The cardiofaciocutaneous (CFC) syndrome

Authors: Professor Giovanni Neri[1] and Dr. Maria Ines Kavamura
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[1]Istituto di Genetica Medica, Facoltà di Medicina e Chirurgia "A.Gemelli", Università Cattolica del S. Cuore, Largo F. Vito 1, 00168 Roma, Italy; gneri@rm.unicatt.it

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Abstract
The cardiofaciocutaneous (CFC) syndrome (OMIM 115150) is a multiple congenital anomalies/mental retardation (MCA/MR) syndrome characterized by psychomotor delay, muscular hypotonia, feeding problems, short stature, relative macrocephaly, typical face, ectodermal abnormalities consisting typically of sparse and curly hair, absent eyebrows and ulerythema ophryogenes, congenital heart defects, mainly pulmonic stenosis, atrial septal defects and hypertrophic cardiomyopathy. All known bona fide *cases are sporadic, possibly due to new autosomal dominant mutations of an as yet unknown gene(s). Differential diagnosis is usually made with Noonan and Costello syndromes. The frequency of the condition is unknown. Its management is symptomatic, including special education, occupational and speech therapy, appropriate care of the skin. Feeding problems may require tube feeding or even gastrostomy. Heart defects may require surgical correction.*

Keywords
multiple physical anomalies, developmental delay, mental retardation, short stature, macrocephaly, ectodermal abnormalities, heart defects, Noonan syndrome, Costello syndrome

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Disease name
Cardiofaciocutaneous or CFC syndrome. No other synonyms.

Definition/diagnostic criteria
The cardiofaciocutaneous (CFC) syndrome (OMIM 115150), first described by Reynolds *et al.* (1986), is a multiple congenital anomalies/mental retardation (MCA/MR) syndrome of unknown etiology. Its diagnosis is purely clinical (Kavamura *et al.*, 2002). No specific laboratory tests are available.

Differential diagnosis
Noonan syndrome and Costello syndrome, especially the former, can be phenotypically similar to CFC and should be excluded. Noonan syndrome differs by less severe psychomotor delay bordering to normality, low posterior hairline with thick hair, cubitus valgus, neck abnormalities, ectodermal involvement characterized by nevi and café-au-lait spots, familial occurrence (Neri *et al.*, 1991). In approximately 60% of cases the diagnosis can be confirmed by mutational analysis of the *PTPN11* gene (Tartaglia *et al.*, 2001). Involvement of this gene has been excluded in all *bona fide* cases of CFC syndrome tested so far

(Kavamura *et al.*, 2003a). Costello syndrome differs by the presence of "coarse" face, nasal and/or anal papillomata and a predisposition to childhood tumors such as neuroblastoma, redundant skin of the hands and feet with deep palmar and plantar creases, elbow joint limitation.

Etiology
The cause of the CFC syndrome is unknown. *De novo* autosomal dominant mutations of an as yet unidentified gene(s) appear to be a likely cause. Mutations of the *PTPN11* gene as well as subtelomeric rearrangements have been excluded in a large series of cases (Kavamura *et al.*, 2003b). Rauen *et al.* (2000 and 2002) described two patients with an interstitial deletion of chromosome 12q and a phenotype resembling the CFC syndrome. Most likely these patients do not have the CFC syndrome (Neri *et al.*, 2003) and deletions of the critical 12q region have been excluded as possible cause of the condition (Kavamura *et al.*, 2003b).

Clinical description
A typical case of CFC syndrome is characterized by the following clinical findings:
- psychomotor retardation, usually of moderate degree, with speech delay
- congenital muscular hypotonia
- failure to thrive with feeding difficulties, resulting in short stature
- relative macrocephaly, short neck and typical face with high forehead, bitemporal constriction, supraorbital hypoplasia, downslanting eyes with epicanthic folds, hypertelorism and palpebral ptosis, short nose with depressed nasal bridge and anteverted nostrils, low-set and posteriorly angulated ears
- ectodermal abnormalities consisting of sparse, slow-growing and curly hair, sparse or absent eyelashes and eyebrows, follicular keratosis or ulerythema ophryogenes, ichthyosis, hyperkeratosis, generalized hyperpigmentation, hyperelastic skin, hemangiomas, café-au-lait spots
- congenital heart defects, consisting more frequently of pulmonic stenosis, atrial septal defect and hypertrophic cardiomyopathy.

Diagnostic methods
Clinical evaluation, including MRI and ultrasound imaging of brain and heart respectively, as deemed appropriate. A skin biopsy can be offered to evaluate the type of skin involvement, but it does not appear to be of high diagnostic value. Chromosome abnormalities and *PTPN11* mutations should be excluded.

Epidemiology
All *bona fide* cases reported so far are sporadic. The frequency of the condition is unknown.

Genetic counselling
Parents who had an affected child should be given an empirical recurrence risk of 1-3% to allow for such rare occurrences as parental germinal mosaicism or cryptic chromosomal translocation. An affected person should be given a recurrence risk of 50% in his/her offspring.

Prenatal diagnosis
Presently not available.

Management
Since there is no specific treatment for the CFC syndrome, management should be symptomatic, including special education, occupational and speech therapy, appropriate care of the skin. Feeding problems may require tube feeding or even gastrostomy. Heart defects may require surgical correction.

Support group
CFC International Inc. President & Director: Brenda Conger, Vestal, New York.
E-mail: bconger@stny.rr.com Web page: http://www.cfcsyndrome.org Mail: CFC International, Inc. 183 Brown Road Vestal, NY 13850 USA Phone: (607) 772-9666 evenings and weekends.

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