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Cardiofaciocutaneous Syndrome

Synonym: CFC Syndrome

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Summary

Clinical characteristics

Cardiofaciocutaneous (CFC) syndrome is characterized by cardiac abnormalities (pulmonic stenosis and other valve dysplasias, septal defects, hypertrophic cardiomyopathy, rhythm disturbances), distinctive craniofacial appearance, and cutaneous abnormalities (including xerosis, hyperkeratosis, ichthyosis, keratosis pilaris, ulerythema ophryogenes, eczema, pigmented moles, hemangiomas, and palmoplantar hyperkeratosis). The hair is typically sparse, curly, fine or thick, woolly or brittle; eyelashes and eyebrows may be absent or sparse. Nails may be dystrophic or fast growing. Some form of neurologic and/or cognitive delay (ranging from mild to severe) is seen in all affected individuals. Neoplasia, mostly acute lymphoblastic leukemia, has been reported in some individuals.

Diagnosis/testing

Diagnosis is based on clinical findings and molecular genetic testing. The four genes known to be associated with CFC syndrome are: *BRAF* (~75%), *MAP2K1* and *MAP2K2* (~25%), and *KRAS* (<2%).

Management

Treatment of manifestations: Care by a multidisciplinary team; management of cardiac structural defects, hypertrophic cardiomyopathy, and arrhythmias as in the general population; increased ambient humidity or hydrating lotions for xerosis and pruritus; increased caloric intake and a nasogastric tube or gastrostomy for severe feeding problems; surgical intervention for severe gastroesophageal reflux; routine management of growth hormone deficiency, ocular abnormalities; management of seizures may require polytherapy; occupational therapy, physical therapy, and speech therapy as needed. Consensus medical management guidelines have been published.

Prevention of secondary complications: Antibiotic prophylaxis for subacute bacterial endocarditis primarily for those with valve dysplasias; evaluation for hypertrophic cardiomyopathy or a predisposition to cardiac rhythm disturbances prior to anesthesia.

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Surveillance: Periodic echocardiogram (hypertrophic cardiomyopathy), electrocardiogram (rhythm disturbances), neurologic and eye examination, scoliosis check, and assessment of growth and cognitive development.

Genetic counseling

Cardiofaciocutaneous (CFC) syndrome is inherited in an autosomal dominant manner. Most affected individuals have CFC as the result of a *de novo* pathogenic variant. The offspring of an affected individual are at a 50% risk of inheriting a CFC-related pathogenic variant. Prenatal testing for pregnancies at risk is possible if the *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* pathogenic variant has been identified in an affected family member.

Diagnosis

Cardiofaciocutaneous (CFC) syndrome is one the RASopathies: a group of syndromes having overlapping clinical features resulting from a common pathogenetic mechanism [Tidyman & Rauen 2009a]. No diagnostic criteria have been established. The diagnosis of CFC syndrome is suspected by clinical findings and confirmed on molecular testing.

Suggestive Findings

Cardiofaciocutaneous (CFC) syndrome **should be suspected** in individuals with the following phenotypic features involving the heart, face, and ectodermal structures:

- **Cardiac.** Pulmonic stenosis; atrial septal defects; ventricular septal defects; hypertrophic cardiomyopathy; heart valve anomalies (mitral valve dysplasia, tricuspid valve dysplasia, and bicuspid aortic valve); and rhythm disturbances. These defects may be identified at birth or diagnosed later. Hypertrophic cardiomyopathy may be progressive.
- **Craniofacial.** High forehead, relative macrocephaly, bitemporal narrowing, hypoplasia of the supraorbital ridges, ocular hypertelorism, telecanthus, downslanting palpebral fissures, epicanthal folds, ptosis, short nose with depressed bridge and anteverted nares, ear lobe creases, low-set ears that may be posteriorly rotated, deep philtrum, cupid's bow configuration of the upper lip, high-arched palate, relative micrognathia (Figure 1). The face is broader and longer, overall more coarse, than in Noonan syndrome (a clinically similar disorder often confused with CFC syndrome), but usually not as coarse as typically seen in Costello syndrome.
- **Ectodermal**
  - **Skin.** Xerosis; hyperkeratosis of arms, legs, and face; ichthyosis; keratosis pilaris; ulerythema ophryogenes; eczema; hemangiomas; café-au-lait macules; erythema; pigmented moles; palmoplantar hyperkeratosis over pressure zones
  - **Hair.** Sparse, curly, fine or thick, woolly or brittle; sparse to absent, or normal eyelashes and eyebrows
  - **Nails.** Dystrophic with flat broad nails; nails may be fast growing.

Additional features variably present

- **Musculoskeletal.** Short neck, pterygium colli, pectus deformity, kyphosis, and/or scoliosis, pes planus
- **Lymphatic.** Lymphedema, chylothorax
- **Ocular.** Ocular hypertelorism, strabismus, nystagmus, astigmatism, myopia and/or hyperopia. Optic nerve hypoplasia, cortical blindness, and cataracts have been described. Although most individuals with CFC syndrome have ocular manifestations, some have a normal ophthalmologic examination.
- **Feeding/gastrointestinal.** Severe feeding problems manifest as gastroesophageal reflux (GER), aspiration, vomiting, and oral aversion. Other GI problems include dysmotility, intestinal malrotation, hernia, and/or

constipation. Some individuals have splenomegaly or hepatomegaly. Most children have failure to thrive. Fatty liver and anal stenosis have also been reported.

- **Growth delays.** Feeding issues contribute to growth delay. Growth may be normal with appropriate birth weight and length; however, weight and length may drop to below the fifth centile during early infancy while head circumference remains within the normal range (resulting in relative macrocephaly).
- **Endocrine abnormalities.** Growth hormone deficiency in some individuals. Some may have precocious puberty.
- **Neurologic.** Some aspect of neurologic or neurocognitive findings present in nearly all individuals. Cognitive delay typically ranges from mild to severe, although a few individuals with CFC syndrome have IQs in the normal range. The most common neurologic findings include hypotonia and developmental delay. Other abnormalities can include seizure disorders, abnormal EEG, corticospinal tract findings, hydrocephalus, cortical atrophy versus dilated perivascular spaces, ventriculomegaly, frontal lobe hypoplasia, agenesis of the corpus callosum, abnormal myelination, Chiari malformation, and pachygyria.
- **Urogenital.** Renal, uterine, and/or cervical anomalies in some individuals

Note: Individuals with CFC syndrome display phenotypic variability and therefore not all have every finding.

Establishing the Diagnosis

The diagnosis of CFC syndrome **is established** in a proband by the identification of a heterozygous pathogenic variant in *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* by molecular genetic testing (see Table 1).

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Consensus guidelines have been developed for a genetic testing strategy for CFC syndrome [Pierpont et al 2014]

Based on current published information, sequencing can be approached stepwise:

1. **A multigene panel** for RASopathies / Noonan spectrum disorders that includes *BRAF*, *MAP2K1*, *MAP2K2*, and *KRAS* and other genes of interest (see Differential Diagnosis) is usually the preferred initial test.

   For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

2. If multigene panel testing is not available, **serial single-gene testing** is recommended, beginning with *BRAF*, *MAP2K1*, and *MAP2K2*, and *KRAS*; if no pathogenic variants are found follow with sequencing of *HRAS* (all exons) even though the patient appears to have a clinical diagnosis of CFC syndrome. Individuals who have an *HRAS* pathogenic variant by definition have Costello syndrome.

3. If no pathogenic variant is identified in these genes using sequencing analysis, gene-targeted deletion/duplicaton analysis or array CGH can be considered. Rare deletions in MEK genes (i.e., *MAP2K1* and *MAP2K2*) may cause phenotypic features that are reminiscent of CFC syndrome [Nowaczyk et al 2014].

More comprehensive genomic testing (when available) including exome sequencing or genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes *BRAF*, *MAP2K1*, *MAP2K2*, and *KRAS*) fails to confirm a diagnosis in an individual with features of CFC syndrome. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

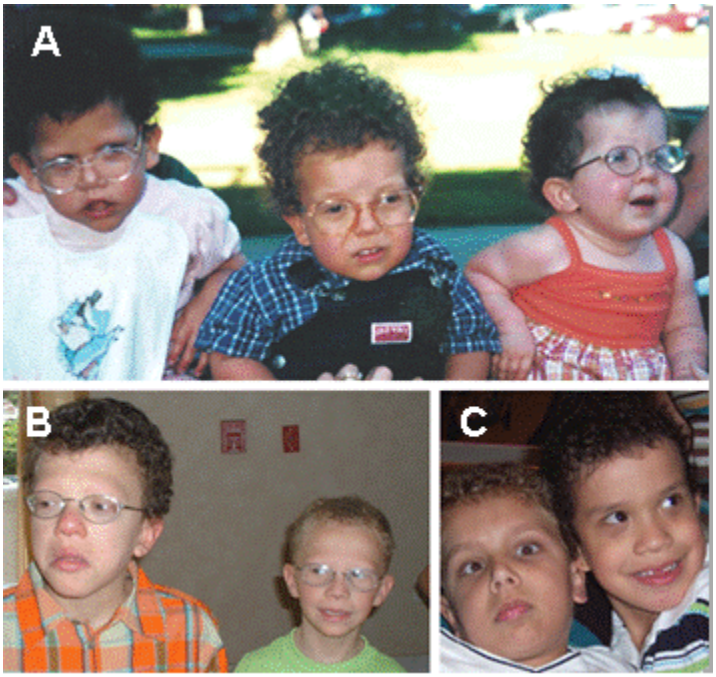

Figure 1. Children with CFC syndrome who have known pathogenic variants in *BRAF* or *MAP2K2*

A. Three young children with *BRAF* pathogenic variants: p.Thr470del, in exon 11 (left); p.Ser467Ala, in exon 11 (middle); and p.Gln257Arg, in exon 6 (right). Ages are 2.5, 2, and 2 years.

B. Two boys, age 12 and eight years, with *MAP2K2* pathogenic missense variants: p.Phe57Cys, in exon 2 (left) and p.Tyr134Cys, in exon 3 (right)

C. Two boys age six years, previously clinically diagnosed with Costello syndrome, at the 2005 Costello Syndrome Family Conference. Both have *BRAF* pathogenic variants: p.Gly534Arg, a missense substitution in exon 13 (left) and p.Leu485Phe, a missense substitution in exon 12 (right).

Courtesy of CFC International

Table 1. Molecular Genetic Testing Used in Cardiofaciocutaneous Syndrome

Gene [1]	Proportion of CFC Attributed to Pathogenic Variants in Gene [2]	Proportion of Pathogenic Variants [3] Detected by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
BRAF	~75%	~100%	Unknown [6], but single case reported [7]
MAP2K1	~25%	~100%	Unknown [6]
MAP2K2		~99%	Unknown [6] but several cases have been reported [8]
KRAS	<2%-3%	~100%	Unknown [6]

Table 1. continued from previous page.

Gene [1]	Proportion of CFC Attributed to Pathogenic Variants in Gene [2]	Proportion of Pathogenic Variants [3] Detected by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
Unknown [9]		NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Rauen [2013]
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.
7. A single report of a *BRAF* deletion associated with a CFC-like phenotype [Yu & Graf 2011] which was not supported by functional data
8. Nowaczyk et al [2014] reported several individuals with *MAP2K2* deletion associated with a CFC-like phenotype. This was supported by functional data of MAPK pathway dysregulation.
9. It is unclear at this time whether pathogenic variants in additional, unidentified genes cause CFC syndrome.

Clinical Characteristics

Clinical Description

Cardiofaciocutaneous (CFC) syndrome affects males and females equally.

Prenatally, polyhydramnios is present in the vast majority of cases. Maternal hyperemesis gravidarum may occur and subjective decrease in fetal movement may be observed. Newborns may be premature and large for gestational age, although the majority are appropriate for gestational age.

In the neonate, distinctive craniofacial features are present. Chylothorax and lymphedema have been reported at birth. Cardiac abnormalities, when present, typically present at birth, although hypertrophic cardiomyopathy and rhythm disturbances may present later in life. Feeding difficulties may be present.

In infancy, severe feeding difficulties are common, resulting in failure to thrive. Many children require nasogastric or gastrostomy feeding, while some undergo a Nissen fundoplication procedure for severe gastroesophageal reflux. Constipation is typically reported and continues to be an issue throughout childhood and adolescence.

All children have some form of neurologic abnormalities, neurocognitive delay, or learning issues. Overall, developmental delay typically ranges from mild to profoundly severe. A few individuals have IQs in the normal range. Children have speech delays and the vast majority have hypotonia, causing motor delays.

Childhood and adolescence. At present, no longitudinal or natural history studies have been done for CFC syndrome. However, CFC syndrome does have an evolving phenotype.

- **Feeding issues.** Later in childhood, feeding difficulties and hypotonia improve. Oral feedings are achieved usually in early childhood.
- **Growth failure** affects most individuals with CFC syndrome. Although the vast majority of children may not be tested, some have growth hormone deficiency.

- **Neurodevelopmental delay** may be less obvious in mildly or moderately affected children, but speech delays and difficulty walking become apparent in those who are more severely affected. Some young adults participate in assisted living programs.
- **Seizures.** Nearly 50% of individuals with CFC and a pathogenic variant in one of its associated genes have a seizure disorder. Most seizures begin in infancy or early childhood [Yoon et al 2007]; however, a seizure disorder may develop later in childhood as well.
- **Otolaryngologic problems.** Many children have recurrent otitis media and are found to have narrow external auditory canals.
- **Ocular abnormalities** including strabismus, nystagmus, optic nerve hypoplasia, astigmatism, myopia, and/or hyperopia are present in most individuals and may result in decreased vision and acuity.
- **Cardiac issuesabnormalities** occur in approximately 75%-80% of indiividuals and include hypertrophic cardiomyopathy, structural anomalies, and (more rarely) rhythm disturbances.
- **Renal/ urogenital anomalies.** Anomalies can occur in up to 33% of individuals, with cryptorchidism in males being the most common. Renal cysts and stones as well as hydronephrosis and hydroureter can also occur.
- **Bleeding diathesis.** von Willebrand disorder has been reported.
- **Dermatologic.** With age, the dryness of the skin and the follicular hyperkeratosis tend to improve, allowing the hair to grow on the face and scalp [Roberts et al 2006]; however, palmoplantar hyperkeratosis and lymphedema may become more severe. Nevi, when present, increase in number over time [Siegel et al 2011]. Individuals with CFC syndrome have been known to develop severe skin infections.
- **Musculoskeletal.** The vast majority of individuals have musculoskeletal findings including hypotonia with a paucity of muscle mass and lax joints. Orthopedic issues include pectus deformity, scoliosis, kyphosis, and/or gait disturbances.
- **Appearance.** By late adolescence to early adulthood, the craniofacial appearance becomes less like that seen in Noonan syndrome.
- **Neoplasias** (e.g., benign papillomas or malignancies observed in the other RASopathies including Costello syndrome, Noonan syndrome, or neurofibromatosis type 1) have not been reported in CFC syndrome. However, acute lymphoblastic leukemia (ALL) has now been reported in a few individuals [Niihori et al 2006, Makita et al 2007, Rauen et al 2010], hepatoblastoma in an immunocompromised individual [Al-Rahawan et al 2007], non-Hodgkin lymphoma [Ohtake et al 2011], and large B-cell lymphoma [Rauen et al 2010].

Genotype-Phenotype Correlations

Further evaluation of more individuals with CFC syndrome is necessary to clarify genotype-phenotype correlations, thereby permitting more accurate prognoses.

Ongoing correlations include the following:

- Pulmonic stenosis is present in 50% of CFC individuals with a *BRAF* pathogenic variant as opposed to 37% with a MEK pathogenic variant [Allanson et al 2011].
- Individuals with the *BRAF*p.Gln257Arg pathogenic variant, the most common CFC pathogenic variant, have many phenotypic features in common, including characteristic facies, cardiac defects, short stature, failure to thrive, abnormal brain imaging, musculoskeletal and ocular abnormalities, and relatively mild developmental delay [Niihori et al 2006, Rodriguez-Viciana et al 2006].
- Individuals with a *MAP2K1* or *MAP2K2* pathogenic variant are more likely to have keratosis pilaris and progressive nevi formation than those with a *BRAF* pathogenic variant [Siegel et al 2011].

Penetrance

Penetrance is complete in CFC syndrome.

Nomenclature

Blumberg et al [1979] at the March of Dimes Birth Defects Conference reported three individuals with intellectual disability who also had characteristic craniofacial dysmorphology, ectodermal anomalies, and cardiac defects. These three persons, along with five others, were subsequently reported by Reynolds et al [1986], who designated this new disorder cardiofaciocutaneous syndrome. Also Baraitser & Patton [1986] reported on a Noonan syndrome-like short stature syndrome with ectodermal anomalies that was presumed to be the same entity.

Prevalence

More than 100 individuals with CFC syndrome have been reported in the literature. The total number of individuals worldwide with CFC syndrome is estimated to be several hundred, yet this may be an underestimation because of underdiagnosis of mildly affected individuals. Overall prevalence is not known; prevalence in Japan is estimated at one in 810,000 [Abe et al 2012].

Genetically Related (Allelic) Disorders

BRAF

Noonan syndrome with multiple lentigines (NSML). *BRAF* pathogenic variants have been reported in a few individuals who were given a clinical diagnosis of NSML (previously referred to as LEOPARD syndrome).

Noonan syndrome. *BRAF* pathogenic variants have been reported in a few individuals who were given a clinical diagnosis of Noonan syndrome.

Note: While individuals with a clinical diagnosis of either NSML or Noonan syndrome have been reported in the medical literature to be associated with pathogenic variants in *BRAF* [Sarkozy et al 2009], the author feels strongly that a pathogenic variant in *BRAF* molecularly defines CFC syndrome.

KRAS

Noonan syndrome. *KRAS* pathogenic variants have been identified in fewer than 5% of individuals with the clinical diagnosis of Noonan syndrome [Carta et al 2006, Schubbert et al 2006, Zenker et al 2007].

Differential Diagnosis

Multigene panels may include testing for a number of the genes associated with disorders discussed in this section.

Costello syndrome is characterized by failure to thrive in infancy as a result of severe postnatal feeding difficulties; short stature; developmental delay or intellectual disability; coarse facial features (full lips, large mouth, full nasal tip); curly or sparse, fine hair; loose, soft skin with deep palmar and plantar creases; papillomata of the face and perianal region; diffuse hypotonia and joint laxity with ulnar deviation of the wrists and fingers; tight Achilles tendons; and cardiac involvement including: cardiac hypertrophy (usually typical hypertrophic cardiomyopathy [HCM]), congenital heart defect (usually valvar pulmonic stenosis), and arrhythmia (usually supraventricular tachycardia, especially chaotic atrial rhythm/multifocal atrial tachycardia or ectopic atrial tachycardia). Relative or absolute macrocephaly is typical, and postnatal cerebellar overgrowth can result in the development of a Chiari I malformation with associated anomalies including hydrocephalus or syringomyelia. Individuals with Costello syndrome are at an approximately 15% lifetime risk for malignant tumors including rhabdomyosarcoma and neuroblastoma in young children and transitional cell carcinoma of the bladder in adolescents and young adults.

Germline pathogenic variants in *HRAS* are causative [Aoki et al 2005]. Inheritance is autosomal dominant as demonstrated by germline mosaicism [Sol-Church et al 2009].

Individuals identified with *HRAS* pathogenic variants by definition have the diagnosis of Costello syndrome. *BRAF* pathogenic variants have been identified in individuals with a Costello syndrome-like phenotype who did not have an *HRAS* pathogenic variant [Rauen 2006]. However, with closer clinical examination, the clinical diagnosis was consistent with CFC syndrome. Costello syndrome and cardiofaciocutaneous (CFC) syndrome have many overlapping phenotypic features, underscoring the difficulty in making a clinical diagnosis based on phenotypic features alone. Individuals with *BRAF* pathogenic variants have the diagnosis of CFC syndrome, even if they have features that may be present in Costello syndrome or have phenotypic overlap with Noonan syndrome (see following).

Noonan syndrome is characterized by short stature, congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, characteristic facies, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities. Although birth length is usually normal, final adult height approaches the lower limit of normal. Congenital heart disease occurs in 50%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. Other structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Up to one third of affected individuals have mild intellectual disability.

Pathogenic variants in *PTPN11* have been identified in approximately 50% of individuals with clinically diagnosed Noonan syndrome [Tartaglia et al 2001]. *SOS1* pathogenic variants have been identified in approximately 13% of individuals with Noonan syndrome [Roberts et al 2006, Tartaglia et al 2007]. *KRAS* pathogenic variants have been reported in fewer than 5% [Schubbert et al 2006]. *RAF1* pathogenic variants have been reported in 3% to 17%. Other genes in which pathogenic variants have been reported to cause Noonan syndrome in fewer than 1% of cases include *NRAS* [Cirstea et al 2010], *BRAF*, and *MAP2K1*.

Craniofacial findings in CFC syndrome are reminiscent of those described in Noonan syndrome (macrocephaly, broad forehead, bitemporal narrowing, hypoplasia of the supraorbital ridges, downslanting palpebral fissures with ptosis, short nose with depressed nasal bridge and anteverted nares, low-set ears with prominent helices which may be posteriorly rotated, and high-arched palate), underscoring the importance of molecular testing to establish the correct diagnosis.

Inheritance is autosomal dominant; however, many affected individuals most likely have *de novo* pathogenic variants.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with or suspected to have cardiofaciocutaneous (CFC) syndrome, the following evaluations are recommended. Evaluations are based on published consensus guidelines for workup at initial diagnosis or as ongoing medical management throughout an individual's life span [Pierpont et al 2014]

- Consultation with a clinical geneticist and/or genetic counselor
- Complete physical examination including measurement of growth parameters
- Nutrition and feeding evaluation; consideration of swallow study
- Endocrine evaluation
- Psychomotor developmental evaluation

- Neurologic evaluation
- MRI of the brain to detect any structural changes
- Electroencephalogram if seizures are suspected
- Audiologic examination
- Ophthalmologic examination
- Cardiac evaluation including echocardiogram and electrocardiogram
- Full abdominal ultrasound examination to evaluate for renal and urogenital anomalies
- Obtain history for possible bleeding diathesis
- Dermatologic evaluation

Treatment of Manifestations

Consensus guidelines for workup at initial diagnosis or as ongoing medical management throughout an individual's life span have been published [Pierpont et al 2014].

CFC syndrome affects many organ systems and, therefore, the vast majority of individuals require ongoing care by a multidisciplinary team of healthcare providers. At present, phenotypic features caused by germline pathogenic variants in *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* are treated as in the general population.

- Severe feeding issues during the first years of life require management by a pediatric gastroenterologist. Many children with CFC syndrome require nasogastric or gastrostomy tube feeding because of failure to thrive. Increasing caloric intake may be of benefit. Children with severe gastroesophageal reflux may require a Nissen fundoplication. Constipation affects the majority of individuals; increased fiber in the diet, under the direction of a pediatrician, may be beneficial.
- Some individuals are growth hormone- and or thyroid hormone-deficient and may benefit from management by an endocrinologist. Individuals with a diagnosis of hypertrophic cardiomyopathy must be monitored closely while on growth hormone therapy.
- Enrollment in early-intervention therapies to promote motor and intellectual development (e.g., occupational therapy, physical therapy, or speech therapy) is highly recommended.
- Seizures are treated as in the general population. However, seizures may be refractory to single-agent therapy and may require polytherapy.
- Recurrent otitis media may require placement of PE tubes.
- Ocular abnormalities such as myopia or hyperopia are corrected with lenses as in the general population.
- Cardiovascular management is dictated by the abnormality, with treatment similar to that in the general population: structural defects are managed surgically as needed; hypertrophic cardiomyopathy is followed by serial echocardiograms, and cardiac arrhythmias are medically managed in an aggressive manner.
- Xerosis and pruritus may be relieved by increasing the ambient humidity or using hydrating lotions. Hyperkeratoses are treated as in the general population.
- Signs and symptoms of skin infection, especially in the presence of lymphedema, warrant thorough and immediate evaluation by a physician for the consideration of antibiotic treatment.
- Musculoskeletal abnormalities, such as scoliosis or pectus deformity, are managed as in the general population.

Note: Specialized NF/Ras pathway genetics clinics are available in the US and United Kingdom.

Prevention of Secondary Complications

Cardiac. Certain congenital heart defects (notably valve dysplasias) require antibiotic prophylaxis for subacute bacterial endocarditis (SBE).

Anesthesia. Individuals with CFC syndrome may have an unrecognized hypertrophic cardiomyopathy, tracheomalacia, or a predisposition to cardiac rhythm disturbances and should be evaluated for these issues prior to anesthetic administration.

Surveillance

If anomalies are identified in any organ system, lifelong periodic follow up is warranted. Consensus guidelines for surveillance in CFC syndrome have been established [Pierpont et al 2014].

- **Gastrointestinal.** Monitor for signs and symptoms of gastrointestinal reflux, constipation, and generalized dysmotility.
- **Endocrine.** Monitor growth parameters to identify evidence of growth failure that may be associated with growth hormone deficiency. Monitor for signs of precocious puberty.
- **Cognitive development.** Assess periodically to be certain that school programs or other supports are addressing learning needs.
- **Neurologic.** Monitor neurologic signs and symptoms with period neurologic evaluations and MRI if indicated. Chiari malformation and later onset of seizures have been observed.
- **Audiologic**. Annual evaluation of hearing is recommended.
- **Ophthalmologic.** Periodic evaluation by an ophthalmologist to monitor for ocular issues (such as myopia, hyperopia, cataracts) is recommended.
- **Cardiac.** If the initial cardiac evaluation is normal, periodic follow-up evaluations including an echocardiogram and an electrocardiogram are necessary as hypertrophic cardiomyopathy and rhythm disturbances may develop later in life.
- **Dermatologic.** As affected individuals age, formation of nevi may be progressive. At present, the natural history of the nevi is unknown. Periodic and routine dermatologic evaluation of nevi may be warranted to monitor for malignant change, although **no** individuals with CFC syndrome have been reported to have a malignant change.
- **Musculoskeletal.** Periodic evaluation for scoliosis during young childhood is recommended.
- **Malignancy.** No screening protocol exists at present, as it is unclear if individuals with CFC syndrome are at an increased risk for malignancies.

Agents/Circumstances to Avoid

Over-exposure to heat. Individuals with CFC syndrome report heat intolerance.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

A pregnant female suspected of having CFC syndrome warrants obstetric care from a trained maternal-fetal-medicine physician due to possible polyhydramnios, cardiac issues, and/or hypertension.

Therapies Under Investigation

Because the Ras/MAPK pathway has been studied intensively in the context of cancer, numerous therapeutics that specifically target this pathway are in development.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Cardiofaciocutaneous (CFC) syndrome is transmitted in an autosomal dominant manner [Rauen et al 2010]. Most affected individuals reported to date have had a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- The vast majority of individuals with CFC syndrome reported to date have the disorder as the result of a *de novoBRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* pathogenic variant.
- In rare cases, individuals diagnosed with CFC have an affected parent. Autosomal dominant inheritance of *MAP2K2* and *KRAS*-related CFC has been reported in several families [Rauen et al 2010, Stark et al 2012].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing for the pathogenic variant identified in the proband or, if a pathogenic variant has not been identified in the proband, a detailed medical history as well as physical examination of the parents to identify phenotypic features of CFC.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (although no instances of germline mosaicism have been reported, it remains a possibility).

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the proband's parents.
- As most affected individuals reported to date have had a *de novoBRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* pathogenic variant, risk to sibs is presumed to be low. However, because of the possibility of germline mosaicism in a parent, the risk may be greater than in the general population.

Offspring of a proband. Each child of an individual with CFC syndrome has a 50% chance of inheriting the *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to couples if one of the two has CFC syndrome or if they have had an affected child.

The importance of determining the genetic etiology using molecular genetic testing. Noonan syndrome and CFC syndrome have phenotypic overlap; thus, determining the genetic etiology by molecular testing is important to establish the correct diagnosis in the proband and allow for accurate genetic counseling.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *BRAF*, *KRAS*, *MAP2K2*, *or MAP2K1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for CFC are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **CFC International**
  183 Brown Road
  Vestal NY 13850
  Phone: 607-772-9666
  Fax: 607-748-0409
  Email: info@cfcsyndrome.org
  www.cfcsyndrome.org
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Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Cardiofaciocutaneous Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BRAF	7q34	Serine/threonine-protein kinase B-raf	BRAF database	BRAF	BRAF
KRAS	12p12.1	GTPase KRas	KRAS database	KRAS	KRAS

Table A. continued from previous page.

MAP2K1	15q22.31	Dual specificity mitogen-activated protein kinase kinase 1	MAP2K1 @ LOVD	MAP2K1	MAP2K1
MAP2K2	19p13.3	Dual specificity mitogen-activated protein kinase kinase 2	MAP2K2 database	MAP2K2	MAP2K2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Cardiofaciocutaneous Syndrome (View All in OMIM)

115150	CARDIOFACIOCUTANEOUS SYNDROME 1; CFC1
164757	B-RAF PROTOONCOGENE, SERINE/THREONINE KINASE; BRAF
176872	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 1; MAP2K1
190070	KRAS PROTOONCOGENE, GTPase; KRAS
601263	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 2; MAP2K2
615278	CARDIOFACIOCUTANEOUS SYNDROME 2; CFC2
615279	CARDIOFACIOCUTANEOUS SYNDROME 3; CFC3
615280	CARDIOFACIOCUTANEOUS SYNDROME 4; CFC4

Molecular Pathogenesis

The four genes currently known to be associated with cardiofaciocutaneous (CFC) syndrome are in the Ras/mitogen-activated protein kinase (MAPK) signaling cascade. The MAPK signaling cascade of dual-specificity kinases [Rauen et al 2011] (see Figure 1) is highly conserved among eukaryotic organisms and is critically involved in cell proliferation, differentiation, motility, apoptosis, and senescence. The Ras/Raf/MEK/ERK signal transduction pathway is activated by extracellular stimuli. Activated Ras recruits Raf, the first kinase of the cascade, to the cell membrane. Activated Raf phosphorylates MEK1 (encoded by *MAP2K1*) and/or MEK2 (encoded by *MAP2K2*), which then phosphorylates ERK1 and/or ERK2 (aka MAPK). Noonan syndrome has been associated with pathogenic variants in *PTPN11* (protein product SHP2), *SOS1*, *SOS2*, *RAF1* (protein product CRAF), *NRAS*, *RIT1*, *LZTR1*, *RRAS* and *KRAS*. Pathogenic variants in *HRAS* are causative for Costello syndrome. CFC syndrome is associated with pathogenic variants in *BRAF*, *MAP2K1*, and *MAP2K2*. Because *KRAS* pathogenic variants were identified in individuals clinically diagnosed with CFC syndrome or with Noonan syndrome [Niihori et al 2006, Schubbert et al 2006], the role of its protein product GTPase KRas (KRAS) in CFC syndrome has yet to be clarified.

BRAF

Gene structure. *BRAF* encodes BRAF, a member of the Raf family, which also includes CRAF and ARAF encoded by the X-linked gene *ARAF*. *BRAF* spans approximately 190 kb and contains 18 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The spectrum of *BRAF* pathogenic variants in individuals with CFC syndrome is similar to the spectrum of somatic pathogenic variants observed in cancer. However, pathogenic variants associated with CFC syndrome are more widely distributed within the gene and many are novel, never having been identified in cancer. Pathogenic variants are heterogeneous and cluster mainly in two regions, the cysteine-rich domain of the CR1 and the protein kinase domain. Nearly all pathogenic variants published to date have been *de novo* missense variants. However, rare in-frame deletions have been identified in *BRAF* exon 11 [Yoon et al 2007].

Table 2. Selected *BRAF* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.770A>G	p.Gln257Arg [1]	NM_004333.4 NP_004324.2
c.1399T>G	p.Ser467Ala [1]	
c.1408_1410del	p.Thr470del [1]	
c.1455G>C	p.Leu485Phe [2]	
c.1600G>C	p.Gly534Arg [2]	
c.1787G>T	p.Gly596Val	
c.1799T>A	p.Val600Glu [3]	
c.1799T>G	p.Val600Gly	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Figure 1.
2. Associated with Costello syndrome; see Figure 1.
3. p.Val600Glu is a somatic pathogenic variant found in some solid tumors (see Genetically Related Disorders).

Normal gene product. The protein product of *BRAF* is BRAF, a serine/threonine protein kinase that is one of the many direct downstream effectors of Ras. The Raf/MEK/ERK module of kinases is critically involved in cell proliferation, differentiation, motility, apoptosis, and senescence. BRAF has only two known downstream effectors, mitogen-activated protein kinase 1 and 2 (also known as MEK1 and MEK2). There are three conserved regions in BRAF. Conserved region 1 (CR1) contains the Ras binding domain and the cysteine-rich domain, both of which are required for recruitment of BRAF to the cell membrane. CR2 is the smallest of the conserved regions and CR3 is the kinase domain containing the glycine-rich loop (exon 11) and the activation segment (exon 15) of the catalytic domain.

Abnormal gene product. The type of *BRAF* pathogenic variants found in CFC syndrome is similar to the types of somatic pathogenic variants found in cancers with high kinase and kinase-impaired activities [Niihori et al 2006, Rodriguez-Viciana et al 2006]. In addition, CFC syndrome BRAF mutated proteins activate downstream effectors in vitro, as determined by measuring phosphorylated species of MEK and ERK. Both cancer and CFC syndrome-associated BRAF mutated proteins with elevated kinase activity induce higher levels of MEK and ERK phosphorylation compared with wild-type BRAF, whereas kinase-impaired BRAF mutated proteins are impaired in their ability to induce phosphorylation of MEK and ERK [Rodriguez-Viciana et al 2006]. The most common *BRAF* pathogenic variant identified in cancer, p.Val600Glu, has not been identified in CFC syndrome. Presumably, such a gain-of-function variant would be incompatible with life. However, a germline p.Val600Gly pathogenic variant has recently been reported in CFC [Champion et al 2011] and, like the *BRAF* p.Val600Glu pathogenic variant, has also been reported in cancer.

Cancer and benign tumors – solid tumors. Somatic pathogenic variants in *BRAF* have been reported in approximately 8% of tumors with *BRAF* most frequently mutated in melanoma, thyroid, colorectal, and ovarian. The vast majority of *BRAF* pathogenic variants are missense substitutions found in (but not limited to) exon 11 (the glycine-rich loop) and exon 15 (the activation segment) in the BRAF kinase domain [Wellbrock et al 2004]. One pathogenic variant, p.Val600Glu, which results in increased kinase activity, accounts for more than 90% of *BRAF* pathogenic variants identified in human cancer. Somatic *BRAF* p.Val600Glu pathogenic variants are also found in benign nevi and premalignant colon polyps. The common p.Val600Glu cancer pathogenic variant has never been identified in CFC syndrome. However, a *BRAF* p.Val600Gly pathogenic variant has been reported recently in an individual with CFC syndrome [Champion et al 2011].

MAP2K1, MAP2K2

Gene structure. MEK, like Raf, exists as a multigene family. *MAP2K1* spans approximately 104 kb. *MAP2K2* spans approximately 34 kb. Each gene contains 11 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Missense variants in *MAP2K1* and *MAP2K2* cause CFC syndrome in approximately 25% of clinically diagnosed individuals. Pathogenic variants are heterogeneous missense substitutions, with the majority identified in exons 2 and 3 of both *MAP2K1* and *MAP2K2*. The amino acid substitutions in MEK1 and MEK2 are similar, suggesting that the functional consequences in the two family isoforms may be similar.

Table 3. Selected *MAP2K1* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.389A>G	p.Tyr130Cys	NM_002755.3 NP_002746.1
c.199G>A	p.Asp67Asn	
c.171G>T	p.Lys57Asn	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Table 4. Selected *MAP2K2* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.170T>G	p.Phe57Cys [1]	NM_030662.3 NP_109587.1
c.383C>A	p.Pro128Gln	
c.401A>G	p.Tyr134Cys [1]	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Figure 1.

Normal gene product. *MAP2K1* and *MAP2K2* encode threonine/tyrosine kinases with both isoforms having the ability to activate ERK1 and ERK2. *MAP2K1* encodes the mitogen activated protein kinase 1 (MEK1). *MAP2K2* encodes MEK2. The proteins have approximately 85% amino acid identity. MEK1 and MEK2 proteins do not serve redundant purposes as determined in mouse development.

Abnormal gene product. In vitro functional studies of MEK proteins encoded by CFC syndrome-associated *MAP2K1* and *MAP2K2* pathogenic variants determine that they overstimulate ERK phosphorylation compared to wild-type MEK; however, they are less stimulating than artificially generated constitutively active MEK pathogenic variants [Rodriguez-Viciana et al 2006].

Cancer and benign tumors. The first functional *MAP2K1* pathogenic variant, p.Asp67Asn, was identified in an ovarian cancer cell line with functional studies determining that this mutated protein has increased activity as measured by an increase in ERK phosphorylation [Estep et al 2007]. Subsequently, *MAP2K1* p.Lys57Asn pathogenic variants were identified in non-small-cell lung carcinoma [Marks et al 2008]. Since these initial publications, somatic pathogenic variants in *MAP2K1* and *MAP2K2* have been reported in various tumor types.

KRAS

Gene structure. *KRAS* has four coding exons with intervening sequences and spans approximately 45 kb. Two alternative splice variants exist, with KRAS4b being ubiquitously expressed. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Germline missense *KRAS* variants, which are distinct from those identified in cancer, have been identified in coding exons 1, 2, and 4b [Carta et al 2006, Niihori et al 2006, Schubbert et al 2006, Zenker et al 2007].

Normal gene product. The GTPase KRAS belongs to a large superfamily of small GTPases; it and its major counterparts H-Ras and N-Ras are the most extensively studied of the Ras proteins. Ras proteins regulate cell growth, proliferation, and differentiation. Ras activates several downstream cascades, some of which include the mitogen-activated protein kinase (MAPK), phosphotidylinositol 3-kinase (PI3K), RAL guanine nucleotide dissociation stimulator (RALGDS), and phospholipase Cε (PLCε).

Abnormal gene product. Abnormal protein products deregulate single transduction and cause growth factor hypersensitivity of hematopoietic cells. Functional studies of NS/CFC syndrome-associated *KRAS* pathogenic variants revealed reduced intrinsic GTPase activity compared to the wild-type protein, although not to the level of mutated K-Ras protein typically found in cancer [Schubbert et al 2006]. Such a gain-of-function pathogenic variant would presumably be incompatible with life.

Cancer and benign tumors. Aberrant activation of Ras is frequently found in cancer, occurring in approximately 20% of all tumors. The vast majority of oncogenic pathogenic variants occur in hotspots in codons 12, 13, or 61. These are not the same pathogenic variants found in Noonan syndrome or CFC syndrome. Single-nucleotide variants in *KRAS* account for approximately 85% of pathogenic variants in the Ras gene family. *NRAS* (~15% of total) and *HRAS* (~1% of total) pathogenic variants are found less frequently. Amino acid substitutions caused by pathogenic missense variants in *KRAS* affect guanine nucleotide binding and cause a reduction of GTP hydrolysis, resulting in a gain of function of the protein.

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Chapter Notes

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Revision History

- 3 March 2016 (ha) Comprehensive update posted live
- 6 September 2012 (cd) Revision: multigene panels for Noonan / Costello / LEOPARD / cardiofaciocutaneous syndrome(s) (RAS/MAPK pathway) available clinically
- 23 December 2010 (me) Comprehensive update posted live
- 18 January 2007 (me) Review posted live
- 14 September 2006 (kar) Original submission

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