If you’re preparing for the United States Medical Licensing Examination® (USMLE®) Step 1 exam, you might want to know which questions are most often missed by test-prep takers. Check out this example from Kaplan Medical, and read an expert explanation of the answer. Also check out all posts in this series.

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This month’s stumper

A 4-year-old girl is brought to the physician by her mother. The mother is concerned about the child's ravenous appetite and rapid weight gain. Her mother says that at birth, the child had a poor sucking reflex and fed poorly. As a baby, she was floppy and did not meet motor development milestones. Her older brother and sister are both normal. The patient's karyotype shows no abnormalities, but Southern blotting shows a microdeletion in one of her chromosomes.

Which of the following is the most likely additional finding in this patient?

A. Abnormal methylation pattern on chromosome 15.

B. Deletion of a tumor suppression gene.

C. Deletion of the short arm of chromosome 5.

D. Microsatellite instability.
The correct answer is A.

Kaplan Medical explains why

This child has Prader-Willi syndrome, and the deletion is from the paternal chromosome region, within 15q11.2. This region of 15q11.2 can be amplified by an allele-specific polymerase chain reaction (AS-PCR) in which one set of primers amplifies the methylated sequence and a different set of primers amplifies the nonmethylated sequence. In a normal individual, the methylation pattern at 15q11.2 would be heterozygous, one allele (maternal) methylated and the other (paternal) nonmethylated.

A child with Prader-Willi due to a microdeletion at 15q11.2 would be hemizygous for the methylated allele. Patients with Prader-Willi are characterized by hypotonia and poor feeding in infancy, development of hyperphagia and obesity in childhood, delayed psychomotor development (late...
walking), hypogonadism, and, often, significant behavioral problems. It should be noted that Angelman syndrome (happy puppet syndrome) is similar genetically to Prader-Willi, but due to deletion of a different gene on the maternal chromosome 15 while the same gene is imprinted on paternally inherited chromosome 15.

Why the other answers are wrong

Choice B: Increased risk of multiple cancers would be characteristic of an inherited loss-of-function mutation or deletion of a tumor suppressor gene. An example would be Li-Fraumeni syndrome, in which individuals are at greatly increased risk for breast and colon carcinomas, soft-tissue sarcomas, osteosarcomas, brain tumors, leukemia, and adrenocortical carcinoma. The features described in the present child would not occur.

Choice C: A terminal deletion of 5p causes cri-du-chat syndrome, which is characterized by a high-pitched, monotonic cry. Children with cri-du-chat have microcephaly, wide-set eyes, and significant intellectual disability. Obesity and hyperphagia are not characteristic of this disorder.

Choice D: Microsatellite instability is characteristic of individuals with loss-of-function mutations in the mismatch repair genes (hMLH, hMSH). Areas of DNA with dinucleotide repeats (an example of microsatellites) are often associated with strand slippage during DNA replication that can change the number of repeats on the newly synthesized strand (microsatellite instability). This replication error is normally corrected by the mismatch repair enzymes. Loss of mismatch repair is associated with a form of colon cancer (hereditary nonpolyposis colorectal cancer, HNPCC), endometrial cancer, and microsatellite instability in the tumor cells.

Choice E: T-cell immunodeficiency is a characteristic of DiGeorge anomaly, often associated with a deletion at 22q.11.2. This anomaly is characterized by structural/functional defects of the thymus, hypoparathyroidism, and secondary hypocalcemia. DiGeorge anomaly is associated, in some cases, with palate abnormalities and a characteristic facial appearance.

Tips to remember

Prader-Willi syndrome:

- Caused by genomic imprinting; expression of the gene depends on the gender of the parent donating the gene.
- Usually due to the loss of the paternal copy of 15q11.2.

For more prep questions on USMLE Steps 1, 2 and 3, view other posts in this series.