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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.

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Congenital Contractural Arachnodactyly (CCA) or Beals Syndrome (MIM #121050) is a connective tissue disorder characterized by congenital contractures of small and large joints, marfanoïd habitus with arachnodactyly, crumpled ears and muscular hypoplasia[1]. 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 CCA[1]. 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 CCA[3].

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 reported[4]. 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 CCA[5].

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 neonatally[2]. 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:

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Legends

Figure 1:

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

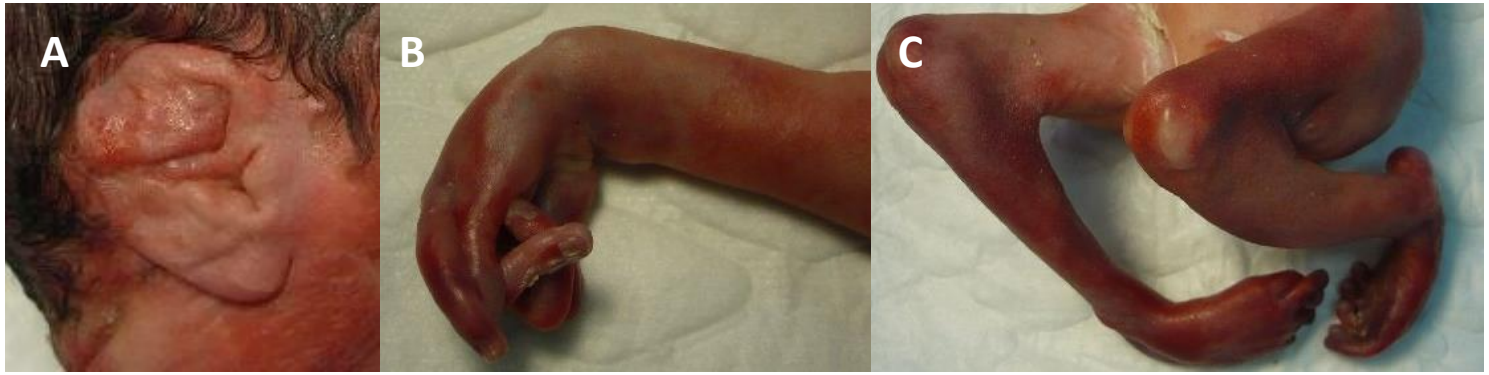
A: Crumpled ear,

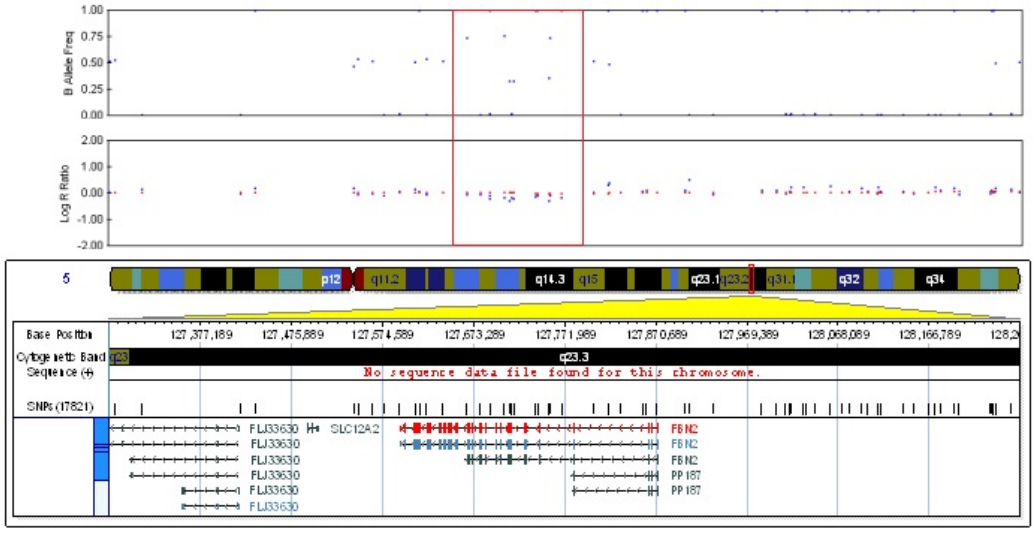
B-C: arachnodactyly, bilateral club feet, thin limbs, reduced muscle mass

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




B Allele Freq
1.00
0.75
0.50
0.25
0.00
Log R Ratio
2.00
1.00
0.00
-1.00
-2.00
5
p12
q11.2
q14.3
q15
q23.1
q23.2
q31.1
q32
q34
Base Position
127,377,189
127,475,889
127,574,589
127,673,289
127,771,989
127,870,689
127,969,389
128,068,089
128,166,789
Cytoband
q23.3
Sequence (+)
No sequence data file found for this chromosome.
SNPs (17821)
FLJ33630
SLC12A2
FBN2
PPI87