GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Cardiofaciocutaneous Syndrome

[*CFC Syndrome. Includes: BRAF-Related Cardiofaciocutaneous Syndrome; KRAS-Related Cardiofaciocutaneous Syndrome; MAP2K1-Related Cardiofaciocutaneous Syndrome: MAP2K2-Related Cardiofaciocutaneous Syndrome*]

Katherine A Rauen, MD, PhD
Assistant Adjunct Professor
Division of Medical Genetics
Department of Pediatrics
University of California San Francisco Comprehensive Cancer Center
rauen@cc.ucsf.edu

Initial Posting: January 18, 2007.

Summary

Disease 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 oophorogenes, eczema, pigmented moles, palmoplantar hyperkeratosis). The hair is typically sparse, curly, fine or thick, woolly or brittle; eyelashes and eyebrows may be absent. Nails may be dystrophic or fast growing. Cognitive delay (ranging from mild to severe) is seen in all affected individuals. Neoplasias have not been reported.

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%-80%), *MAP2K1* and *MAP2K2* (~10%-15%), and *KRAS* (<5%). Molecular genetic testing is clinically available for all known genes.

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 pruritis; increased caloric intake and a nasogastric tube or gastrostomy for severe feeding problems; surgical intervention for severe gastroesophageal reflux; routine management of seizures, growth hormone deficiency, ocular abnormalities; occupational therapy, physical therapy, and speech therapy as needed. *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. *Surveillance:* periodic echocardiogram (hypertrophic cardiomyopathy), electrocardiogram (rhythm disturbances), neurologic and eye examination, scoliosis check, and assessment of growth.

Genetic counseling. Cardiofaciocutaneous (CFC) syndrome is the result of a *de novo* dominant mutation. The risk to the sibs of a proband is small. To date, no individuals with CFC syndrome have been known to reproduce. Prenatal diagnosis for pregnancies at increased risk because of the possibility of germline mosaicism or for couples needing reassurance is possible if the disease-causing allele of the affected family member has been identified.

Diagnosis

Clinical Diagnosis

The diagnosis of cardiofaciocutaneous (CFC) syndrome is made by clinical findings. Currently, no diagnostic criteria have been established.

Individuals with CFC syndrome display phenotypic variability and therefore not all have every finding. Phenotypic features **may** include the following:

Cardiac. Pulmonic stenosis, atrial septal defects, ventricular septal defects, hypertrophic cardiomyopathy, heart valve anomalies (mitral valve dysplasia, tricuspid valve dysplasia, bicuspid aortic valve), and rhythm disturbances. These defects may be identified at birth or diagnosed later. The hypertrophic cardiomyopathy may be progressive.

Craniofacial. High forehead, relative macrocephaly, bitemporal narrowing, hypoplasia of the supraorbital ridges, hypertelorism, telecanthus, down-slanting 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 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 oophorogenes; eczema; hemangiomas; café-au-lait macules; erythema; pigmented moles; palmoplantar hyperkeratosis over pressure zones
- **Hair.** Sparse, curly, fine or thick, woolly or brittle; absent or normal eyelashes and eyebrows
- **Nails.** Dystrophic with flat broad nails; nails may be fast growing.

Musculoskeletal. Short neck, pterygium colli, pectus deformity, kyphosis, and/or scoliosis

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). Some individuals have growth hormone deficiency.

Neurologic. Neurologic findings are present in nearly all individuals and include hypotonia and developmental delay. Other findings can include cognitive delay (ranging from mild to

severe), seizure disorders, abnormal EEG, hydrocephalus, cortical atrophy, ventriculomegaly, frontal lobe hypoplasia, agenesis of the corpus callosum, Chiari malformation, and pachygyria.

Other. Some affected individuals may have renal anomalies.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. The four genes currently known to be associated with CFC syndrome are in the Ras/mitogen-activated protein kinase (MAPK) signaling cascade (Figure 2):

- ***BRAF***[Niihori et al 2006, Rodriguez-Viciana et al 2006]
- ***MAP2K1***[Rodriguez-Viciana et al 2006]
- ***MAP2K2***[Rodriguez-Viciana et al 2006]
- ***KRAS.*** Because *KRAS* mutations 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 (K-Ras) in CFC syndrome has yet to be clarified.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis**

  BRAF. *BRAF* mutations are the most common in CFC syndrome. Utilizing strict diagnostic criteria for the classic CFC syndrome phenotype, Rodriguez-Viciana et al (2006) identified *BRAF* mutations in 18 of 23 (78%) affected individuals. In a separate cohort of 43 individuals, Niihori et al (2006) identified *BRAF* mutations in 16 of 43 (37%).

  The exon 6 mutation p.Q257R is the most common. Other exons in which mutations have been reported include exons 11, 12, 14, and 15. Of note, reevaluation of individuals with the clinical diagnosis of Costello syndrome but without *HRAS* mutations revealed *BRAF* missense mutations in exons 13 and 16 and a phenotype consistent with CFC syndrome [Rauen 2006]. No mosaicism has been reported to date.

  MAP2K1(MEK1), MAP2K2(MEK2). MEK mutations (including *MAP2K1* and *MAP2K2* collectively) have been reported in approximately 10%-15% of individuals with the clinical diagnosis of CFC syndrome [Rodriguez-Viciana et al 2006; Rauen, unpublished data]. To date, all published *MAP2K1* mutations have occurred in exon 2 and exon 3. Mutations within these exons functionally correspond with missense alterations that have been identified in exons 2 and 3 of *MAP2K2* [Rauen, unpublished data]. All identified mutations have been *de novo* missense mutations. No mosaicism has been reported to date.

KRAS. *KRAS* mutations have been identified in a small percentage of individuals with Noonan syndrome and fewer than 5% of individuals with CFC syndrome [Carta et al 2006; Niihori et al 2006; Schubbert et al 2006; Zenker et al, in press]. Mutations reported in coding exons 1, 2, and 4b have been *de novo* missense substitutions, possibly implying that classic CFC syndrome is not caused by *KRAS* mutations. No mosaicism has been reported to date.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Cardiofaciocutaneous Syndrome

Test Method	Mutations Detected	Proportion of CFC Syndrome Caused by Mutations in This Gene [1]	Mutation Detection Rate	Test Availability
Sequence analysis	*BRAF* sequence variants	~75%-80%	98%	Clinical Testing
	MAP2K1 sequence variants	~10%-15%	98%	Clinical Testing
	MAP2K2 sequence variants		98%	Clinical Testing
	KRAS sequence variants	<5%	98%	Clinical Testing

1. It is unclear at this time if all the genes associated with CFC syndrome have been identified.

Interpretation of test results. If a mutation in *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* is not identified in an individual who has phenotypic features consistent with the clinical diagnosis of CFC syndrome, reasons may include the following:

- Presence of a mutation in another gene associated with a similar but different phenotype, such as *HRAS* (Costello syndrome), *PTPN11* (Noonan syndrome), or *SOS1* (Noonan syndrome)
- Presence of a mutation in gene affecting the Ras/MAPK pathway that has yet to be identified
- Presence of low-level tissue mosaicism, which to date has not been reported for CFC syndrome
- Testing-related issues

For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

- Clinical evaluation should include detailed family history and prenatal history.
- Identification of mutations in *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* by direct gene sequencing establishes the diagnosis.
- Based on current published information, sequencing can be approached stepwise:
  1. Direct sequencing of the seven *BRAF* exons in which causative mutations have been identified (exons 6, 11-16). If no causal mutation is identified:
  2. Direct sequencing of *MAP2K1* (exons 2 and 3) and *MAP2K2* (exons 2 and 3). If no causal mutation is identified:

3 Consider sequencing the remaining *BRAF* exons and remaining *MAP2K1* and *MAP2K2* exons in which causal mutations have not yet been reported. If no causal mutation is identified in *BRAF*, *MAP2K1*, and *MAP2K2*:

4 Direct sequencing of *KRAS* (exons 1, 2, 3, and 4b) where additional causal mutations have been demonstrated in individuals with a phenotype that overlaps CFC syndrome. If no causal mutation is identified:

5 Direct sequencing of *HRAS* (all exons). Individuals who have an *HRAS* mutation by definition have Costello syndrome.

Genetically Related (Allelic) Disorders

***BRAF*—Solid tumors.** Somatic mutations in *BRAF* have been reported at a high frequency in numerous cancers including melanoma, thyroid, colorectal, and ovarian. The vast majority of *BRAF* mutations are missense substitutions found in, but not limited to, exon 11 (the glycine-rich loop) and exon 15 (the activation segment) in the B-Raf kinase domain [Wellbrock et al 2004]. One mutation, p.V600E, which results in increased kinase activity, accounts for more than 90% of *BRAF* mutations identified in human cancer. Somatic B-Raf p.V600E mutants are also found in benign nevi and premalignant colon polyps.

***KRAS*—Cancer.** Aberrant activation of Ras is frequently found in cancer, occurring in approximately 20% of all tumors. The vast majority of oncogenic mutations occur in mutation hotspots in codons 12, 13, or 61. Point mutations in *KRAS* account for approximately 85% of Ras mutations. *NRAS* (~15% of total) and *HRAS* (~1% of total) mutations are found less frequently. Amino acid substitutions caused by missense mutations in *KRAS* affect guanine nucleotide binding and cause a reduction of GTP hydrolysis, resulting in a gain of function of the protein.

Noonan syndrome. *KRAS* mutations 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, in press].

Clinical Description

Natural History

Cardiofaciocutaneous (CFC) syndrome affects males and females equally.

Prenatally, polyhydramnios is present in the vast majority of cases. Although newborns may be premature and large for gestational age, most 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.

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 developmental delay, typically ranging from moderate to profoundly severe. Rarely, developmental delays are mild. Children have speech delays and the vast majority have hypotonia, causing motor delays.

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

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 are not tested, some have growth hormone deficiency.

Many children have recurrent otitis media.

Ocular abnormalities including strabismus, nystagmus, optic nerve hypoplasia, astigmatism, myopia and/or hyperopia may result in decreased vision and acuity.

Nearly 50% of individuals with CFC and a mutation in one of its associated genes have a seizure disorder. Most seizures begin in infancy or early childhood [Yoon et al, manuscript in preparation]. However, a seizure disorder may develop later in childhood as well.

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 [Rauen, unpublished observation]. Individuals with CFC syndrome have been known to develop severe skin infections.

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.

The craniofacial appearance becomes less like that seen in Noonan syndrome.

Some young adults participate in assisted living programs.

Neoplasias, such as benign papillomas or malignancies observed in Costello syndrome, Noonan syndrome, or neurofibromatosis type 1, have not been reported in CFC syndrome. To date, only one individual with CFC syndrome and acute lymphoblastic leukemia has been reported. Whether the association is coincidental or causal is unknown [Van Den Berg & Hennekam 1999, Niihori et al 2006].

Genotype-Phenotype Correlations

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

Preliminary correlations include the following:

- Individuals with the B-Raf p.Q257R mutation 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].
- The two individuals reported with the kinase-impaired B-Raf p.G596V mutation have a milder phenotype as indicated by normal growth and development, and no cardiac, GI, or brain abnormalities [Rodriguez-Viciana et al 2006].
- Two individuals with the B-Raf missense amino acid substitutions reported to be altered in cancer had severe phenotypes [Rodriguez-Viciana et al 2006].

- Three persons reported with *MAP2K1* or *MAP2K2* mutations had typical craniofacial features of CFC syndrome except one child (with *MAP2K1* p.Y130C), whose features were very mild [Rodriguez-Viciana et al 2006]. All had cardiac defects, ectodermal anomalies (curly hair, hyperkeratosis, keratosis pilaris, and progressive nevi formation with age), gastrointestinal dysfunction, short stature, and abnormal brain imaging with developmental delay. In addition, all had hypotonia, heat intolerance, and excessive sweating.
- Common phenotypic findings in individuals reported with *KRAS* mutations include CFC syndrome/Noonan syndrome-like craniofacial features, cardiomyopathy, curly hair, and no skin findings [Niihori et al 2006; Schubbert et al 2006; Zenker et al, in press].

Penetrance

Penetrance is complete in CFC syndrome.

Nomenclature

A mental retardation syndrome having characteristic craniofacial dysmorphology, ectodermal anomalies, and cardiac defects in three individuals was reported by Blumberg et al (1979) at the March of Dimes Birth Defects Conference. All three had characteristic facial features, ichthyosis with abnormal hair, ocular and cardiac abnormalities, postnatal growth failure, and mental retardation. These three persons, along with five others, were subsequently reported by Reynolds et al (1986), who designated this new disorder CFC syndrome.

Also in 1986,Baraitser and Patton reported on a Noonan syndrome-like short stature syndrome with ectodermal anomalies that was presumed to be the same entity.

Prevalence

CFC syndrome is rare, with over 100 individuals reported in the literature. The total number of individuals worldwide with CFC syndrome is estimated to be 200-300, yet this may be an underestimation because of under-diagnosis of mildly affected individuals.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Costello syndrome is characterized by distinctive craniofacial features, cardiac defects, ectodermal and musculoskeletal anomalies, short stature, developmental delay, and a predisposition to neoplasia, both benign and malignant. Facial features are coarse and typically include macrocephaly with a prominent forehead, epicanthal folds, down-slanting palpebral fissures, short nose with a depressed nasal bridge and a broad base, and low-set, posteriorly rotated ears with thickened helices and lobes. The cheeks may be full and the mouth large with full lips. The skin is soft with excessive wrinkling and redundancy over the dorsum of the hands and the feet; plantar and palmar creases are deep. Other ectodermal features may include hyperpigmentation, papillomas, and curly hair. Musculoskeletal abnormalities include limited range of motion at the elbows, tight calcaneal tendons, ulnar deviation of the hands, laxity of the small joints, and broad distal phalanges. Cardiac anomalies (structural defects, hypertrophic cardiomyopathy, and rhythm disturbances) are present in the majority. Neurodevelopmental delays range from moderate to severe. Structural brain anomalies include enlarged ventricles, frontal atrophy, Chiari malformation, and dysmyelinization of the basal ganglia and white matter. Endocrine and ophthalmologic abnormalities as well as unique behavioral characteristics may be observed.

Germline mutations in *HRAS* are causative [Aoki et al 2005]. Inheritance is presumably autosomal dominant. Individuals reported to date have *de novo* mutations.

Individuals identified with *HRAS* mutations by definition have the diagnosis of Costello syndrome. *BRAF* mutations have been identified in individuals with a Costello syndrome-like phenotype who were *HRAS*-mutation negative [Rauen 2006]. 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* mutations have the diagnosis of CFC syndrome.

Noonan syndrome is characterized by distinctive craniofacial features (although many features overlap with CFC syndrome); cardiac defects; short stature; musculoskeletal, ophthalmologic, and renal anomalies; lymphatic dysplasia; bleeding diathesis; cryptorchidism in males; and a predisposition to leukemia. Developmental delay of variable degree is present in 25%-30%. Congenital heart defects occur in the majority, with pulmonary valve stenosis being the most common, followed by hypertrophic cardiomyopathy. Other frequent structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, tetralogy of Fallot, and coarctation of the aorta. Neurologic findings are not as common in Noonan syndrome as in CFC syndrome; however, Chiari malformation has been reported in Noonan syndrome.

Mutations in *PTPN11* have been identified in approximately 50% of individuals with clinically diagnosed Noonan syndrome [Tartaglia et al 2001]. *SOS1* mutations have been identified in approximately 20% of individuals with Noonan syndrome [Roberts et al 2006, Tartaglia et al 2007]. *KRAS* mutations have been reported in fewer than 5% [Schubbert et al 2006]. Inheritance is autosomal dominant; however, many affected individuals have *de novo* mutations.

Craniofaciafl findings in CFC syndrome are reminiscent of those described in Noonan syndrome including macrocephaly, broad forehead, bitemporal narrowing, hypoplasia of the supraorbital ridges, down-slanting 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 a high-arched palate.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

The following evaluations are recommended in an individual known to have cardiofaciocutaneous (CFC) syndrome:

- Genetics consultation
- Complete physical examination including measurement growth parameters
- Cardiac evaluation including echocardiogram and electrocardiogram
- Neurologic evaluation
- MRI of the brain to detect any structural changes
- Electroencephalogram if seizures are suspected
- Abdominal ultrasound examination to evaluate for renal anomalies
- Psychomotor developmental evaluation
- Endocrine evaluation if growth delay is suspected
- Ophthalmologic examination

- Audiologic examination
- Nutrition and feeding evaluation
- Dermatologic evaluation

Treatment of Manifestations

CFC syndrome affects many organ systems and, therefore, the vast majority of individuals require a multidisciplinary team of healthcare providers.

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.

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.

Seizures are treated as in the general population.

Some individuals are growth hormone deficient and may benefit from management by an endocrinologist. Hypertrophic cardiomyopathy is considered by some to be a contraindication to growth hormone therapy.

Ocular abnormalities such as myopia or hyperopia are corrected with lenses as in the general population.

Musculoskeletal abnormalities, such as scoliosis or pectus deformity, are managed as in the general population.

Xerosis and pruritis may be relieved by increasing the ambient humidity or using hydrating lotions.

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.

Recurrent otitis media may require placement of PE tubes.

Enrollment in early-intervention therapies to promote motor and intellectual development (e.g., occupational therapy, physical therapy, or speech therapy) is recommended.

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 or a predisposition to cardiac rhythm disturbances.

Surveillance

If anomalies are identified in any organ system, lifelong periodic follow-up is warranted. At present, no guidelines have been established for surveillance in CFC syndrome. However, based on phenotypic findings and anecdotal observations, the following may apply:

- **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.
- **Neurologic.** Monitor neurologic signs and symptoms with period neurologic evaluations and MRI if indicated. Chiari malformation and later onset of seizures have been observed [Rauen, unpublished observation].
- **Gastrointestinal.** Monitor for signs and symptoms of gastrointestinal refux.
- **Ophthalmologic.** Periodic evaluation by an ophthalmologist to monitor for ocular issues (such as myopia, hyperopia, cataracts) is recommended.
- **Musculoskeletal.** Periodic evaluation for scoliosis during young childhood is recommended.
- **Endocrine.** Monitor growth parameters to identify evidence of growth failure that may be associated with growth hormone deficiency.
- **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.

Therapies Under Investigation

At present there are no therapies for CFC syndrome under investigation. However, because the Ras/MAPK pathway has been studied intensively in the context of cancer, numerous therapeutics that specifically target this pathway are in development. Systemic therapies that reduce MAPK activity may merit investigation.

Search ClinicalTrials.gov 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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Cardiofaciocutaneous (CFC) syndrome is the result of a *de novo* dominant mutation.

Risk to Family Members

Parents of a proband

- To date, all individuals with CFC syndrome have the disorder as the result of a *de novo* mutation.

- The parents of a proband are not affected.

Sibs of a proband

- The risk to the sibs of a proband depends upon the genetic status of the proband's parents.
- Because CFC syndrome occurs as a *de novo* mutation, the risk to the sibs of a proband is small.
- Currently, no instance of germline mosaicism has been reported, although it remains a possibility. Thus, the risk to sibs of a proband may be on the order of one in 500, as in other disorders cause by *de novo* dominant mutations.

Offspring of a proband. Little is known about the fertility of individuals with CFC syndrome. To date, no individuals with CFC syndrome have been known to reproduce.

Other family members of a proband. Because CFC syndrome occurs as a *de novo* mutation, other family members of a proband are not at increased risk.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

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 as Noonan syndrome may be familial and thus inherited in an autosomal dominant manner.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk because of the possibility of germline mosaicism or for couples needing reassurance is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of the affected family member should be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Cardiofaciocutaneous Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
BRAF	7q34	B-Raf proto-oncogene serine/threonine-protein kinase
KRAS	12p12.1	GTPase KRas
MAP2K1	15q21	Dual specificity mitogen-activated protein kinase kinase 1
MAP2K2	7q32	Dual specificity mitogen-activated protein kinase kinase 2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Cardiofaciocutaneous Syndrome

115150	CARDIOFACIOCUTANEOUS SYNDROME
164757	V-RAF MURINE SARCOMA VIRAL ONCOGENE HOMOLOG B1; BRAF
176872	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 1; MAP2K1
190070	V-KI-RAS2 KIRSTEN RAT SARCOMA 2 VIRAL ONCOGENE HOMOLOG; KRAS2
601263	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 2; MAP2K2

Table C. Genomic Databases for Cardiofaciocutaneous Syndrome

Gene Symbol	Entrez Gene
BRAF	673 (MIM No. 164757)
KRAS	3845 (MIM No. 190070)
MAP2K1	5604 (MIM No. 176872)
MAP2K2	5605 (MIM No. 601263)

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

The MAPK signaling cascade of dual specificity kinases (Figure 2) 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 mutations in *PTPN11* (protein product Shp2), *SOS1*, and *KRAS*. The causal gene for Costello syndrome is *HRAS*. Cardiofaciocutaneous (CFC) syndrome is associated with mutations in *BRAF*, *MAP2K1*, and *MAP2K2*. The role of *KRAS* in Noonan syndrome and CFC syndrome has yet to be defined and may represent a new syndrome.

BRAF

Normal allelic variants: The *BRAF* gene encodes B-Raf, a member of the Raf family, which also includes C-Raf-1 and the X-linked A-Raf. *BRAF* spans approximately 190 kb, and contains 18 exons with intervening sequences. There are three conserved regions in B-Raf. Conserved region 1 (CR1) contains the Ras binding domain and the cysteine-rich domain, both of which are required for recruitment of B-Raf 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.

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

Normal gene product: The protein product of *BRAF*, a serine/threonine protein kinase, 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. B-Raf has only two known downstream effectors, MEK1 and MEK2.

Abnormal gene product: The type of *BRAF* mutations found in CFC syndrome are similar to the different types of somatic mutations found in cancers with high kinase and kinase-impaired activities [Niihori et al 2006, Rodriguez-Viciana et al 2006]. In addition, CFC syndrome B-Raf mutant proteins activate downstream effectors in vitro, as determined by measuring phosphorylated species of MEK and ERK. Both cancer and CFC syndrome-associated B-Raf mutant proteins with elevated kinase activity induce higher levels of MEK and ERK phosphorylation compared with wild-type B-Raf, whereas kinase-impaired B-Raf mutant proteins are impaired in their ability to induce phosphorylation of MEK and ERK [Rodriguez-Viciana et al 2006]. The most common B-Raf mutant identified in cancer, p.V600E, has not been identified in CFC syndrome. Presumably, such a gain-of-function mutation would be incompatible with life.

MAP2K1, *MAP2K2*

Normal allelic variants: MEK, like Raf, exists as a multigene family. The *MAP2K1* gene spans approximately 104 kb. *MAP2K2* spans approximately 34 kb. Each gene contains 11 exons with intervening sequences.

Pathologic allelic variants: Missense mutations in the *MAP2K1* and *MAP2K2* genes cause CFC syndrome in approximately 10%-15% of clinically diagnosed individuals [Rodriguez-Viciana et al 2006; Rauen, unpublished observation]. Mutations are heterogeneous with missense substitutions 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. No somatic or constitutional mutations have been previously described in *MAP2K1* or *MAP2K2*.

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

Abnormal gene product: Functional studies of these novel *MAP2K1* and *MAP2K2* mutations have determined that all CFC syndrome-associated mutations are more active than wild-type MEK in stimulating in vitro ERK phosphorylation, but that the CFC syndrome-associated mutations are not as active as artificially generated constitutively active MEK mutations [Rodriguez-Viciana et al 2006].

KRAS

Normal allelic variants: The *KRAS* gene has four coding exons with intervening sequences and spans approximately 45 kb. Two alternative splice variants exist, with K-Ras4b being ubiquitously expressed.

Pathologic allelic variants: Unlike somatic mutations identified in cancer, novel germline missense *KRAS* mutations in coding exon 1, 2, and 4b have been identified [Carta et al 2006; Niihori et al 2006; Schubbert et al 2006; Zenker et al, in press].

Normal gene product: GTPase KRas (K-Ras) 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* mutations revealed reduced intrinsic GTPase activity compared to the wild-type protein; however, not to the level of mutant K-Ras protein typically found in cancer [Schubbert et al 2006]. Such a gain-of-function mutation would presumably be incompatible with life.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

CFC International
183 Brown Rd.
Vestal NY 13850
Phone: 607-772-9666
Fax: 607-748-0409
Email: bconger@cfcsyndrome.org
www.cfcsyndrome.org

CFC International Registry
183 Brown Rd.
Vestal NY 13850
Phone: 607-772-9666
Fax: 607-748-0409
Email: bconger@cfcsyndrome.org
CFC Registry

Genetic Alliance BioBank
A centralized biological and data [consent/clinical/environmental] repository to enable translational genomic research on rare genetic diseases.
Phone: 202-966-5557
Email: sterry@geneticalliance.org
www.biobank.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, Tanaka Y, Filocamo M, Kato K, Suzuki Y, Kure S, Matsubara Y. Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nat Genet. 2005;37:1038–40. [PubMed: 16170316]

Baraitser M, Patton MA. A Noonan-like short stature syndrome with sparse hair. J Med Genet. 1986;23:161–4. [PubMed: 3712393]

Blumberg B, Shapiro L, Punnett HH, Rimoin D, Kirtenmacher M. A new mental retardation syndrome with characterisitc facies, ichthyosis and abnormal hair. Paper presented at March of Dimes Birth Defects Conference. Chicago, Il. 1979

Carta C, Pantaleoni F, Bocchinfuso G, Stella L, Vasta I, Sarkozy A, Digilio C, Palleschi A, Pizzuti A, Grammatico P, Zampino G, Dallapiccola B, Gelb BD, Tartaglia M. Germline missense mutations affecting KRAS Isoform B are associated with a severe Noonan syndrome phenotype. Am J Hum Genet. 2006;79:129–35. [PubMed: 16773572]

Niihori T, Aoki Y, Narumi Y, Neri G, Cave H, Verloes A, Okamoto N, Hennekam RC, Gillessen-Kaesbach G, Wieczorek D, Kavamura MI, Kurosawa K, Ohashi H, Wilson L, Heron D, Bonneau D, Corona G, Kaname T, Naritomi K, Baumann C, Matsumoto N, Kato K, Kure S, Matsubara Y. Germline KRAS and BRAF mutations in cardio-facio-cutaneous syndrome. Nat Genet. 2006;38:294–6. [PubMed: 16474404]

Rauen KA. Distinguishing Costello versus cardio-facio-cutaneous syndrome: BRAF mutations in patients with a Costello phenotype. Am J Med Genet A. 2006;140:1681–3. [PubMed: 16804887]

Reynolds JF, Neri G, Herrmann JP, Blumberg B, Coldwell JG, Miles PV, Opitz JM. New multiple congenital anomalies/mental retardation syndrome with cardio-facio-cutaneous involvement--the CFC syndrome. Am J Med Genet. 1986;25:413–27. [PubMed: 3789005]

Roberts A, Allanson J, Jadico SK, Kavamura MI, Noonan J, Opitz JM, Young T, Neri G. The cardiofaciocutaneous syndrome. J Med Genet. 2006;43:833–42. [PubMed: 16825433]

Rodriguez-Viciana P, Estep AL, Tidyman WE, Rauen KA. MAPK pathway mutations in CFC syndrome: delineation of molecular heterogeneity and genotype-phenotype correlation. in preparation

Rodriguez-Viciana P, Tetsu O, Tidyman WE, Estep AL, Conger BA, Cruz MS, McCormick F, Rauen KA. Germline mutations in genes within the MAPK pathway cause cardio-facio-cutaneous syndrome. Science. 2006;311:1287–90. [PubMed: 16439621]

Schubbert S, Zenker M, Rowe SL, Boll S, Klein C, Bollag G, van der Burgt I, Musante L, Kalscheuer V, Wehner LE, Nguyen H, West B, Zhang KY, Sistermans E, Rauch A, Niemeyer CM, Shannon K, Kratz CP. Germline KRAS mutations cause Noonan syndrome. Nat Genet. 2006;38:331–6. [PubMed: 16474405]

Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, van der Burgt I, Crosby AH, Ion A, Jeffery S, Kalidas K, Patton MA, Kucherlapati RS, Gelb BD. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet. 2001;29:465–8. [PubMed: 11704759]

Tartaglia M, Pennacchio LA, Zhao C, Yadav KK, Fodale V, Sarkozy A, Pandit B, Oishi K, Martinelli S, Schackwitz W, Ustaszewska A, Martin J, Bristow J, Carta C, Lepri F, Neri C, Vasta I, Gibson K, Curry CJ, Siguero JP, Digilio MC, Zampino G, Dallapiccola B, Bar-Sagi D, Gelb BD. Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. Nat Genet. 2007;39:75–9. [PubMed: 17143282]

van Den Berg H, Hennekam RC. Acute lymphoblastic leukaemia in a patient with cardiofaciocutaneous syndrome. J Med Genet. 1999;36:799–800. [PubMed: 10528867]

Wellbrock C, Karasarides M, Marais R. The RAF proteins take centre stage. Nat Rev Mol Cell Biol. 2004;5:875–85. [PubMed: 15520807]

Zenker M, Lehmann K, Schulz AL, Barth H, Hansmann D, Koenig R, Korinthenberg R, Kreiss-Nachtsheim M, Meinecke P, Morlot S, Mundlos S, Quante AS, Raskin S, Schnabel D, Wehner LE, Kratz CP, Horn D, Kutsche K. Expansion of the genotypic and phenotypic spectrum in patients with KRAS germline mutations. J Med Genet . in press

Suggested Readings

Hancock JF. Ras proteins: different signals from different locations. Nat Rev Mol Cell Biol. 2003;4:373–84. [PubMed: 12728271]

Roberts A, Allanson J, Jadico SK, Kavamura MI, Noonan J, Opitz JM, Young T, Neri G. The cardiofaciocutaneous syndrome. J Med Genet. 2006;43:833–42. [PubMed: 16825433]

Chapter Notes

Author Notes

Dr. Rauen serves on the Medical Advisory Board for CFC International and is co-director and member of the Professional Advisory Board for The Costello Syndrome Family Network.

Acknowledgments

Special thanks to Brenda Conger, President, and Molly Santa Cruz, Vice President, of CFC International and all the families of CFC International and the Costello syndrome Family Network for their ongoing support of research in genetic medicine. This work was supported in part by NIH grant HD048502.

Revision History

- 18 January 2007 (me) Review posted to live Web site
- 14 September 2006 (kar) Original submission

Figure 1. Clinical images of individuals with CFC syndrome who have known *BRAF* or *MAP2K1* or *MAP2K2* mutations (courtesy of CFC International)
Top panel. Three young children with *BRAF* mutations: p.T470del, in exon 11 (left); p.S467A, in exon 11 (middle); and p.Q257R, in exon 6 (right). Ages are 2.5, 2, and 2 years, respectively.
Lower left. Two boys, age 12 and eight years, with *MAP2K2* missense mutations: p.F57C, in exon 2 (left) and p.Y134C, in exon 3 (right)
Lower right. Two boys age six years, previously diagnosed clinically with Costello syndrome, at the 2005 Costello Syndrome Family Conference. Both have *BRAF* mutations: p.G534R, a missense substitution in exon 13 (left) and p.L485F, a missense substitution in exon 12 (right).

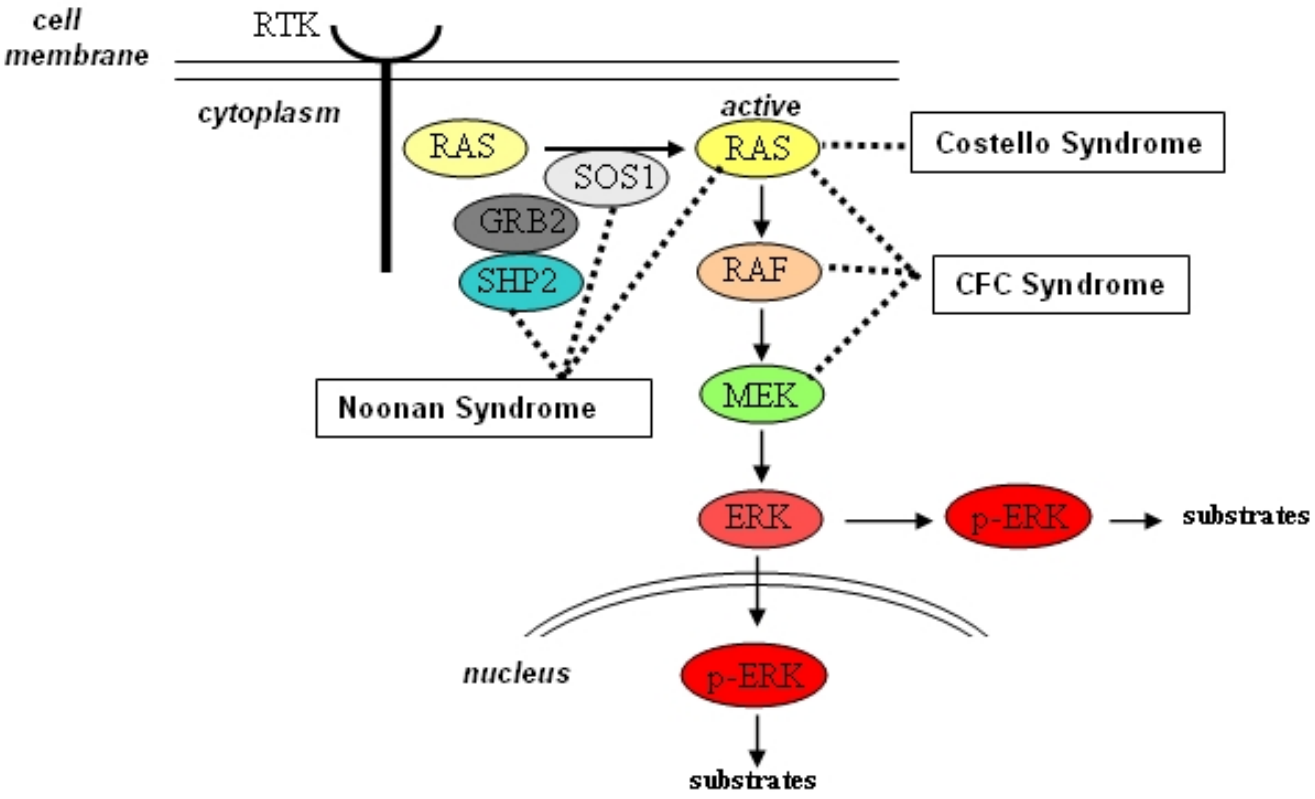

Figure 2. The mitogen-activated protein kinase (MAPK) signaling cascade, also known as the Raf/MEK/ERK (extracellular signal-related kinase)