Costello syndrome

Description

Costello syndrome is a rare disorder that affects many parts of the body. This condition is characterized by delayed development, loose folds of skin (which are especially noticeable on the hands and feet), unusually flexible joints, heart problems, short stature, and distinctive facial features.

Children with Costello syndrome are often delayed in reaching developmental milestones, such as speaking, sitting, and walking. Affected individuals may also have intellectual disabilities that can vary in severity.

Distinctive facial features in people with Costello syndrome typically include a prominent forehead, full cheeks, and full lips. Infants with Costello syndrome may be larger than average at birth, but most have difficulty eating and grow more slowly than other children. Affected individuals may have gastrointestinal problems that include constipation or a backflow of stomach acids into the esophagus (gastroesophageal reflux or GERD). People with this condition have short stature compared to their family and peers and may have reduced growth hormone levels.

Heart problems are common, including an abnormal heartbeat (arrhythmia), structural heart defects, and a type of heart disease that enlarges and weakens the heart muscle (hypertrophic cardiomyopathy). Neurological problems in people with Costello syndrome include seizures, weak muscle tone (hypotonia), and a structural abnormality of the brain called a Chiari I malformation. Costello syndrome can cause vision problems, such as nearsightedness (myopia), farsightedness (hyperopia), or eyes that do not point in the same direction (strabismus). Hearing loss may also occur.

Other signs and symptoms of Costello syndrome can include tight Achilles tendons (which connect the calf muscles to the heel), recurrent respiratory infections, dry and thickened skin, skeletal abnormalities, and dental problems.

Beginning in early childhood, people with Costello syndrome have a higher risk of developing certain cancerous and noncancerous tumors compared to the general population. The most common noncancerous tumors associated with this condition are papillomas, which are small, wart-like growths that usually develop around the nose and mouth or near the anus. The most common cancerous tumor associated with Costello syndrome is a childhood cancer called rhabdomyosarcoma, which begins in muscle tissue. Neuroblastoma, a tumor that arises in developing nerve cells, has also been

reported in children and adolescents with this syndrome. In addition, some teenagers with Costello syndrome have developed transitional cell carcinoma, a form of bladder cancer that is usually seen in older adults.

The signs and symptoms of Costello syndrome overlap significantly with those of two other genetic conditions, cardiofaciocutaneous syndrome (CFC syndrome) and Noonan syndrome. In affected infants, it can be difficult to tell the three conditions apart based on their physical features. However, the conditions can be distinguished by their genetic causes and by the specific patterns of signs and symptoms that develop later in childhood.

Frequency

This condition is very rare; it probably affects 100 to 1,500 people worldwide. The estimates of Costello syndrome prevalence range from 1 in 300,000 to 1 in 1.25 million people.

Causes

Variants (also called mutations) in the *HRAS* gene cause Costello syndrome. This gene provides instructions for making a protein called H-Ras, which is part of a pathway that helps control cell growth and division. Variants that cause Costello syndrome lead to the production of an H-Ras protein that is abnormally turned on (active). The overactive protein directs cells to grow and divide constantly, which can lead to the development of tumors. It is unclear how variants in the *HRAS* gene cause the other features of Costello syndrome, but many of the signs and symptoms probably result from cell overgrowth and abnormal cell division.

Some people with signs and symptoms like those of Costello syndrome do not have an identified variant in the *HRAS* gene. These individuals may actually have CFC syndrome or Noonan syndrome, which are caused by variants in related genes. The proteins produced from these genes interact with one another and with the H-Ras protein as part of the same cell growth and division pathway. This pathway is called the RAS/MAPK signaling pathway, so these three conditions are sometimes referred to as RASopathies. These interactions help explain why variants in different genes can cause conditions with overlapping signs and symptoms.

Learn more about the gene associated with Costello syndrome

- HRAS

Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Most cases of this condition result from new (de novo) variants in the gene that occur during the formation of reproductive cells (eggs or sperm) in an affected individual's parent or in early

embryonic development. These affected individuals have no history of the disorder in their family.

Other Names for This Condition

- Faciocutaneoskeletal syndrome
- FCS syndrome

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Costello syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0587248/)

Genetic and Rare Diseases Information Center

- Costello syndrome (https://rarediseases.info.nih.gov/diseases/1550/index)

Patient Support and Advocacy Resources

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

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Costello syndrome%22)

Catalog of Genes and Diseases from OMIM

- COSTELLO SYNDROME; CSTLO (https://omim.org/entry/218040)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=(costello+syndrome%5BTIAB%5D)+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+6000+days%22%5Bdp%5D)

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