

Cardiofaciocutaneous Syndrome

Subjects: Genetics & Heredity

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Cardiofaciocutaneous syndrome is a disorder that affects many parts of the body, particularly the heart (cardio-), facial features (facio-), and the skin and hair (cutaneous). People with this condition also have delayed development and intellectual disability, usually ranging from moderate to severe.

Keywords: genetic conditions

1. Introduction

Heart defects occur in most people with cardiofaciocutaneous syndrome. The heart problems most commonly associated with this condition include malformations of one of the heart valves that impairs blood flow from the heart to the lungs (pulmonic stenosis), a hole between the two upper chambers of the heart (atrial septal defect), and a form of heart disease that enlarges and weakens the heart muscle (hypertrophic cardiomyopathy).

Cardiofaciocutaneous syndrome is also characterized by distinctive facial features. These include a high forehead that narrows at the temples, a short nose, widely spaced eyes (ocular hypertelorism), outside corners of the eyes that point downward (down-slanting palpebral fissures), droopy eyelids (ptosis), a small chin, and low-set ears. Overall, the face is broad and long, and the facial features are sometimes described as "coarse."

Skin abnormalities occur in almost everyone with cardiofaciocutaneous syndrome. Many affected people have dry, rough skin; dark-colored moles (nevi); wrinkled palms and soles; and a skin condition called keratosis pilaris, which causes small bumps to form on the arms, legs, and face. People with cardiofaciocutaneous syndrome also tend to have thin, dry, curly hair and sparse or absent eyelashes and eyebrows.

Infants with cardiofaciocutaneous syndrome typically have weak muscle tone (hypotonia), feeding difficulties, and a failure to grow and gain weight at the normal rate (failure to thrive). Additional features of this disorder in children and adults can include an unusually large head (macrocephaly), short stature, problems with vision, and seizures.

The signs and symptoms of cardiofaciocutaneous syndrome overlap significantly with those of two other genetic conditions, Costello syndrome and Noonan syndrome. The three conditions are distinguished by their genetic cause and specific patterns of signs and symptoms; however, it can be difficult to tell these conditions apart, particularly in infancy. Unlike Costello syndrome, which significantly increases a person's cancer risk, cancer does not appear to be a major feature of cardiofaciocutaneous syndrome.

2. Frequency

Cardiofaciocutaneous syndrome is a very rare condition whose incidence is unknown. Researchers estimate that 200 to 300 people worldwide have this condition.

3. Causes

Cardiofaciocutaneous syndrome can be caused by mutations in several genes. Mutations in the *BRAF* gene are most common, accounting for 75 to 80 percent of all cases. Another 10 to 15 percent of cases result from mutations in one of two similar genes, *MAP2K1* and *MAP2K2*. Fewer than 5 percent of cases are caused by mutations in the *KRAS* gene.

The *BRAF*, *MAP2K1*, *MAP2K2*, and *KRAS* genes provide instructions for making proteins that work together to transmit chemical signals from outside the cell to the cell's nucleus. This chemical signaling pathway, known as the RAS/MAPK pathway, is essential for normal development before birth. It helps control the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), cell movement, and the self-destruction of cells (apoptosis).

Mutations in any of these genes can result in the characteristic features of cardiofaciocutaneous syndrome. The protein made from the mutated gene is overactive, which alters tightly regulated chemical signaling during development. The altered signaling interferes with the development of many organs and tissues, leading to the signs and symptoms of cardiofaciocutaneous syndrome.

Some people with the signs and symptoms of cardiofaciocutaneous syndrome do not have an identified mutation in the *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* gene. In these cases, affected individuals may actually have Costello syndrome or Noonan syndrome, which are also caused by mutations in genes involved in RAS/MAPK signaling. The proteins produced from these genes are all part of the same chemical signaling pathway, which helps explain why mutations in different genes can cause conditions with such similar signs and symptoms. The group of related conditions that includes cardiofaciocutaneous syndrome, Costello syndrome, and Noonan syndrome is often called the RASopathies.

3.1. The Genes Associated with Cardiofaciocutaneous Syndrome

- *BRAF*
- *KRAS*
- *MAP2K1*
- *MAP2K2*

4. Inheritance

Cardiofaciocutaneous syndrome is considered to be an autosomal dominant condition, which means one copy of an altered gene in each cell is sufficient to cause the disorder.

Cardiofaciocutaneous syndrome usually results from new gene mutations and occurs in people with no history of the disorder in their family. In a few reported cases, an affected person has inherited the condition from an affected parent.

5. Other Names for This Condition

- cardio-facio-cutaneous syndrome
- CFC syndrome

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