Cardiofaciocutaneous Syndrome

Synonym: CFC Syndrome

Katherine A Rauen, MD, PhD
Professor, Department of Pediatrics
Chief, Division of Genomic Medicine
Albert Holmes Rowe Endowed Chair in Human Genetics II
Director, NF/Ras Pathway Clinic
University of California Davis MIND Institute
Sacramento, California
rauen@ucdavis.edu

Initial Posting: January 18, 2007; Last Revision: September 6, 2012.

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 ophryogenes, eczema, pigmented moles, hemangiomas, and palmoplantar hyperkeratosis). The hair is typically sparse, curly, fine or thick, woolly or brittle; eyelashes and eyebrows may be absent or sparse. Nails may be dystrophic or fast growing. Some form of neurologic and/or cognitive delay (ranging from mild to severe) is seen in all affected individuals. Neoplasia, mostly acute lymphoblastic leukemia (ALL), has been reported in some individuals.

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

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

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 usually the result of a de novo dominant mutation. The risk to the sibs of a proband is small. To date, one family with transmission of an autosomal dominant germline mutation (MAP2K2) through multiple generations has been reported. Prenatal diagnosis for pregnancies at increased risk because of the theoretic possibility of germline mosaicism or for couples needing reassurance is possible if the disease-causing allele in the affected family member is known.

Diagnosis

Clinical Diagnosis

Cardiofaciocutaneous (CFC) syndrome is one of the RASopathies: a group of syndromes having overlapping clinical features resulting from a common pathogenetic mechanism [Tidyman & Rauen 2009a].

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, and bicuspid aortic valve); and rhythm disturbances. These defects may be identified at birth or diagnosed later. Hypertrophic cardiomyopathy may be progressive.

Craniofacial. High forehead, relative macrocephaly, bitemporal narrowing, hypoplasia of the supraorbital ridges, ocular hypertelorism, telecanthus, downslanting palpebral fissures, epicanthal folds, ptosis, short nose with depressed bridge and anteverted nares, ear lobe creases, low-set ears that may be posteriorly rotated, deep philtrum, cupid's bow lip, high-arched palate, relative micrognathia (Figure 1). The face is broader and longer, overall more coarse, than in Noonan syndrome (a clinically similar disorder often confused with CFC syndrome), but usually not as coarse as typically seen in Costello syndrome.

Ectodermal

- Skin. Xerosis; hyperkeratosis of arms, legs, and face; ichthyosis; keratosis pilaris; ulerythema ophryogenes; eczema; hemangiomas; café-au-lait macules; erythema; pigmented moles; palmoplantar hyperkeratosis over
pressure zones

- **Hair.** Sparse, curly, fine or thick, woolly or brittle; sparse to absent, or normal eyelashes and eyebrows

- **Nails.** Dystrophic with flat broad nails; nails may be fast growing.

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

**Lymphatic.** Lymphedema, chylothorax.

**Ocular.** Ocular hypertelorism, strabismus, nystagmus, astigmatism, myopia and/or hyperopia. Optic nerve hypoplasia, cortical blindness, and cataracts have been described. Although most individuals with CFC syndrome have ocular manifestations, some have a normal ophthalmologic examination.

**Feeding/gastrointestinal.** Severe feeding problems manifest as gastroesophageal reflux (GER), aspiration, vomiting, and oral aversion. Other GI problems include dysmotility, intestinal malrotation, hernia, and/or constipation. Some individuals have splenomegaly or hepatomegaly. Most children have failure to thrive. Fatty liver and anal stenosis have also been reported.

**Growth delays.** Feeding issues contribute to growth delay. Growth may be normal with appropriate birth weight and length; however, weight and length may drop to below the fifth centile during early infancy while head circumference remains within the normal range (resulting in relative macrocephaly).

**Endocrine abnormalities.** Some individuals have growth hormone deficiency. Some may have precocious puberty.

**Neurologic.** Some aspect of neurologic or neurocognitive findings are present in nearly all individuals. Cognitive delay typically ranges from mild to severe, although a few individuals with CFC syndrome have IQs in the normal range. The most common neurologic findings include hypotonia and developmental delay. Other abnormalities can include seizure disorders, abnormal EEG, corticospinal tract findings, hydrocephalus, cortical atrophy versus dilated perivascular spaces, ventriculomegaly, frontal lobe hypoplasia, agenesis of the corpus callosum, abnormal myelination, Chiari malformation, and pachygyria.

**Malignancy.** The risk for malignancies may be increased, although at the present time this is still unclear. Individuals with a mutation in one of the four genes associated with CFC syndrome have been reported with acute lymphoblastic leukemia (ALL); immunosuppression and hepatoblastoma; non-Hodgkin lymphoma; and large B-cell lymphoma.

**Urogenital.** Some affected individuals may have renal, uterine, and/or cervical anomalies.

**Molecular Genetic Testing**

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

- **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 (KRAS) in CFC syndrome has yet to be clarified.

**Clinical testing**

- **Sequence analysis**
  - **BRAF**. BRAF mutations are the most common in CFC syndrome. Utilizing strict diagnostic criteria for the classic CFC syndrome phenotype, initial studies by Rodriguez-Viciana et al [2006] identified BRAF mutations in 18 of 23 (78%) affected individuals and Niihori et al [2006] identified BRAF mutations in 16 of 43 (37%). However, more recent studies have determined BRAF mutations in about 75% of mutation-positive individuals with CFC syndrome [Tidyman & Rauen 2009b].

  At present, about 40 novel BRAF mutations affecting 28 different codons have been identified in individuals with CFC syndrome. The exon 6 mutation p.Gln257Arg is the most common and represents about 25% of all BRAF mutations. Other exons in which mutations have been reported include exons 11, 12, 14, 15, and 17. About 80% of the mutations in BRAF occur in exons 6, 11, and 12. 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 25% of individuals with the clinical diagnosis of CFC syndrome [Rodriguez-Viciana et al 2006, Tidyman & Rauen 2009b]. To date, all published MAP2K1 mutations have occurred in exon 2, 3, and 6; mutations that have been identified in MAP2K2 have occurred in exons 2, 3, and 7. Most identified mutations have been de novo missense mutations with the exception of a four-generation family with autosomal dominant transmission of a MAP2K1 p.Pro128Gln mutation [Rauen et al 2010]. 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 2007]. 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.

- **Deletion/duplication analysis.** Preliminary data suggest that large deletions are rare; thus, mutation detection frequency is unknown.

Table 1. Summary of Molecular Genetic Testing Used in Cardiofaciocutaneous Syndrome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Proportion of CFC Syndrome Attributed to Mutations in This Gene</th>
<th>Test Method</th>
<th>Mutations Detected</th>
<th>Mutation Detection Frequency by Gene and Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF</strong></td>
<td>~75%</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td>98%</td>
</tr>
<tr>
<td><strong>MAP2K1</strong></td>
<td>~25%</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sequencing of select exons</td>
<td>Sequence variants in selected exons</td>
<td>~98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis</td>
<td>Exonic or whole-gene deletions</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>MAP2K2</strong></td>
<td></td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sequencing of select exons</td>
<td>Sequence variants in selected exons</td>
<td>~98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis</td>
<td>Exonic or whole-gene deletions</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>KRAS</strong></td>
<td>&lt;2%-3%</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td>98%</td>
</tr>
</tbody>
</table>
1. See Table A. Genes and Databases for chromosome locus and protein name.

2. It is unclear at this time whether mutations in additional, unidentified genes cause CFC syndrome.

3. See Molecular Genetics for information on allelic variants.

4. The ability of the test method used to detect a mutation that is present in the indicated gene

5. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations; typically, exonic or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

6. Exons 2, 3, and 6 of MAP2K1, and exons 2, 3, and 7 of MAP2K2. Exons screened may vary among laboratories.

7. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

8. No exonic or whole-gene MAP2K1 deletions or duplications have been reported in CFC syndrome; therefore, the mutation detection rate is unknown and may be very low.

9. Several large deletions encompassing MAP2K2 have been identified in persons with CFC-like features [Author, personal observation]; however, no functional data are available to document that haploinsufficiency contributes to the phenotype.

**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, SOS1, RAF1, NRAS, or SHOC2 (Noonan syndrome)
- Presence of a mutation in a 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 Strategy**

To confirm/establish the diagnosis in a proband. Clinical evaluation should include detailed family history with a three-generation pedigree and detailed prenatal history.

Identification of mutations in BRAF, MAP2K1, MAP2K2, or KRAS by direct gene sequencing establishes the diagnosis.

**Single gene testing.** Based on current published information, sequencing can be approached stepwise:
1. Direct sequencing of the seven \textit{BRAF} exons in which causative mutations have been identified (exons 6, 11-17). If no causal mutation is identified:

2. Direct sequencing of select exons of \textit{MAP2K1} (exons 2, 3, and 6) and \textit{MAP2K2} (exons 2, 3, and 7). If no causal mutation is identified:

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

4. Direct sequencing of \textit{KRAS} 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 \textit{HRAS} (all exons). Individuals who have an \textit{HRAS} mutation by definition have Costello syndrome.

6. Consider array GH genome scanning for copy number variants. Rare deletions in MEK genes (i.e., \textit{MAP2K1} and \textit{MAP2K2}) may cause phenotypic features that are reminiscent of CFC syndrome [Author, personal observation].

\textbf{Multi-gene panel.} Another strategy for molecular diagnosis of a proband suspected of having CFC syndrome is use of a multi-gene panel. The genes included and the methods used in multi-gene panels vary by laboratory and over time; a panel may not include a specific gene of interest. See Differential Diagnosis.

\textbf{Prenatal diagnosis and preimplantation genetic diagnosis (PGD)} for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

\textbf{Genetically Related (Allelic) Disorders}

\textbf{BRAF}

\textbf{LEOPARD syndrome.} \textit{BRAF} mutations have been reported in a few individuals who had the clinical diagnosis of LEOPARD syndrome.

\textbf{Solid tumors.} Somatic mutations in \textit{BRAF} have been reported at a high frequency in numerous cancers including melanoma, thyroid, colorectal, and ovarian. The vast majority of \textit{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.Val600Glu, which results in increased kinase activity, accounts for more than 90% of \textit{BRAF} mutations identified in human cancer. Somatic B-Raf p.Val600Glu mutations are also found in benign nevi and premalignant colon polyps. The common p.Val600Glu cancer mutation has never been identified in CFC syndrome. However, a \textit{BRAF} p.Val600Glu mutation has been reported recently in an individual with CFC syndrome [Champion et al 2011].

\textbf{KRAS}

\textbf{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. These are not the same mutations found in Noonan syndrome or CFC syndrome. Point mutations in KRAS account for approximately 85% of mutations in the Ras gene family. 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 2007].

**MAP2K1, MAP2K2**

The first functional MAP2K1 mutation, p.Asp67Asn, was identified in an ovarian cancer cell line with functional studies determining that this mutant protein has increased activity as measured by an increase in ERK phosphorylation [Estep et al 2007]. Subsequently, MAP2K1 p.Lys57Asn mutations were identified in non-small-cell lung carcinoma [Marks et al 2008].

**Clinical Description**

**Natural History**

Cardiofaciocutaneous (CFC) syndrome affects males and females equally.

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

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

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

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

**Childhood and adolescence.** At present, no longitudinal or natural history studies have been done for CFC syndrome. However, CFC syndrome does have an evolving phenotype.
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 and are found to have narrow external auditory canals.

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

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 2007]; 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 [Siegel et al 2011]. 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 the other RASopathies including Costello syndrome, Noonan syndrome, or neurofibromatosis type 1, have not been reported in CFC syndrome. However, acute lymphoblastic leukemia (ALL) has now been reported in a few individuals [Niihori et al 2006, Makita et al 2007, Rauen et al 2010], hepatoblastoma in an immunocompromised individual [Al-Rahawan et al 2007], non-Hodgkin lymphoma [Ohtake et al 2011], and large B-cell lymphoma [Rauen et al 2010].

**Genotype-Phenotype Correlations**

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

Preliminary correlations include the following:

- Individuals with the *BRAF* p.Gln257Arg mutation, the most common CFC causing 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 *BRAF* p.Gly596Val...
mutation have a milder phenotype as indicated by normal growth and development, and no cardiac, GI, or brain abnormalities [Rodriguez-Viciana et al 2006].

- Individuals with a \textit{MAP2K1} or \textit{MAP2K2} mutation are more likely to have keratosis pilaris and progressive nevi formation than those with a \textit{BRAF} mutation [Siegel et al 2011].

\textbf{Penetrance}

Penetrance is complete in CFC syndrome.

\textbf{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.

\textbf{Prevalence}

More than 100 individuals with CFC syndrome have been reported in the literature. The total number of individuals worldwide with CFC syndrome is estimated to be 200 to 300, yet this may be an underestimation because of underdiagnosis of mildly affected individuals.

\textbf{Differential Diagnosis}

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

\textbf{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, downslanting 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 dysmyelination 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 autosomal dominant as demonstrated by germline mosaicism [Sol-Church et al 2009]. 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]. However, with closer clinical examination, the clinical diagnosis was consistent with CFC syndrome. Costello syndrome and cardiofaciocutaneous (CFC) syndrome have many overlapping phenotypic features, underscoring the difficulty in making a clinical diagnosis based on phenotypic features alone.

Individuals with BRAF mutations have the diagnosis of CFC syndrome, even if they have features that may be present in Costello 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]. Mutations in SHOC2 [Cordeddu et al 2009] and NRAS [Cirstea et al 2010] have also been reported.

Craniofacial findings in CFC syndrome are reminiscent of those described in Noonan syndrome (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 high-arched palate), underscoring the importance of molecular testing to establish the correct diagnosis.

Inheritance is autosomal dominant; however, many affected individuals have de novo mutations.

**Note to clinicians:** For a patient-specific ‘simultaneous consult’ related to this disorder, go to [SimulConsult®](#), an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).
Management

Evaluations Following Initial Diagnosis

The following evaluations are recommended in an individual known to have or suspected 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
- Full abdominal ultrasound examination to evaluate for renal and urogenital anomalies
- Psychomotor developmental evaluation
- Endocrine evaluation if growth delay is suspected
- Ophthalmologic examination
- Audiologic examination
- Nutrition and feeding evaluation, consider swallow study
- Dermatologic evaluation

Treatment of Manifestations

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

Cardiovascular management is dictated by the abnormality, with treatment similar to that in the general population: structural defects are managed surgically as needed; hypertrophic cardiomyopathy is followed by serial echocardiograms, and cardiac arrhythmias are medically managed in an aggressive manner.

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. However, seizures may be
refractory to single agent therapy and may require polytherapy.

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 pruritus may be relieved by increasing the ambient humidity or using hydrating lotions. Hyperkeratoses are treated as in the general population.

Signs and symptoms of skin infection, especially in the presence of lymphedema, warrant thorough and immediate evaluation by a physician for the consideration of antibiotic treatment.

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 highly recommended.

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

Prevention of Secondary Complications

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

**Anesthesia.** Individuals with CFC syndrome may have an unrecognized hypertrophic cardiomyopathy, tracheomalacia, or a predisposition to cardiac rhythm disturbances.

**Surveillance**

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

- **Audiologic.** Annual evaluation of hearing is recommended.

- **Cardiac.** If the initial cardiac evaluation is normal, periodic follow-up evaluations including an echocardiogram and an electrocardiogram are necessary as hypertrophic cardiomyopathy and rhythm disturbances may develop later in life.

- **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 reflux.

• **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. Monitor for signs of precocious puberty.

• **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, though no individuals with CFC syndrome have been reported to have a malignant change.

• **Malignancy.** At present there is no screening protocol as it is unclear if individuals with CFC syndrome are at an increased risk for malignancies.

**Agents/Circumstances to Avoid**

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

**Evaluation of Relatives at Risk**

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

**Therapies Under Investigation**

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

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

**Genetic Counseling**

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

**Mode of Inheritance**

Cardiofaciocutaneous (CFC) syndrome is transmitted in an autosomal dominant manner [Rauen et al 2010]. However, in most cases, it is the result of a de novo dominant mutation.
Parents of a proband

- The vast majority of individuals with CFC syndrome have the disorder as the result of a de novo mutation.
- The parents of a proband with a de novo mutation are not affected.

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the proband’s parents.
- Because the vast majority of 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. Each child of an individual with CFC syndrome has a 50% chance of inheriting the mutation.

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

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

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

Prenatal Testing

If the disease-causing mutation has been identified in the family, 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 ~15-18 weeks’ gestation) or chorionic villus sampling (usually performed at ~10-12 weeks’ gestation).

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

**Preimplantation genetic diagnosis (PGD)** may be an option for some families in which the disease-causing mutation has been identified.

**Resources**

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

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

- **RASopathiesNet**
  244 Taos Road
  Atlandena CA 91001
  **Phone:** 626-676-7694
  **Email:** lisa@rasopathies.org
  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

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Chromosomal Locus</th>
<th>Protein Name</th>
<th>Locus Specific</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>7q34</td>
<td>B-Raf proto-oncogene serine/threonine-protein kinase</td>
<td>BRAF homepage - Mendelian genes</td>
<td>BRAF</td>
</tr>
<tr>
<td>KRAS</td>
<td>12p12.1</td>
<td>GTPase KRas</td>
<td>KRAS homepage - Mendelian genes Resource of Asian Primary Immunodeficiency Diseases (KRAS)</td>
<td>KRAS</td>
</tr>
</tbody>
</table>
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, RAF1, NRAS, SHOC2, and KRAS. The gene in which mutations are causative for Costello syndrome is HRAS. Cardiofaciocutaneous (CFC) syndrome is associated with mutations in BRAF, MAP2K1, and MAP2K2.

**BRAF**

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

**Pathogenic 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 [Yoon et al 2007].

Table 2. Selected BRAF Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Protein Amino Acid Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.770A&gt;G</td>
<td>p.Gln257Arg¹</td>
<td>NM_004333.4</td>
</tr>
<tr>
<td>c.1399T&gt;G</td>
<td>p.Ser467Ala¹</td>
<td>NP_004324.2</td>
</tr>
<tr>
<td>c.1408_1410del</td>
<td>p.Thr470del¹</td>
<td></td>
</tr>
<tr>
<td>c.1455G&gt;C</td>
<td>p.Leu485Phe²</td>
<td></td>
</tr>
<tr>
<td>c.1600G&gt;C</td>
<td>p.Gly534Arg²</td>
<td></td>
</tr>
<tr>
<td>c.1787G&gt;T</td>
<td>p.Gly596Val</td>
<td></td>
</tr>
<tr>
<td>c.1799T&gt;A</td>
<td>p.Val600Glu³</td>
<td></td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the author. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. See Figure 1.
2. Associated with Costello syndrome, see Figure 1.
3. p.Val600Glu is a somatic mutation found in some solid tumors (see Genetically Related Disorders).

**Normal gene product.** The protein product of BRAF is B-Raf, a serine/threonine protein kinase that is one of the many direct downstream effectors of Ras. The Raf/MEK/ERK module of kinases is critically involved in cell proliferation, differentiation, motility, apoptosis, and senescence. B-Raf has only two known downstream effectors, mitogen-activated protein kinase 1 and 2 (also known as MEK1 and MEK2). There are three conserved regions in 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.

**Abnormal gene product.** The type of BRAF mutations found in CFC syndrome is 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 BRAF mutation identified in cancer, p.Val600Glu, has not been identified in CFC syndrome. Presumably, such a gain-of-function mutation would be incompatible with life. However, a germline p.Val600Gly mutation has recently been reported in CFC [Champion et al 2011] and, like the BRAF p.Val600Glu mutation, has also been reported in cancer.

**MAP2K1, MAP2K2**

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

**Pathogenic allelic variants.** Missense mutations in MAP2K1 and MAP2K2 cause CFC syndrome in approximately 25% of clinically diagnosed individuals. Mutations are heterogeneous with missense substitutions, with the majority identified in exons 2 and 3 of both MAP2K1 and MAP2K2. The amino acid substitutions in MEK1 and MEK2 are similar, suggesting that the functional consequences in the two family isoforms may be similar. Somatic mutations have recently been reported in ovarian [Estep et al 2007] and lung cancer [Marks et al 2008].

Table 3. Selected MAP2K1 Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Protein Amino Acid Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.389A&gt;G</td>
<td>p.Tyr130Cys</td>
<td>NM_002755.3</td>
</tr>
<tr>
<td>c.199G&gt;A</td>
<td>p.Asp67Asn</td>
<td>NP_002746.1</td>
</tr>
<tr>
<td>c.171G&gt;T</td>
<td>p.Lys57Asn</td>
<td></td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the author. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Table 4. Selected MAP2K2 Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Protein Amino Acid Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.170T&gt;G</td>
<td>p.Phe57Cys¹</td>
<td>NM_030662.3</td>
</tr>
</tbody>
</table>
c.383C>A  p.Pro128Gln  NP_109587.1

c.401A>G  p.Tyr134Cys

Note on variant classification: Variants listed in the table have been provided by the author. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. See Figure 1.

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

**Abnormal gene product.** 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**

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

**Pathogenic allelic variants.** Unlike somatic mutations identified in cancer, novel germline missense KRAS mutations in coding exons 1, 2, and 4b have been identified [Carta et al 2006, Niihori et al 2006, Schubbert et al 2006, Zenker et al 2007].

**Normal gene product.** The GTPase 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, although 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.


(10) Makita Y, Narumi Y, Yoshida M, Niihori T, Kure S, Fujieda K, Matsubara Y,


Suggested Reading


Chapter Notes

Author Notes

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

Dr Rauen is the Director of the UCSF NF/Ras Pathway Genetics Clinic (www.ucsfhealth.org/clinics/nf_ras_pathway).

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

- 6 September 2012 (cd) Revision: multi-gene 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 to live Web site
- 14 September 2006 (kar) Original submission

Copyright © 1993-2014, University of Washington, Seattle. All rights reserved.
For more information, see the GeneReviews Copyright Notice and Usage Disclaimer.
For questions regarding permissions: admasst@uw.edu.
Bookshelf ID: NBK1186    PMID: 20301365