



AA

apps.uworld.com



Item 7 of 20

Question Id: 633



Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

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 expression of disease is called mosaicism. Examples of mosaicism include milder forms of Turner (genotype 46XX/45X0), Klinefelter (46XY/47XXY), and Down syndromes.

**(Choice F)** Sometimes, one gene mutation leads to multiple, seemingly unrelated phenotypic abnormalities, a genetic phenomenon termed pleiotropy.

### Educational objective:

An increased number of trinucleotide repeats on the *HTT* gene is associated with Huntington disease. The larger the number of repeats, the earlier the onset of the disease. Trinucleotide expansion occurs more frequently during paternal transmission, causing a genetic phenomenon called anticipation.

### References

- Genetics and neuropathology of Huntington's disease.

Genetics

Genetics (General Principles)

Subject

System

Huntington disease

Topic

apps.uworld.com

Item 8 of 20 Question Id: 596

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

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

Omitted  
Correct answer  
D

Collecting Statistics

01 sec  
Time Spent

2023  
Version

Explanation

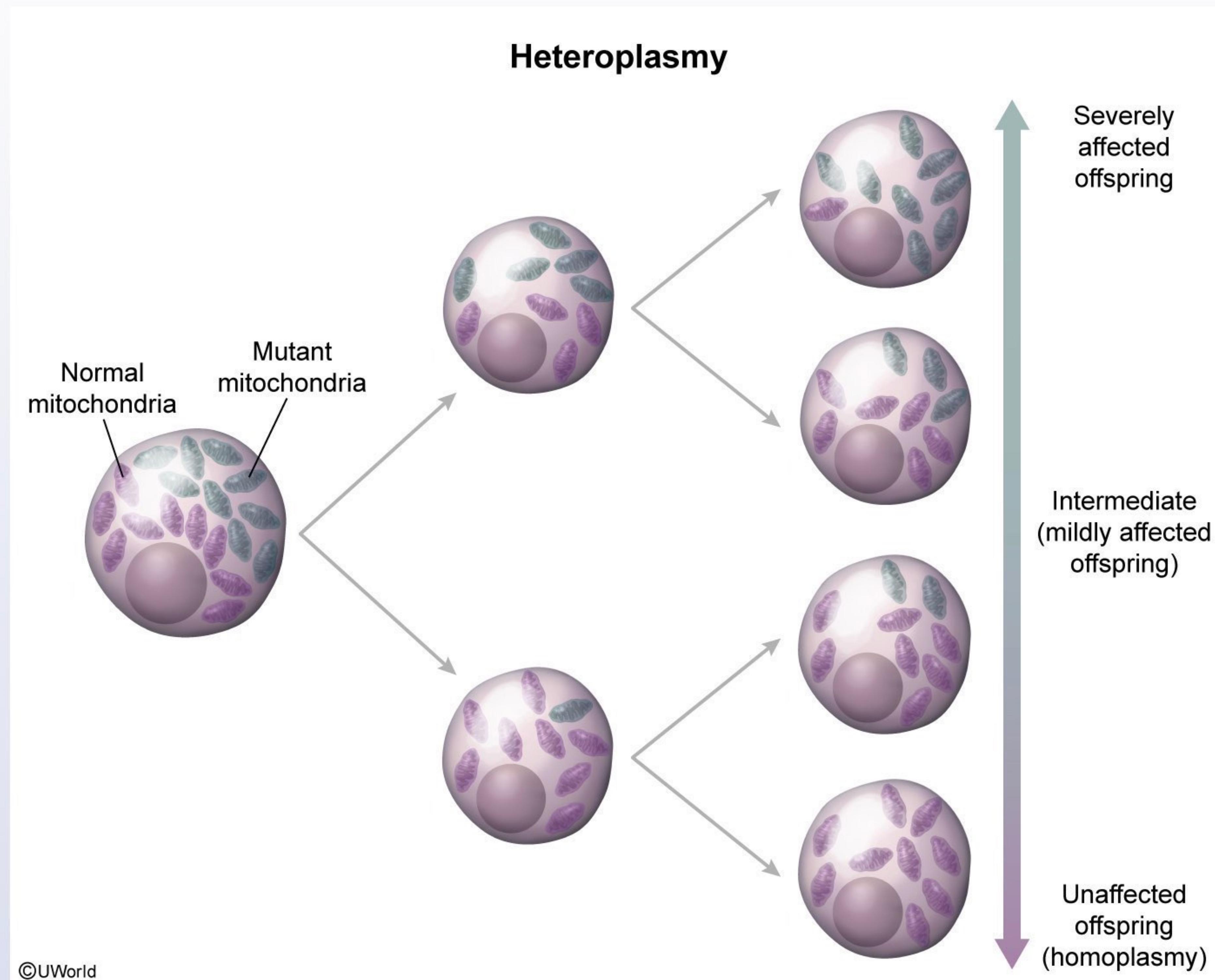
Heteroplasmy

Severely

apps.uworld.com

Item 8 of 20 Question Id: 596

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings



This patient has a genetic condition with a **maternal inheritance pattern**, a finding characteristic of mitochondrial disease. Unlike nuclear DNA (inherited from both parents), **mitochondrial DNA** (mtDNA) is inherited almost exclusively through the maternal line.

apps.uworld.com

Item 8 of 20 Question Id: 596 ©UWorld

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

This patient has a genetic condition with a **maternal inheritance pattern**, a finding characteristic of mitochondrial disease. Unlike nuclear DNA (inherited from both parents), **mitochondrial DNA** (mtDNA) is inherited almost exclusively through the maternal line.

Inheritance of mtDNA mutations affects male and female offspring with equal frequency, but disease often presents with **varying severity** even in those with the **same mtDNA mutation**. This variability is the result of **heteroplasmy**. Cells contain thousands of mitochondria, each with several copies of its own genome.

Mitochondria containing more mutant mtDNA copies are less likely to function normally, and random distribution of mitochondria during mitosis/meiosis results in **variable amounts** of mutant and normal mitochondria among daughter cells. The relative balance of mutated and normal mtDNA explains the variability in symptom severity between this patient and his sibling, who presumably has less mutant mitochondria.

Because mitochondrial defects lead to impaired oxidative phosphorylation (ie, decreased ATP production), tissues with the highest energy requirements (eg, brain, skeletal muscle) are most affected, as seen in this child. This patient likely has mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), one of the most common mitochondrial disorders.

**(Choice A)** **Anticipation** is the increasing severity or earlier onset of a genetic disease in subsequent generations. This phenomenon is often seen in conditions with an increasing number of trinucleotide repeats with each generation (eg, Huntington disease).

**(Choice B)** Genetic heterogeneity refers to varying genotypes among individuals with the same phenotype, such as sensorineural hearing loss, which can be caused by >100 different mutations. In contrast, this patient has the same mutation as his sister but a more severe phenotype.

**(Choice C)** Genetic imprinting refers to selective inactivation of paternal or maternal alleles. This phenomenon

Item 8 of 20  
Question Id: 596

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

tissues with the highest energy requirements (eg, brain, skeletal muscle) are most affected, as seen in this child. This patient likely has mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), one of the most common mitochondrial disorders.

**(Choice A)** Anticipation is the increasing severity or earlier onset of a genetic disease in subsequent generations. This phenomenon is often seen in conditions with an increasing number of trinucleotide repeats with each generation (eg, Huntington disease).

**(Choice B)** Genetic heterogeneity refers to varying genotypes among individuals with the same phenotype, such as sensorineural hearing loss, which can be caused by >100 different mutations. In contrast, this patient has the same mutation as his sister but a more severe phenotype.

**(Choice C)** Genetic imprinting refers to selective inactivation of paternal or maternal alleles. This phenomenon explains the difference in presentation between Prader-Willi and Angelman syndromes.

**(Choice E)** Pleiotropy refers to the seemingly unrelated phenotypic effects of a single genetic mutation. This is seen in Marfan syndrome, in which a fibrillin gene mutation affects various organs (eg, heart, eye). Pleiotropy would not explain variable symptom severity between siblings.

#### Educational objective:

Mitochondrial DNA (mtDNA) is inherited through the maternal line, and identical mutations can cause varying disease severity due to heteroplasmy. Mitochondrial heteroplasmy describes cells that contain both mutant and normal mitochondria; the relative amount of each determines disease severity.

Genetics

Subject

Genetics (General Principles)

System

Mitochondrial disorders

Topic

apps.uworld.com

Item 9 of 20 Question Id: 1788

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

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 (10%)
- B. 1/2 (8%)
- C. 1/4 (29%)
- D. 1/8 (45%)
- E. 1/16 (5%)
- F. 1/32 (1%)

Omitted  
Correct answer  
D

45%  
Answered correctly

01 sec  
Time Spent

2023  
Version

### Explanation

#### Hemophilia inheritance probability

apps.uworld.com

Item 9 of 20 Question Id: 1788

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

## Hemophilia inheritance probability

P1 = 50% chance of being carrier

P2 = 50% chance of passing on mutant allele

P3 = 50% chance of baby being male (therefore affected)

$P1 \times P2 \times P3 = 1/8$

Affected

Unaffected

apps.uworld.com

This patient is a boy with excessive bleeding and hemarthroses, suggesting a diagnosis of **hemophilia A** or B. Both diseases are **X-linked recessive** coagulation factor deficiencies. The probability that his sister will give birth to an affected child can be calculated by multiplying the following probabilities:

- The probability (p1) that the sister is a **carrier** = 0.5. The patient's father does not carry the mutation on his X chromosome because he would be affected by the disease if he did. That means the mother carries the mutation on 1 of her 2 X chromosomes. This gives the daughter a 50% chance of having inherited the mutated X chromosome and therefore being a carrier.
- The probability (p2) that the offspring of a female carrier will **inherit** the X chromosome with the hemophilia gene = 0.5. Assuming the daughter is a carrier, the probability of passing on the mutant allele is 50% as only 1 of her 2 X chromosomes is passed to her offspring.
- The probability (p3) that his sister will have a **boy** = 0.5. If the sister's child is female, the child could be a carrier of the disease but would not be affected by it. If a male child inherits the mutated X chromosome, he will have the disease.

The probability that the sister will have an affected son is the probability that all 3 of the above events will take place (ie, the product of their individual probabilities):  $p1 \times p2 \times p3 = 1/2 \times 1/2 \times 1/2 = 1/8$ .

#### Educational objective:

Given phenotypically normal parents, the probability that a female sibling of a male affected by an X-linked recessive disease will give birth to an affected child is 1/8.



AA

apps.uworld.com



Item 10 of 20

Question Id: 1970



Previous

Next

Full Screen

Tutorial



Lab Values

Notes



Calculator



Reverse Color

A A A

Text Zoom

Settings

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 (5%)
- B. Genetic linkage (3%)
- C. Incomplete penetrance (2%)
- D. Locus heterogeneity (10%)
- E. Pleiotropy (74%)
- F. Polyploidy (3%)
- G. Segregation (0%)

Omitted

Correct answer

E



74%

Answered correctly



01 sec

Time Spent



2023

Version

Explanation

apps.uworld.com

Item 10 of 20 Question Id: 1970 Explanation AA

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

This patient presenting with skeletal abnormalities, lens dislocation, intellectual deficits, vascular thromboses, and a genetic defect in the cystathione beta-synthase enzyme likely has [homocystinuria](#). The occurrence of **multiple**, seemingly unrelated **phenotypic manifestations**, often in different organ systems, as a result of a **single genetic defect** is termed **pleiotropy**. Most syndromic genetic illnesses including homocystinuria exhibit pleiotropy.

**(Choice A)** Dominant negative mutations occur when an abnormal gene negatively affects the product of the wild-type gene in the same cell. For example, certain oncogene *p53* mutations can lead to translation of a protein product that prevents wild-type *p53* from binding to the promoter of its target genes.

**(Choice B)** Genetic linkage describes the tendency of alleles located near one another on the same chromosome to be inherited jointly.

**(Choice C)** Penetrance refers to the proportion of individuals with a given genotype that express the associated phenotype. In incomplete penetrance, less than 100% of individuals with a given genotype express its associated phenotype.

**(Choice D)** Locus heterogeneity refers to the ability of one disease or trait to be caused by mutations in multiple different genes. An example is familial hypercholesterolemia, which can be caused by different mutations affecting cholesterol metabolism genes (eg, LDL receptor, apo B-100).

**(Choice F)** Polyploidy occurs when more than 2 complete sets of homologous chromosomes exist within an organism or cell. In a partial hydatidiform mole, for example, there are cells of nonstandard ploidy (typically 69,XXX; 69,XXY; or 69,XYY). The chromosomes in this case are derived from 1 haploid maternal set and 2 haploid paternal sets of chromosomes.

Item 10 of 20  
Question Id: 1970

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

**(Choice C)** Penetrance refers to the proportion of individuals with a given genotype that express the associated phenotype. In incomplete penetrance, less than 100% of individuals with a given genotype express its associated phenotype.

**(Choice D)** Locus heterogeneity refers to the ability of one disease or trait to be caused by mutations in multiple different genes. An example is familial hypercholesterolemia, which can be caused by different mutations affecting cholesterol metabolism genes (eg, LDL receptor, apo B-100).

**(Choice F)** Polyploidy occurs when more than 2 complete sets of homologous chromosomes exist within an organism or cell. In a partial hydatidiform mole, for example, there are cells of nonstandard ploidy (typically 69,XXX; 69,XXY; or 69,XYY). The chromosomes in this case are derived from 1 haploid maternal set and 2 haploid paternal sets of chromosomes.

**(Choice G)** The law of segregation (Mendel's first law) describes the phenomenon whereby gametogenesis within the parent organism results in the separation of paired alleles so that each offspring inherits only half of each parent's genetic composition.

### Educational objective:

Pleiotropy describes instances where multiple phenotypic manifestations result from a single genetic mutation. Most syndromic genetic illnesses exhibit pleiotropy.

### References

- [Pleiotropy in complex traits: challenges and strategies.](#)

Genetics

Genetics (General Principles)

Subject

System

Pleiotropy

Topic



AA

apps.uworld.com



Item 11 of 20



Question Id: 1728

Previous

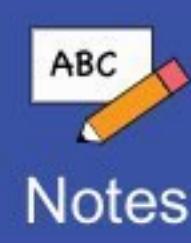
Next

Full Screen

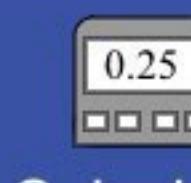
Tutorial



Lab Values



Notes



Calculator

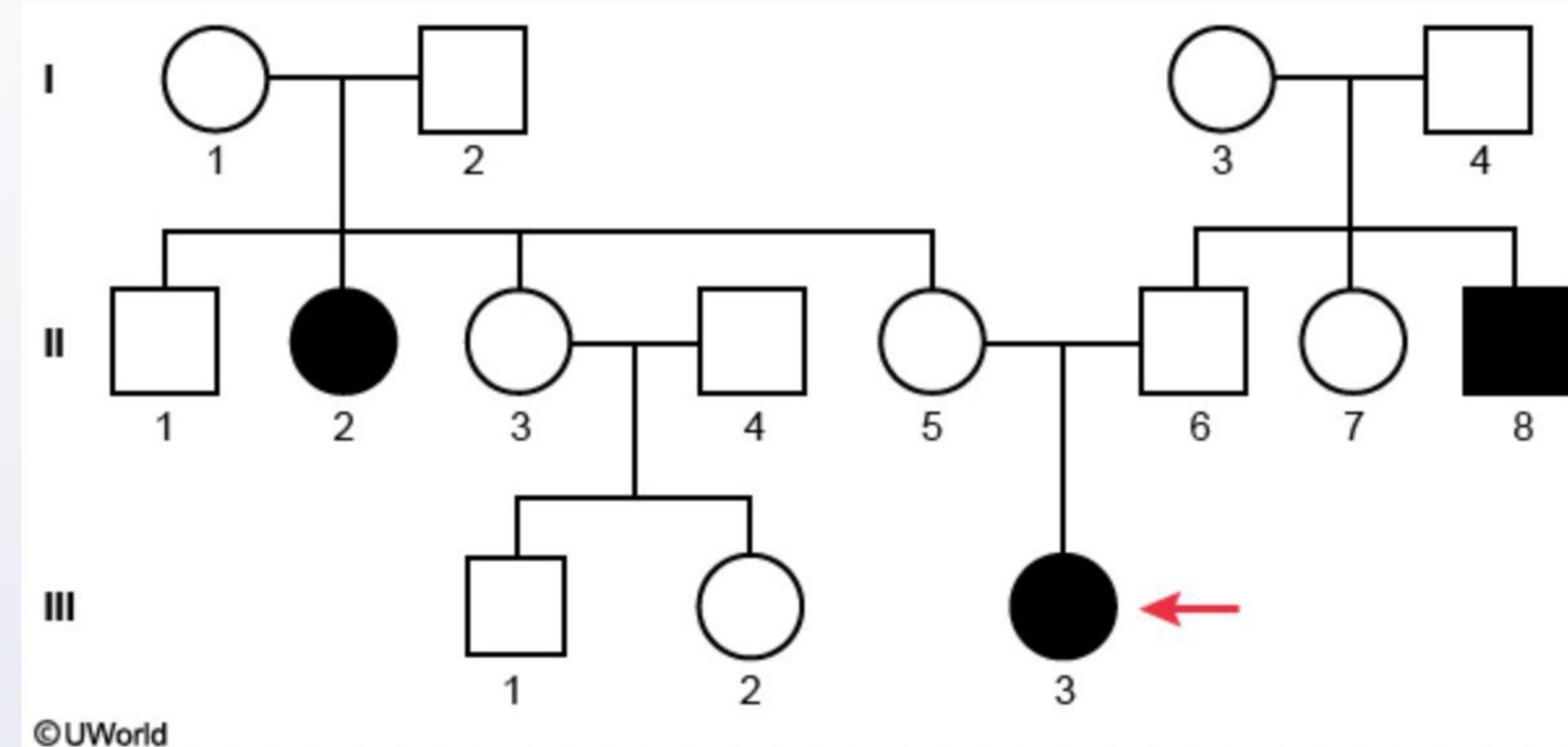


Reverse Color

Text Zoom



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 (64%)
- B. Hemophilia B (16%)
- C. Huntington disease (6%)
- D. Leber hereditary optic neuropathy (6%)
- E. Rett syndrome (6%)

Omitted

Correct answer

A



64%

Answered correctly



01 sec

Time Spent



2023

Version

AA apps.uworld.com

Item 11 of 20 Question Id: 1728 Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

### Autosomal recessive inheritance

Carrier parent (Aa)

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

Offspring have 25% chance of being affected

©UWorld

Each of the affected individuals on this pedigree inherited the disorder from **asymptomatic carrier parents**, which is consistent with a recessive inheritance pattern. Because **both males and females** inherit the condition, it is an **autosomal recessive** disorder. Based on this inheritance pattern, 50% of offspring will be asymptomatic carriers, 25% will be unaffected, and 25% will express the disorder.

**Classic galactosemia** is the most common and most severe of the galactosemic disorders. It is an autosomal recessive disorder leading to complete enzymatic absence of galactose-1-phosphate uridyl transferase.

apps.uworld.com

Item 11 of 20 Question Id: 1728

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Each of the affected individuals on this pedigree inherited the disorder from **asymptomatic carrier parents**, which is consistent with a recessive inheritance pattern. Because **both males and females** inherit the condition, it is an **autosomal recessive** disorder. Based on this inheritance pattern, 50% of offspring will be asymptomatic carriers, 25% will be unaffected, and 25% will express the disorder.

**Classic galactosemia** is the most common and most severe of the galactosemic disorders. It is an autosomal recessive disorder leading to complete enzymatic absence of galactose-1-phosphate uridyl transferase.

Newborns present within days of birth with jaundice, vomiting, and hepatomegaly.

In general, most **enzyme deficiency conditions** follow an autosomal recessive inheritance pattern whereas diseases due to defective noncatalytic proteins follow an autosomal dominant pattern.

**(Choice B)** Hemophilia B (Christmas disease) is an [X-linked recessive disorder](#) affecting **males** that causes factor IX deficiency with easy bruising and bleeding (eg, hemarthrosis, oral bleeding, intracranial hemorrhage). Affected males will have asymptomatic carrier mothers.

**(Choice C)** Huntington disease is an [autosomal dominant disorder](#) affecting males and females equally. It causes progressive neurodegeneration of the caudate and putamen, leading to chorea, dementia, and death. Patients usually have an affected parent.

**(Choice D)** Leber hereditary optic neuropathy is a [mitochondrial inheritance disorder](#) affecting all offspring of an affected mother; there is no father-child transmission. It is characterized by progressive bilateral optic neuropathy leading to blindness.

**(Choice E)** Rett syndrome is an [X-linked dominant disorder](#) affecting females (affected males die in utero) that presents in early childhood with progressive neurodegeneration and stereotypical hand movements. X-linked dominant conditions are characterized by a lack of father-son transmission whereas all daughters of an affected father are affected. Half of all offspring of an affected mother are also affected.

diseases due to defective noncatalytic proteins follow an autosomal dominant pattern.

**(Choice B)** Hemophilia B (Christmas disease) is an [X-linked recessive disorder](#) affecting **males** that causes factor IX deficiency with easy bruising and bleeding (eg, hemarthrosis, oral bleeding, intracranial hemorrhage). Affected males will have asymptomatic carrier mothers.

**(Choice C)** Huntington disease is an [autosomal dominant disorder](#) affecting males and females equally. It causes progressive neurodegeneration of the caudate and putamen, leading to chorea, dementia, and death. Patients usually have an affected parent.

**(Choice D)** Leber hereditary optic neuropathy is a [mitochondrial inheritance disorder](#) affecting all offspring of an affected mother; there is no father-child transmission. It is characterized by progressive bilateral optic neuropathy leading to blindness.

**(Choice E)** Rett syndrome is an [X-linked dominant disorder](#) affecting females (affected males die in utero) that presents in early childhood with progressive neurodegeneration and stereotypical hand movements. X-linked dominant conditions are characterized by a lack of father-son transmission whereas all daughters of an affected father are affected. Half of all offspring of an affected mother are also affected.

#### Educational objective:

Autosomal recessive disorders affect 25% of offspring of asymptomatic heterozygous carrier parents. Classical galactosemia is the most common and severe galactosemic disorder and presents within days of birth with jaundice, vomiting, and hepatomegaly.

Genetics

Subject

Genetics (General Principles)

System

Genetic inheritance

Topic



AA

apps.uworld.com



Item 12 of 20

Question Id: 21307



Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

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 (26%)
- B. Heteroplasm (3%)
- C. Incomplete penetrance (5%)
- D. Linkage disequilibrium (11%)
- E. Locus heterogeneity (47%)
- F. Pleiotropy (4%)

Omitted

Correct answer

E



47%

Answered correctly



01 sec

Time Spent



2023

Version

Explanation

Locus heterogeneity in oculocutaneous albinism

apps.uworld.com

Item 12 of 20

Mark

Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

## Locus heterogeneity in oculocutaneous albinism

Mutations at different genetic loci result in similar phenotypes.

**Father**

Homozygous abnormal chromosome 11

Homozygous normal chromosome 15

**Mother**

Homozygous normal chromosome 11

Homozygous abnormal chromosome 15

Paternal abnormal chromosome 11

Maternal normal chromosome 11

Paternal normal chromosome 15

Maternal abnormal chromosome 15

Child

Double heterozygote, phenotypically normal

The screenshot shows a mobile application interface for a quiz. At the top, there's a header bar with a back arrow, a forward arrow, and a double A icon. The URL 'apps.uworld.com' is displayed in the center. On the right side of the header are icons for sharing, adding, and a grid. Below the header is a blue navigation bar with various icons and text: 'Item 12 of 20', 'Question Id: 21307', 'Mark' (with a red flag icon), 'Previous' (with a left arrow), 'Next' (with a right arrow), 'Full Screen' (with a screen icon), 'Tutorial' (with a question mark icon), 'Lab Values' (with a test tube icon), 'Notes' (with a pencil icon), 'Calculator' (with a calculator icon), 'Reverse Color' (with a black circle icon), 'Text Zoom' (with a double A icon), and 'Settings' (with a gear icon). The main content area contains text about locus heterogeneity in oculocutaneous albinism.

This case is an example of **locus heterogeneity**, in which mutations at different genetic loci result in similar phenotypes. Both parents have oculocutaneous albinism, an inherited **autosomal recessive** disorder. However, although their phenotype is similar, their recessive mutations occur on **different chromosomes**.

In this case, the child would inherit one normal (paternal) allele and one abnormal (maternal) allele at location 15q12-q13 and one normal (maternal) allele and one abnormal (paternal) allele at location 11q14.3. Because the child would have **one normal, dominant allele at each location**, they would be a **double heterozygote** and therefore would not express an oculocutaneous albinism phenotype.

**(Choice A)** In contrast to this case, **allelic heterogeneity** describes *different mutations at the same genetic locus* causing similar phenotypes (eg, cystic fibrosis). Children born to parents who have autosomal recessive genetic conditions resulting from different mutations at the same genetic locus would inherit two abnormal copies of the gene and likely display the corresponding phenotype.

**(Choice B)** Mitochondrial diseases (eg, MELAS syndrome, Leber hereditary optic neuropathy) are maternally inherited. The variable severity of these diseases is explained by **heteroplasmy**, the random distribution of normal and mutated mitochondrial DNA between daughter cells during meiosis. As a result, some eggs may have completely healthy mitochondria, while other cells contain mitochondria affected by genetic mutation.

**(Choice C)** Penetrance is the probability that a person with a given genotype will express its associated phenotype. Incomplete penetrance means that some individuals with an abnormal genotype will not express the corresponding phenotype (eg, breast cancer in individuals with *BRCA1/2* mutations).

**(Choice D)** Two allele loci are said to be in **linkage disequilibrium** when a pair of alleles is inherited together in the same gamete (haplotype) more often or less often than would be expected given random pairing. This most often occurs when the genes are in close physical proximity on the same chromosome.

gene and likely display the corresponding phenotype.

**(Choice B)** Mitochondrial diseases (eg, MELAS syndrome, Leber hereditary optic neuropathy) are maternally inherited. The variable severity of these diseases is explained by [heteroplasmy](#), the random distribution of normal and mutated mitochondrial DNA between daughter cells during meiosis. As a result, some eggs may have completely healthy mitochondria, while other cells contain mitochondria affected by genetic mutation.

**(Choice C)** Penetrance is the probability that a person with a given genotype will express its associated phenotype. Incomplete penetrance means that some individuals with an abnormal genotype will not express the corresponding phenotype (eg, breast cancer in individuals with *BRCA1/2* mutations).

**(Choice D)** Two allele loci are said to be in [linkage disequilibrium](#) when a pair of alleles is inherited together in the same gamete (haplotype) more often or less often than would be expected given random pairing. This most often occurs when the genes are in close physical proximity on the same chromosome.

**(Choice F)** The occurrence of multiple, seemingly unrelated phenotypic manifestations (often in different organ systems as a result of a single genetic defect) is termed pleiotropy. Although this may apply to features of oculocutaneous albinism (eg, absence of melanin in skin, reduced visual acuity, nystagmus), it does not explain why a child of two affected parents would be unaffected.

#### Educational objective:

Locus heterogeneity describes when a similar phenotype is produced by mutations in different genetic loci (eg, oculocutaneous albinism).

Genetics

Genetics (General Principles)

Subject

System

Albinism

Topic

apps.uworld.com

Item 13 of 20 Question Id: 8283

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

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 (11%)
- B. Increased penetrance (8%)
- C. Linkage disequilibrium (60%)
- D. Pleiotropy (13%)
- E. Segregation (7%)

Omitted  
Correct answer  
C

60%  
Answered correctly

01 sec  
Time Spent

2023  
Version

### Explanation

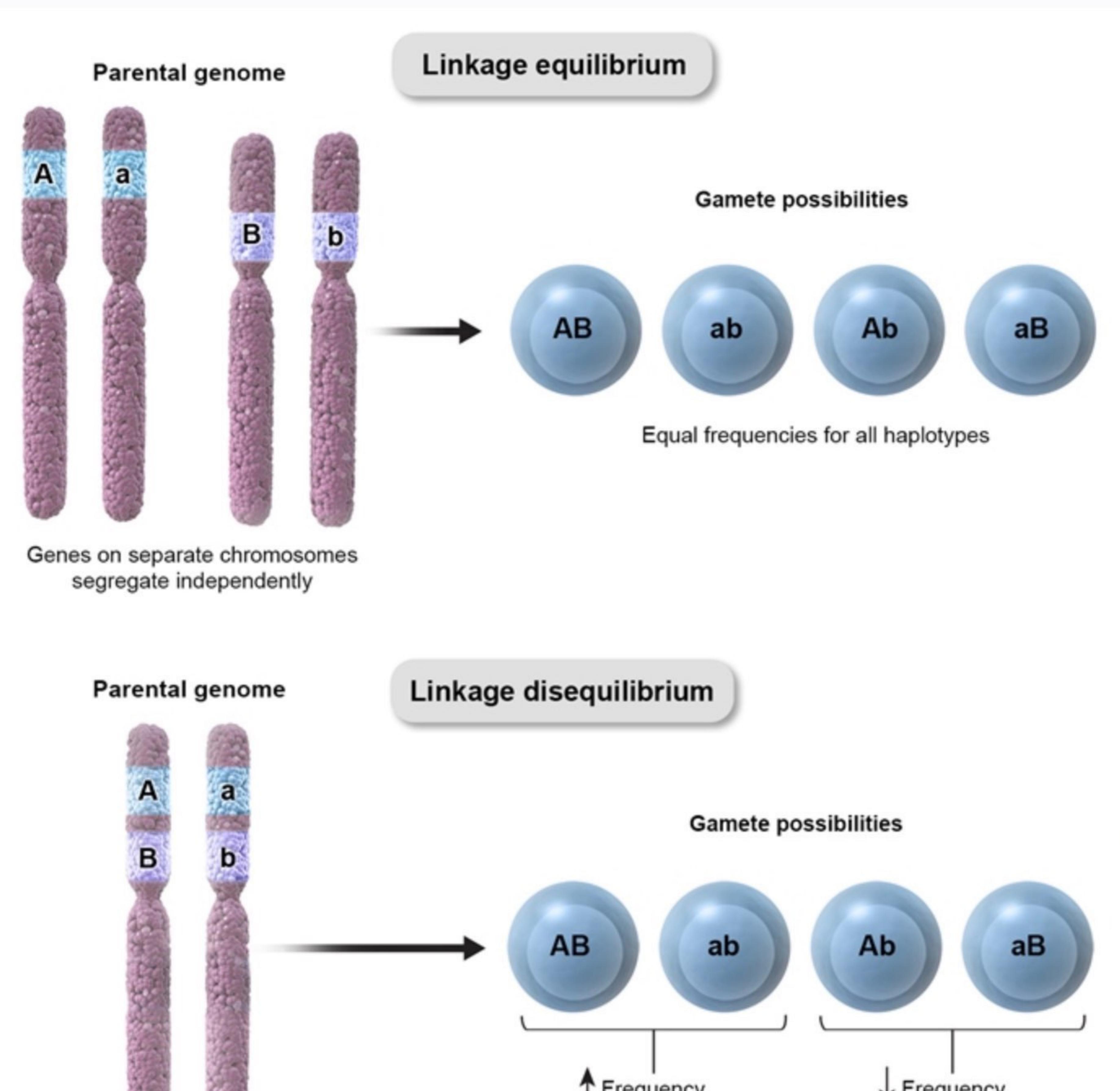
Parental genome

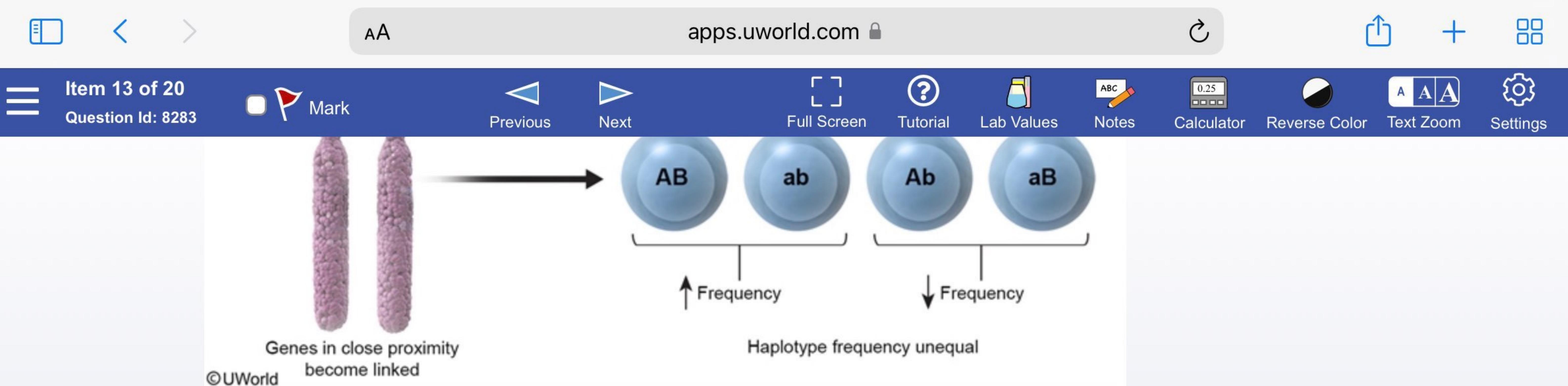
Linkage equilibrium

AA apps.uworld.com

Item 13 of 20 Question Id: 8283

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings





Two genetic loci are said to be in **linkage disequilibrium** when their respective alleles are **inherited together** in the same gamete (haplotype) **more or less often than expected** by chance alone given their corresponding allele frequencies. Although linkage disequilibrium is often the result of **physical proximity** of genes on the same chromosome, it does not always imply physical linkage between the allelic loci.

To estimate the expected probability of 2 alleles from separate loci appearing together, multiply their occurrence rates. Note that the Hardy-Weinberg principle ( $2pq$ ) is not applicable when considering alleles at different loci.

DQA1\*0501-DQB1\*0201  
haplotype frequency

$$\begin{aligned}
 &= [\text{Frequency of DQA1*0501}] \times [\text{Frequency of DQB1*0201}] \\
 &= 0.3 \times 0.2 \\
 &= \mathbf{0.06}
 \end{aligned}$$

In this example, the observed frequency of both alleles being inherited together is **0.2**, which is greater than the expected frequency of 0.06; therefore, the population is said to be in linkage disequilibrium. This disequilibrium is explained by the close proximity of the HLA-DQA1 and HLA-DQB1 loci that code for  $\alpha$  and  $\beta$  chains of class II major histocompatibility complex.

apps.uworld.com

Item 13 of 20 Question Id: 8283

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

is explained by the close proximity of the HLA-DQAT and HLA-DQB1 loci that code for  $\alpha$  and  $\beta$  chains of class II major histocompatibility complex.

**(Choice A)** Heteroplasmy describes the presence of different mitochondrial genomes (eg, mutated and wild type) within a single cell. The severity of mitochondrial diseases is often related to the proportion of abnormal to normal mitochondria.

**(Choice B)** Penetrance is the proportion of people with a given genotype who express its associated phenotype. If all individuals with a given gene express its phenotype, that gene is said to have full penetrance.

**(Choice D)** Pleiotropy is the occurrence of multiple phenotypic manifestations, often in different organ systems, which result from a mutation in a single gene.

**(Choice E)** The law of segregation describes the phenomenon in which gametogenesis results in the separation of paired chromosomes so that the offspring inherit only half of each parent's genetic composition.

### Educational objective:

Two allele loci are said to be in linkage disequilibrium when a pair of alleles are inherited together in the same gamete (haplotype) more often or less often than would be expected given random pairing. This most often occurs when the genes are in close physical proximity on the same chromosome.

### References

- Gene polymorphisms, inflammatory diseases and cancer.
- Linkage disequilibrium and its expectation in human populations.

Genetics

Genetics (General Principles)

Subject

System

Linkage disequilibrium

Topic

apps.uworld.com

Item 14 of 20 Question Id: 14781

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

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 (7%)
- B. 1/16 (15%)
- C. 1/8 (10%)
- D. 1/4 (55%)
- E. 1/2 (10%)

Omitted  
Correct answer  
D

55%  
Answered correctly

01 sec  
Time Spent

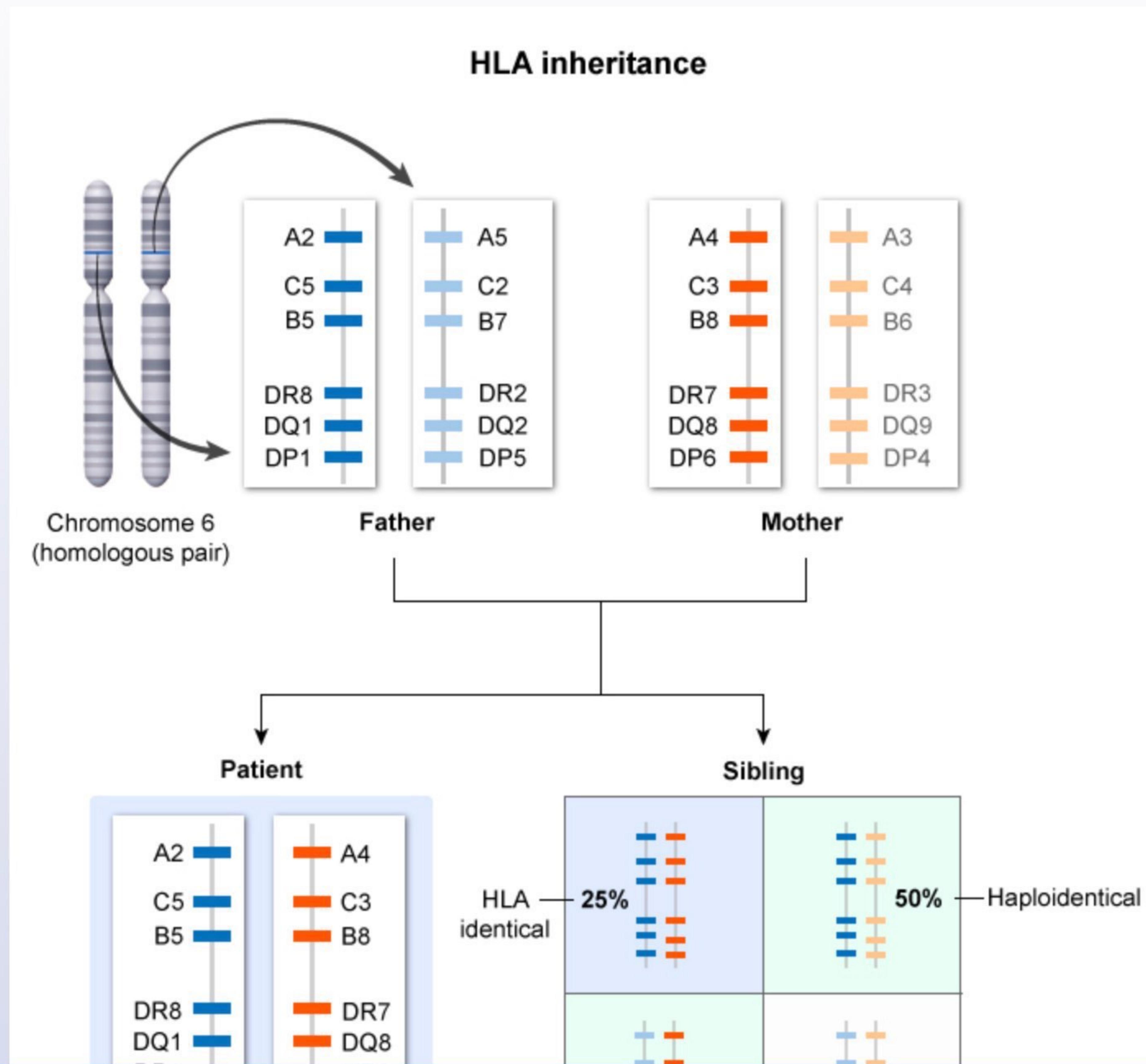
2023  
Version

### Explanation

#### HLA inheritance

AA apps.uworld.com

Item 14 of 20 Question Id: 14781 Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings



apps.uworld.com

Item 14 of 20 Question Id: 14781

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Chromosome 6 (homologous pair)

Father

Mother

Patient

Sibling

HLA identical

25% 50% Haploidentical

25% HLA mismatch

A2 A4  
C5 C3  
B5 B8  
DR8 DR7  
DQ1 DQ8  
DP1 DP6

©UWorld

The human leukocyte antigen (**HLA**) genes encode major histocompatibility complex (**MHC**) molecules that are expressed on the cell surface and are key to recognition of cells as **self or non-self** by the immune system. These include major class I genes (eg, HLA-A, HLA-B, HLA-C) and class II genes (eg, HLA-DP, HLA-DQ, HLA-DR), along with other minor HLA genes.

Although there are thousands of HLA alleles in the human population with millions of potential combinations, the HLA genes are **clustered** within a short region of a **single chromosome**. This results in a **low rate of crossover**, allowing the HLA gene cluster to be treated as an **HLA haplotype** (a series of **linked genes** on the same chromosome). Each child inherits 2 HLA haplotypes - one from the mother and one from the father. Therefore,

apps.uworld.com

expressed on the cell surface and are key to recognition of cells as **self or non-self** by the immune system.

These include major class I genes (eg, HLA-A, HLA-B, HLA-C) and class II genes (eg, HLA-DP, HLA-DQ, HLA-DR), along with other minor HLA genes.

Although there are thousands of HLA alleles in the human population with millions of potential combinations, the HLA genes are **clustered** within a short region of a [single chromosome](#). This results in a **low rate of crossover**, allowing the HLA gene cluster to be treated as an **HLA haplotype** (a series of **linked genes** on the same chromosome). Each child inherits 2 HLA haplotypes, one from the mother and one from the father. Therefore, the probabilities that a given sibling will share some or all of the same HLA genes are as follows:

- **1/4** chance of inheriting all the same HLA genes (ie, **identical HLA match**).
- **1/2** chance of inheriting half of the same HLA genes (ie, haploidentical HLA match) (**Choice E**).
- **1/4** chance of inheriting none of the same HLA genes (ie, HLA mismatch).

**Molecular typing** of HLA antigens is performed prior to transplants (eg, allogeneic stem cell transplant) to evaluate potential donors for mismatch in HLA alleles (eg, HLA-DR8 versus HLA-DR3), which is associated with higher rates of posttransplant complications (eg, graft versus host disease, graft failure). An **HLA-identical sibling donor** would drastically reduce the likelihood of serious complications and increase the likelihood of a **successful transplant**.

#### **Educational objective:**

The human leukocyte antigen (HLA) genes encode major histocompatibility complex (MHC) molecules that are key to activation of the immune system in response to foreign (non-self) antigens. All the HLA genes are clustered together, meaning that there is a low rate of crossover and that offspring essentially inherit 2 HLA haplotypes, one from each parent. Therefore, the probability that a sibling would be an identical HLA match is **1/4**.



AA

apps.uworld.com



Item 15 of 20



Question Id: 11914

Previous Next

Full Screen

Tutorial

Lab Values

Notes

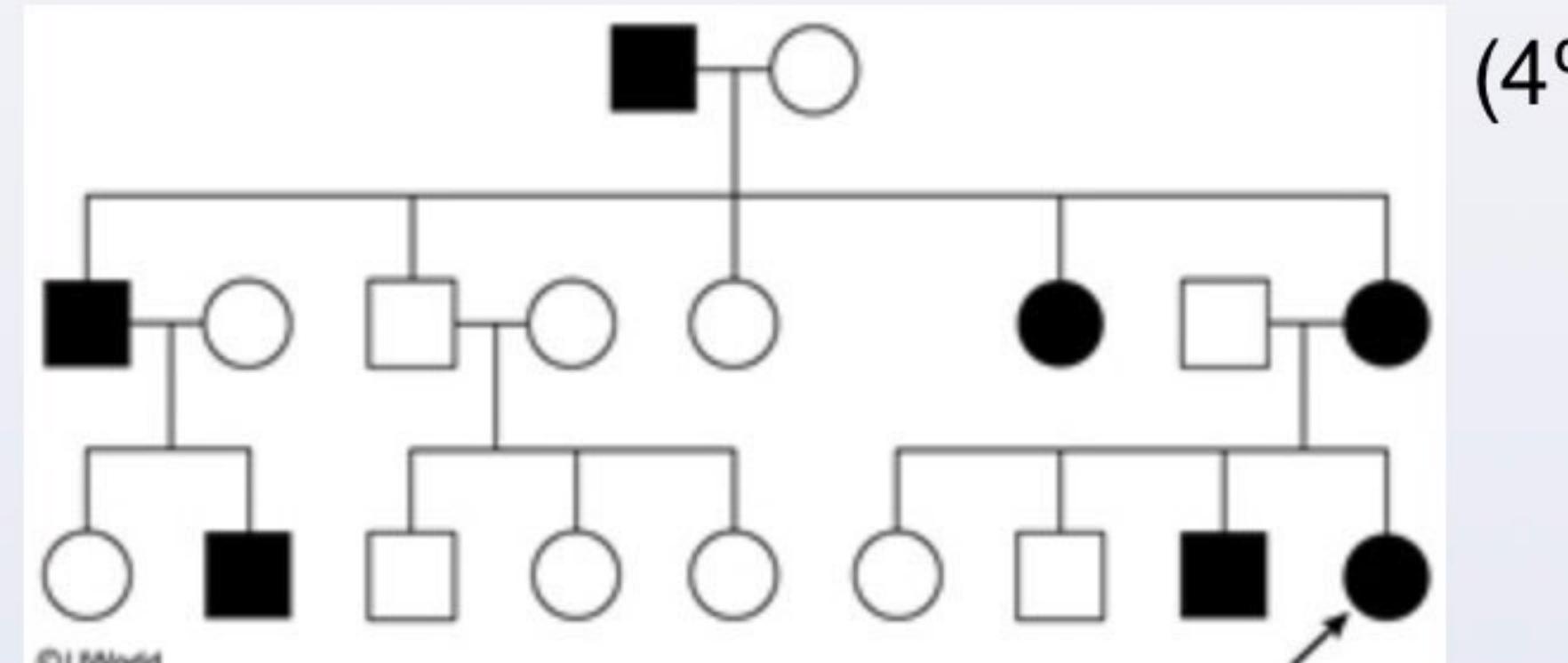
Calculator

Reverse Color

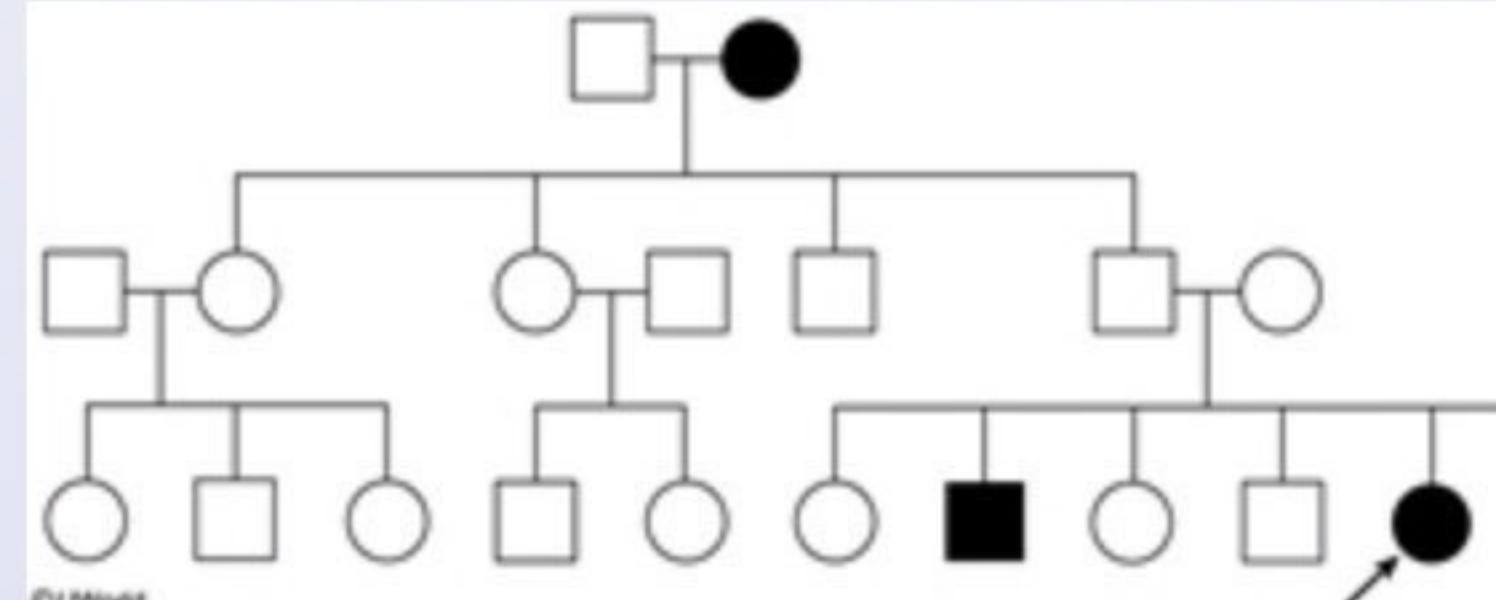
Text Zoom

Settings

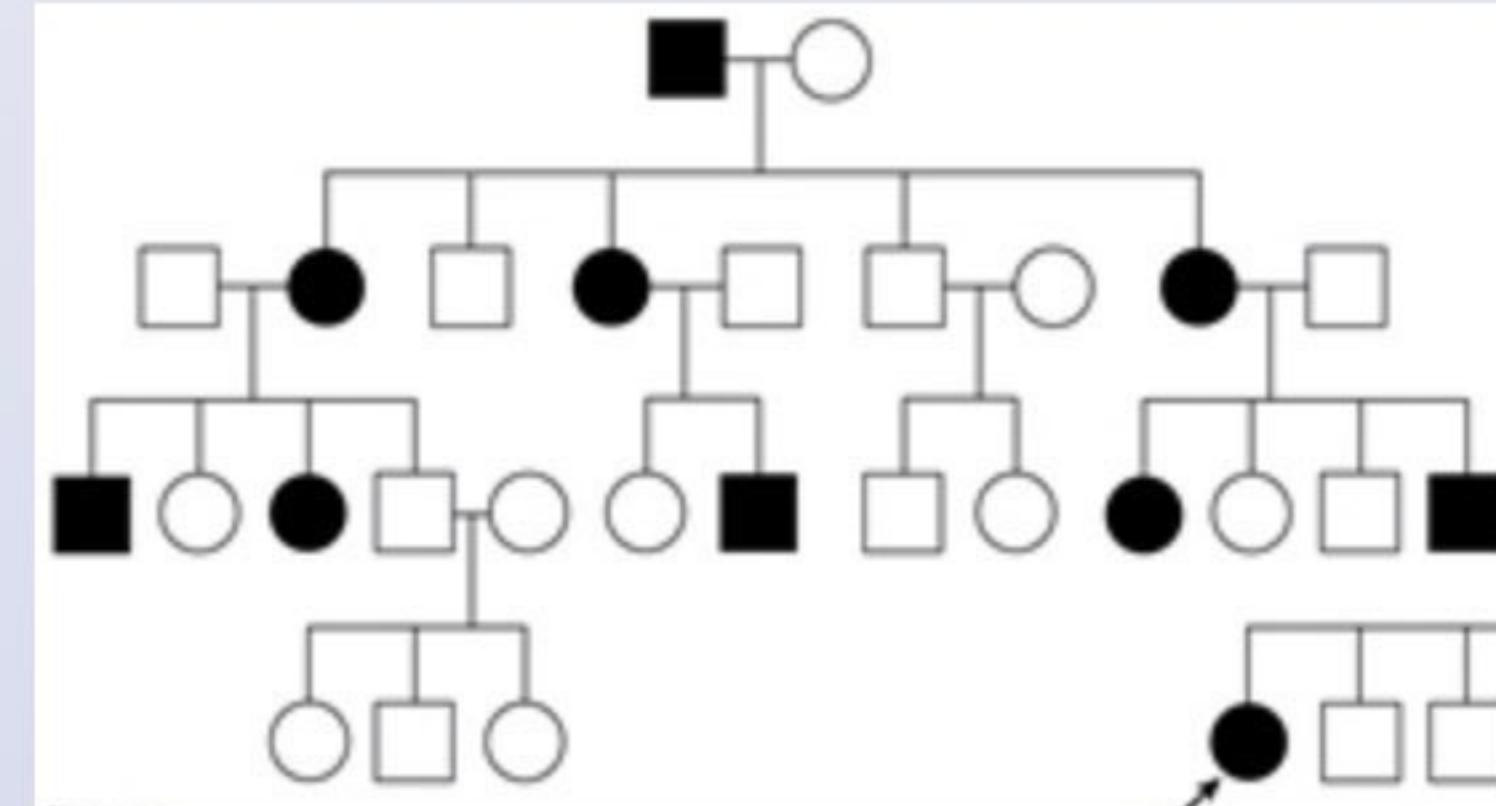
A 19-year-old woman is evaluated for new onset generalized tonic-clonic seizures. For the past several years, she has also been having erratic jerks of her arms and legs, and intermittent muscle weakness. The girl has multiple family members with similar symptoms. Neurological examination reveals decreased 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.

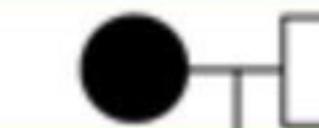
(4%)

 B.

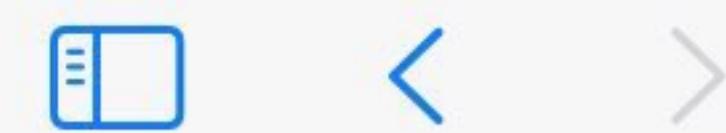
(3%)

 C.

(4%)

 D.

(3%)



AA

apps.uworld.com

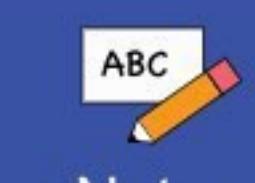


Item 15 of 20

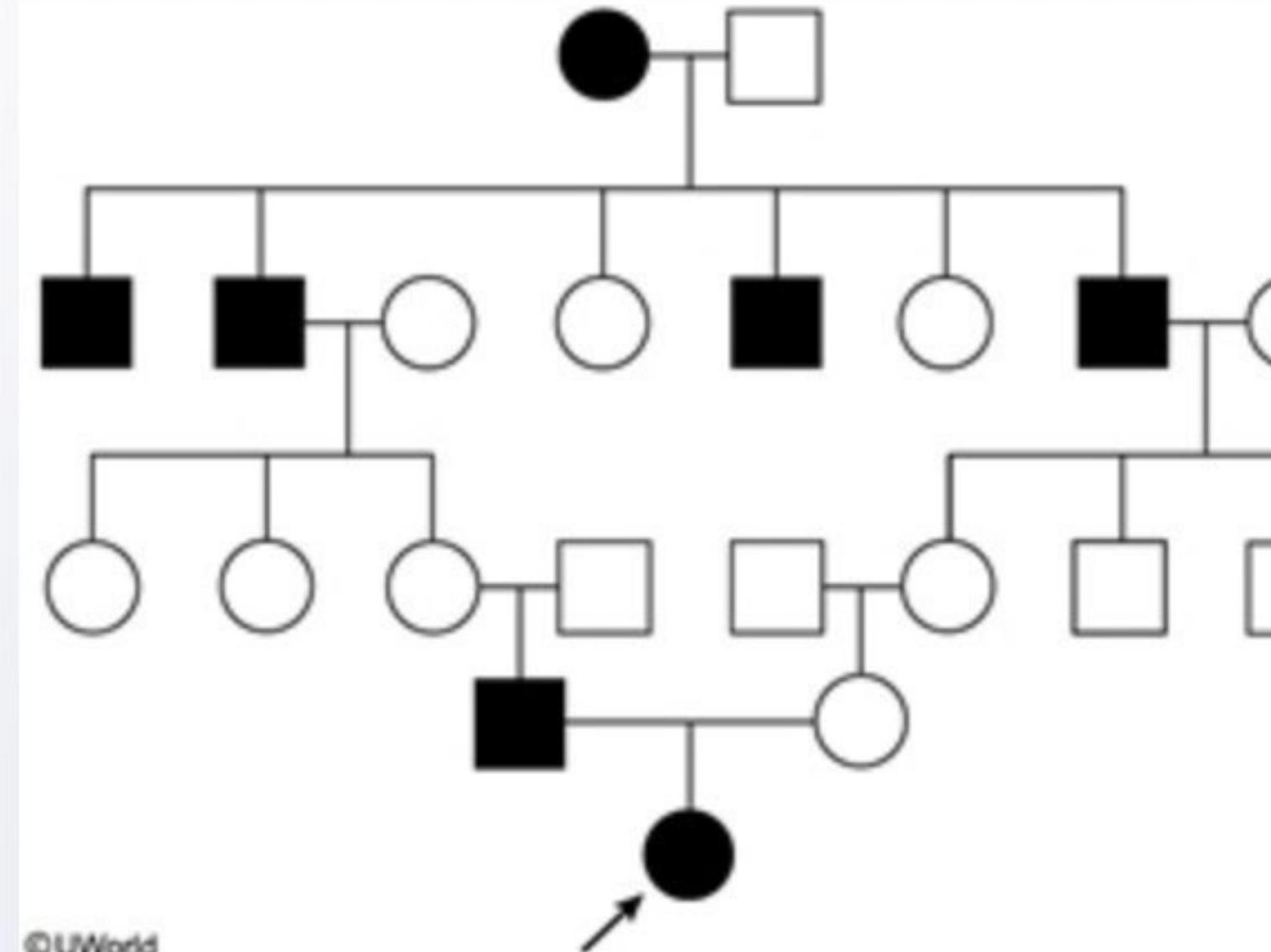
Question Id: 11914



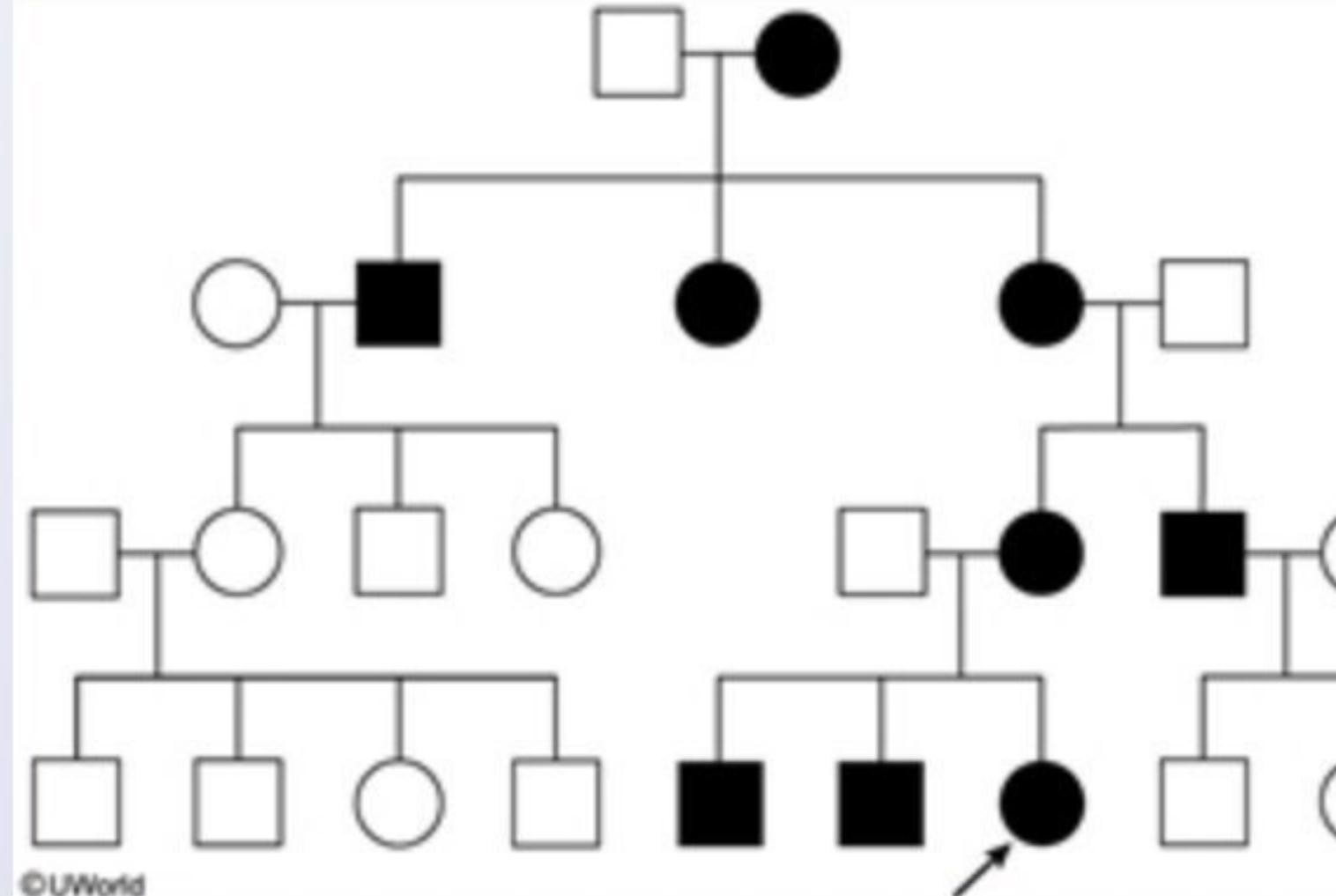
Previous

 D.

(3%)

 E.

(84%)



Omitted

Correct answer

E

84%  
Answered correctly07 secs  
Time Spent2023  
Version

## Explanation

Item 15 of 20 Question Id: 11914

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

This patient most likely has a form of **mitochondrial myopathy**. Without properly functioning mitochondria, cells are unable to use oxidative phosphorylation to efficiently produce adequate levels of ATP. Organ systems such as the brain and skeletal muscle will be affected first due to their high metabolic demand relative to other tissues. Affected patients often present with myopathy (eg, **muscle weakness**, myalgia), lactic acidosis due to impaired aerobic glycolysis, and **nervous system dysfunction** (eg, neuropathy, seizures). Muscle biopsy classically shows **ragged red fibers**.

Mitochondria are unique organelles because they contain their own DNA, known as **mtDNA**. Offspring inherit mtDNA in a maternal fashion with no paternal contribution (**maternal inheritance**). Only affected females transmit abnormal mitochondria to offspring; transmission never occurs through males (even if they are affected).

**(Choice A)** Autosomal dominant disorders affect 50% of all children (males and females) born to one affected parent. The disease will appear in consecutive generations, and father-to-son transmission can occur.

**(Choice B)** Autosomal recessive conditions affect about 25% of all children (males and females) with two carrier parents. Offspring of a single affected parent will be carriers for the disorder. As a result, the disease can skip generations, but consanguineous families will show increased incidence.

**(Choice C)** In **X-linked dominant** disorders, all female children of affected males will have the condition, but both female and male children of an affected female have a 50% chance of being affected. There is no father-to-son transmission.

**(Choice D)** In **X-linked recessive** conditions, male offspring of a carrier female have a 50% chance of being affected, whereas female offspring have a 50% chance of being carriers. Female children of an affected father are obligate carriers. The disease can skip generations, and there is no father-to-son transmission.

#### Educational objective:

The image shows a screenshot of the UWorld mobile application. At the top, there's a navigation bar with icons for back, forward, and search. The URL 'apps.uworld.com' is displayed in the address bar. Below the address bar is a toolbar with various functions: 'Item 15 of 20', 'Mark' (with a red flag icon), 'Previous' and 'Next' buttons, 'Full Screen', 'Tutorial', 'Lab Values', 'Notes' (with a pencil icon), 'Calculator' (with a '0.25' icon), 'Reverse Color' (with a black circle icon), 'Text Zoom' (with a 'A A A' icon), and 'Settings' (with a gear icon). The main content area contains four choices labeled A, B, C, and D, each describing a different inheritance pattern. Choice A describes autosomal dominant disorders. Choice B describes autosomal recessive conditions. Choice C describes X-linked dominant disorders. Choice D describes X-linked recessive disorders. Below the choices is a section titled 'Educational objective:' followed by a paragraph about mitochondrial dysfunction and inheritance.

**(Choice A)** Autosomal dominant disorders affect 50% of all children (males and females) born to one affected parent. The disease will appear in consecutive generations, and father-to-son transmission can occur.

**(Choice B)** Autosomal recessive conditions affect about 25% of all children (males and females) with two carrier parents. Offspring of a single affected parent will be carriers for the disorder. As a result, the disease can skip generations, but consanguineous families will show increased incidence.

**(Choice C)** In [X-linked dominant](#) disorders, all female children of affected males will have the condition, but both female and male children of an affected female have a 50% chance of being affected. There is no father-to-son transmission.

**(Choice D)** In [X-linked recessive](#) conditions, male offspring of a carrier female have a 50% chance of being affected, whereas female offspring have a 50% chance of being carriers. Female children of an affected father are obligate carriers. The disease can skip generations, and there is no father-to-son transmission.

### Educational objective:

Mitochondrial dysfunction frequently presents with myopathy, nervous system dysfunction, lactic acidosis, and ragged red fibers on muscle biopsy. Mitochondrial myopathies due to mtDNA mutations are inherited solely in a maternal fashion (ie, maternal inheritance). Therefore, transmission occurs only through affected females and never through males.

### References

- [Maternal inheritance of mitochondrial DNA by diverse mechanisms to eliminate paternal mitochondrial DNA.](#)

Genetics  
Subject

Genetics (General Principles)  
System

Mitochondrial disorders  
Topic

apps.uworld.com

Item 16 of 20 Question Id: 1789

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

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 (5%)
- B. 1/32 (0%)
- C. 1/16 (3%)
- D. 1/8 (4%)
- E. 1/4 (79%)
- F. 1/2 (5%)

Omitted  
Correct answer  
E

79%  
Answered correctly

06 secs  
Time Spent

2023  
Version

### Explanation

Intellectual disability, gait abnormalities, a musty body odor, and eczema are signs consistent with [phenylketonuria](#) (PKU). PKU is caused by a mutation in a single gene that codes for phenylalanine hydroxylase. This enzyme normally synthesizes tyrosine from phenylalanine, and a buildup of phenylalanine in the CNS results in neurologic dysfunction. In the United States, phenylalanine levels are measured in neonates via

apps.uworld.com

Item 16 of 20

Question Id: 1789

Mark

Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Intellectual disability, gait abnormalities, a musty body odor, and eczema are signs consistent with [phenylketonuria](#) (PKU). PKU is caused by a mutation in a single gene that codes for phenylalanine hydroxylase. This enzyme normally synthesizes tyrosine from phenylalanine, and a buildup of phenylalanine in the CNS results in neurologic dysfunction. In the United States, phenylalanine levels are measured in neonates via routine newborn screening.

PKU is an [autosomal recessive](#) disease. Therefore, when a child is affected but **parents are unaffected**, the parents are very likely to be **heterozygous carriers** of the mutation. The probability of a child inheriting any disease with an autosomal recessive inheritance pattern, including PKU, depends on the following factors:

$p_1$  = probability that the mother transmits the mutant allele = 1/2

$p_2$  = probability that the father transmits the mutant allele = 1/2

The probability that a child will inherit a mutant allele from each carrier parent is equal to  $p_1 \times p_2 = 1/4$  because these are independent events (**Choices A, B, and D**).

**(Choice C)** The probability of having two future children both inherit an autosomal recessive disease from parents who are heterozygous carriers is  $1/4 \times 1/4 = 1/16$  (each 1/4 representing the likelihood of 1 child inheriting the disease). In this case, this family already has an affected child, making the probability of a single subsequent child with the disease remain at 1/4.

**(Choice F)** The probability that a child will inherit an [autosomal dominant](#) disorder if one parent is affected is 1/2.

#### Educational objective:

Intellectual disability, gait abnormalities, and a musty body odor are signs of phenylketonuria, an autosomal recessive disorder. The probability that a child will inherit an autosomal recessive disease from heterozygous carrier parents is 1/4.

apps.uworld.com

Item 17 of 20 Question Id: 1487

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

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 (3%)
- B. UAA → UAG (19%)
- C. UAC → CAC (5%)
- D. UCA → UGA (69%)
- E. UUU → UUC (1%)

Omitted  
Correct answer  
D

69%  
Answered correctly

01 sec  
Time Spent

2023  
Version

### Explanation

#### Types of DNA mutations

apps.uworld.com

Item 17 of 20  
Question Id: 1487

Mark

Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Types of DNA mutations	
<b>Silent</b>	Base substitution codes for same amino acid
<b>Missense</b>	Base substitution codes for different amino acid
<b>Conservative</b>	Base substitution codes for different amino acid with similar chemical structure
<b>Nonsense</b>	Base substitution introduces premature stop codon
<b>Nonstop</b>	Base substitution within stop codon results in continued translation
<b>Splice site</b>	Mutation at splice site alters intron removal from pre-mRNA
<b>Frameshift</b>	Deletion/insertion of bases causes downstream misreading

This young boy with progressive proximal muscle weakness, calf pseudohypertrophy, [Gowers sign](#), and elevated creatine kinase likely has **Duchenne muscular dystrophy**, an X-linked recessive disorder caused by mutations in the dystrophin gene. Although Duchenne muscular dystrophy is most commonly caused by **deletions** resulting in frameshift mutations, **nonsense mutations** may also occur, leading to the formation of a truncated dystrophin protein.

After messenger RNA (mRNA) is produced from DNA and posttranscriptionally modified, it is transported to the cytoplasm for translation into protein. mRNA is composed of groups of 3 sequential nucleotide bases known as codons. These nucleotide triplets code for specific amino acids and signal for the initiation (eg, start codon [AUG]) or termination of translation (eg, **stop codons** [UAA, UAG, UGA]). In this case, a single base substitution from UCA (serine) to UGA has introduced a **premature** stop codon in the middle of the protein sequence (nonsense mutation), resulting in early termination of protein synthesis.

The screenshot shows a mobile application interface for a medical question. At the top, there's a header with a back arrow, a forward arrow, and a double-letter icon labeled 'AA'. The URL 'apps.uworld.com' is displayed in the address bar. To the right of the address bar are icons for refresh, share, plus, and square. Below the header, a blue navigation bar contains the text 'Item 17 of 20' and 'Question Id: 1487'. It also includes icons for 'Mark' (with a red flag), 'Previous' (left arrow), 'Next' (right arrow), 'Full Screen' (monitor), 'Tutorial' (info circle), 'Lab Values' (test tube), 'Notes' (pencil), 'Calculator' (calculator), 'Reverse Color' (circle with dot), 'Text Zoom' (text A), and 'Settings' (gear). The main content area of the screen displays the following text:

sequence (nonsense mutation), resulting in early termination or protein synthesis.

Dystrophin normally links with actin fibers and provides mechanical reinforcement to glycoprotein complexes in the plasma membrane of skeletal muscle cells. Consequently, dystrophin dysfunction leads to increased breakdown of the sarcolemma, muscle fiber degeneration, and the clinical findings described above.

**(Choices A and C)** Changing CUU (leucine) to AUU (isoleucine) or UAC (tyrosine) to CAC (histidine) would result in an amino acid substitution at one position (missense mutation). The function of this protein may be altered depending on a variety of factors, but the ultimate size of the protein will remain the same. Missense mutations that result in the substitution of a new amino acid with similar chemical properties are called conservative mutations.

**(Choice B)** Changing UAA to UAG would not affect protein structure or function because both of these sequences are stop codons. Stop codons are normally located at the end of the translated region of mRNA.

**(Choice E)** Changing UUU to UUC would not affect the protein as both sequences code for phenylalanine. Point mutations that do not change the amino acid sequence of a protein are called silent mutations.

### Educational objective:

Duchenne muscular dystrophy presents with progressive proximal muscle weakness in young boys due to increased muscle fiber degeneration. It is caused by frameshift mutations (most common) or nonsense mutations in the dystrophin gene that lead to the formation of a truncated, defective protein. Nonsense mutations introduce premature stop codons (eg, UAA, UAG, UGA) in the coding sequence of mRNA.

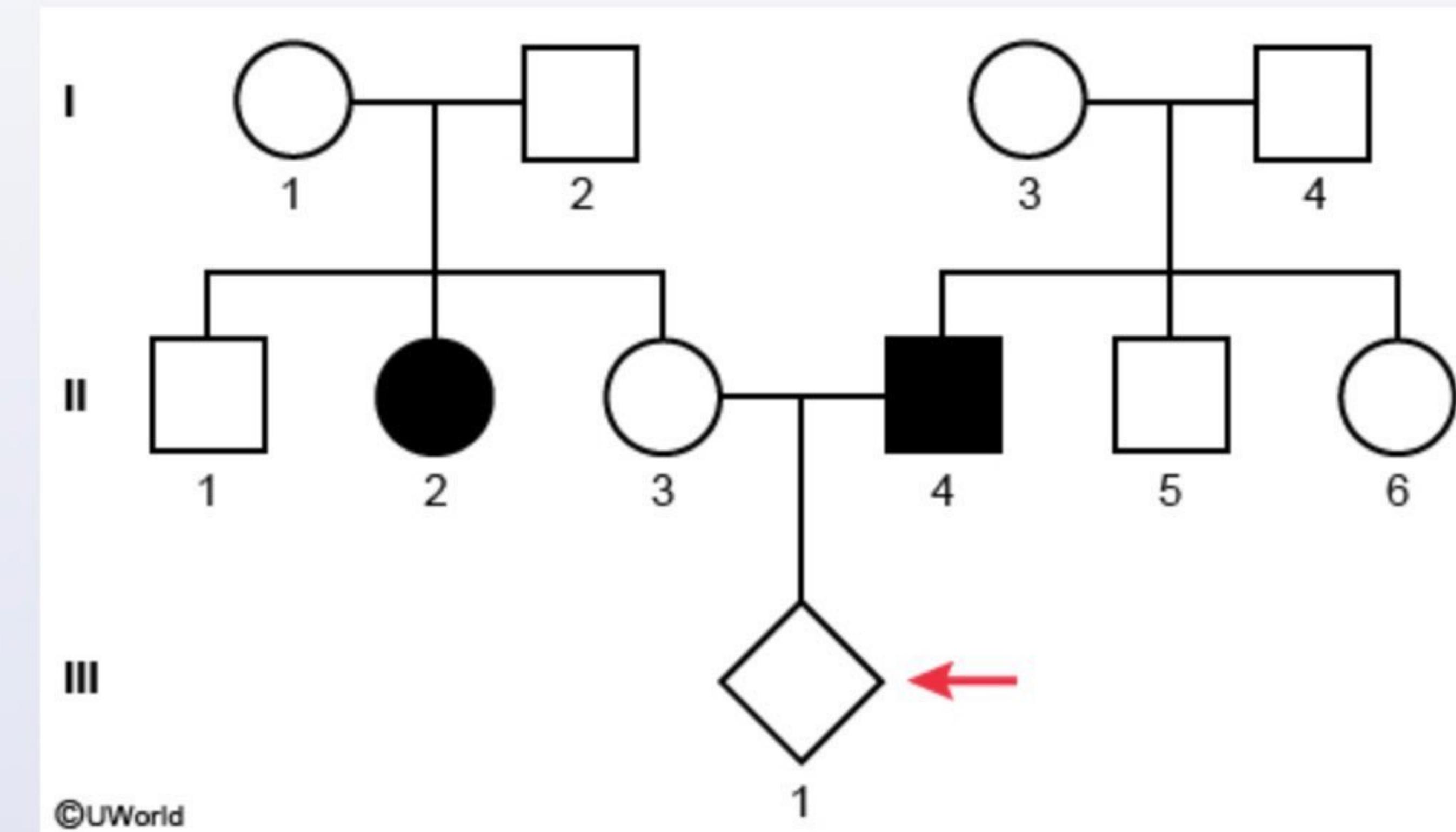
### References

- Mutation spectrum of the dystrophin gene in 442 Duchenne/Becker muscular dystrophy cases from one Japanese referral center.

apps.uworld.com

Item 18 of 20    Mark    Previous    Next    Full Screen    Tutorial    Lab Values    Notes    Calculator    Reverse Color    Text Zoom    Settings

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?

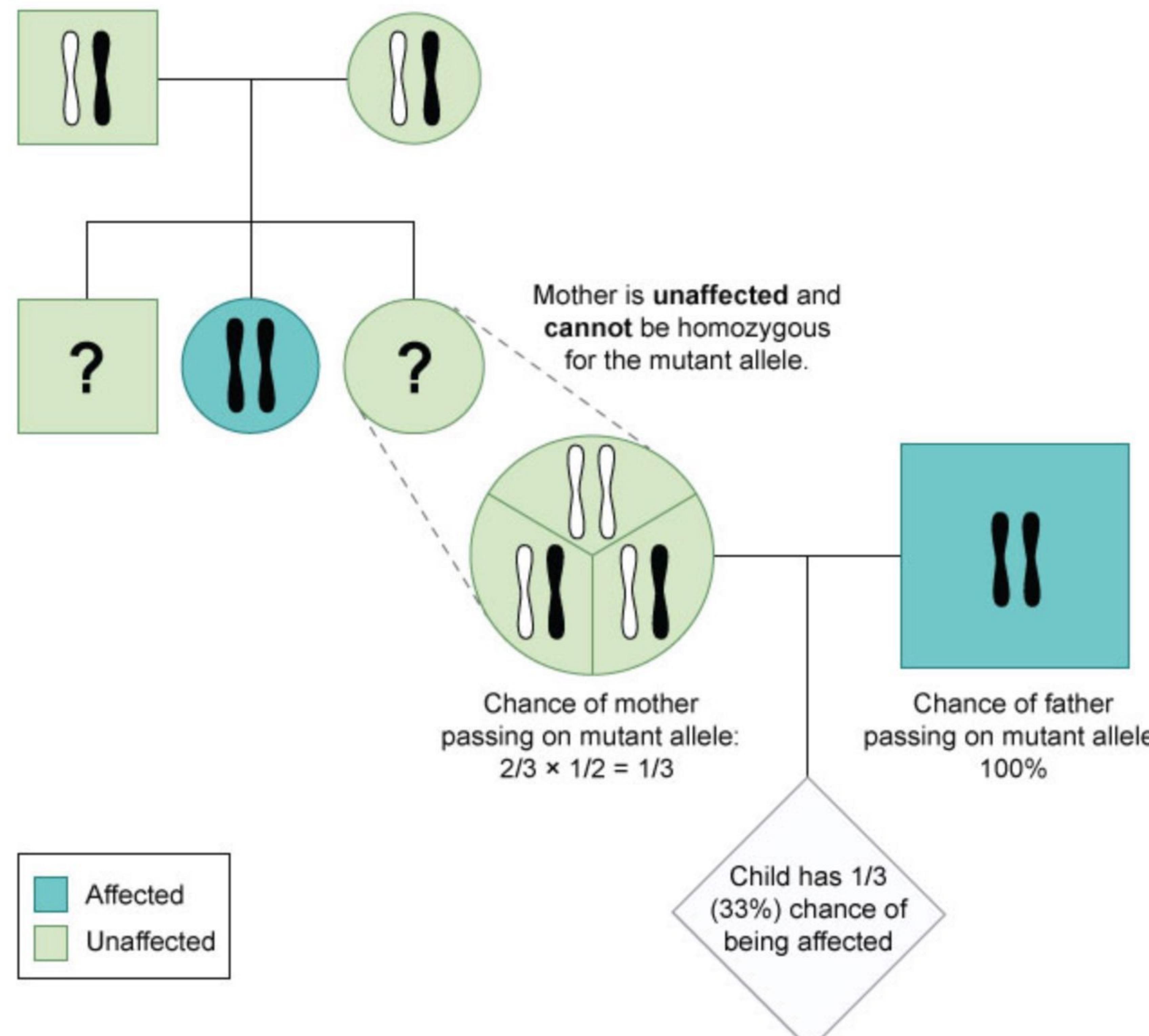
- A. 1/16 (3%)
- B. 1/8 (12%)
- C. 1/4 (31%)
- D. 1/3 (35%)

AA apps.uworld.com

Item 18 of 20 Question Id: 1790 Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

## Probability of the child having cystic fibrosis

Unaffected grandparents with a diseased child are likely heterozygous for the mutant allele.



apps.uworld.com

Item 18 of 20 Question Id: 1790 © UWorld

Mark Previous Next Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Cystic fibrosis (CF) results from an **autosomal recessive** defect in the CF transmembrane conductance regulator (*CFTR*) gene. Although most men with CF are infertile due to congenital absence of the vas deferens, they are **not sterile** and can have children via assisted reproductive technology.

Calculating the probability that the unborn child will have CF can be done by analyzing the above pedigree as follows:

1. Because the **father** is homozygous for the mutant *CFTR* allele, he will **always** transmit the mutant allele to his offspring.
2. Because the **mother** has an affected sibling and neither of her parents is affected, she most likely had 2 heterozygous carrier parents. Therefore, the mother's 4 possible genotypes are: homozygous for the normal allele, heterozygous with her mother's mutant allele, heterozygous with her father's mutant allele, and homozygous for the mutant allele. However, the mother does **not have CF** and therefore is **not homozygous for the mutant allele**. This leaves 3 possible genotypes for the mother. Two of the 3 remaining genotypes result in her being a **carrier** for the mutant *CFTR* allele, while the last one results in her being homozygous normal. Therefore, the mother's probability of being a carrier equals **2/3**.
3. If the mother is a carrier (2/3 chance), the probability that she will transmit the mutant allele to the child is 1 in 2. As a result, the probability that the child will inherit a mutant allele from the mother (and therefore have CF as the father will always contribute a mutant allele) is:  $2/3 \times 1/2 = 1/3$ .

#### Educational objective:

The probability that an autosomal recessive disease will be transmitted to a child can be calculated based on the maternal and paternal pedigrees. An unaffected individual (with unaffected parents) who has a sibling affected by an autosomal recessive condition has a 2/3 chance of being a carrier for that condition.