



HAL
open science

Mosaic intragenic deletion of FBN2 and severe congenital contractural arachnodactyly

A. Lavillaureix, S. Heide, S. Chantot-Bastaraud, I. Marey, B. Keren, R. Grigorescu, J.M. Jouannic, A. Gelot, S. Whalen, D. Héron, et al.

► To cite this version:

A. Lavillaureix, S. Heide, S. Chantot-Bastaraud, I. Marey, B. Keren, et al.. Mosaic intragenic deletion of FBN2 and severe congenital contractural arachnodactyly. *Clinical Genetics*, 2017, 92 (5), pp.556-558. 10.1111/cge.13062 . inserm-03867929

HAL Id: inserm-03867929

<https://inserm.hal.science/inserm-03867929>

Submitted on 28 Jul 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright

Mosaic intragenic deletion of *FBN2* and severe congenital contractural arachnodactyly

A. Lavillaureix¹, S. Heide^{1,2}, S. Chantot-Bastaraud¹, I. Marey², B. Keren²,
R. Grigorescu¹, J-M. Jouannic³, A. Gelot^{4,7}, S. Whalen⁵, D. Héron^{2,5,6}, JP. Siffroi¹

1 APHP, Hôpital Armand-Trousseau, Département de Génétique médicale, Paris, 75012, France.

2 APHP, Groupe Hospitalier Pitié-Salpêtrière, Département de Génétique, Paris, 75013, France.

3 APHP, Hôpital Armand-Trousseau, Service de Médecine Fœtale, Paris, 75012, France.

4 APHP, Hôpital Armand-Trousseau, Service d'Anatomie Pathologique, Paris, 75012, France.

5 APHP, Hôpital Armand-Trousseau, Unité de Génétique clinique, Paris, 75012, France.

6 UPMC Univ Paris 06, UMR_S975, Groupe de Recherche Clinique (GRC) Déficience intellectuelle et autisme, CRICM, Team Molecular Bases, F-75013, Paris, France.

7 INMED INSERM U901 Parc Scientifique de Luminy, Marseille, France 13273

Conflict of interest statement :

The authors A. Lavillaureix, S. Heide, S. Chantot-Bastaraud, I. Marey, B. Keren, R. Grigorescu, J-M. Jouannic, A. Gelot, S. Whalen, D. Héron and JP. Siffroi, have no conflict of interest to declare.

Corresponding author:

Alinoë Lavillaureix, MD
Medical Genetics Resident
Département de Génétique médicale, Hôpital Armand-Trousseau, APHP
26 Avenue du Dr. Arnold Netter
75012 Paris, France
Phone : +33 1 44 73 52 83
Fax : + 33 1 44 73 52 82
alinoe.lavillaureix@gmail.com

Congenital Contractural Arachnodactyly (CCA) or Beals Syndrome (MIM #121050) is a connective tissue disorder characterized by congenital contractures of small and large joints, marfanoid habitus with arachnodactyly, crumpled ears and muscular hypoplasia¹. High arched palate and pectus deformity are frequently associated. Scoliosis causes the greatest morbidity although life expectancy is usually normal. In many cases, this autosomal dominant syndrome is caused by a mutation in the fibrillin-2 gene *FBN2* on chromosome 5q23.

Nine patients also had gastrointestinal and cardiac manifestations and did not live past infancy. This severe form of CCA is also termed lethal CCA¹. In only two of these patients, a *FBN2* defect was shown, one with a 103.3 intragenic deletion and the other with a splice site variant^{2,3}. This latter resulted in an exon 34 skip and abnormal protein. The proband's mother was mosaic for the variant and presented with classic CCA³.

We report the first case of mosaic intragenic deletion of the *FBN2* gene associated with a phenotype of severe and probably lethal CCA in a fetus presenting with multiple flexion contractures, arachnodactyly, crumpled ears, muscle hypoplasia and cardiovascular malformation.

The proband presented prenatally with hypokinesia, arthrogryposis and frequent respiratory movements suggesting fetal distress. The parents decided to terminate the pregnancy at 28 weeks of gestation. Autopsy showed a male eutrophic but dysmorphic fetus with crumpled ears, high arched palate and retrognathia. He had joint contractures, flexed fingers, rocker-bottom feet and muscular hypoplasia of the limbs and of the pectoral muscles (Figure 1, A-C). Internal examination revealed pulmonary hypoplasia, bifid heart apex and ostium secundum atrial septal defect with backward failure of the right heart. Neuropathological examination was normal as well as morphological studies performed on muscles and nerves.

Array-CGH revealed an intragenic *FBN2* mosaic deletion on chromosome 5q23.3 (Figure 1 D). FISH analysis confirmed the deletion in liver, muscle and skin tissue samples and showed that it was present in 55% to 70% of the nuclei examined. The minimal deleted segment was about 116Kb in size (chr5:127663810-127779670) and maximal 135Kb (chr5:127656238-127791139) (<http://genome.ucsc.edu/>, GRCh37/hg19). Exons 7-8 to 34 of the 65 *FBN2* exons (NM_001999.3) were included in the deleted area (Figure 1 E). FISH and array-CGH in parents were normal, thus indicating that the deletion was *de novo*. Further information concerning material and methods is available upon request.

CCA syndrome is usually associated with in-frame *FBN2* variants (missense point mutations, one duplication resulting in an in-frame insertion or in-frame splice-site mutations)⁴ located between exons 23 and 34, the so-called "neonatal region" in the homologous *FBN1* gene leading to severe neonatal presentations of Marfan syndrome. *FBN2* variants leading to a premature termination codon are significantly underrepresented, with only one nonsense mutation reported⁴. Recently, large deletions that include the *FBN2* gene have been described in five unrelated patients who presented with a spectrum of clinical manifestations associated with CCA⁵.

Some intragenic deletions of the *FBN2* gene can lead to more severe CCA phenotypes than haploinsufficiency due to larger deletions encompassing the whole gene, thus suggesting a possible

dominant negative effect. Indeed, fibrillin-1 and fibrillin-2 homo and heterodimers are an integral component of the extracellular matrix (ECM) where they form microfibrils which provide a scaffold for the organization of elastin in elastic tissues. Fibrillin-2 protein appears in the early stages of embryogenesis and an abnormal protein might affect the structure and function of the 10 nm extensible microfibrils within the ECM.

Another case of intragenic deletion of *FBN2* (103,3kb) has been described in a premature neonate with CCA and global hypotonia who died neonatally². The intragenic deletion we report includes the “neonatal” region and is likely in-frame thus resulting in a drastically shorter protein disrupting the microfibril assembly more severely than other variants in classical CCA. Unfortunately, genetic analyses were carried out after medical termination of pregnancy and RNA extraction was not performed.

In conclusion, the existence of deletions within the *FBN2* gene should be tested in every CCA proband to allow a more accurate prognosis and an adequate genetic counseling in pregnancies with an arthrogryposis affected fetus.

Ethics approval:

Informed written consent was obtained from the parents of the patient.

References:

1. Callewaert BL, Loeys BL, Ficcadenti A, et al. Comprehensive clinical and molecular assessment of 32 probands with congenital contractural arachnodactyly: Report of 14 novel mutations and review of the literature. *Hum Mutat.* 2009;30(3):334–341.
2. Inbar-Feigenberg M, Meirowitz N, Nanda D, Toi A, Okun N, Chitayat D. Beals syndrome (congenital contractural arachnodactyly): prenatal ultrasound findings and molecular analysis. *Ultrasound Obstet Gynecol.* 2014;44(4):486-490.
3. Wang M, Clericuzio CL, Godfrey M. Familial occurrence of typical and severe lethal congenital contractural arachnodactyly caused by missplicing of exon 34 of fibrillin-2. *Am J Hum Genet.* 1996;59(5):1027-1034.
4. Frédéric MY, Monino C, Marschall C, et al. The FBN2 gene: new mutations, locus-specific database (Universal Mutation Database FBN2), and genotype-phenotype correlations. *Hum Mutat.* 2009;30(2):181–190.
5. Ansari M, Rainger JK, Murray JE, et al. A syndromic form of Pierre Robin sequence is caused by 5q23 deletions encompassing FBN2 and PHAX. *Eur J Med Genet.* 2014;57(10):587-595.

Legends

Figure 1:

Photographs and array-CGH results for the fetus, intragenic *FBN2* mosaic deletion.

A: Crumpled ear,

B-C: arachnodactyly, bilateral club feet, thin limbs, reduced muscle mass

D: Log₂ratio of means for oligonucleotides covering chromosome 5. A mosaic copy loss is clearly seen in band q23.3 (Log₂ratio values between 0 and -1 for 12 oligonucleotides).

E: Exons 7 to 34 of the 65 *FBN2* exons are included in the 135 Kb maximum deleted region (chr5:127656238-127791139) (<http://genome.ucsc.edu/>, GRCh37/hg19).

Figure 1:

Photographs of the fetus

A : Crumpled ear,

B, C : arachnodactyly, bilateral club feet, thin limbs, reduced muscle mass



