Mosaic variegated aneuploidy syndrome

Description

Mosaic variegated aneuploidy (MVA) syndrome is a rare disorder in which some cells in the body have an abnormal number of chromosomes instead of the usual 46 chromosomes, a situation known as aneuploidy. Most commonly, cells have an extra chromosome, which is called trisomy, or are missing a chromosome, which is known as monosomy. In MVA syndrome, some cells are aneuploid and others have the normal number of chromosomes, which is a phenomenon known as mosaicism. Typically, at least one-quarter of cells in affected individuals have an abnormal number of chromosomes. Because the additional or missing chromosomes vary among the abnormal cells, the aneuploidy is described as variegated.

In MVA syndrome, growth before birth is slow (intrauterine growth restriction). After birth, affected individuals continue to grow at a slow rate and are shorter than average. In addition, they typically have an unusually small head size (microcephaly). Another common feature of MVA syndrome is an increased risk of developing cancer in childhood. Cancers that occur most frequently in affected individuals include a cancer of muscle tissue called rhabdomyosarcoma, a form of kidney cancer known as Wilms tumor, and a cancer of the blood-forming tissue known as leukemia.

Less commonly, people with MVA syndrome have eye abnormalities or distinctive facial features, such as a broad nasal bridge and low-set ears. Some affected individuals have brain abnormalities, the most common of which is called Dandy-Walker malformation. Intellectual disability, seizures, and other health problems can also occur in people with MVA syndrome.

There are at least three types of MVA syndrome, each with a different genetic cause. Type 1 is the most common and displays the classic signs and symptoms described above. Type 2 appears to have slightly different signs and symptoms than type 1, although the small number of affected individuals makes it difficult to define its characteristic features. Individuals with MVA syndrome type 2 grow slowly before and after birth; however, their head size is typically normal. Some people with MVA syndrome type 2 have unusually short arms. Individuals with MVA syndrome type 2 do not seem to have an increased risk of cancer. Another form of MVA syndrome is characterized by a high risk of developing Wilms tumor. Individuals with this form may also have other signs and symptoms typical of MVA syndrome type 1.

Frequency

MVA syndrome is a rare condition. Its prevalence is unknown.

Causes

BUB1B gene mutations cause MVA syndrome type 1, *CEP57* gene mutations cause MVA syndrome type 2, and *TRIP13* gene mutations cause the other form of MVA syndrome. Some people with MVA syndrome do not have mutations in any of these genes. Other genes that have not been identified are likely also involved in the condition.

The proteins produced from the *BUB1B*, *CEP57*, and *TRIP13* genes have roles in the proper separation of chromosomes during cell division. Before cells divide, they copy all of their chromosomes. To aid in the equal sorting of chromosomes to the two new cells, structures called spindle microtubules attach to the chromosomes and pull one copy of each to opposite sides of the cell. Then the cell divides such that each new cell has a full set of chromosomes. The CEP57 protein helps organize and stabilize the spindle microtubules. The BUBR1 protein, produced from the *BUB1B* gene, and the TRIP13 proteins help ensure that each copy of the duplicated chromosomes is attached to a spindle microtubule, and they prevent cell division if any remain unattached.

The *BUB1B* gene mutations reduce the amount of functional BUBR1 protein, and *TRIP13* gene mutations lead to an absence of TRIP13 protein in cells. Without BUBR1 or TRIP13, cell division can proceed, even if not all the chromosomes are attached to spindle microtubules. The resulting errors in the sorting of chromosomes typically leads to the aneuploidy that occurs in MVA syndrome. (Some people with *TRIP13* gene mutations have chromosome abnormalities that indicate problems with chromosome sorting but do not develop aneuploidy. These individuals do have the other signs and symptoms of MVA syndrome.) Research suggests that impairment of the process that delays cell division until the correct time underlies the increased risk of cancer in MVA syndrome, although the mechanism is not completely understood. It is also unclear how *BUB1B* or *TRIP13* gene mutations or aneuploidy is involved in the other features of the condition.

CEP57 gene mutations are thought to reduce the amount of functional CEP57 protein in cells. The resulting problems with spindle microtubule organization may prevent the normal separation of chromosomes during cell division, leading to aneuploidy, although the mechanism is unknown. Researchers are working to understand how these genetic changes lead to the other features of MVA syndrome type 2 and why individuals with this form of the condition do not seem to have an increased risk of cancer.

Learn more about the genes associated with Mosaic variegated aneuploidy syndrome

- BUB1B
- CEP57
- TRIP13

Inheritance

All types of MVA syndrome are inherited in an autosomal recessive pattern, which means both copies of the *BUB1B*, *CEP57*, or *TRIP13* gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Parents of individuals with MVA syndrome type 1, who have a mutation in one copy of the *BUB1B* gene, can have a related problem with their chromosomes called premature chromatid separation trait. Although these individuals have chromosome abnormalities that indicate trouble with normal chromosome separation during cell division, affected individuals usually have no health problems related to the trait.

Other Names for This Condition

- Mosaic variegated aneuplody microcephaly syndrome
- MVA syndrome
- Warburton-Anyane-Yeboa syndrome

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Mosaic variegated aneuploidy syndrome 1 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1850343/)
- Genetic Testing Registry: Mosaic variegated aneuploidy syndrome 2 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3279843/)

Genetic and Rare Diseases Information Center

- Mosaic variegated aneuploidy syndrome (https://rarediseases.info.nih.gov/diseases/3007/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- MOSAIC VARIEGATED ANEUPLOIDY SYNDROME 1; MVA1 (https://omim.org/entry/257300)
- MOSAIC VARIEGATED ANEUPLOIDY SYNDROME 2; MVA2 (https://omim.org/entry/614114)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28mosaic+variegated+aneuploidy%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

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