Electron microscopy of a eukaryotic cell during interphase of the cell cycle shows 10-nm thick chromatin fibers with a "beads on a string" appearance. These chromatin fibers are extracted and treated with an endonuclease, which preferentially cleaves the "string" portions of the chromatin. Further evaluation of the "beads" reveals that they are composed of DNA wrapped around a core of proteins. Which of the following proteins is most likely found outside of this core and helps promote chromatin compaction?

- A. Histone H1
- B. Histone H3
- C. Histone H4
- D. snRNP
- E. Topoisomerase II
- F. Ubiquitin

A. Histone H1 (73%)
B. Histone H3 (6%)
C. Histone H4 (11%)
D. snRNP (2%)
E. Topoisomerase II (3%)
F. Ubiquitin (2%)

Correct

73%
Answered correctly

44 secs
Time Spent

02/28/2021
Last Updated

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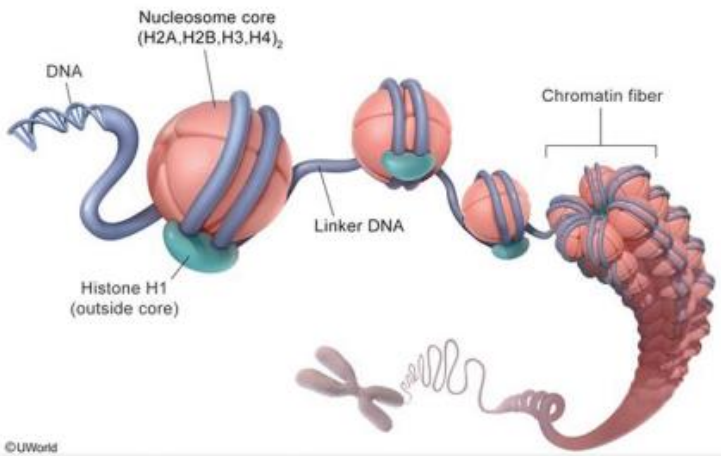
Eukaryotic DNA organization



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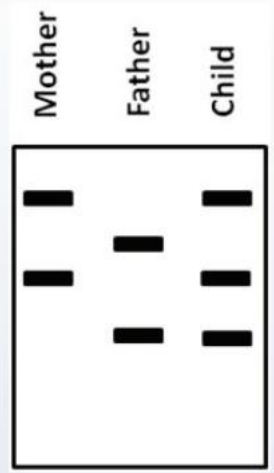
An infant born to a 34-year-old woman has a flat facial profile, prominent epicanthal folds, and a holosystolic murmur heard loudest at the left sternal border. Karyotype analysis is consistent with trisomy 21. Maternal and paternal karyotypes are normal. A restriction fragment length polymorphism (RFLP) 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
- B. Maternal meiosis II
- C. Paternal meiosis I
- D. Paternal meiosis II

A. Maternal meiosis I (52%)

B. Maternal meiosis II (36%)

C. ~~Paternal meiosis I~~ (5%)

D. ~~Paternal meiosis II~~ (5%)

Incorrect

52%

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12/22/2020

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Question Id: 8328

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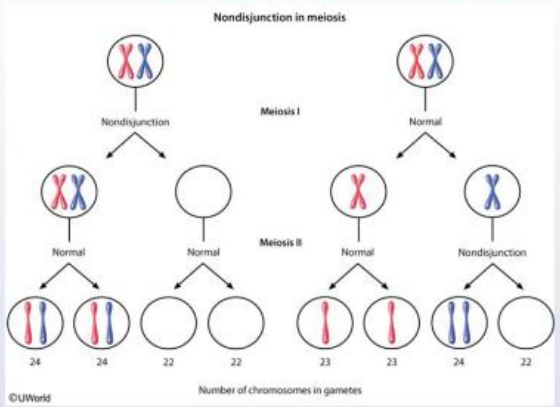

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Question Id: 8328

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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 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.

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
- B. Mosaicism
- C. Partial deletion
- D. Triplet expansion
- E. Uniparental disomy

A. ~~Aberrant genomic imprinting~~ (2%)

✓ B. Mosaicism (46%)

C. ~~Partial deletion~~ (5%)

D. ~~Triplet expansion~~ (12%)

E. Uniparental disomy (33%)

Inheritance of Down syndrome

Mechanism	Pathogenesis	Recurrence risk
Meiotic nondisjunction (~95%)	• Extra copy of chromosome 21 present in every cell	Based on maternal age
Unbalanced translocation	• All or part of additional chromosome 21 **attached** to another chromosome	**High** if balanced translocation is present in one parent
Mosaicism	• **Some** (not all) cells have an extra copy of chromosome 21 • Nondisjunction event in early embryonic life	Similar to normal population

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many of the characteristic features of Down syndrome (DS), a condition that results from an **ne dosage** effect due to an **extra copy** of chromosome 21. Three cytogenetic abnormalities S:

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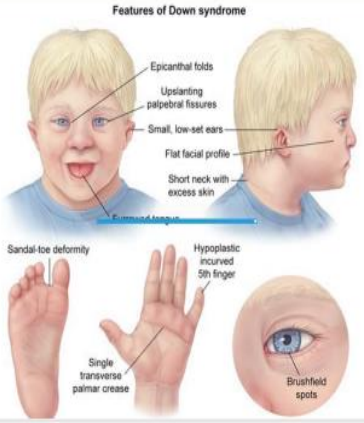
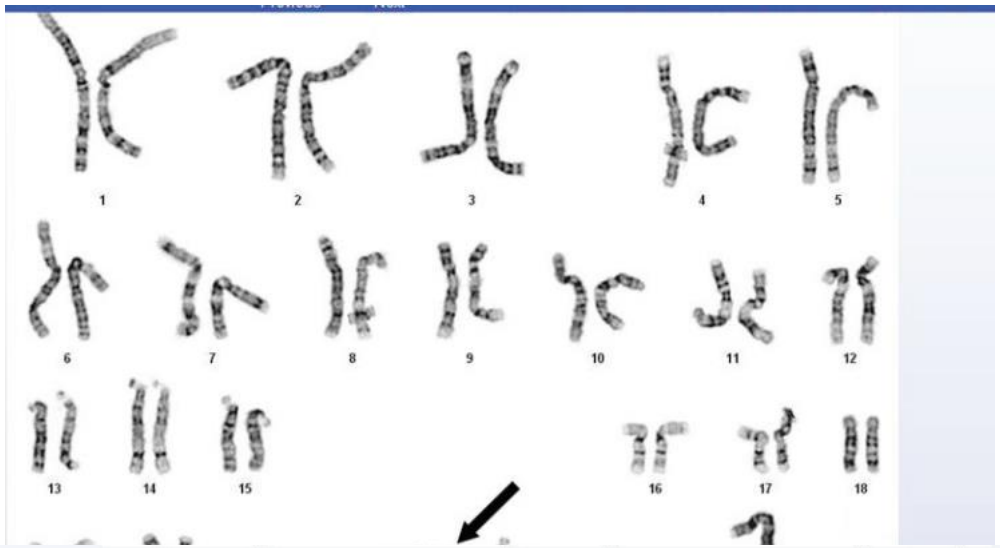


can lead to DS:

- 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, 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.

A 35-year-old woman and her husband have been trying to conceive for more than a year and are being followed by an infertility specialist. The woman is found to have significant scarring and fibrosis involving her fallopian tubes secondary to pelvic inflammatory disease that she had at a young age. After a long struggle, the woman finally becomes pregnant. She gives birth to a boy who is evaluated by a pediatrician and found to have a flat nasal bridge, small mouth, and low-set ears. The pediatrician orders a karyotype analysis on the infant, which is shown below.



The infant is most likely to be diagnosed with which of the following conditions?

- A. Acute lymphoblastic leukemia
- B. Chronic myelogenous leukemia
- C. Immotile cilia
- D. Macroorchidism
- E. Red blood cell sickling
- F. Rickets

- ✓ A. Acute lymphoblastic leukemia (85%)
- B. Chronic myelogenous leukemia (8%)
- C. Immotile cilia (1%)
- D. Macroorchidism (3%)
- E. Red blood cell sickling (0%)
- F. Rickets (0%)

This karyotype shows **trisomy 21** (47, XY, +21), which is diagnostic for **Down syndrome**, the most common genetic cause of congenital **intellectual disability**. In most cases, Down syndrome results from meiotic nondisjunction in the ovum; the parents themselves are usually genetically normal. **Advanced maternal age** is a risk factor for having a child with Down syndrome.

Individuals with Down syndrome are at an increased risk of developmental abnormalities (eg, cardiac septal defects, duodenal atresia) and health complications (eg, early-onset Alzheimer disease, ophthalmologic disorders). They also have **increased risk** of hematologic malignancies such as **acute lymphoblastic leukemia** and acute megakaryoblastic leukemia.

A 46-year-old woman is evaluated for a 2-month history of progressive abdominal distension, vague abdominal discomfort, and a bloating sensation. Physical examination shows moderate ascites. Laboratory evaluation reveals markedly elevated CA-125 and imaging studies show an ovarian mass. Molecular analysis of the malignant cells in ascitic fluid is performed, and these cells are found to have high telomerase activity. This enzyme promotes cell growth and malignancy by directly causing which of the following actions?

- A. Enhancing tissue invasion and metastasis
- B. Increasing transcription factor expression
- C. Preventing chromosomal shortening
- D. Promoting G1/S progression
- E. Sustaining angiogenesis

C

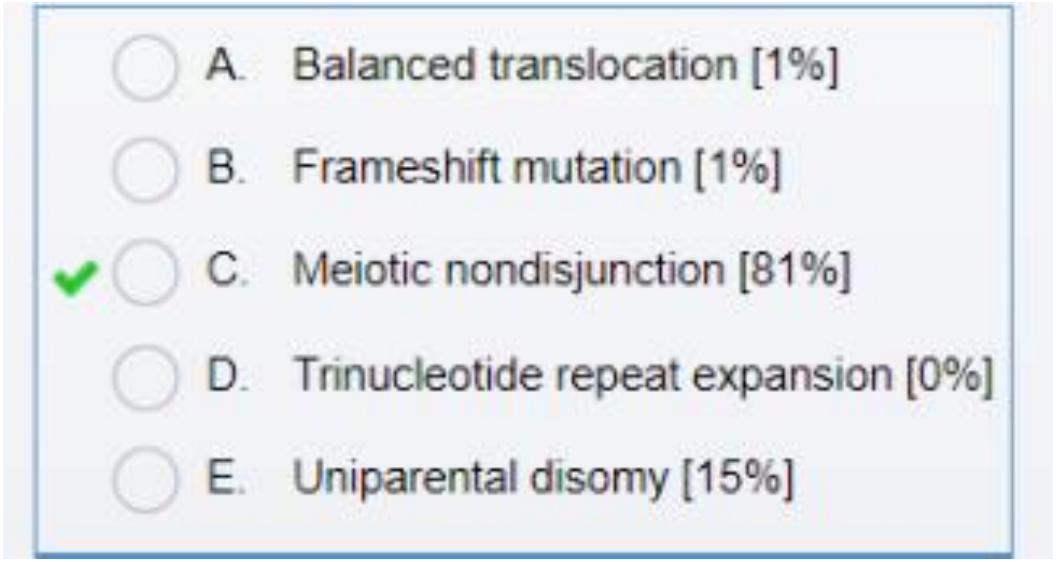
A newborn is examined immediately after an induced vaginal delivery for fetal growth retardation. On visual inspection, the infant has low-set ears, a small mandible, and a prominent occiput. The neonate has a weak cry and increased tone of the extremities, including clenched hands with second and fifth digits on top of the third and fourth digits. Cardiac auscultation reveals a harsh, IV/VI holosystolic murmur heard best at the left sternal border. The infant is transferred to the neonatal intensive care unit for further workup and management. Which of the following is the most likely chromosomal abnormality in this infant?

- A. 5p deletion
- B. 22q11 deletion
- C. 47, XX, +13
- D. 47, XX, +18
- E. 47, XX, +21

D

A 10-year-old girl is brought to the office for evaluation of short stature. She was an average-sized infant, but over the past few years, her height growth velocity has plateaued. The patient has not menstruated and has no symptoms. She takes no medications, has no allergies, and has received all recommended immunizations. Menarche occurred in her mother at age 14 and both of her parents are tall. The patient's height is at the <5th percentile and weight is at the 50th percentile for age and sex. She has no breast buds and no axillary or pubic hair. She has a low hairline, a short and wide neck, a broad chest, and widely spaced nipples. Which of the following is the most likely underlying mechanism for this patient's condition?

- A. Balanced translocation
- B. Frameshift mutation
- C. Meiotic nondisjunction
- D. Trinucleotide repeat expansion
- E. Uniparental disomy



Turner syndrome is a genetically heterogeneous condition that is most commonly due to **meiotic nondisjunction** during gametogenesis. The loss of one X chromosome in the sperm or egg results in a missing X chromosome in all of the patient's cells (**45,X**). In other patients, the nondisjunction event occurs during mitosis in early embryogenesis; these patients are missing the X chromosome in only some of their cells (mosaic Turner syndrome [45,X/46,XX]). A minority of patients have both X chromosomes, but one is structurally abnormal and missing some genetic material (eg, X fragments, isochromosomes).

The loss of all or part of the X chromosome in Turner syndrome results in a **missing *SHOX* gene**, which normally promotes long bone growth. Therefore, patients with this syndrome typically have **short stature**. Meiotic nondisjunction is also responsible for Klinefelter syndrome and trisomies 13, 18, and 21.

A 22-year-old woman, who recently relocated, comes to the office for a new patient visit. She has mild intellectual disability and has completed a high school level of education. The patient has no major health problems but reports persistent swelling of the hands and feet. Menarche occurred at age 13, and she has regular menstrual cycles. Physical examination shows short stature and a webbed neck. Karyotype analysis performed on peripheral leukocytes shows that 40% of the cells have a 45,X genotype and that the remaining 60% contain a 46,XX genotype. Which of the following is the most likely cause of this patient's condition?

- A. Chromosomal deletion
- B. Complete monosomy X
- C. Germline mosaicism
- D. Somatic mosaicism
- E. Uniparental disomy
- F. X chromosome inactivation

A. Chromosomal deletion [1%]

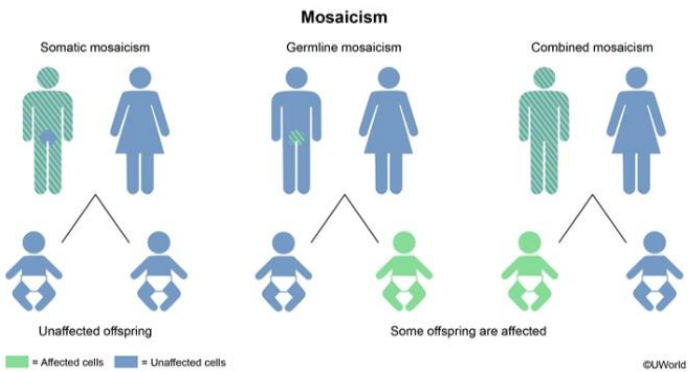
B. Complete monosomy X [2%]

C. Germline mosaicism [34%]

✔ D. Somatic mosaicism [53%]

E. Uniparental disomy [2%]

F. X chromosome inactivation [5%]



This patient with mild intellectual disability, lymphedema, short stature, webbed neck, and 2 karyotypes evident on analysis likely has **mosaic Turner syndrome**. Mosaicism is defined as the presence of multiple, **genetically different cell lines** within the body. It can result from several processes, including chromosomal nondisjunction and mutations during the first stages of embryonic development. The earlier the error happens, the more daughter cells are affected.

Mosaicism can be classified as germline, somatic, or both:

- **Somatic mosaicism** affects the cells forming the body, causing **disease manifestations** to develop in affected individuals. 45,X/46,XX is the most commonly diagnosed mosaicism affecting sex chromosomes. These patients typically have a milder form of Turner syndrome or can be asymptomatic, depending on the ratio of abnormal to normal cells.
- **Germline mosaicism** affects the cells that give rise to gametes, allowing the affected genes to **pass to the offspring**. The chance of a child being affected depends on the proportion of gametes that carry the mutation. When mosaicism is limited to the germline, the affected parent does not develop clinical manifestations.

(Choice A) Chromosomal deletions can be either macro or micro, depending on how many base pairs are eliminated. Neither process results in the elimination of entire chromosomes or the presence of multiple cell lines within the body.

(Choice B) Complete monosomy X also causes Turner syndrome. However, it would not explain the 2 separate genotypes seen on karyotyping.

(Choice C) This patient has manifestations of Turner syndrome and peripheral cells with multiple distinct genotypes, which indicates that she has somatic mosaicism. If the mitotic error occurred very early in embryogenesis, before separation of the germline, she could also have germline mosaicism. However, germline mosaicism would not be the cause of her clinical manifestations and would not be detectable on karyotyping of a blood sample.