son most likely inherited the mutation (91%)

Omitted

Correct answer

E



91%

Answered correctly



12 secs

Time Spent



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### Explanation

This patient most likely has **heterozygous familial hypercholesterolemia**, an autosomal dominant LDL receptor defect that causes **high LDL levels** and increases the risk of **premature atherosclerosis**.

*Homozygous familial hypercholesterolemia* (a rarer and more severe form of the disease due to inheritance of 2 defective LDL receptor alleles) often presents with coronary heart disease in childhood/adolescence.

**Southern blotting** is a technique that can be used to detect DNA mutations. The process involves the following steps:

1. DNA extraction from the individual's cells
2. Restriction endonuclease digestion of the DNA sample into fragments
3. Gel electrophoresis to separate the various sizes of DNA fragments; larger fragments move slowly and shorter fragments move faster

- 3. Gel electrophoresis to separate the various sizes of DNA fragments; larger fragments move slowly and shorter fragments move faster
- 4. DNA probe (a single-stranded segment of labeled DNA complementary to the gene of interest) to identify the target gene

Once the gene of interest is identified by the DNA probe, various family members' Southern blots can be compared. Because **both** the patient and his father are affected, the common DNA segment between them (**8 kb segment**) most likely represents the mutated gene. The patient's **son** also has the 8 kb segment, meaning that he is probably affected as well.

**(Choice A)** Familial hypercholesterolemia is an autosomal dominant disorder. X-linked recessive mutations are transmitted from unaffected carrier mothers to their sons. Father-to-son transmission does not occur.

**(Choices B and D)** The patient (affected by the disease) does not possess the 10 kb segment, so this segment does not correspond to the mutated gene. The patient's brother inherited the 10 kb segment from his father (not the 8kb mutated segment), so he would not be affected.

**(Choice C)** The patient and his brother, but not their father, have a 12 kb segment on Southern blot analysis. Therefore, this segment was likely inherited from the mother and does not carry the mutation.

### Educational objective:

Southern blotting is a technique used to identify DNA mutations. It involves restriction endonuclease digestion of sample DNA, gel electrophoresis, and gene identification with a labeled DNA probe.

### References

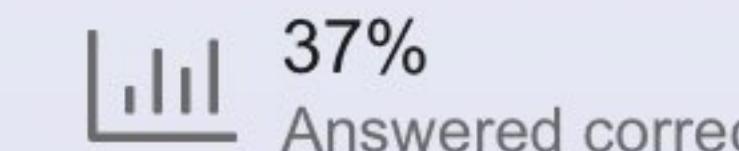
- Genetic defects causing familial hypercholesterolaemia: identification of deletions and duplications in the LDL-receptor gene and summary of all mutations found in patients attending the Hammersmith Hospital Lipid Clinic.

A 33-year-old woman, gravida 2 para 1, comes to the office for a prenatal visit at 20 weeks gestation. She feels well and reports experiencing fetal movements. The patient and her husband have no medical conditions, but their first child, a 3-year-old boy, was born with spina bifida. Physical examination is unremarkable, and uterine size is in accordance with dates established using ultrasonography. The patient is worried that the fetus may develop the same birth defect as her first child. The inheritance pattern of her child's birth defect is most similar to which of the following conditions?

- A. Hereditary hemorrhagic telangiectasia (12%)
- B. Lesch-Nyhan syndrome (18%)
- C. Leukocyte adhesion deficiency (18%)
- D. Myoclonic epilepsy with ragged red fibers (11%)
- E. Sjögren syndrome (37%)

## Omitted

Correct answer  
E

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## Explanation

Spina bifida is a neural tube defect in which incomplete fusion of the caudal neural tube leads to a cleft in the vertebral column, with or without an overlying epithelial defect and exposed neural tissue. Isolated spina bifida has a **multifactorial inheritance pattern** that is determined by genetic and environmental factors.

- **Genetic factors:** Disorders with a multifactorial inheritance pattern tend to **cluster in families**, suggesting that certain genetic variants contribute to the pathogenesis. In spina bifida, genetic factors may include



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- **Genetic factors:** Disorders with a multifactorial inheritance pattern tend to **cluster in families**, suggesting that certain genetic variants contribute to the pathogenesis. In spina bifida, genetic factors may include inherited polymorphisms involving folate metabolism and variable epigenetic modifications (eg, methylation). Because this couple's first child has spina bifida, their subsequent children are at a slightly increased risk for the condition compared to the general population.
- **Environmental factors:** Maternal **folic acid deficiency** is a preventable risk factor for spina bifida. Similarly, in utero exposure to medications that interfere with folic acid metabolism (eg, valproic acid) is also associated with spina bifida. Other risk factors include maternal obesity and poorly controlled pregestational diabetes mellitus.

Like spina bifida, **Sjögren syndrome** has a multifactorial inheritance pattern. Sjögren syndrome is an autoimmune disorder in which chronic inflammation leads to exocrine gland (eg, salivary, lacrimal) destruction, causing dry eyes and mouth. Although certain genotypes are associated with Sjögren syndrome, environmental factors also determine its incidence. A recent viral illness, for example, can lead to the production of autoantibodies (eg, anti-Ro/SSA, anti-La/SSB) that target exocrine glands.

A multifactorial inheritance pattern is also characteristic of many other birth defects (eg, cleft palate) and autoimmune disorders (eg, type 1 diabetes mellitus) as well as atopic disease (eg, asthma).

**(Choice A)** Hereditary hemorrhagic telangiectasia is characterized by development of multiple arteriovenous malformations (absent capillary beds). It is inherited in an autosomal dominant pattern rather than a multifactorial inheritance pattern.

**(Choice B)** Lesch-Nyhan syndrome is characterized by impaired purine salvage resulting in neurobehavioral



causing dry eyes and mouth. Although certain genotypes are associated with Sjögren syndrome, environmental factors also determine its incidence. A recent viral illness, for example, can lead to the production of autoantibodies (eg, anti-Ro/SSA, anti-La/SSB) that target exocrine glands.

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**(Choice A)** Hereditary hemorrhagic telangiectasia is characterized by development of multiple arteriovenous malformations (absent capillary beds). It is inherited in an autosomal dominant pattern rather than a multifactorial inheritance pattern.

**(Choice B)** Lesch-Nyhan syndrome is characterized by impaired purine salvage resulting in neurobehavioral symptoms (eg, developmental delay, self-mutilating behavior). This condition is inherited in an X-linked recessive pattern.

**(Choice C)** Leukocyte adhesion deficiency is due to impaired neutrophil migration, which causes recurrent infections. It is an autosomal recessive disorder.

**(Choice D)** Myoclonic epilepsy with ragged red fibers is a mitochondrial disorder that causes myopathy and CNS disease (eg, myoclonus, epilepsy). Offspring generally inherit mitochondrial disorders only from an affected mother.

### Educational objective:

Spina bifida has a multifactorial inheritance pattern, and incidence is determined by complex interactions between genetic and environmental factors. Sjögren syndrome also has a multifactorial inheritance pattern.

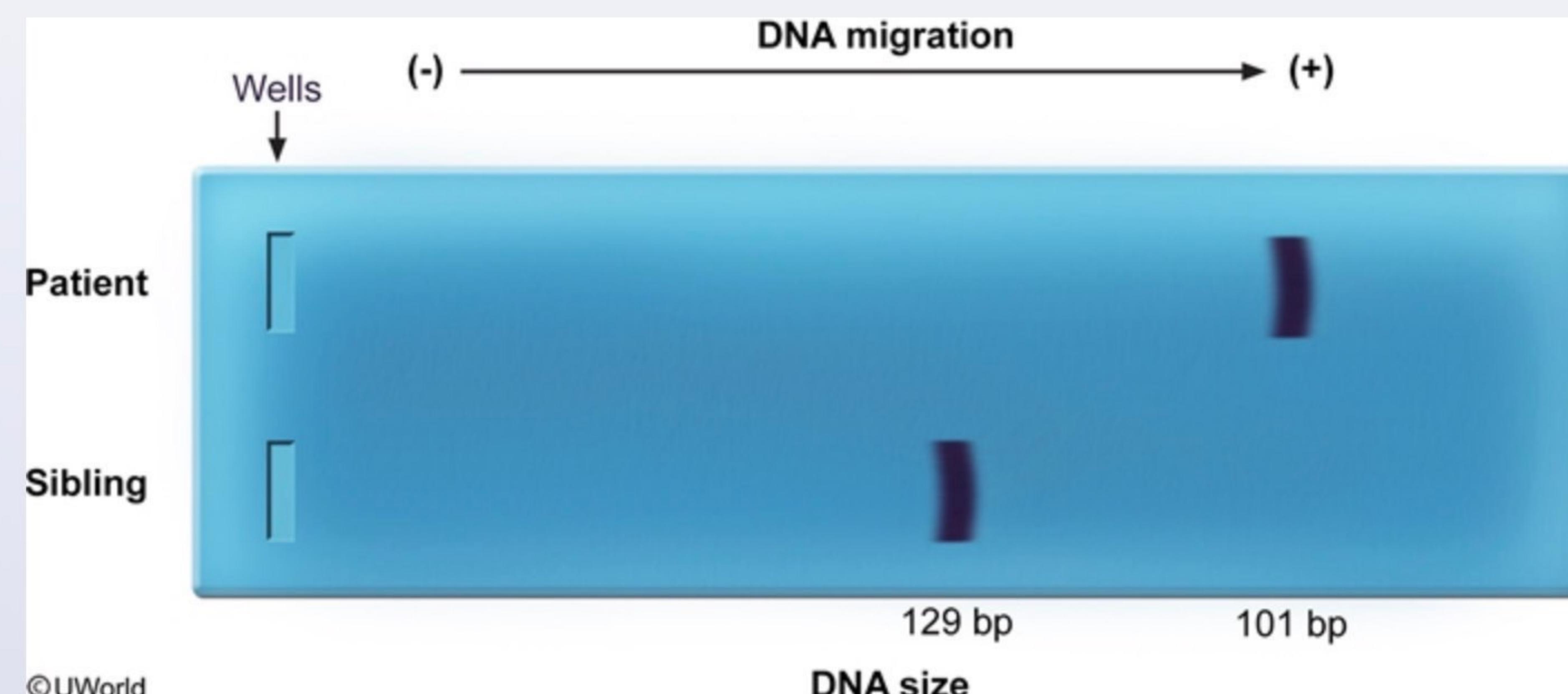
### References

- Genetics and epigenetics in primary Sjögren's syndrome.



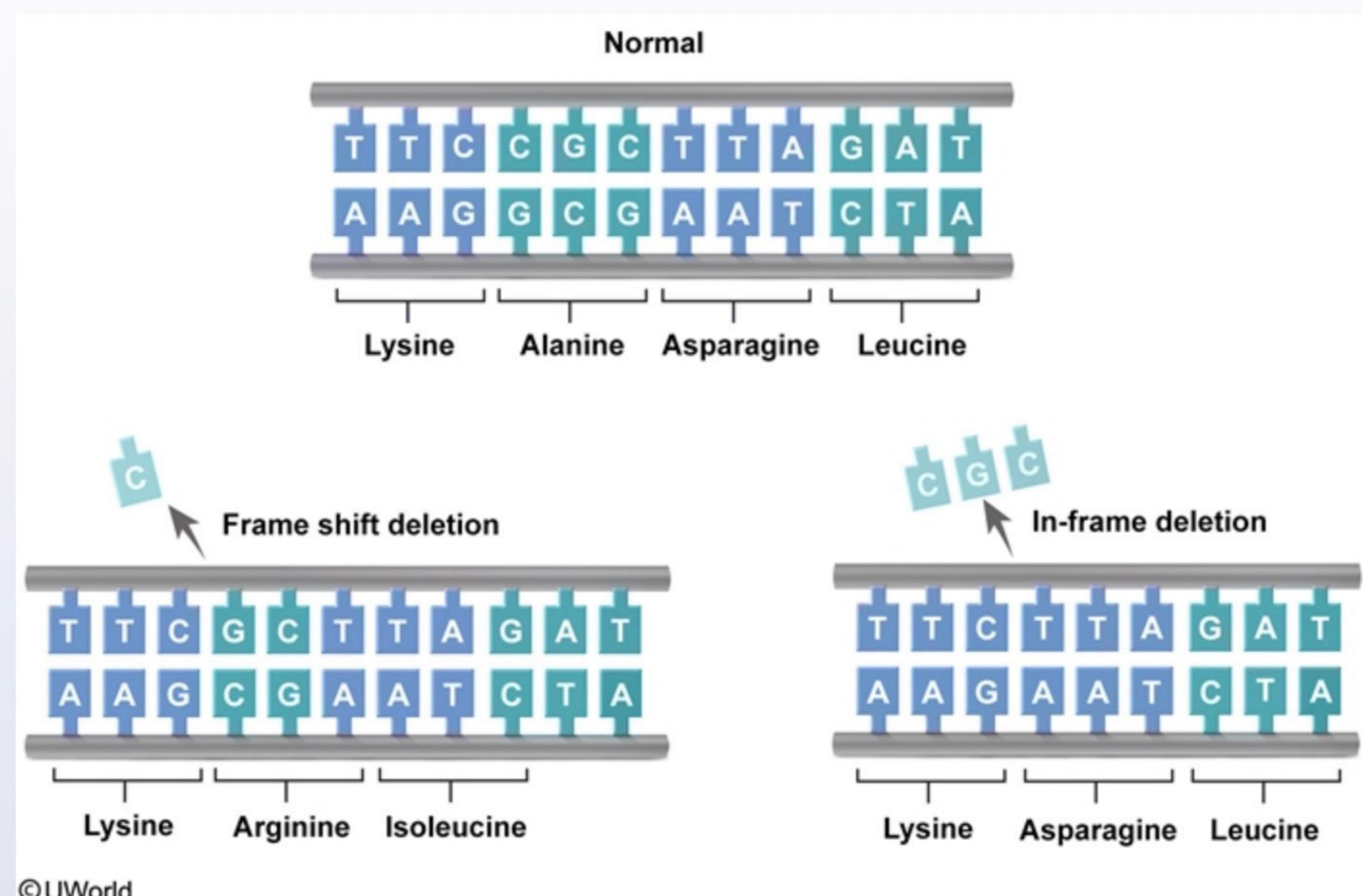
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A 3-year-old boy is being evaluated for recurrent respiratory infections. The patient's family immigrated to the United States 5 months after his birth. Since then, the boy has experienced multiple episodes of pneumonia and bronchitis, and has developed a persistent cough and failure to thrive. His older brother has no medical issues. A genetic test is performed and reveals a mutation in an exon of a gene that codes for a transmembrane chloride channel. The abnormal mRNA is isolated from cultured epithelial cells, and its complementary DNA is synthesized. Amplified cDNA samples from both the patient and his healthy sibling are analyzed using gel electrophoresis and compared to DNA fragments of known size to determine base pair length. The results are shown below.



Which of the following is most likely responsible for this patient's condition?

- A. Frameshift mutation (24%)
- B. In-frame deletion (15%)
- C. Missense mutation (10%)



This patient has cystic fibrosis, which occurs due to mutations affecting the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The vignette states that the patient's **mutation affects an exon**, meaning that the mutation will be **detectable in the mRNA sequence**. Complementary DNA (cDNA) is double-stranded DNA that is synthesized from an mRNA template. In this case, cDNA was synthesized using *CFTR* mRNA from the patient and his brother. Subsequent gel electrophoresis shows that the patient's cDNA is 28 base pairs shorter than that of his brother, indicating the patient has a **28-base pair deletion** affecting the coding region of *CFTR*. Deletion or insertion of a number of bases that is **not divisible by 3** results in **frameshift mutations**. As the name implies, frameshift mutations alter the reading frame of the genetic code, resulting in the formation of



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the name implies, frameshift mutations alter the reading frame of the genetic code, resulting in the formation of nonfunctional proteins due to the incorporation of many incorrect amino acids.

**(Choice B)** One or more complete codons (genetic triplet codes) are removed in an in-frame deletion, which does not affect the reading frame of subsequent codons. This patient's 28-base pair deletion is not divisible by 3, so it will result in a reading frame shift.

**(Choices C and D)** Missense and nonsense mutations are due to single base substitutions that result in the placement of an incorrect amino acid or introduction of a premature stop codon, respectively. These mutations occur in exons and affect protein translation. However, in this scenario, **gel electrophoresis** is being performed on **cDNA (not protein)** and the results indicate the **length of the mature RNA transcript**. Termination of RNA transcription occurs by specific sequences in the 3' untranslated region that cause RNA hairpin loop formation and/or recruitment of termination factors. As a result, point mutations in the exons of a gene (such as those responsible for causing nonsense mutations) are unlikely to affect total mRNA (cDNA) size.

**(Choice E)** Silent mutations can occur in both coding and noncoding regions, but they do not alter protein quantity or function and do not affect phenotype. This patient's mutation caused him to develop cystic fibrosis, so it is not a silent mutation.

**(Choice F)** Trinucleotide expansions increase the number of trinucleotide repeats in the coding region of a gene, often resulting in large proteins with abnormal function. This patient's abnormal *CFTR* gene is shorter (not longer) than the normal gene from his sibling, which indicates a deletion has occurred.

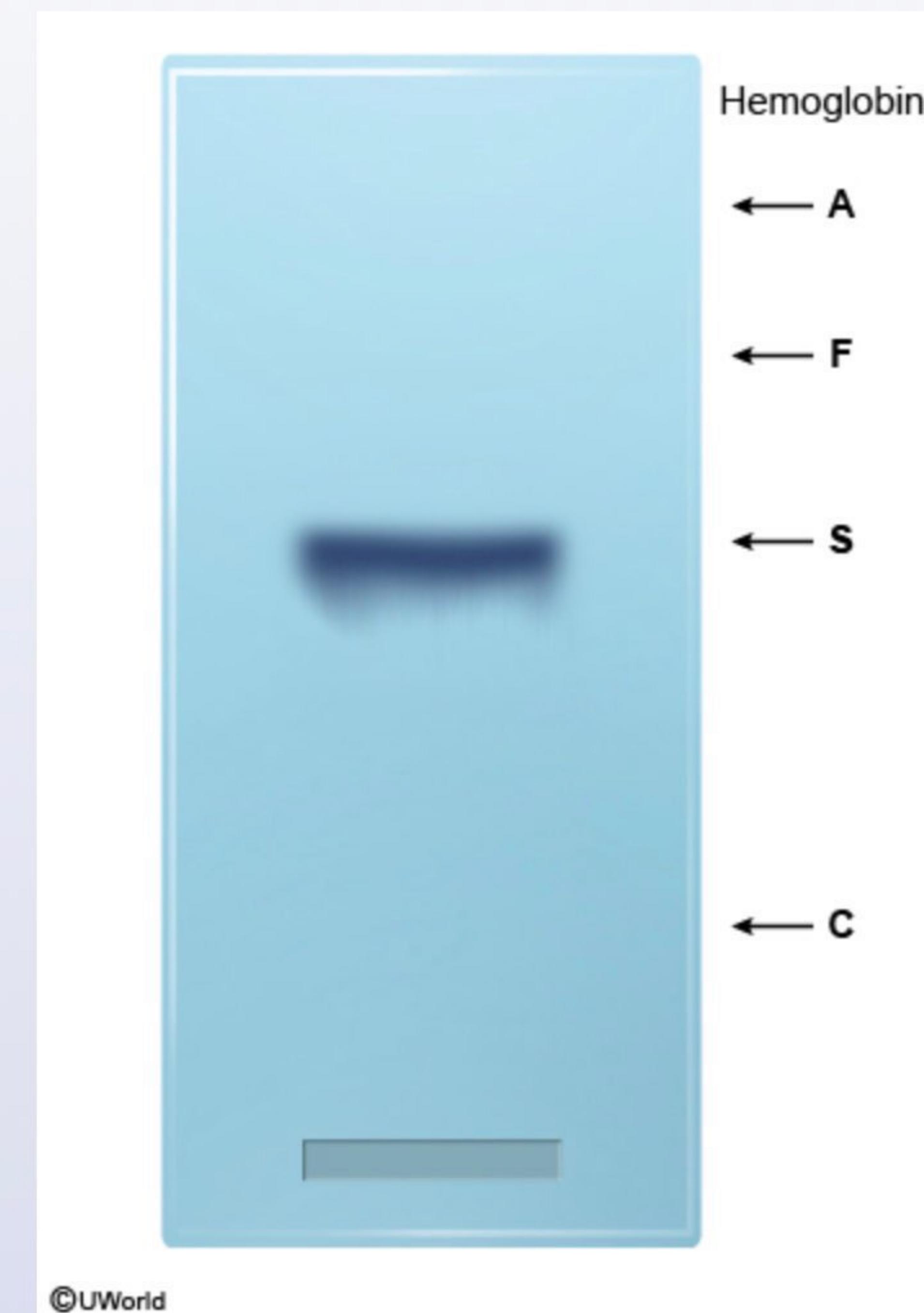
### Educational objective:

Deletion or addition of a number of bases that is not divisible by 3 in the coding region of a gene will cause a frameshift mutation. Frameshift mutations alter the reading frame of the genetic code, resulting in the formation of nonfunctional proteins.

### References



A 26-year-old woman comes to the office with her husband for genetic counseling. Both of them are healthy with no chronic medical conditions, but their firstborn son has had recurrent episodes of anemia, jaundice, and painful swelling of the hands and feet. Hemoglobin electrophoresis is performed on the son at alkaline pH to determine the predominant hemoglobin variants present in his red blood cells. The results are shown below.



The parents are considering having another child. What is the probability they will conceive a child who inherits  $\geq 1$  mutated alleles?



AA

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The parents are considering having another child. What is the probability they will conceive a child who inherits ≥1 mutated alleles?

- A. Near 0%
- B. 25%
- C. 50%
- D. 75%
- E. 100%

Omitted

Correct answer

D

Collecting Statistics

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Version

Explanation

### Autosomal recessive inheritance

**Carrier parent (Aa)**

		A	a
		A	
Carrier parent (Aa)	A	AA Normal child	Aa Carrier child
	a		

### Autosomal recessive inheritance

Carrier parent (Aa)

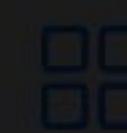
		A	a
A	A	AA Normal child	Aa Carrier child
	a	Aa Carrier child	aa Affected child

Offspring have 75% chance of inheriting at least 1 mutant allele.

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This couple's son has **sickle cell disease** (SCD), an **autosomal recessive** disorder characterized by the production of hemoglobin S and sickled red blood cells that undergo hemolysis (eg, anemia, jaundice) and cause vascular obstruction (eg, painful swelling of the hands/feet). SCD is diagnosed using **hemoglobin electrophoresis**, which separates different types of **hemoglobin** according to the electrical charge of their amino acid composition. In this case, electrophoresis shows a predominance of hemoglobin S, consistent with SCD.

For autosomal recessive disorders such as SCD, affected offspring must inherit a mutant allele from each parent. In this case, both **parents are unaffected** but have **affected offspring**. Therefore, both parents must be **carriers**, and the probability of inheriting each of the 3 possible genotypes (AA, Aa, aa) can be determined



AA



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This couple's son has sickle cell disease (SCD), an autosomal recessive disorder characterized by the

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For autosomal recessive disorders such as SCD, affected offspring must inherit a mutant allele from each parent. In this case, both **parents are unaffected** but have **affected offspring**. Therefore, both parents must be **carriers**, and the probability of inheriting each of the 3 possible genotypes (AA, Aa, aa) can be determined using a Punnett square.

- 25% probability (1 in 4) of inheriting 2 normal alleles (AA, unaffected)
- 50% probability (2 in 4) of inheriting 1 normal allele and 1 mutated allele (Aa, carrier)
- 25% probability (1 in 4) of inheriting 2 mutated alleles (aa, affected)

Although the couple already has an affected child, each child's genotype is determined independently, and the probability of this couple's second child inheriting  $\geq 1$  mutant alleles is neither more nor less likely than that of their first. Therefore, the probability of this couple's second child inheriting  **$\geq 1$  mutated alleles** is 50% + 25% = **75%**.

### Educational objective:

Sickle cell disease is an autosomal recessive disorder characterized by a predominance of hemoglobin S, causing red blood cells to sickle, hemolyze, and cause vascular obstruction. Offspring of carrier parents have a 3 in 4 (75%) chance of inheriting at least 1 mutated allele (ie, genotype Aa or aa).

Genetics

Subject

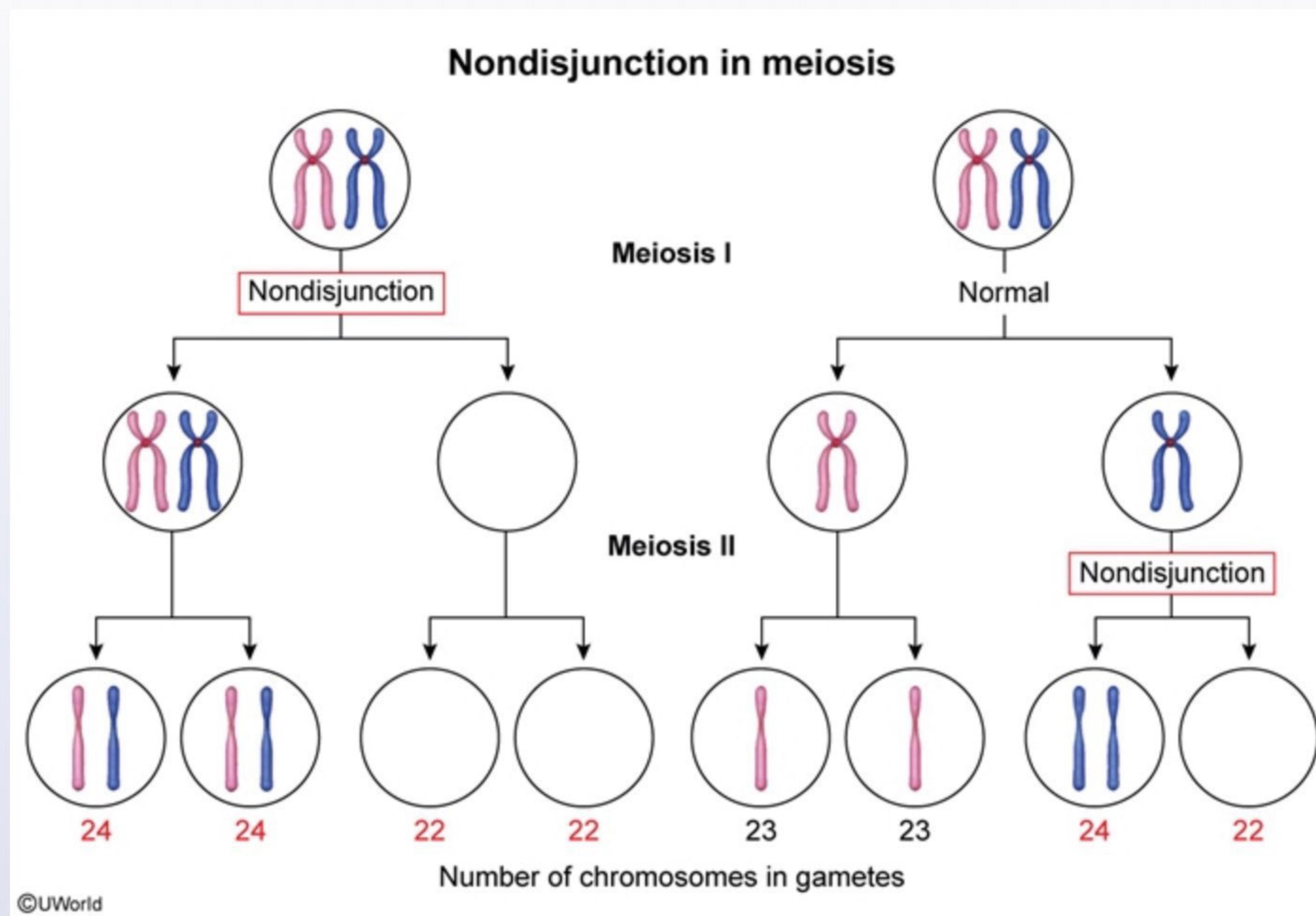
Genetics (General Principles)

System

Genetic inheritance

Topic

## Explanation



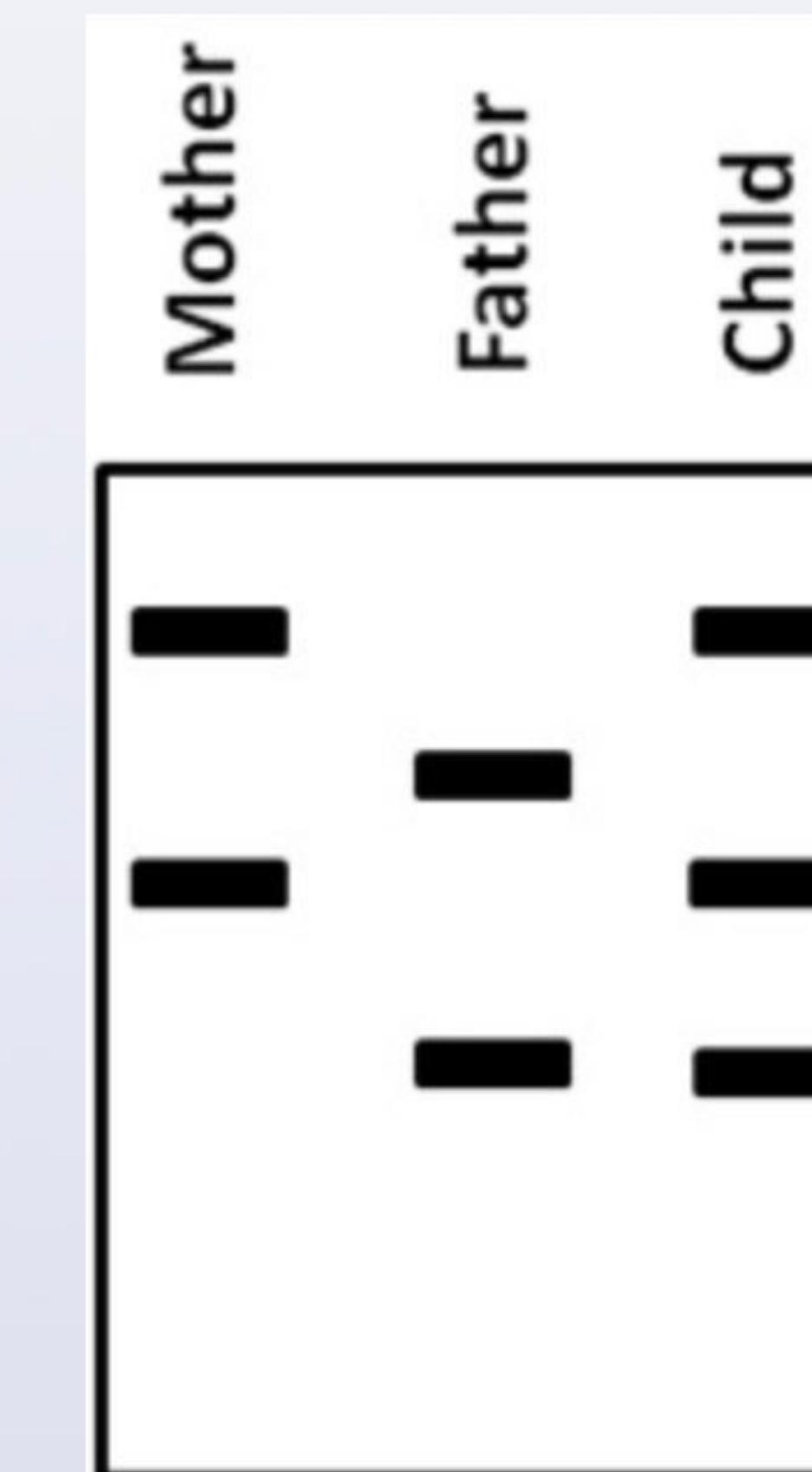
**Nondisjunction** is the failure of chromosome pairs to separate properly during cell division. This could be due to a failure of **homologous chromosomes** to separate in **meiosis I** or a failure of **sister chromatids** to separate during **meiosis II or mitosis**. In monosomy, a single chromosome is lost. In trisomy, a single chromosome is gained. **Monosomies or trisomies** can result from nondisjunction in meiosis I or II.

Restriction fragment length polymorphism (RFLP) analysis shows that both parents demonstrate 2 bands. Each

Item 5 of 20 Question Id: 8328

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An infant born to a 34-year-old woman has a flat facial profile, prominent epicanthal folds, and a holosystolic murmur heard loudest at the left sternal border. Karyotype analysis is consistent with trisomy 21. Maternal and paternal karyotypes are normal. A restriction fragment length polymorphism (RFLP) analysis is conducted to determine the parental origin of the extra chromosome. DNA samples from the child, mother, and father are obtained and the DNA is fragmented with a restriction enzyme. The fragments are then sorted by size using the Southern blot technique. Labeling is done using a probe that binds to a specific DNA sequence close to the centromere of chromosome 21. RFLP analysis for the child, mother, and father is shown below.



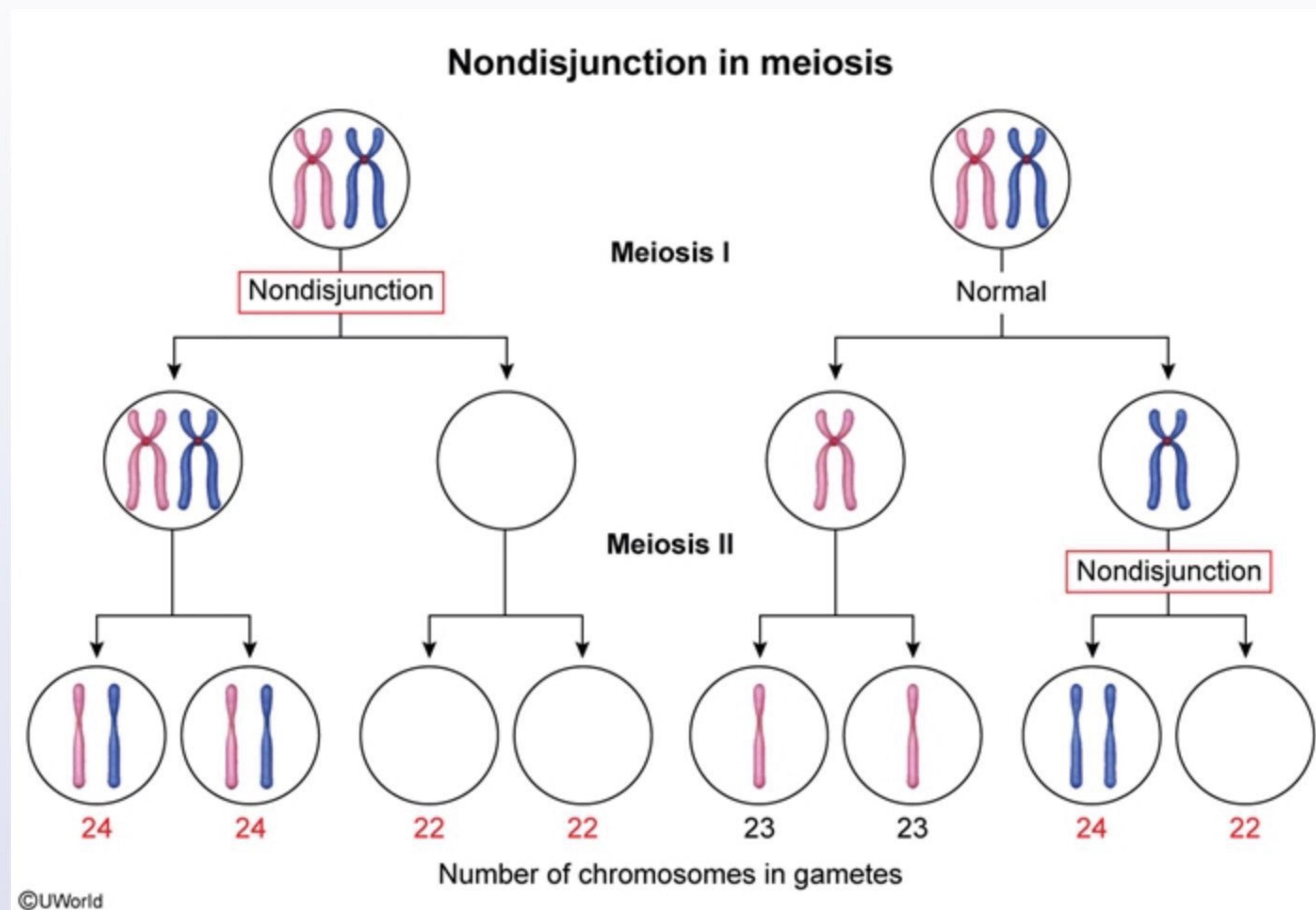
In which of the following meiosis events did the nondisjunction most likely occur?

- A. Maternal meiosis I (52%)
- B. Maternal meiosis II (36%)

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**Nondisjunction** is the failure of chromosome pairs to separate properly during cell division. This could be due to a failure of **homologous chromosomes** to separate in **meiosis I** or a failure of **sister chromatids** to separate during **meiosis II or mitosis**. In monosomy, a single chromosome is lost. In trisomy, a single chromosome is gained. **Monosomies or trisomies** can result from nondisjunction in meiosis I or II.

Restriction fragment length polymorphism (RFLP) analysis shows that both parents demonstrate 2 bands. Each

Restriction fragment length polymorphism (RFLP) analysis shows that both parents demonstrate 2 bands. Each parental band represents a homologous chromosome 21. The child has 3 bands, indicating that he has 3 different versions of chromosome 21 that he obtained from his parents. He received the lower band from the father and both of the upper bands from the mother. The fact that he received 2 different bands from the mother indicates that he inherited both of her homologous chromosomes. Therefore, the problem occurred in the mother during meiosis I, when homologous chromosomes are separated. In fact, the vast majority of **Down syndrome** cases arise due to nondisjunction during maternal meiosis I.

**(Choice B)** If the mother had a failure in meiosis II, the child's RFLP analysis would reveal only two bands ([see example](#)). There would be a single band from the father and a darker, thicker band from the mother. The darker, thicker band signifies the inheritance of both sister chromatids, which will produce equal-size restriction fragments (but twice the normal amount).

**(Choice C)** If the father had a failure in meiosis I, the child's RFLP analysis would reveal 3 bands ([see example](#)). In this instance, there would be a single band inherited from the mother with two bands inherited from the father.

**(Choice D)** If the father had a failure in meiosis II, the child's RFLP analysis would reveal two bands ([see example](#)). In this instance, there would be a single band inherited from the mother and a second band from the father. The father's band would be darker and thicker, signifying the inheritance of both sister chromatids.

#### Educational objective:

Nondisjunction is the failure of chromosome pairs to separate properly during cell division. This could be due to a failure of homologous chromosomes to separate in meiosis I or a failure of sister chromatids to separate during meiosis II or mitosis.

#### References

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Item 6 of 20 Question Id: 1610

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A 1-hour-old girl born to a 40-year-old woman is brought to the nursery for evaluation. The pregnancy and delivery were uncomplicated. Physical examination shows mid-face hypoplasia with a flat nasal bridge, up-slanting palpebral fissures, a small mouth, and a single palmar crease bilaterally. Cardiac auscultation reveals a blowing holosystolic murmur heard best along the sternal border. Which of the following abnormalities is most likely to be present in this patient?

- A. Aberrant genomic imprinting (2%)
- B. Mosaicism (46%)
- C. Partial deletion (5%)
- D. Triplet expansion (12%)
- E. Uniparental disomy (33%)

Omitted

Correct answer

B



46%

Answered correctly



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Time Spent



2023

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### Explanation

#### Inheritance of Down syndrome

Mechanism	Pathogenesis	Recurrence risk
Meiotic	Extra copy of chromosome 21 present in	

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Item 6 of 20 Question Id: 1610

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Inheritance of Down syndrome		
Mechanism	Pathogenesis	Recurrence risk
Meiotic nondisjunction (~95%)	<ul style="list-style-type: none"><li>Extra copy of chromosome 21 present in every cell</li></ul>	Based on maternal age
Unbalanced translocation	<ul style="list-style-type: none"><li>All or part of additional chromosome 21 attached to another chromosome</li></ul>	High if balanced translocation is present in one parent
Mosaicism	<ul style="list-style-type: none"><li>Some (not all) cells have an extra copy of chromosome 21</li><li>Nondisjunction event in early embryonic life</li></ul>	Similar to normal population

This child has many of the characteristic features of [Down syndrome](#) (DS), a condition that results from an **increased gene dosage** effect due to an **extra copy** of chromosome 21. Three cytogenetic abnormalities can lead to DS:

- **Meiotic nondisjunction** accounts for nearly 95% of DS cases. Failure of homologous chromosomes or sister chromatids to separate during meiosis can result in the inheritance of 3 copies of chromosome 21 in one daughter cell (trisomy) and 1 copy in the other daughter cell (monosomy). Nondisjunction during meiosis is almost always of maternal origin.
- **Unbalanced translocations** account for 2%-3% of DS cases. These individuals have 46 chromosomes, but have extra genetic material (consisting of duplicate chromosome 21 genes) attached to one of their chromosomes. Approximately one third of these cases are due to a balanced translocation in one parent,

The screenshot shows a mobile application interface for a medical question. At the top, there is a header with the URL "apps.uworld.com". Below the header is a toolbar with various icons: a blue square icon, a left arrow, a right arrow, a double arrow, a magnifying glass, a "Mark" icon, a "Previous" button, a "Next" button, a "Full Screen" button, a "Tutorial" button, a "Lab Values" button, a "Notes" button, a "Calculator" button, a "Reverse Color" button, a "Text Zoom" button, and a "Settings" button. The main content area displays the following text:

which confers a high recurrence risk.

- **Mosaicism** accounts for <2% of DS cases. Affected individuals have 2 distinct cell lines as a result of **nondisjunction during mitosis**: one with a normal genotype and one with trisomy 21. The proportion of affected cells determines the severity of DS features.

Of the available answer options, only mosaicism is consistent with a **third copy** of chromosome 21 existing in at least a portion of the patient's cells.

**(Choices A and E)** Genomic imprinting is a normal process that refers to selective activation of gene expression depending on the parent of origin. Aberrant imprinting occurs with uniparental disomy, or when a person receives **2 copies** of a chromosome from the same parent and no copy from the other parent. Prader-Willi syndrome and Angelman syndrome (15q) are examples of conditions caused by dysfunctional imprinting due to uniparental disomy.

**(Choice C)** Many genetic syndromes are caused by deletions (loss of genetic material). Cri du chat syndrome (5p deletion) is an example of a syndrome caused by a partial deletion of chromosome 5.

**(Choice D)** Increased trinucleotide repeats (triplet expansion) on certain genes can lead to silencing of a gene or synthesis of an abnormal gene product. Huntington disease and fragile X syndrome are examples of conditions caused by triplet expansion.

#### Educational objective:

Common findings in Down syndrome include cognitive impairment, facial dysmorphism, and cardiac defects; 95% of cases are caused by the presence of an extra chromosome 21 (trisomy) resulting from nondisjunction. Unbalanced Robertsonian translocations or mosaicism are less common causes.

#### References

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Item 7 of 20 Question Id: 633

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A 28-year-old man is evaluated for abnormal movements of the hands and face. The patient reports that he started experiencing involuntary grimacing a year ago, which has gradually worsened. He is taking a selective serotonin reuptake inhibitor for major depression but has not taken any antipsychotic medications. His 52-year-old father was diagnosed with an inherited movement disorder 2 months ago. Physical examination shows normal strength and normal deep tendon reflexes. No sensory deficits are noted. Which of the following best explains the difference in disease presentation between this patient and his father?

- A. Anticipation (88%)
- B. Genomic imprinting (0%)
- C. Incomplete penetrance (5%)
- D. Microdeletion (0%)
- E. Mosaicism (1%)
- F. Pleiotropy (2%)

Omitted  
Correct answer  
A

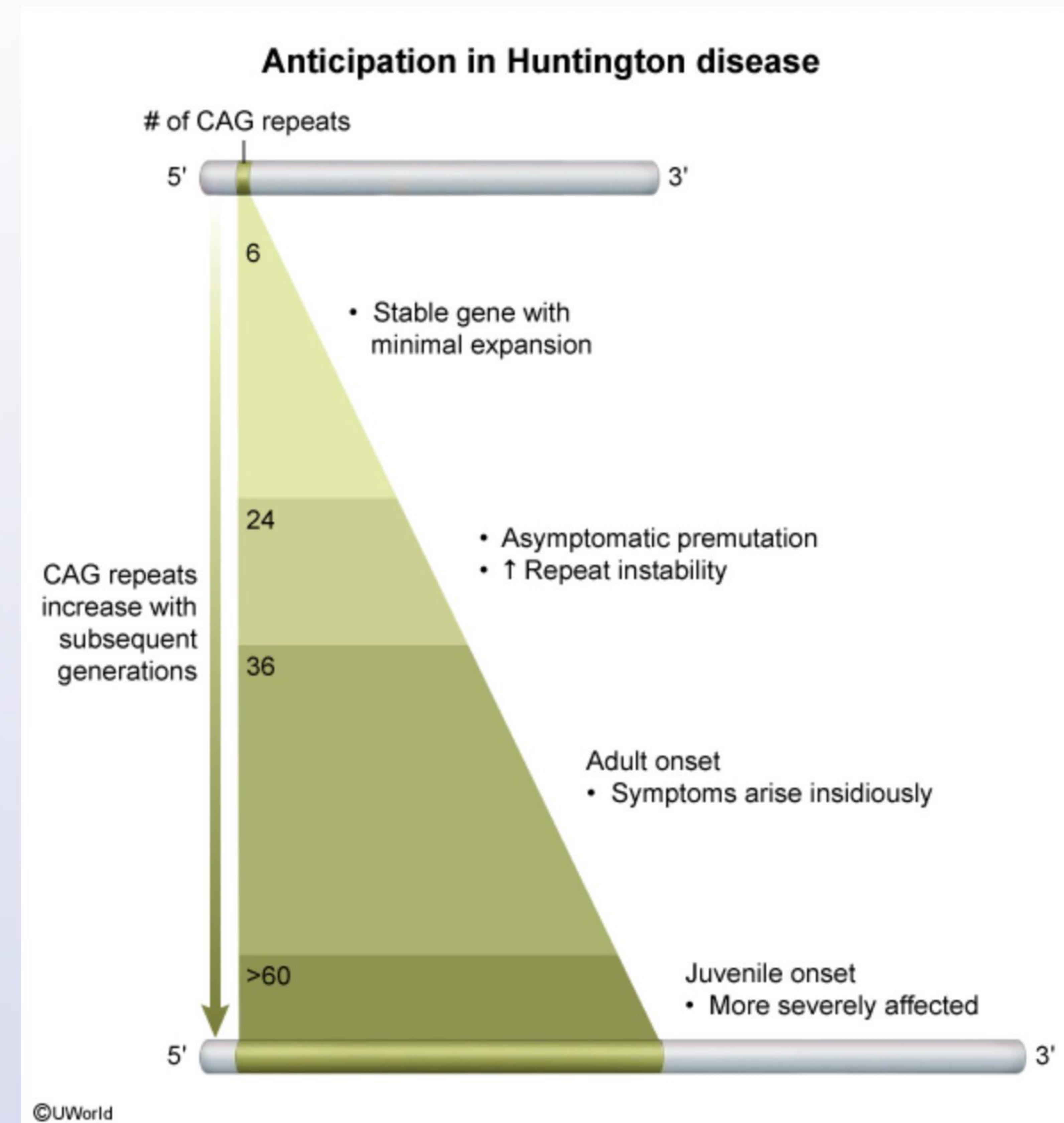
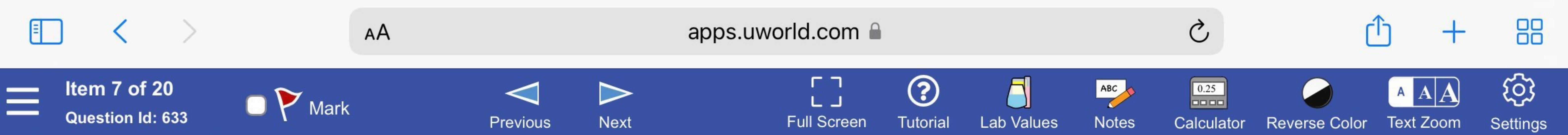
88%  
Answered correctly

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Time Spent

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### Explanation

#### Anticipation in Huntington disease



This patient presenting with involuntary movements, depression, and a family history of a movement disorder

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Item 7 of 20  
Question Id: 633

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This patient presenting with involuntary movements, depression, and a family history of a movement disorder likely has **Huntington disease** (HD), which typically manifests with the triad of movement disorder (chorea), behavioral abnormalities (aggressiveness, apathy, or depression), and dementia. HD is caused by an expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats. Most patients develop symptoms in their 40s or 50s, but an earlier age of onset and more severe symptoms are associated with a larger number of **trinucleotide repeats**.

During spermatogenesis, CAG repeats in the abnormal *HTT* gene (chromosome 4p) can rapidly increase (much more than during oogenesis). Therefore, patients who receive an abnormal gene from their fathers tend to develop the disease earlier in life. The tendency for clinical symptoms to worsen and/or occur earlier in subsequent generations is called **anticipation**. Anticipation is common in disorders associated with trinucleotide repeats, as in Fragile X syndrome, myotonic dystrophy, and Friedreich ataxia.

**(Choice B)** Genomic imprinting is a selective inactivation of the genes of either maternal or paternal origin. It results in Prader-Willi and Angelman syndromes, which involve deletions of the same region on chromosome (15q) but have very different clinical manifestations due to the differential expression of parental genes. When the chromosome with the deleted region comes from the father, the lack of expression of maternally imprinted genes results in Prader-Willi syndrome. Likewise, deletions affecting the maternal chromosome result in Angelman syndrome due to absent expression of paternally imprinted genes.

**(Choice C)** HD is transmitted in an autosomal dominant pattern with complete penetrance, which means that a child who inherits the abnormal gene will inevitably develop Huntington disease.

**(Choice D)** Microdeletion is the loss of genetic material too small to be visible via light microscopy. For example, microdeletion of 22q11 is responsible for DiGeorge syndrome.

**(Choice E)** The presence of 2 populations of cells with different genotypes in one patient resulting in the mixed