Craniometaphyseal dysplasia

Description

Craniometaphyseal dysplasia is a rare condition characterized by thickening (overgrowth) of bones in the skull (cranium) and abnormalities in a region at the end of long bones known as the metaphysis. The abnormal bone growth continues throughout life. Except in the most severe cases, the lifespan of people with craniometaphyseal dysplasia is normal.

Bone overgrowth in the head causes many of the signs and symptoms of craniometaphyseal dysplasia. Affected individuals typically have distinctive facial features such as a wide nasal bridge, a prominent forehead, wide-set eyes (hypertelorism), and a prominent jaw. Excess bone formation in the jaw can delay teething (dentition) or result in absent (non-erupting) teeth. Infants with craniometaphyseal dysplasia may have breathing or feeding problems caused by narrow nasal passages. In severe cases, abnormal bone growth can pinch (compress) the nerves that extend from the brain to various areas of the head and neck (cranial nerves). Compression of the cranial nerves can lead to paralyzed facial muscles (facial nerve palsy), blindness, or deafness.

The x-rays of individuals with craniometaphyseal dysplasia show unusually shaped long bones, particularly long bones in the legs. The ends of these bones are wider and appear less dense than usual in people with this condition.

There are two types of craniometaphyseal dysplasia, which are distinguished by their pattern of inheritance and genetic cause. They are known as the autosomal dominant and autosomal recessive types.

Frequency

Craniometaphyseal dysplasia is a very rare disorder; its incidence is unknown.

Causes

Mutations in the *ANKH* gene cause autosomal dominant craniometaphyseal dysplasia. The *ANKH* gene provides instructions for making a protein that plays a role in the development and function of cells that build bones (osteoblasts) and cells that break down bone (osteoclasts). Osteoclasts are involved in bone remodeling, a normal process in which old bone is removed and new bone is created to replace it. In addition,

the ANKH protein transports a molecule called pyrophosphate out of cells. The pyrophosphate found outside of cells (extracellular pyrophosphate) helps control bone formation by preventing mineralization, the process by which minerals such as calcium and phosphorus are deposited in developing bones. The ANKH protein may have other, unknown functions.

Mutations in the *ANKH* gene that cause autosomal dominant craniometaphyseal dysplasia impair the maturation (differentiation) of osteoclasts, which likely disrupts bone remodeling. Reduced breakdown of bone tissue can contribute to the bone thickening characteristic of craniometaphyseal dysplasia. *ANKH* gene mutations may also reduce the protein's ability to transport pyrophosphate out of cells. A shortage of extracellular pyrophosphate can increase bone mineralization, which may also contribute to the bone abnormalities.

A mutation in the *GJA1* gene causes some cases of autosomal recessive craniometaphyseal dysplasia. This gene provides instructions for making a protein called connexin 43, which is involved in the development of many tissues in the body, including bone. The protein may be involved in bone remodeling. It is unclear how a mutation in the *GJA1* gene leads to the particular bone abnormalities of craniometaphyseal dysplasia.

The genetic cause of many cases of autosomal recessive craniometaphyseal dysplasia is unknown. It is likely that other, unidentified genes are involved in this form of the disorder.

Learn more about the genes associated with Craniometaphyseal dysplasia

- ANKH
- GJA1

Inheritance

When caused by mutations in the *ANKH* gene, craniometaphyseal dysplasia follows an autosomal dominant pattern, which means one altered copy of the *ANKH* gene in each cell is sufficient to cause the disorder. Individuals with autosomal dominant craniometaphyseal dysplasia typically have one parent who also has the condition. Less often, cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

When caused by mutations in the *GJA1* gene, craniometaphyseal dysplasia has an autosomal recessive inheritance pattern, which means both copies of the *GJA1* gene in each cell are altered. 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 disorder.

Other Names for This Condition

- Autosomal dominant craniometaphyseal dysplasia
- Autosomal recessive craniometaphyseal dysplasia
- CMD
- CMDD
- CMDJ
- CMDR
- Craniometaphyseal dysplasia, Jackson type

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Craniometaphyseal dysplasia, autosomal dominant (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1852502/)
- Genetic Testing Registry: Craniometaphyseal dysplasia, autosomal recessive (https://www.ncbi.nlm.nih.gov/gtr/conditions/C2931244/)

Genetic and Rare Diseases Information Center

- Craniometaphyseal dysplasia, autosomal dominant (https://rarediseases.info.nih.gov/diseases/1581/index)
- Craniometaphyseal dysplasia, autosomal recessive (https://rarediseases.info.nih.gov/diseases/1582/index)

Patient Support and Advocacy Resources

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

Clinical Trials

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

Catalog of Genes and Diseases from OMIM

- CRANIOMETAPHYSEAL DYSPLASIA, AUTOSOMAL DOMINANT; CMDD (https://omim.org/entry/123000)

Scientific Articles on PubMed

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

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