GENEReviews

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Congenital Contractural Arachnodactyly

[*Beals Syndrome, Beals-Hecht Syndrome*]

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Initial Posting: January 23, 2001.
Last Update: May 4, 2007.

Summary

Disease characteristics. Congenital contractural arachnodactyly (CCA) is characterized by a Marfan-like appearance (tall, slender habitus in which arm span exceeds height) and long, slender fingers and toes (arachnodactyly). Most affected individuals have "crumpled" ears that present as a folded upper helix of the external ear and most have contractures of major joints (knees and ankles) at birth. The proximal interphalangeal joints also have flexion contractures (i.e., camptodactyly), as do the toes. Hip contractures, adducted thumbs, and club foot may occur. The majority of affected individuals have muscular hypoplasia. Contractures usually improve with time. Kyphosis/scoliosis is present in about half of all affected individuals. It begins as early as infancy, is progressive, and causes the greatest morbidity in CCA. Dilatation of the aorta is occasionally present. Infants have been observed with a severe/lethal form characterized by multiple cardiovascular and gastrointestinal anomalies in addition to the typical skeletal findings.

Diagnosis/testing. CCA is diagnosed on the basis of clinical findings. Molecular genetic testing of the *FBN2* gene encoding the extracellular matrix microfibril, fibrillin 2, is clinically available.

Management. *Treatment of manifestations:* physical therapy for joint contractures beginning in childhood to increase joint mobility and ameliorate the effects of muscle hypoplasia (usually calf muscles); surgical release of contractures as needed; bracing and/or surgical correction of kyphoscoliosis; standard management of aortic root dilation. *Surveillance:* echocardiogram every two years until absence of aortic involvement is evident; at least annual physical examination for evidence of kyphosis/scoliosis.

Genetic counseling. Congenital contractural arachnodactyly is inherited in an autosomal dominant manner. Many individuals with CCA have an affected parent, although a proband may have the disorder as the result of a *de novo* gene mutation. The risk to the sibs of the proband depends upon the status of the parents. If the parent of a proband has clinical features of CCA, the risk to the sibs is 50%. Germline mosaicism has been reported. Offspring of affected individuals have a 50% chance of inheriting the abnormal *FBN2* allele. Prenatal testing is available if the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Classic congenital contractural arachnodactyly (CCA) is diagnosed based on a constellation of clinical findings [Godfrey 2004]. Individuals with CCA typically have the following:

- A marfanoid habitus (long, thin limbs, narrow head and body)
- Flexion contractures of multiple joints including elbows, knees, hips, and fingers
- Kyphoscoliosis (sometimes severe)
- Muscular hypoplasia
- Abnormal pinnae ("crumpled" outer helices)

Severe/lethal CCA is a rare form of CCA [Wang et al 1996, Snape et al 2006]. In addition to the typical features described for classic CCA, infants with severe/lethal CCA have the following anomalies:

- Cardiovascular: atrial or ventricular septal defect, interrupted aortic arch, single umbilical artery, and aortic root dilatation (rare)
- Gastrointestinal: duodenal or esophageal atresia and intestinal malrotation

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.

Gene. *FBN2* is the only gene known to be associated with congenital contractural arachnodactyly.

Clinical uses

- Diagnostic testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis**

  Classic CCA. Although earlier studies identified mutations in about 75% of affected individuals [Carmical et al 2000, Gupta et al 2002], a recent study by Nishimura et al (2007) identified mutations in only 27% of individuals with CCA.

  Severe/lethal CCA. Only a small number of infants with severe/lethal CCA have been reported. A mutation in the same *FBN2* region was identified in the one infant analyzed [Snape et al 2006].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Congenital Contractural Arachnodactyly

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*FBN2* sequence variants	27%-75%	Clinical Testing
RNA-based sequencing	*FBN2* mutations	~40%	Research only

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

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

Genetically Related (Allelic) Disorders

No other phenotypes are known to be caused by mutations in *FBN2*. Because all mutations that cause CCA are clustered in a rather limited region of *FBN2* (i.e., exons 24 through 36), one can hypothesize that mutations falling outside of this region may cause disorders or syndromes not yet attributed to *FBN2*, or may have no phenotypic effect.

Clinical Description

Natural History

Congenital contractural arachnodactyly (CCA) appears to comprise a broad phenotypic spectrum. At the most severe end is "severe/lethal CCA." This form of CCA is rare, with few cases reported in the literature, one of which has been confirmed using molecular testing.

Phenotypic expression is variable within and between families. In one report, a mother with somatic mosaicism that affected the germline had features of classic CCA, while her daughter, who inherited the mutant *FBN2* allele, had the severe/lethal form of CCA [Wang et al 1996].

Classic CCA. The following are seen in individuals with CCA:

- **Marfan syndrome-like appearance** characterized by a tall and slender habitus with arm span exceeding height
- **Arachnodactyly** (long slender fingers and toes)
- **"Crumpled" ears** that present as a folded upper helix of the external ear
- **Contractures** of major joints at birth, especially the knees (81%) and elbows (86%). The proximal interphalangeal joints of the fingers and toes display flexion contractures (i.e., camptodactyly). Hip contractures (26%) are also seen. Adducted thumbs (46%) and club foot may occur. Contractures usually improve with time.
- **Bowed long bones** (31%) and **muscular hypoplasia** (65%)
- **Kyphosis/scoliosis,** present in about half of affected individuals. It begins as early as infancy and is progressive, causing the greatest morbidity in CCA.
- **Aortic root dilatation,** documented in individuals with CCA with a characterized *FBN2* mutation [Park et al 1998, Carmical et al 1999, Gupta et al 2002, Snape et al 2006]. Its frequency is unknown.
- **Additional craniofacial abnormalities** (significantly less common): mild micrognathia, high arched palate, scaphocephaly, brachycephaly, dolichocephaly, and frontal bossing

Severe/lethal CCA. In addition to the typical skeletal findings (arachnodactyly, joint contractures, scoliosis) and abnormally shaped ears of CCA, infants with the severe/lethal form have multiple cardiovascular and gastrointestinal anomalies [Wang et al 1996]. Although data are limited, all individuals with severe/lethal CCA have required surgery for various congenital malformations as early as the first week of life. Respiratory complications have been the cause of death in most. The age of death has ranged from eight days to 11.5 months.

Genotype-Phenotype Correlations

No genotype-phenotype correlations exist.

Penetrance

Penetrance is complete.

Nomenclature

Congenital contractural arachnodactyly has been referred to as CCA.

Prevalence

The prevalence is not known, but appears to be lower than that of the Marfan syndrome.

CCA does not have any specific geographic or ethnic predilection.

Differential Diagnosis

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

A number of disorders have features that overlap with those of congenital contractural arachnodactyly (CCA).

The disorder most similar to CCA is the **Marfan syndrome**, caused by mutations in the *FBN1* gene. Individuals with Marfan syndrome have lens subluxation, high myopia, and progressive aortic root dilation not characteristic of CCA; they also lack the "crumpled" ears and joint contractures seen at birth in individuals with CCA. Until genetic linkage studies distinguished the two disorders, it was speculated that they could be allelic. Differentiating the two disorders is most important given the severe cardiovascular complications and cardiac monitoring essential in individuals with the Marfan syndrome.

The Marfan syndrome and CCA can be distinguished by clinical findings. Diagnosis of either requires the presence of a constellation of clinical features. In both cases, clinical diagnosis is the gold standard; molecular genetic testing can be used for confirmation of the diagnosis in some instances.

The severe/lethal form of CCA may be mistaken for the neonatal Marfan syndrome, the most severe end of the spectrum of the Marfan syndrome, in which the cardiovascular abnormalities include mitral and tricuspid valve anomalies and dilated aorta, while those in severe/lethal CCA include atrial and/or ventricular septal defects and interrupted aortic arch.

Stickler syndrome is a connective tissue disorder that can include ocular findings of myopia, cataract, and retinal detachment; hearing loss that is both conductive and sensorineural; midfacial underdevelopment and cleft palate (either alone or as part of the Robin sequence); and mild spondyloepiphyseal dysplasia and/or precocious arthritis. Variable phenotypic expression of Stickler syndrome occurs both within and among families. At present, no consensus minimal clinical diagnostic criteria exist. Mutations affecting one of three genes

(COL2A1, *COL11A1*, and *COL11A2*) have been associated with Stickler syndrome. Some individuals with Stickler syndrome have a marfanoid body habitus and typically the fingers are long and gracile, which may suggest the diagnosis of CCA. However, in Stickler syndrome joint laxity is present, as are other findings not typical for CCA, including myopia and retinal detachment, hearing loss that is both conductive and sensorineural, and midfacial underdevelopment and cleft palate (either alone or as part of the Robin sequence).

Homocystinuria, a multisystem disorder of amino acid metabolism caused by cystathionine β-synthase deficiency, typically affects the skeleton, joints, eye, and central nervous system. Skeletal features are similar to those seen in CCA and Marfan syndrome, and include limited joint mobility, dolichostenomelia, arachnodactyly, and kyphoscoliosis. Homocystinuria is clinically distinguishable from CCA by its other manifestations, such as lens subluxation, osteoporosis, and often developmental delay, as well as predisposition to thromboembolism. It can be definitively diagnosed by serum amino acid analysis.

Distal arthrogryposis is a hereditary congenital joint contracture disorder, characterized by involvement of the hands and feet. Typical joint findings are medially overlapping fingers, clenched fists, ulnar deviation of fingers, camptodactyly, positional foot deformities, and clubfoot. Distal arthrogryposis can be clinically distinguished from CCA by absence of marfanoid habitus, arachnodactyly, contractures of knees and elbows, and crumpled ears.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with congenital contractural arachnodactyly (CCA), the following evaluations are recommended:

- Echocardiogram
- Musculoskeletal examination for the presence of contractures and kyphosis/scoliosis

Treatment of Manifestations

- Physical therapy for joint contractures helps increase joint mobility and ameliorate the effects of muscle hypoplasia (usually calf muscles). This type of therapy is best instituted in childhood. As affected individuals age, spontaneous improvement in camptodactyly is frequently observed.
- Surgical release of contractures may be necessary.
- The kyphoscoliosis tends to be progressive, requiring bracing and/or surgical correction. Consultation with an orthopedist is encouraged.
- Aortic root dilation, if present, is managed in a standard manner.
- In severe/lethal CCA no general recommendations exist; findings need to be managed in a standard manner as they arise.

Surveillance

- Echocardiogram every two years until it is clear that the aorta is not involved
- At least annual physical examination for evidence of kyphosis/scoliosis

Testing of Relatives at Risk

Establishing the diagnosis of CCA early in at-risk relatives may permit more careful surveillance of affected individuals (see Surveillance).

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

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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

Congenital contractural arachnodactyly (CCA) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with CCA have an affected parent.
- A proband with CCA may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- It is appropriate to evaluate the parents of a proband by physical examination and molecular genetic testing if the mutation in the proband has been identified.

Sibs of a proband

- The risk to the sibs of the proband depends upon the status of the parents.
- If a parent of the proband has clinical features of CCA, the risk to the sibs is 50%.
- If neither parent is clinically affected and if the disease-causing mutation identified in the proband cannot be detected in the DNA extracted from the leukocytes of either parent, there is still a small (but unknown) risk to the sibs because germline mosaicism has been reported in three unrelated families; in one case, an unaffected father had two children with CCA [Putnam et al 1997].

Offspring of a proband. Each child of an individual with CCA has a 50% chance of inheriting the mutation.

Other family members of the proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected or to have a *FBN2* mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

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 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 an affected family member must 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.

Fetal ultrasound examination. While joint contractures may be identified by ultrasound examination of an at-risk fetus, a normal fetal ultrasound examination does not exclude the diagnosis of CCA.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

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

Table A. Molecular Genetics of Congenital Contractural Arachnodactyly

Gene Symbol	Chromosomal Locus	Protein Name
FBN2	5q23-q31	Fibrillin-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 Congenital Contractural Arachnodactyly

121050	CONTRACTURAL ARACHNODACTYLY, CONGENITAL

Table C. Genomic Databases for Congenital Contractural Arachnodactyly

Gene Symbol	Entrez Gene	HGMD
FBN2	2201 (MIM No. 121050)	FBN2

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

Molecular Genetic Pathogenesis

Fibrillin 2 was serendipitously discovered during the search for the molecular basis of the Marfan syndrome and the identification of *FBN1*. Fibrillin 2 is co-distributed with fibrillin 1 in many tissues of the developing embryo. Fibrillin 2 expression appears to be greatest in matrices rich in elastic fibers. Studies have compared the distribution of fibrillin 1 and fibrillin 2 in tissues. For example, human ear cartilage shows differential expression of the two fibrillins. Abnormally shaped auricular helices are a hallmark of congenital contractural arachnodactyly (CCA). Immunostaining studies of fetal aorta have shown preferential staining of fibrillin 2 in the elastic-rich media, while fibrillin 1 immunostaining was observed in all three aortic layers. In hyaline cartilage, fibrillin 1 was seen throughout the tissue, while fibrillin 2 was localized to the periphery and perichondrium. Fibrillin 2 expression in the lung was also lower than that of fibrillin 1.

Given the differential expression of the fibrillins in fetal tissue and the much lower expression of fibrillin 2 versus fibrillin 1 in adult tissues, a general hypothesis has emerged: fibrillin 2 directs the assembly of elastic fibers during early embryogenesis, while fibrillin 1 provides the major structural, i.e., "load-bearing" function of the microfibrils [Robinson & Godfrey 2000].

Normal allelic variants: *FBN2* is highly homologous to *FBN1*, mutations in which are known to cause the Marfan syndrome. The structure of *FBN2* has been described by Zhang et al (1994). It encodes a multidomain protein with five distinct structural regions comprising a total of 65 exons. The largest of these structural regions contains 41 calcium binding-epidermal growth factor (cb-EGF)-like domains. The single longest stretch of cb-EGF-like domains is 12; it is here that all mutations causing CCA have been found to date. This is also the region of greatest homology between the fibrillins. Upstream from this region of high homology is a region, encoded by a single exon, with the most divergence. This highly divergent region is proline rich in fibrillin 1 and glycine rich in fibrillin 2.

Pathologic allelic variants: Table 2 lists reported *FBN2* mutations. All mutations identified to date cluster in the single longest stretch of calcium-binding epidermal growth factor-like (cb-EGF) domains of *FBN2* [Park et al 1998,Gupta et al 2002].

Table 2. *FBN2* Mutations Known to Cause Congenital Contractural Arachnodactyly

Amino Acid Change	Exon	Reference
p.Gly1056Asp	24	Park et al 1998
p.Ile1092Thr	25	Park et al 1998
p.Ala1114His	25	Babcock et al 1998
p.Cys1141Phe	26	Belleh et al 2000
p.Cys1252Tyr	29	Putnam et al 1995
p.Cys1252Trp	29	Belleh et al 2000
Deletion of exon 29	29	Putnam et al 1997
Deletion of exon 31	31	Maslen et al 1997, Park et al 1998
p.Cys1433Ser	33	Putnam et al 1995
Deletion of exon 34 [1]	34	Wang et al 1996

1. Found in an individual with severe/lethal CCA and in her mother, who was mosaic for the mutation [Wang et al 1996

Normal gene product: Fibrillin 2 is a glycoprotein of the extracellular matrix microfibrils.

Abnormal gene product: The precise function of fibrillin 2 is not known. Therefore, the mechanism of an abnormal gene product in contributing to the pathophysiology of CCA in not known. Of note, mice lacking the *Fbn2* gene or having a mutation in that gene have syndactyly. This finding suggests that *FBN2* mutations outside the "neonatal region" may cause non-CCA phenotypes in humans [Arteaga-Solis et al 2001, Chaudhry et al 2001].

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.

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National Marfan Foundation
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www.marfan.org

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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.

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Chapter Notes

Revision History

- 4 May 2007 (me) Comprehensive update posted to live Web site
- 5 April 2006 (cd) Revision: *FBN2* testing clinically available
- 29 December 2004 (me) Comprehensive update posted to live Web site
- 5 February 2003 (me) Comprehensive update posted to live Web site
- 23 January 2001 (me) Review posted to live Web site
- June 2000 (mg) Original submission