ACAN GENE SKELETAL DYSPLASIA (SHORT SIZE SYNDROME, WITH OR WITHOUT ADVANCED BONE AGE AND EARLY ONSET OSTEOARTHRITIS)

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Introduction

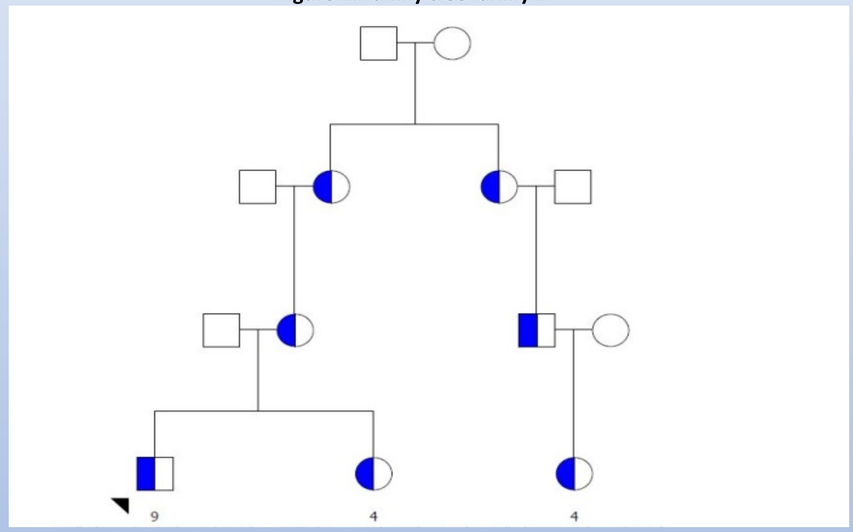
Aggrecan is a structural glycoprotein of the extracellular matrix of cartilage present in the articular cartilage, growth plate and cartilage of the intervertebral disc. Biallelic pathogenic variants are the cause of aggrecan type spondyloepiphyseal dysplasia (OMIM#612813) while the presence of heterozygous pathogenic variants determine Kimberley type spondyloepiphyseal dysplasia (OMIM#608361) and short stature associated or not with acceleration of bone maturation and early onset of osteoarthritis and familial osteochondritis dissecans (OMIM#165800). The clinical characteristics of 5 patients with heterozygous pathogenic variants in the ACAN gene are presented.

Patients

Table 1 Characteristics of the patients with *ACAN variation*

	FAMILY 1	FAMILY 2			FAMILY 3
	Patient	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Female	Masculine	Female	Female	Female
Born weight DE	-0.28	-1.0	-1.5	-0.23	-0.82
Born Length DE	-2.21	-3.5	-2.9	-1.61	-3.0
Father length DE	-2.7	-1.6	-1.6	-3.0	-1.16
Mother length DE	-1.0	-3.7	-3.7	-1.0	-2.6
First visit					
Age (years)	9a 4m	9a 9 m	4a 6 m	4a 3m	9a 8m
Bone age (years)	10	12.6	7	5.7	10
Length (DE)	-2.7	-2	-2.4	-3	-2.6
Sitting / Standing Ratio	p90	p75	p25	p3	p50
Phenotype	Retrognathia / ears set low	Genu sort	Normal	Normal	Normal
Skeletal series	Normal	Short cubes and curved rays	Normal	Widened distal femoral diaphyses	-----
Osteoarthritis	No	Yes	No	No	No
IGF1 ng/ml	198.5 (+1.0 DE)	264.7(+1.1DE)	61.7 (+0.5DE)	140.4 (+1DE)	108 (+0.5DE)
ACAN mutation	c.1097dup	c.7276G>T	c.7276G>T	c.7276G>T	c.11061_1062 del
Protein change	p.Glu367*	p.Glu2426*	p.Glu2426*	p.Glu2426*	p.(Phe354Cys fs*13)

Figure 1: Family tree family 2



Conclusions

- New patients and pathogenic variants of the ACAN gene have been identified with highly variable phenotypic and radiological characteristics, without the skeletal disproportion and the advance of bone maturation being constant.
- Most of our patients have harmonic short stature and advanced bone age, two of them have skeletal abnormalities in the axial skeleton and one with early-onset osteoarthritis.
- The ACAN gene study should be included in the study of patients with idiopathic short stature.
- More studies are required to establish the genotype-phenotype correlation in patients with genetic variants in the ACAN gene.

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