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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, and woolly or brittle; eyelashes and eyebrows may be absent or sparse. Nails may be dystrophic or fast growing. Affected individuals typically have some form of neurologic and/or cognitive delay (ranging from mild to severe). Most individuals have severe feeding issues, which can contribute to poor growth, and many require nasogastric or gastrostomy tube feeding. Many affected individuals have eye findings, including strabismus, nystagmus, refractive errors, and optic nerve hypoplasia. Seizures may be present and can be refractory to therapy.

Diagnosis/testing

The diagnosis of CFC syndrome is established in a proband with suggestive clinical findings by the identification of a heterozygous pathogenic variant in *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* by molecular genetic testing.

Management

Treatment of manifestations: Consensus medical management guidelines have been published. Care by a multidisciplinary team; increased caloric intake and a nasogastric or gastrostomy tube for severe feeding issues; surgical intervention for severe gastroesophageal reflux or malrotation; management of cardiac structural defects, hypertrophic cardiomyopathy, and arrhythmias as in the general population; increased ambient humidity or hydrating lotions for xerosis and pruritus; management of seizures may require polytherapy; routine management of growth hormone deficiency; standard treatment for peripheral neuropathy, Chiari I malformation, developmental delay / intellectual disability, constipation, musculoskeletal anomalies, hypotonia,

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chronic/recurrent otitis media, hearing loss, cryptorchidism, hydronephrosis, bleeding disorders / thrombocytopenia, and sleep disorders.

Surveillance: At each visit: measure blood pressure; measure growth parameters; evaluate nutritional status and safety of oral intake; monitor for GERD, constipation, generalized dysmotility; assess for new manifestations such as seizures or changes in tone; monitor developmental progress, behavior, and educational needs; monitor for signs and symptoms of thyroid and/or growth hormone deficiency. Assess for scoliosis at each visit until skeletal maturity. Monitor for signs/symptoms of precocious or delayed puberty at each visit in childhood and adolescence. Refer to endocrinologist between the ages of two to three years (or earlier if there are concerns about growth) to monitor growth velocity. Monitor for ocular issues every six to 12 months as directed by ophthalmologist. Hearing evaluation every two to three years, or as clinically indicated. Echocardiogram every two to three years up to age 20 years in those who have an initial cardiac evaluation that is normal. Echocardiogram every three to five years in individuals older than age 20 years who have no previous heart disease found. Annual dermatologic evaluation. DXA scan in early adulthood. Reassess platelet count for evidence of thrombocytopenia in those who have evidence of easy bruising or bleeding.

Agents/circumstances to avoid: Avoid overexposure to heat, strenuous activity, and dehydration. In individuals with evidence of peripheral neuropathy, avoid drugs with a neurotoxic effect.

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

Genetic counseling

CFC syndrome is inherited in an autosomal dominant manner. The majority of individuals with CFC syndrome reported to date have the disorder as the result of a *de novo* *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* pathogenic variant. However, instances of familial recurrence of CFC have been reported. Each child of an individual with CFC syndrome has a 50% chance of inheriting the *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* pathogenic variant. Once the CFC syndrome-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CFC are possible.

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 consensus clinical diagnostic criteria have been established. The diagnosis of CFC syndrome is suspected by clinical findings and confirmed by molecular genetic testing.

Suggestive Findings

Cardiofaciocutaneous (CFC) syndrome **should be suspected** in individuals with the following clinical features:

- Dysmorphic facial features (see Figure 1) as outlined in Clinical Characteristics. The face is triangular in shape and overall may be more coarse than in Noonan syndrome (a clinically similar condition often confused with CFC syndrome), but usually not as coarse as is typically seen in Costello syndrome.
- Cardiac anomalies and rhythm disturbance, including pulmonic stenosis, hypertrophic cardiomyopathy, septal defects, and heart valve anomalies
- Severe feeding issues (gastroesophageal reflux disease, aspiration, vomiting, and oral aversion) and poor growth with relative macrocephaly
- Ectodermal findings, such as xerosis; sparse, curly, and woolly or brittle hair; and dystrophic nails
- Lymphedema and/or chylothorax

- Eye anomalies, including strabismus, nystagmus, and/or optic nerve hypoplasia
- Hypotonia
- Developmental delay and cognitive impairment (mild to severe)
- Seizure disorder
- Cryptorchidism in males

Establishing the Diagnosis

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

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous variant of uncertain significance in one of the genes does not establish or rule out the diagnosis of the disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of CFC syndrome or another RASopathy has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A RASopathy multigene panel that includes some or all of the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

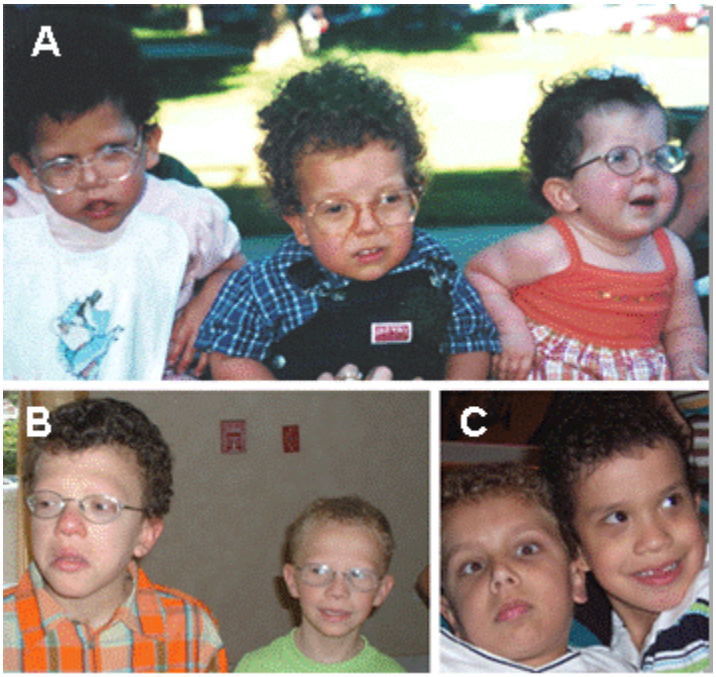

Figure 1. Children with CFC syndrome

A. Three young children with *BRAF* pathogenic variants. Ages are 2.5, 2, and 2 years.

B. Two boys, age 12 and eight years, with *MAP2K2* pathogenic variants.

C. Two boys age six years, with *BRAF* pathogenic variants.

Courtesy of CFC International

Table 1. Molecular Genetic Testing Used in Cardiofaciocutaneous (CFC) Syndrome

Gene [1, 2]	Proportion of CFC Syndrome Attributed to Pathogenic Variants in Gene [3]	Proportion of Probands with a Pathogenic Variant [4] Detectable by Method	
		Sequence analysis [5]	Gene-targeted deletion/ duplication analysis [6]
BRAF	~75%	~100% [7]	Single deletion reported [8]
KRAS	<2%	~100% [7]	Unknown [9]
MAP2K1	~25%	~100% [7]	Unknown [9]
MAP2K2		~100% [7]	Several deletions have been reported, [10] but may not cause CFC syndrome. [11]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of CFC Syndrome Attributed to Pathogenic Variants in Gene [3]	Proportion of Probands with a Pathogenic Variant [4] Detectable by Method	
		Sequence analysis [5]	Gene-targeted deletion/ duplication analysis [6]
Unknown [12]	NA		

NA = not applicable
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Rauen [2013]
4. See Molecular Genetics for information on variants detected in these genes.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
8. A single report of a *BRAF* deletion associated with a CFC-like phenotype [Yu & Graf 2011] that was not supported by functional data
9. No data on detection rate of gene-targeted deletion/duplication analysis are available.
10. Nowaczyk et al [2014] reported several individuals with a *MAP2K2* deletion associated with a CFC-like phenotype. This was supported by functional data of MAPK pathway dysregulation.
11. Lissewski et al [2015] disputed that gene deletions or duplications cause RASopathies.
12. Popov et al [2019] reported several individuals with features of CFC syndrome who had a heterozygous variant in *YWHAZ*.

Clinical Characteristics

Clinical Description

Cardiofaciocutaneous (CFC) syndrome is a multiple congenital anomaly disorder in which individuals may have dysmorphic craniofacial features, cardiac issues, skin and hair abnormalities, hypotonia, eye abnormalities, gastrointestinal dysfunction, seizures, and varying degrees of neurocognitive delay [Pierpont et al 2014] (see Table 2). While many features have been seen in association with this condition, individuals with CFC syndrome display phenotypic variability and therefore not all have every finding.

Polyhydramnios is present in the vast majority of fetal cases diagnosed in utero. Maternal hyperemesis gravidarum, gestational diabetes, gestational hypertension, and preeclampsia may occur, and subjective decrease in fetal movement may be observed prenatally. Second- and third-trimester ultrasound abnormalities may include polyhydramnios, macrocephaly, macrosomia, and renal and cardiac abnormalities. Operative delivery is not uncommon.

Neonatal outcomes of CFC individuals may include irregular heartbeat, intubation, need for feeding tube, edema, chylothorax, and hyperbilirubinemia, which may be confounded by the increased rate of prematurity [Jelin et al 2023].

Table 2. Cardiofaciocutaneous Syndrome: Frequency of Select Features

Feature	Frequency			Comment
	Nearly all	Common	Less frequent	
Prenatal polyhydramnios	●			
Characteristic facial features	●			

Table 2. continued from previous page.

Feature	Frequency			Comment
	Nearly all	Common	Less frequent	
Cardiac issues	●			
Feeding difficulties	●			
Poor growth	●			
Skin issues	●			
Neurocognitive delays	●			Ranging from mild to profound
Eye anomalies	●			
Musculoskeletal abnormalities	●			
Hypotonia & motor developmental delay	●			
Seizures		●		
Behavioral issues		●		
Neonatal chylothorax &/or lymphedema		●		
Otolaryngologic issues		●		Most commonly recurrent otitis media
Urogenital anomalies		●		Most commonly cryptorchidism in males
Malignancy			●	
Hematologic issue			●	
Immunologic issues			●	

Dysmorphic features (see Figure 1) are often helpful in making the diagnosis. By late adolescence to early adulthood, the craniofacial appearance becomes less like that seen in Noonan syndrome. Dysmorphic features in CFC syndrome can include:

- Relative macrocephaly
- Triangular facies
- Bitemporal narrowing
- High anterior hairline
- Hypoplasia of the supraorbital ridges
- Widely spaced eyes
- Telecanthus
- Downslanted 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

Cardiac issues occur in approximately 75%-80% of individuals. Cardiac abnormalities, when present, typically present at birth, although hypertrophic cardiomyopathy and rhythm disturbances may manifest later in life. Cardiac findings can include the following:

- Pulmonic stenosis
- Atrial septal defects and/or ventricular septal defects
- Hypertrophic cardiomyopathy
- Heart valve anomalies (mitral valve dysplasia, tricuspid valve dysplasia, and bicuspid aortic valve)
- Rhythm disturbances

Gastrointestinal/feeding issues. Most affected individuals have severe feeding issues, which can contribute to poor growth. Many children require nasogastric or gastrostomy tube feeding, while some undergo a Nissen fundoplication procedure for severe gastroesophageal reflux. Oral feedings are typically achieved in early childhood. Constipation is typically reported and continues to be an issue throughout childhood and adolescence. Later in childhood, feeding difficulties and hypotonia often improve. Other issues may include the following:

- Aspiration or swallowing problems, which may improve with age
- Recurrent vomiting, which may be association with gastroesophageal reflux disease or malrotation
- Oral aversion
- Dysmotility
- Intestinal malrotation
- Umbilical and inguinal hernia

Poor growth affects most individuals with CFC syndrome. Growth parameters may be normal at birth, with appropriate birth weight and length; however, weight and length may drop to below the fifth centile during early infancy, while head circumference typically remains within the normal range, resulting in relative macrocephaly.

Ectodermal findings. All individuals with CFC syndrome will develop dermatologic issues. With age, the dryness of the skin and the follicular hyperkeratosis tend to improve, allowing 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.

- **Skin findings** can include the following:
  - Xerosis
  - Hyperkeratosis of arms, legs, and face
  - Keratosis pilaris
  - Ichthyosis
  - Ulerythema ophryogenes
  - Eczema
  - Hemangiomas
  - Café au lait macules
  - Erythema, both on the face or generalized
  - Pigmented moles that may be progressive in number
  - Palmoplantar hyperkeratosis over pressure zones
- **Hair** may be sparse to absent, but affected individuals may have normal eyelashes and eyebrows. Hair can be curly; fine or thick; and/or woolly or brittle.
- **Nails** may be dystrophic; flat and broad nails; and/or fast growing.

Developmental delay (DD) and intellectual disability (ID). The vast majority of children, if not all, have some form of neurologic abnormality, neurocognitive delay, or learning issues. Overall, developmental delay typically ranges from mild to profound, although some individuals have IQs in the normal range. Developmental delay may be less obvious in mildly or moderately affected individuals, but speech and motor delays and difficulty walking become apparent in those who are more severely affected.

- The vast majority of affected individuals have hypotonia due to a skeletal muscle myopathy, causing motor delays. The average age of walking in those who become ambulatory is around three years; however, many never achieve this goal.
- A significant number of affected individuals remain nonverbal. In those who develop verbal language skills, the first word is said on average by age two years.
- Some young adults participate in assisted living programs and may have supervised employment.

Other neurologic/neurodevelopmental features

- **Hypotonia.** Global hypotonia is typically evident in the newborn period. Delayed motor skills, muscle weakness, and decreased muscle bulk is commonly present. As children grow older, muscle weakness appears to gradually improve, although individuals still may have gross motor delays.
- **Seizures.** More than 50% of individuals with CFC syndrome develop a seizure disorder. Seizure types may include complex partial seizures, generalized tonic-clonic seizures, absence seizures, and/or infantile spasms. Most seizures begin in infancy or early childhood [Yoon et al 2007, Pierpont et al 2022]; however, a seizure disorder may develop later in childhood as well. Seizures may require polytherapy and can be refractory to therapy (see Treatment of Manifestations).
- **Head MRI** findings may include Chiari I malformation, ventriculomegaly, hydrocephalus, prominent Virchow-Robin spaces, abnormal myelination, and structural anomalies.
- **Neuropathy** may occur and is typically underreported. Musculoskeletal pain is not uncommon and may be acute or chronic [Leoni et al 2019].
- **Neurobehavioral issues** are common and may include irritability, short attention span, stubbornness, and obsessive and/or aggressive behaviors. Anxiety is commonly reported. Autism may also be seen in individuals with CFC syndrome.

Eye abnormalities are present in most individuals and may result in decreased vision and acuity. Findings may include the following:

- Strabismus
- Nystagmus
- Optic nerve hypoplasia
- Astigmatism
- Myopia
- Hyperopia

Musculoskeletal. The vast majority of affected individuals have musculoskeletal findings including a paucity of muscle mass, skeletal myopathy, and lax joints [Tidyman et al 2011]. Orthopedic issues can include pectus deformity, pes planus, hip dysplasia, scoliosis, kyphosis, gait disturbances, and/or joint contractures of the elbow, knee, and/or hip. Contractures may be progressive and require surgical intervention. Many affected individuals require ambulatory assistance. Bone mineral density may also be reduced [Stevenson et al 2011].

Neonatal lymphatic issues. Chylothorax and lymphedema have been reported at birth, although the natural history of these findings has not been reported. Peripheral edema in older individuals may occur.

Otolaryngologic issues. Many affected children experience recurrent otitis media and are found to have narrow external auditory canals. Many require pressure equalization tubes.

Hyperacusis and hearing loss have been reported.

Renal/urogenital anomalies 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. Bladder, uterine, and cervical abnormalities, though rare, have been reported.

Less common features

- **Endocrinology.** Although the vast majority of affected children have not been formally tested, some have true growth hormone deficiency. Affected individuals are also at risk for the development of growth hormone resistance. Both delayed puberty and precocious puberty may occur in males and females. Hypothyroidism has also been reported.
- **Respiratory/sleep.** Laryngotracheal abnormalities such as laryngotracheomalacia and laryngeal clefts have been reported. Sleep issues are common and may include poor sleeping patterns, night sweating, sleep apnea, and/or night terrors.
- **Bleeding diathesis** has rarely been reported, including a case of von Willebrand disorder as well as a rare case of transient thrombocytopenia in a newborn.
- **Malignancy.** Acute lymphoblastic leukemia has been reported in a few individuals [Niihori et al 2006, Makita et al 2007, Rauen et al 2010]. Hepatoblastoma was reported in an immunocompromised individual [Al-Rahawan et al 2007]. Other reported malignancies include non-Hodgkin lymphoma in one individual [Ohtake et al 2011] and large B cell lymphoma in one individual [Rauen et al 2010].

Phenotype Correlations by Gene

BRAF

- Pulmonic stenosis is more common in individuals with CFC syndrome due to a pathogenic variant in *BRAF*. Approximately 50% of individuals with *BRAF*-related CFC syndrome have pulmonic stenosis [Allanson et al 2011].
- The frequency of seizures is higher among individuals with *BRAF*-related CFC syndrome compared to those with *MAP2K2*-related CFC syndrome [Pierpont et al 2022].

MAP2K1. The frequency of seizures is higher among individuals with *MAP2K1*-related CFC syndrome comparted to those with *MAP2K2*-related CFC syndrome [Pierpont et al 2022].

MAP2K2. Individuals with *MAP2K2*-related CFC syndrome have a lower risk of severe neurodevelopmental delay and epilepsy than individuals with *MAP2K1*-related CFC syndrome [Pierpont et al 2022].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified for specific pathogenic variants in *BRAF*, *KRAS*, *MAP2K1*, or *MAP2K2*.

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

Hundreds of individuals with CFC syndrome have been reported in the literature. Overall prevalence is not known; prevalence in Japan is estimated at one in 810,000 [Abe et al 2012].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with **germline** pathogenic variants in *MAP2K2*.

Other phenotypes associated with **germline** pathogenic variants in *BRAF*, *KRAS*, and *MAP2K1* are summarized in Table 3.

Table 3. Allelic Disorders Due to Germline Pathogenic Variants

Gene	Disorder
BRAF	While individuals with a clinical diagnosis of either Noonan syndrome with multiple lentigines or Noonan syndrome have been reported in the medical literature to be associated with pathogenic variants in *BRAF*, [1] the author feels strongly that a pathogenic variant in *BRAF* molecularly defines CFC syndrome.
KRAS	Noonan syndrome (See Differential Diagnosis.)
	RAS-associated autoimmune leukoproliferative disorder (OMIM 614470)
MAP2K1	Noonan syndrome (See Differential Diagnosis.) The author feels strongly that a pathogenic variant in *MAP2K1* molecularly defines CFC syndrome.

1. Sarkozy et al [2009]

Differential Diagnosis

Costello syndrome. By definition, individuals identified as having a heterozygous *HRAS* pathogenic variant have the diagnosis of Costello syndrome. Costello syndrome is characterized by the following:

- Slow growth 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)
- Hair that may be curly, sparse, and fine with synophrys, trichomegaly, and abnormalities of the scalp hair shafts
- 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 (calcaneal) tendons
- 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 (typically). 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.

Although *BRAF* pathogenic variants have been identified in individuals with a Costello syndrome-like phenotype who did not have an *HRAS* pathogenic variant [Rauen 2006], on closer clinical examination, the clinical diagnosis was consistent with cardiofaciocutaneous (CFC) syndrome. Costello syndrome and CFC

syndrome have many overlapping phenotypic features, underscoring the difficulty in making a clinical diagnosis based on phenotypic features alone. The author feels strongly that 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 the following:

- Characteristic facies that includes features similar to CFC, such as triangular facies, macrocephaly, broad forehead, downslanting palpebral fissures, short nose with depressed nasal bridge and anteverted nares, a high-arched palate, and low-set, posteriorly rotated ears.
- Short stature. Although birth length is usually normal, final adult height approaches the lower limit of normal.
- Congenital heart defect. 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 25%-71% of individuals. Hypertrophic cardiomyopathy, found in 20%-29% 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.
- Developmental delay of variable degree. Up to one third of affected individuals have mild intellectual disability.
- Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities.

More than ten genes are known to be associated with Noonan syndrome. More commonly involved genes include *PTPN11*, *SOS1*, *RIT1*, and *RAF1*. Pathogenic variants in *KRAS* (associated with <5% of Noonan syndrome) are also known to be associated with CFC syndrome; see Genetically Related Disorders.

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 that may be posteriorly rotated, and high-arched palate), underscoring the importance of molecular genetic testing to establish the correct diagnosis.

Noonan syndrome is most often inherited in an autosomal dominant manner. While many individuals with autosomal dominant Noonan syndrome have a *de novo* pathogenic variant, an affected parent is recognized in 30%-75% of families. Noonan syndrome caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.

Management

Clinical practice guidelines for cardiofaciocutaneous (CFC) syndrome have been published [Pierpont et al 2014] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with CFC syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Cardiofaciocutaneous (CFC) Syndrome

System/Concern	Evaluation	Comment
Constitutional	Complete physical exam incl measurement of growth parameters	To assess for poor growth
Neurologic	Neurologic eval [1]	• To incl brain MRI in persons w/rapid ↑ in head growth, regression of developmental skills, seizures, changes in neurologic findings, or concerns about optic nerve hypoplasia on ophthalmologic eval • Consider EEG if seizures are a concern. • Consider nerve conduction velocities & electromyogram in those w/suspected peripheral neuropathy. • Education about ↑ risk for development of infantile spasms, seizures, hydrocephalus, & Type 1 Chiari malformation
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider swallowing study &/or studies for GERD. • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk. • Be mindful of possible malrotation. • Assessment for signs/symptoms of constipation
Eyes	Ophthalmologic eval	To assess for ptosis, amblyopia, refractive error, strabismus, optic nerve abnormalities, cataracts, delayed visual maturation, cortical visual impairment, or more complex findings that may require subspecialty referral
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, hip dysplasia, & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Hearing	Audiologic eval	Assess for hearing loss.
Cardiovascular	Cardiac eval incl measurement of blood pressure, echocardiogram, & electrocardiogram	• With special assessment for pulmonary stenosis, hypertrophic cardiomyopathy, &/or septal defects • If there are concerns about arrhythmia, then consider 24-hour Holter eval.
Genitourinary	Abdominal ultrasound	To evaluate for renal & (rarely) splenic anomalies
	Consider pelvic ultrasound.	For uterine anomalies in pubertal/postpubertal females, as clinically indicated
Skin	Dermatologic eval [2]	• Skin issues typically evolve over time. • If there is significant lymphedema or large hemangiomas, consider referral to vascular anomalies specialist or clinic.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Endocrine	Consider obtaining TSH, free T4, IGF-1, & IGFBP-3.	Consider referral to endocrinologist.
	Consider celiac disease screening in those w/growth failure.	
	Physical exam for evidence of precocious puberty in children & for initiation & progression through puberty in adolescents	
	Obtain DXA scan in younger & older adults	To assess for ↓ bone mineralization
Hematologic/Lymphatic	CBC w/platelet count, platelet function studies, & von Willebrand screening	• In persons w/history of bruising or bleeding problems, consider referral to hematologist if there are abnormalities on these screening blood tests. • Eval for bleeding issues should be done prior to any invasive or surgical procedure.
Respiratory/Sleep	Clinical assessment for signs & symptoms of tracheomalacia in infants & young children	Laryngotracheal abnormalities such as laryngotracheomalacia & laryngeal clefts have been reported.
	Consider sleep study.	Sleep issues are common & may incl poor sleeping patterns, night sweating, sleep apnea, &/or night terrors.
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of CFC syndrome to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

Adapted in part from Pierpont et al [2014], Table 1
ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; CBC = complete blood count; DXA = dual-energy x-ray absorptiometry; GERD = gastroesophageal reflux disease; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth factor binding protein 3; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; T4 = thyroxine; TSH = thyroid-stimulating hormone
1. Affected individuals are also at risk for the development of neuropathy and complaints of pain.
2. Skin issues may include keratosis pilaris, ulerythema ophryogenes, eczema, progressive multiple pigmented nevi, dystrophic nails, lymphedema, hemangiomas, hyperkeratosis, and generalized hyperpigmentation.
3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Consensus clinical management guidelines have been published [Pierpont et al 2014] (full text).

There is no cure for CFC syndrome.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5). Specialized NF/Ras pathway genetics clinics are available in the United States, United Kingdom, and European Union.

Table 5. Treatment of Manifestations in Individuals with Cardiofaciocutaneous Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Severe feeding issues	• ↑ caloric intake may be considered. • Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues. • Children w/severe gastroesophageal reflux may require a Nissen fundoplication.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Seizures may be refractory to single-agent therapy & may require polytherapy. • In those w/infantile spasms, consult w/ cardiologist prior to starting steroid medication because of baseline risk of developing cardiomyopathy. • Education of parents/caregivers [1]
Chiari malformation	Standard treatment per neurosurgeon	
Peripheral neuropathy	Standard supportive treatment per neurologist or rehabilitation medicine specialist	Avoidance of drugs that are neurotoxic (See Agents/Circumstances to Avoid.)
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Malrotation	Standard treatment per surgeon	
Constipation	↑ fiber in diet, stool softeners, prokinetics, osmotic agents, or laxatives as needed	Consider referral to gastroenterologist if symptoms are severe.
GERD	Standard treatment	
Eyes	Standard treatment per ohthalmologist	Refractive errors, strabismus
	Standard treatment per ophthalmic subspecialist	More complex findings (e.g., cataract, retinal dystrophy)
	Low vision services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision services / OT / mobility services
Musculoskeletal abnormality	Standard treatment per orthopedist	• Scoliosis, hip dysplasia, joint contractures, or pectus deformity managed as in general population. • Eval for bleeding issues should be done prior to any invasive or surgical procedure.
Chronic/recurrent otitis media	Standard treatment per ENT specialist, which may incl placement of PE tubes	
Hearing loss	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
Cardiovascular defects / Hypertrophic cardiomyopathy	Standard treatment per cardiologist	
Cryptorchidism/ Hydronephrosis	Standard treatment per urologist	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Skin	• Xerosis & pruritus may be relieved by ↑ ambient humidity or using hydrating lotions. • Hyperkeratoses, lymphedema, & hemangiomas are treated as in general population. • Antibiotic treatment for skin infection, esp in presence of lymphedema	• Nevi may be progressive. • For those w/significant lymphedema, mgmt through lymphedema or vascular anomalies clinic may be indicated.
Endocrine	Those persons who are growth &/or thyroid hormone deficient should be managed by an endocrinologist.	• Growth hormone therapy may be considered. • Persons w/diagnosis of hypertrophic cardiomyopathy must be monitored closely while on growth hormone therapy.
	Standard treatment for pubertal abnormalities (precocious or delayed puberty)	
Bleeding disorders / Thrombocytopenia	Standard treatment per hematologist	
Sleep disorders	Standard treatment as in general population	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement and/or home nursing • Consider involvement in adaptive sports or Special Olympics.

Adapted in part from Pierpont et al [2014], Table 1
ASM = anti-seizure medication; GERD = gastroesophageal reflux disease; OT = occupational therapy; PE = pressure equalizer; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC

devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder or anxiety, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 6 are recommended. Lifelong periodic follow up is warranted.

Table 6. Recommended Surveillance for Individuals with Cardiofaciocutaneous Syndrome

System/Concern	Evaluation	Frequency
Growth	• Measurement of growth parameters, incl weight, length/height, & head circumference • Refer to endocrinologist at age 2-3 yrs (or earlier if there are concerns about growth) to monitor growth velocity. [1]	At each visit
Feeding	Eval of nutritional status & safety of oral intake	
Gastrointestinal	Monitor for gastrointestinal reflux, constipation, & generalized dysmotility.	
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations such as seizures, changes in tone, or need for brain MRI. [2]	At each visit, w/periodic neurologist evals as needed
Development	Monitor developmental progress & educational needs.	At each visit
Eyes	Monitor for ocular issues (such as myopia, hyperopia, cataracts) by ophthalmologist	Every 6-12 mos as directed by ophthalmologist
Musculoskeletal	Assess for scoliosis [3, 4]	At each visit until skeletal maturity
Hearing	Hearing eval	Every 2-3 yrs, or more frequently if hearing loss has been identified
Cardiovascular [5]	Blood pressure measurement	At each clinic visit
	Persons up to age 20 yrs	Echocardiogram every 2-3 yrs, if initial cardiac eval is normal
	Persons older than age 20 years	Echocardiogram every 3-5 yrs, if no previous heart disease found
Skin	Dermatologic eval for skin issues, progression of nevi formation, & monitoring of lymphedema	Annually or as directed by dermatologist

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Endocrine	Monitor for signs/symptoms of thyroid &/or growth hormone deficiency.	At each visit
	Monitor for signs of precocious or delayed puberty.	At each visit in childhood & adolescence
	DXA scan	In young adults, w/follow up as clinically indicated
Hematologic	Reassess platelet count for evidence of thrombocytopenia	In those who have evidence of easy bruising or bleeding

Adapted in part from Pierpont et al [2014], Table 1
DXA = dual-energy x-ray absorptiometry
1. Growth failure may be a sign of growth hormone deficiency or thyroid hormone deficiency.
2. Affected individuals are at risk of developing Chari I malformation.
3. Perform spine MRI prior to any spinal surgery to assess for Chiari malformation and/or spinal abnormalities [Pierpont et al 2014].
4. Evaluation for bleeding issues should be done prior to any invasive or surgical procedure [Pierpont et al 2014].
5. Periodic echocardiogram and electrocardiogram are necessary throughout life, as hypertrophic cardiomyopathy and rhythm disturbances may develop later in life.

Agents/Circumstances to Avoid

Individuals with CFC syndrome report heat intolerance; therefore, overexposure to heat and strenuous activity should be avoided. Hydrate as needed.

In individuals with evidence of peripheral neuropathy, drugs with a neurotoxic effect should be avoided, per standard supportive treatment according to the individual's neurologist or rehabilitation medicine specialist.

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 high-risk obstetric care from a trained maternal-fetal medicine physician due to possible polyhydramnios, maternal cardiac issues, and/or maternal hypertension.

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Cardiofaciocutaneous (CFC) syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals with CFC syndrome reported to date have the disorder as the result of a *de novo* *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* pathogenic variant.
- Individuals diagnosed with CFC syndrome may have an affected parent; instances of familial recurrence of CFC are increasingly reported in the medical literature [Rauen et al 2010, Stark et al 2012, Rauen et al 2021]. Therefore, it is critical that the parents of the proband are examined for signs of CFC syndrome and the medical history of the parents obtained.
- Molecular genetic testing for the pathogenic variant identified in the proband is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Geoghegan et al 2018]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with CFC syndrome may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of a proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the CFC-causing pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Geoghegan et al 2018].

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 has the CFC syndrome-causing pathogenic variant identified in the proband, the parent's 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/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected and to the parents of an affected child.

Prenatal Testing and Preimplantation Genetic Testing

Once the CFC syndrome-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for CFC are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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**
  16716 Cory Cactus Drive
  Austin TX 78738
  Phone: 813-503-6033
  Email: info@cfcsyndrome.org
  www.cfcsyndrome.org
- **RASopathies Network**
  Email: info@rasopathiesnet.org
  www.rasopathiesnet.org

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 NSEuroNet database - BRAF	BRAF	BRAF
KRAS	12p12.1	GTPase KRas	KRAS database NSEuroNet database - KRAS	KRAS	KRAS
MAP2K1	15q22.31	Dual specificity mitogen-activated protein kinase kinase 1	MAP2K1 @ LOVD NSEuroNet database - MAP2K1	MAP2K1	MAP2K1
MAP2K2	19p13.3	Dual specificity mitogen-activated protein kinase kinase 2	MAP2K2 database NSEuroNet database - MAP2K2	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

Table B. continued from previous page.

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*, *RRAS2*, *KRAS*, and other rarer genes. 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 warrants further study.

Mechanism of disease causation. The vast majority of pathogenic variants are missense or small in-frame deletions that cause a gain-of-function activation of the protein product BRAF, MEK1, MEK2, or KRAS that leads to activation of the Ras/MAPK pathway. This results in increased phosphorylation and, thus, activation of ERK1 and/or ERK2.

Table 8. Cardiofaciocutaneous (CFC) Syndrome: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
BRAF	NM_004333.6 NP_004324.2	c.770A>G	p.Gln257Arg	Most common pathogenic variant in persons w/CFC syndrome [Niihori et al 2006, Rodriguez-Viciana et al 2006]
MAP2K1	NM_002755.4 NP_002746.1	c.389A>G	p.Tyr130Cys	Most common pathogenic variant [Rodriguez-Viciana & Rauen 2008]
MAP2K2	NM_030662.4 NP_109587.1	401A>G	p.Tyr134Cys	Most common pathogenic variant [Rodriguez-Viciana & Rauen 2008]

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. Genes from Table 1 are in alphabetic order.

Cancer and Benign Tumors

BRAF. Somatic pathogenic variants in *BRAF* have been reported in approximately 8% of tumors, most frequently in melanoma, thyroid, colorectal, and ovarian cancers, and have also been found in benign nevi and premalignant colon polyps. *BRAF* pathogenic variants have also been seen in Langerhans cell histiocytosis and non-Langerhans cell histiocytoses [Badalian-Very et al 2010, Diamond et al 2016, Durham et al 2019].

KRAS. Single-nucleotide variants in *KRAS* account for approximately 85% of pathogenic variants in the Ras gene family. *KRAS* oncogenic variants are common in pancreatic cancer, colon cancer, small intestinal cancer, biliary cancer, and lung cancer. The vast majority of oncogenic pathogenic variants occur in hot spots in codons 12, 13, or 61. These are not the same pathogenic variants that are found in CFC syndrome [Schubbert et al 2006]. Somatic activating *KRAS* variants have been identified in arteriovenous malformations of the brain [Nikolaev et al 2018].

MAP2K1/MAP2K2. Somatic pathogenic variants in *MAP2K1* and *MAP2K2* have been reported in various tumors, including ovarian cancer and non-small cell lung carcinoma [Estep et al 2007, Marks et al 2008]. *MAP2K1* and *MAP2K2* pathogenic variants also occur in Langerhans cell histiocytosis and non-Langerhans cell histiocytoses [Diamond et al 2016, Durham et al 2019]. Somatic *MAP2K1* pathogenic variants are associated with extracranial arteriovenous malformation [Couto et al 2017].

Chapter Notes

Author Notes

Dr Rauen serves on the Medical Advisory Board for CFC International, Inc, and is codirector and member of the Professional Advisory Board for the Costello Syndrome Family Network. She also is a member of the RASopathies Network Scientific Advisory Board and the Global Genes Advisory Board.

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- 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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