Craniofrontonasal syndrome

Description

Craniofrontonasal syndrome is a rare condition characterized by the premature closure of certain bones of the skull (craniosynostosis) during development, which affects the shape of the head and face. The condition is named for the areas of the body that are typically affected: the skull (cranio-), face (fronto-), and nose (nasal).

In people with craniofrontonasal syndrome, the skull bones along the coronal suture, which is the growth line that goes over the head from ear to ear, closes early. These changes can result in an abnormally shaped head and distinctive facial features. The size and shape of facial structures may differ between the right and left sides of the face (facial asymmetry) in individuals with craniofrontonasal syndrome. Affected individuals may also have wide-set eyes (ocular hypertelorism), eyes that do not point in the same direction (strabismus), involuntary eye movements (nystagmus), a slit (cleft) in the tip of the nose, a wide nasal bridge, an upper lip that points outward (called a tented lip), or a cleft in the upper lip with or without a cleft in roof of the mouth (palate). Some affected individuals have brain abnormalities, such as absent or underdeveloped tissue connecting the left and right halves of the brain (agenesis or dysgenesis of the corpus callosum). However, intelligence is usually unaffected in people with this condition. Females with craniofrontonasal syndrome typically have more severe signs and symptoms than affected males, who often have hypertelorism and rarely, cleft lip.

Other common features of craniofrontonasal syndrome include extra folds of skin on the neck (webbed neck), ridged nails, unusual curving of the fingers or toes (clinodactyly), extra fingers (polydactyly) or fingers that are fused together (syndactyly), low-set breasts, a sunken chest (pectus excavatum), a spine that curves to the side (scoliosis), or narrow and sloped shoulders with reduced range of motion. People with this condition may also have eyebrows that grow together in the middle (synophrys), a widow's peak hairline with a low hairline in the back, or wiry hair.

Frequency

Craniofrontonasal syndrome is a very rare condition, although its prevalence is unknown. More than 115 cases have been described in the scientific literature.

Causes

Craniofrontonasal syndrome is caused by mutations in a gene known as *EFNB1*. This gene provides instructions for making a protein called ephrin B1. This protein spans the cell membrane where it can attach (bind) to other proteins on the surface of neighboring cells. Protein binding between nearby cells helps cells stick to one another (cell adhesion) and communicate, which are important for the normal shaping (patterning) of many tissues and organs before birth.

Mutations in the *EFNB1* gene result in a shortage (deficiency) of ephrin B1 protein. Most of these mutations lead to an abnormally short version of the molecule that acts as the genetic blueprint for the ephrin B1 protein. The shortened molecules are quickly broken down before protein can be made. A deficiency of ephrin B1 protein prevents cell adhesion, which disrupts normal patterning in tissues before birth, leading to the signs and symptoms of craniofrontonasal syndrome.

Learn more about the gene associated with Craniofrontonasal syndrome

- EFNB1

Inheritance

Craniofrontonasal syndrome is inherited in an X-linked pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. Males have only one X chromosome and females have two copies of the X chromosome. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Researchers suspect that the signs and symptoms of craniofrontonasal syndrome vary in severity between males and females in part because of a normal process called X-inactivation. Early in embryonic development in females, one of the two X chromosomes is permanently turned off (inactivated) in somatic cells (cells other than egg and sperm cells). X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell. Usually X-inactivation occurs randomly, so that each X chromosome is active in about half the body's cells. This means that in affected females with craniofrontonasal syndrome, the X chromosome with an *EFNB1* gene mutation is active in about half of cells, and the X chromosome with the normal *EFNB1* gene is active in about half. Because X-inactivation leads to some cells that produce functional ephrin B1 protein and some cells that do not, patterning of tissues becomes patchy, which can alter development of the head and face.

In affected males, all cells have a single X chromosome with an *EFNB1* gene mutation. Because ephrin B1 activity is completely missing in all cells, normal tissue patterning cannot occur and it is thought that other proteins perform similar functions to compensate.

Other Names for This Condition

- CFND
- CFNS
- Craniofrontonasal dysplasia
- Craniofrontonasal dystosis

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Craniofrontonasal syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0220767/)

Genetic and Rare Diseases Information Center

- Craniofrontonasal dysplasia (https://rarediseases.info.nih.gov/diseases/1578/index)

Patient Support and Advocacy Resources

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

Clinical Trials

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

Catalog of Genes and Diseases from OMIM

- CRANIOFRONTONASAL SYNDROME; CFNS (https://omim.org/entry/304110)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28craniofrontonasal+syndrome%5BTIAB%5D%29+OR+%28craniofrontonasal+dysplasia%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D)

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