Aggrecan (ACAN) mutations: expanding the clinical spectrum

Mutaciones en Aggrecan (*ACAN*): espectro clínico ampliado

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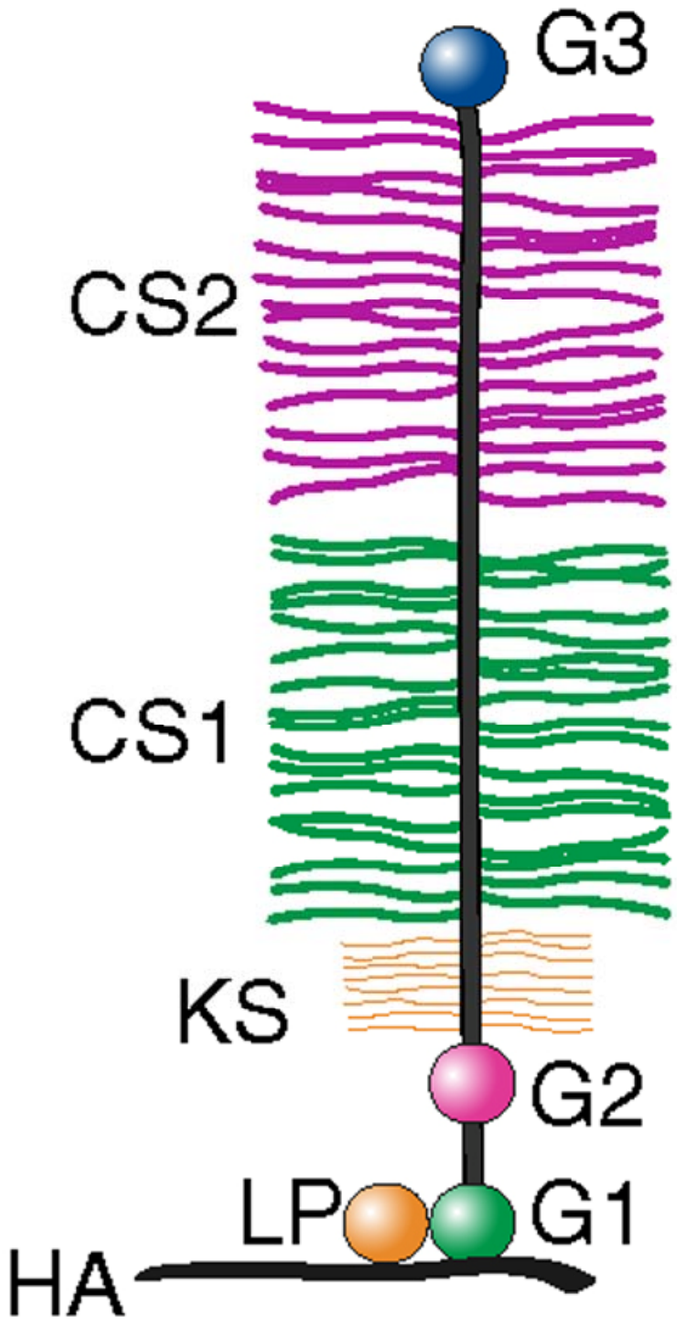
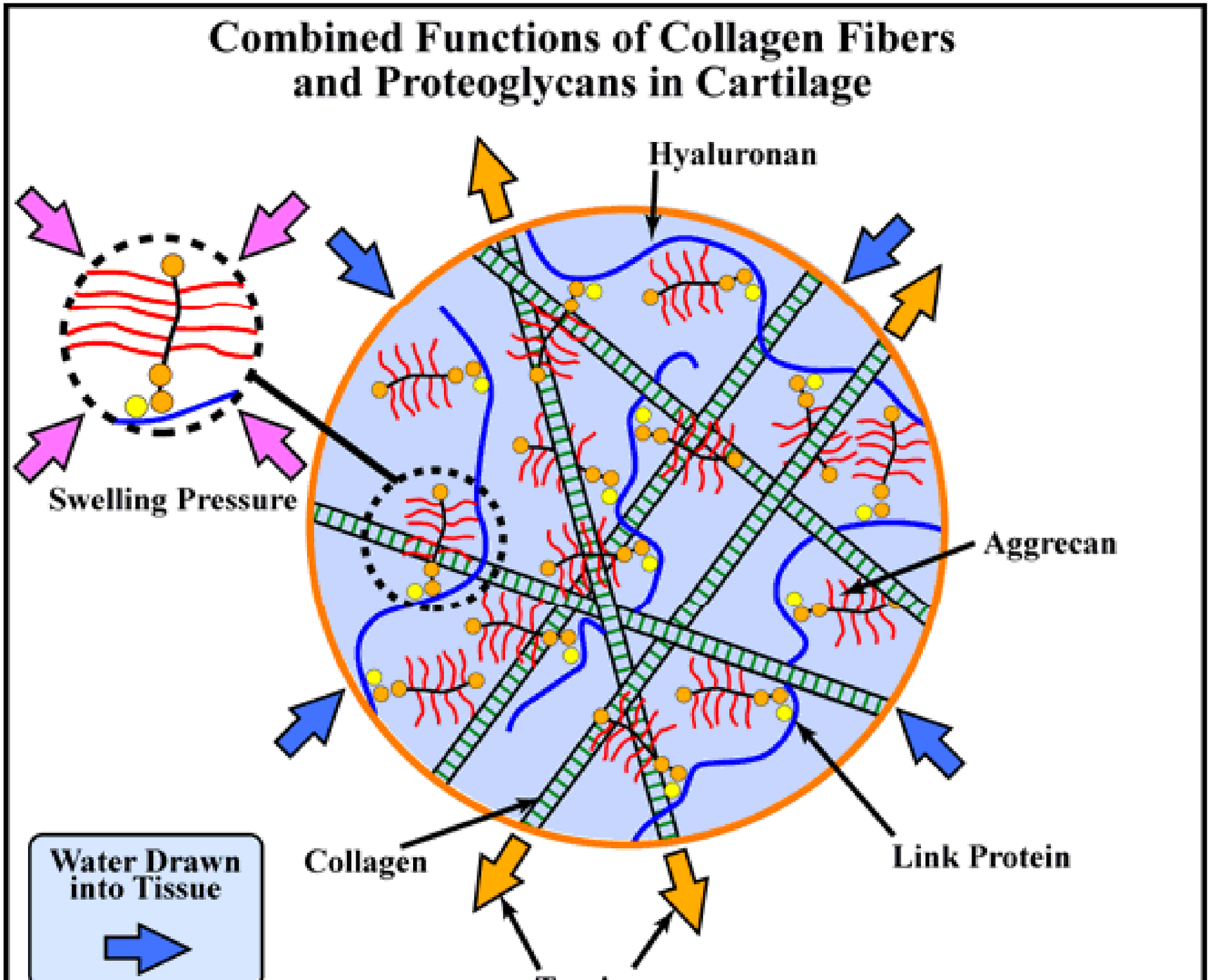
- Aggrecan is a large chondroitin sulphated proteoglycan

- 250 kDa protein core with approximately 100 chondroitin sulphate glycosaminoglycan and 30 keratan sulphate chains attached to a large domain located between three globular domains.

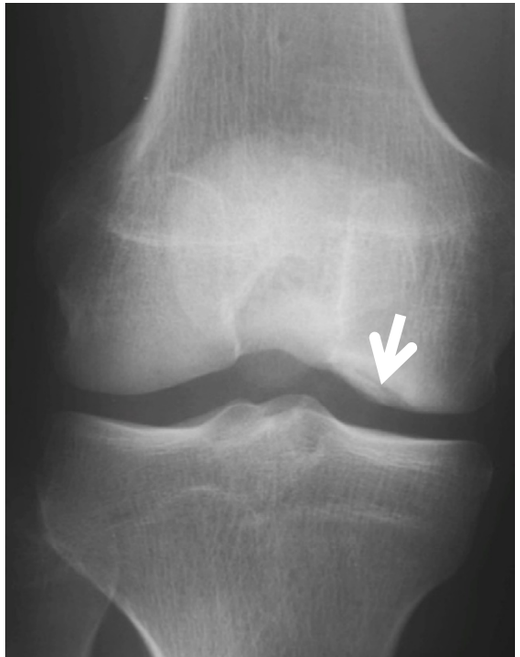
- It is expressed in several tissues including those in the brain, but is a major structural component of cartilage in the cartilage extracellular matrix in the:
  - Growth plate
  - Articular cartilage
  - Intervertebral discs

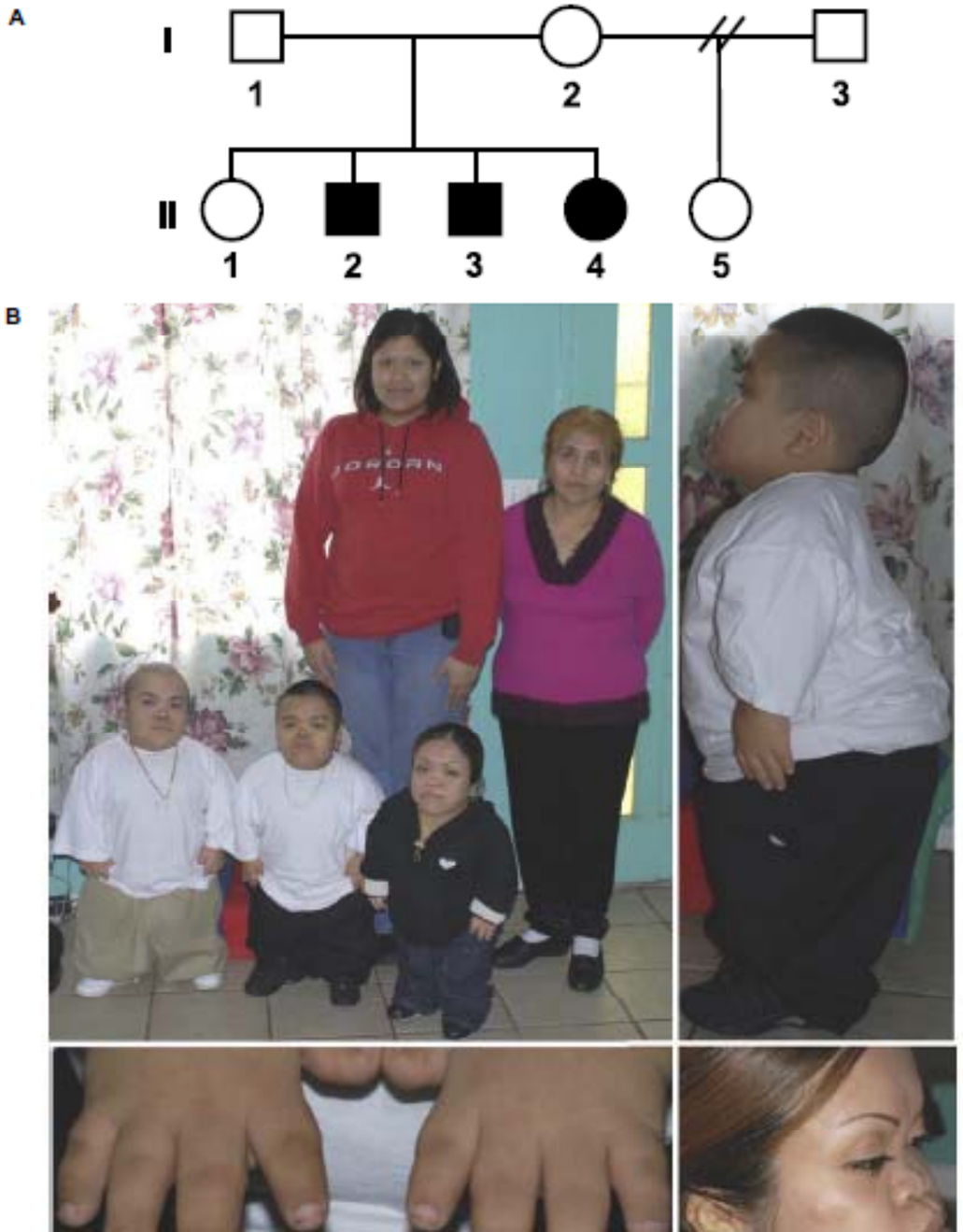
- Function is to allow the cartilage to withstand the high mechanical load found in the skeletal joint




Combined Functions of Collagen Fibers
and Proteoglycans in Cartilage
Hyaluronan
Swelling Pressure
Aggrecan
Collagen
Link Protein
Water Drawn
into Tissue

- Spondyloepiphyseal dysplasia, Kimberley type (SEDK) – AD
- Familial osteochondritis dissecans – AD
- Spondyloepimetaphyseal dysplasia, aggrecan type (SEMD) - AR





Tompson et al, 2004;

CLINICAL RESEARCH ARTICLE

Clinical Characterization of Patients With Autosomal Dominant Short Stature due to Aggrecan Mutations

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- 103 individuals (20 families) with short stature, minor skeletal defects and mild facial dysmorphisms.
- Some had distinct phenotypes showing advanced bone age, poor pubertal spurt and early growth cessation or others with osteochondritis dissecans and precocious osteoarthritis.

Jan 2012 • SKELETALSEQ.V1 - 226 genes (Roche)

Dec 2012 • SKELETALSEQ.V2 - 295 genes Haloplex, Agilent technologies)

Mar 2014 • SKELETALSEQ.V3 - 315 genes (Roche SeqCap, MiSeq) - 16/run

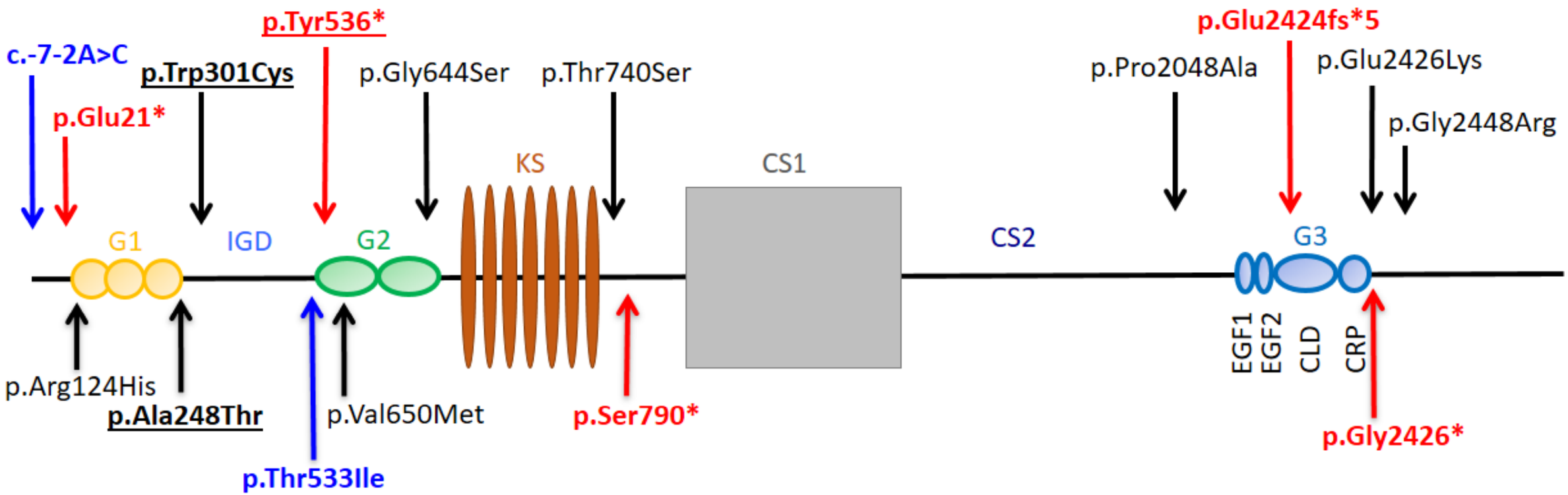
Feb 2015 • SKELETALSEQ.V4 - 327 genes (MiSeq) -18/run

Oct 2015 • SKELETALSEQ.V5 - 362 genes (MiSeq) -18/run

Feb 2016 • SKELETALSEQ.V6 - 368 genes (NextSeq) - 80/run

Jan 2017 • SKELETALSEQ.V7 - 385 genes (NextSeq) - 80/run

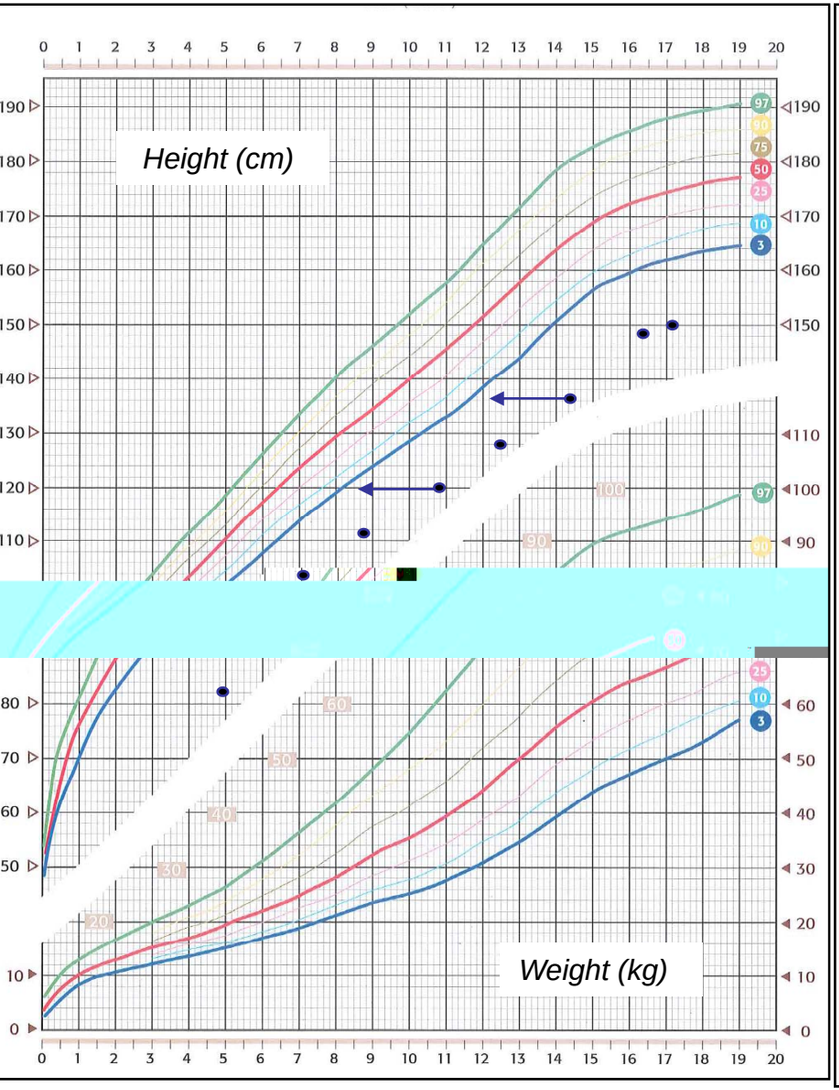
heterozygous ACAN mutations



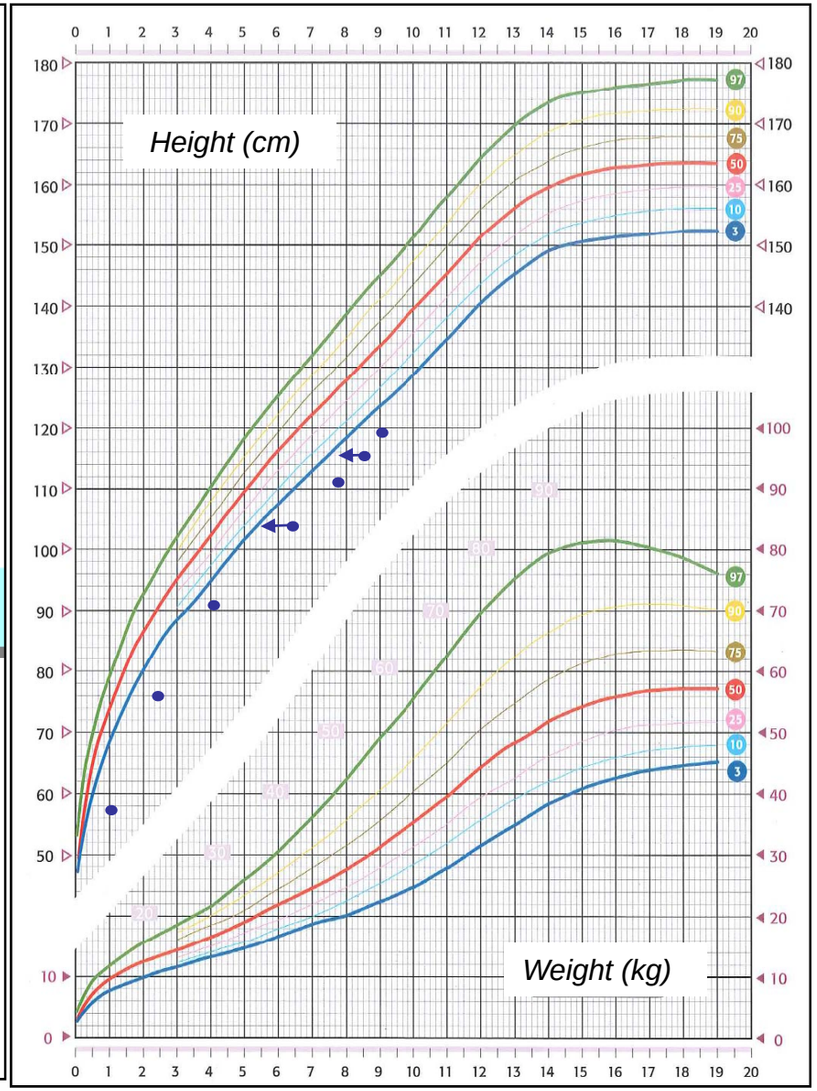
14 mild to moderate short stature and brachydactyly (missense, nonsense and frameshift). Those with osteoarthritis and/or discopathy.

2 Spondyloepiphyseal dysplasia, Kimberley type (SEDK)

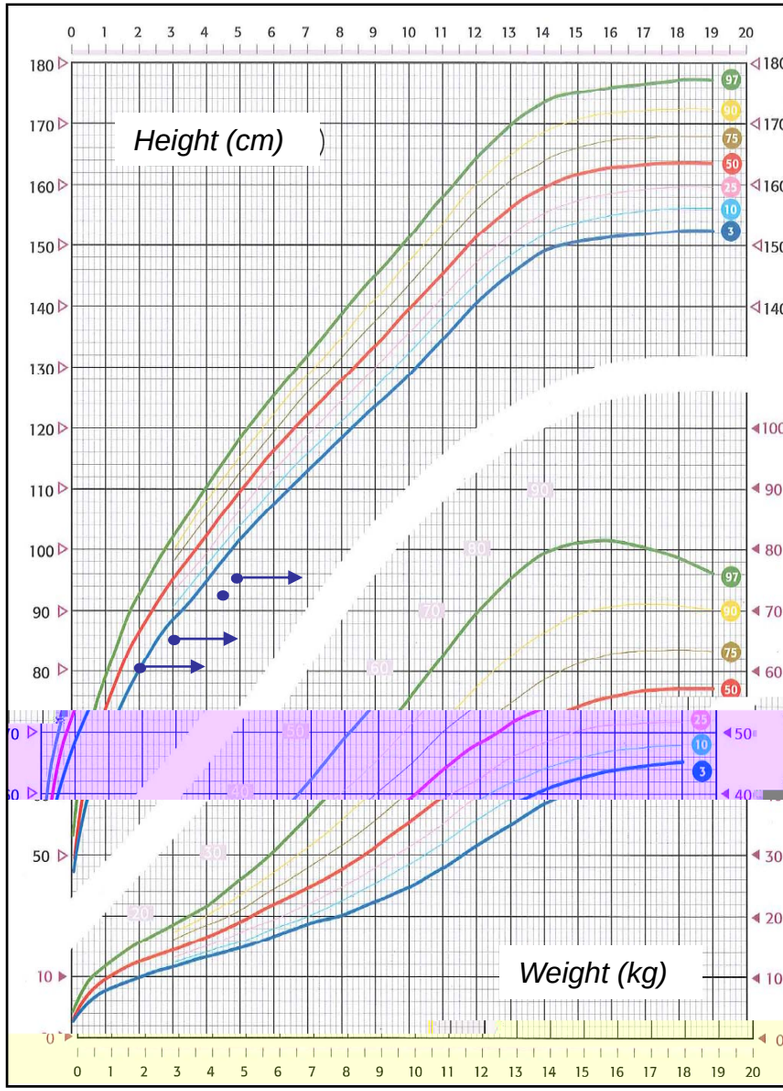
Delayed bone age (n=4)



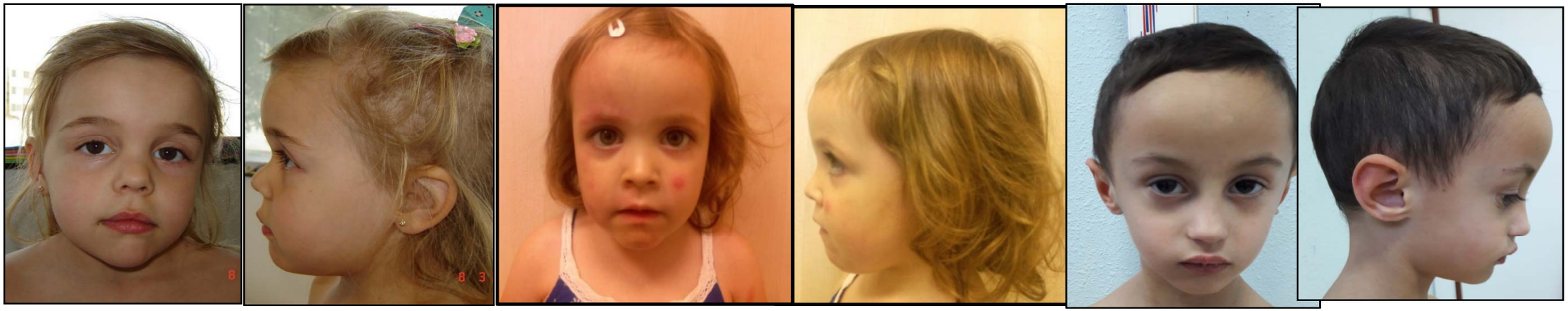
BA=CA (n=5)



Advanced BA (n=5)



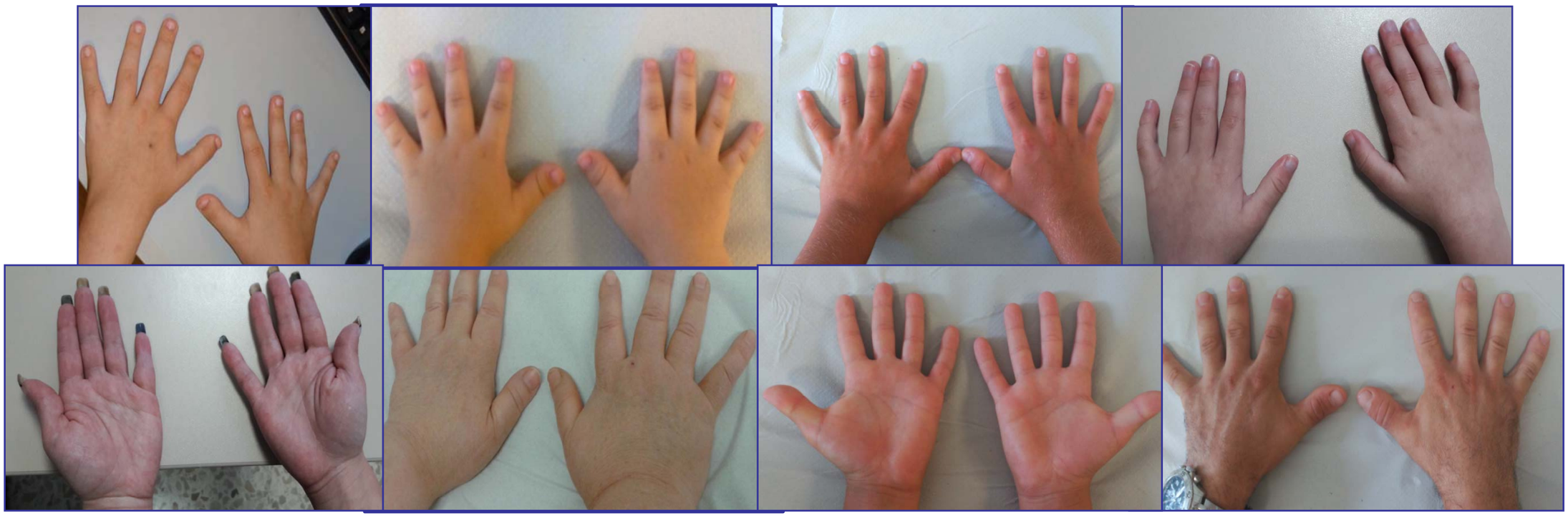
Median height SDS in children was -2.91 (range -4.30/-1.86 SDS)



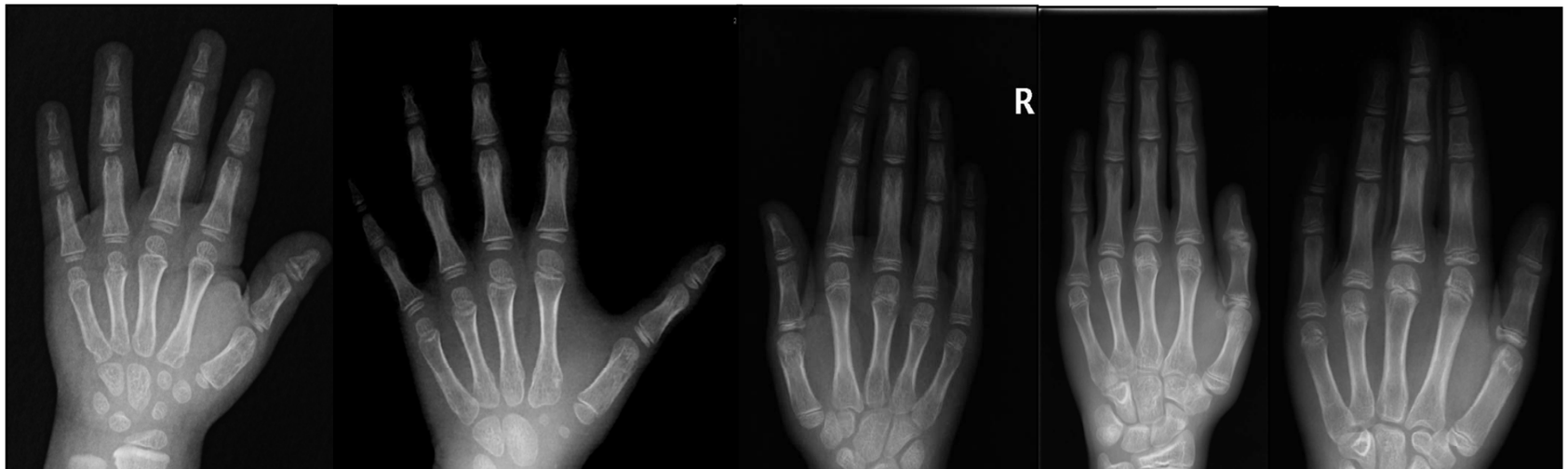
Pediatric cohort

- 53% of patients have a mild dysmorphic phenotype
- 23% frontal bossing, depressed nasal bridge and mid-face hypoplasia

Probands and adults showing brachydactyly and/or short first metacarpal.

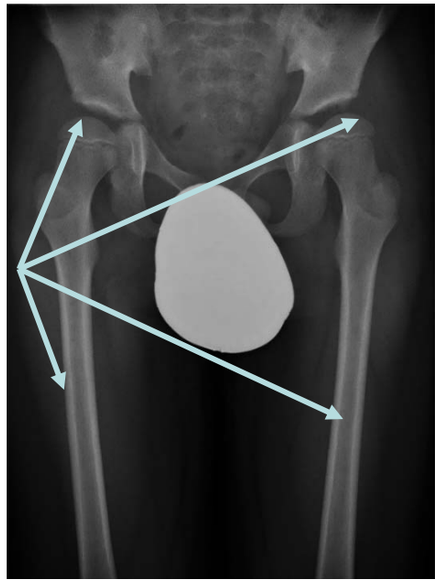


Brachydactyly and first short metacarpal, present in all cases.

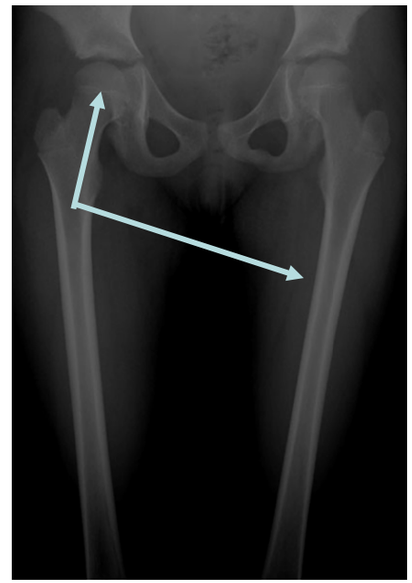


38% had mild hip anomalies

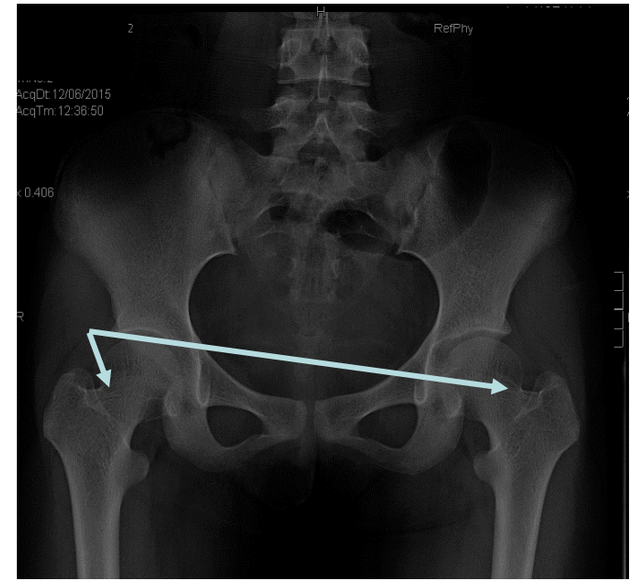
Coxa valga, mildly flattened capital femoral epiphyses and slender femora



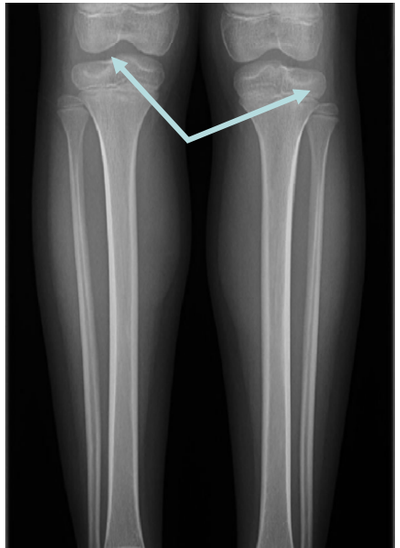
Coxa valga, slender femora

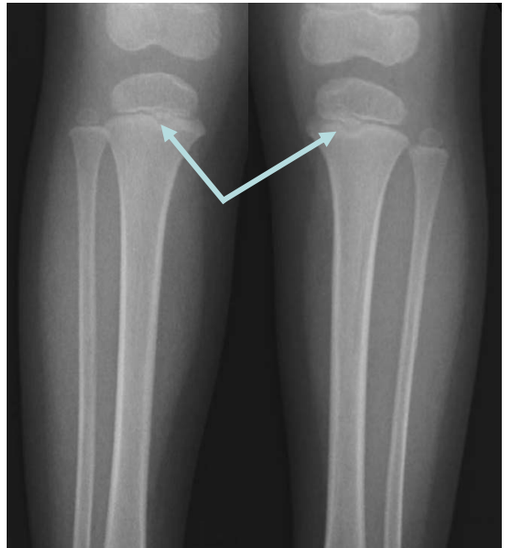


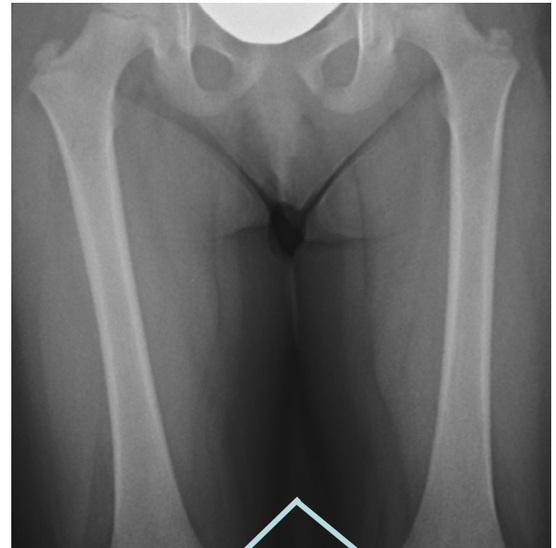
Short femoral necks

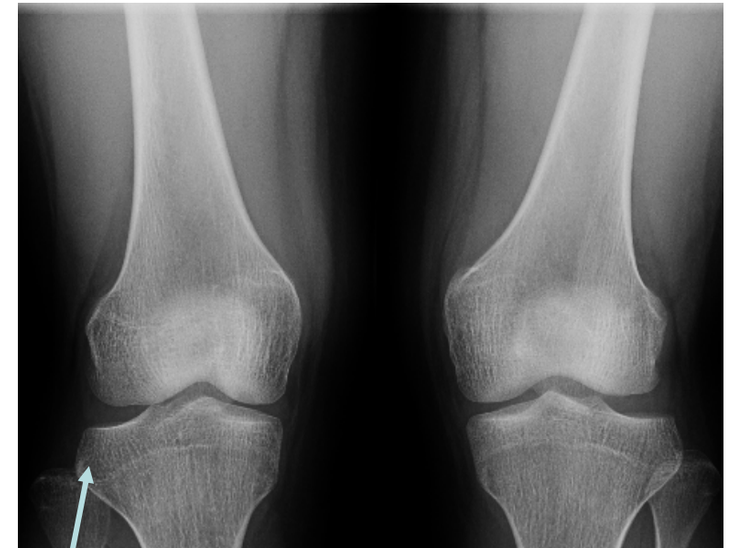


23% had mild epiphyseal knee defects









Study reference	Number of pa (Children/ad from X fam	SGA	Range of heigh Children Adults	Advanced B children	Frontal bos	Flat nasal br	Mid facial hyp	Brachydac	Short thumbs, a short first metac	Broad great	Hyperlordo	Hip anoma	Mild osteoch knee defe	Early growth ce (adults)	Early-onset arth (families	Intervertebra disease (fam
ilsson et al, 2014	14 (5/9)* 3 fams	2/4	-4/-1.2 -3.8/-2.3	3/5	NR	NR	6/9	6/9	3/9	NR	NR	NR	NR	5/5	1/3	0/3
uintos et al, 2015	3 (1/2)** 1 fam	0/1	-2.7 -4.7/-2.6	1/1	NR	NR	1/3	NR	NR	NR	NR	NR	NR	2/2	0/1	0/1
Manouk van der Steen et al, 2016	10 (4/6) 3 fams	3/3	-3.7/-2.4 -5.4/-3.7	3/4	NR	NR	9/10	NR	3/10	6/10	3/10	NR	NR	NR	3/3	0/3
kourogianni et al, 2017	102 (32/70) 20 fams	NR	-4.2/-0.6 -5.9/-0.9	19/23	2/32	8/20	8/20	5/20	3/20	NR	NR	NR	NR	23/70	13/20	8/20
Dateki et al, 2017	4 (2/2) 1 fam	0/2	-2.7/-2.5 -3.1/-3	2/2	NR	NR	3/4	NR	NR	NR	1/4	NR	NR	NR	0/1	1/1
Hu et al, 2017	9(3/6) 3 fams	1/1	-4.3/-2.9 -5.4/-2.9	0/3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0/3	0/3
Hauer et al, 2017	11(6/5) 6 fams	1/6	-3.9/-2 - 3.8/-1.8	2/5	3/6	NR	NR	3/6	2/6	2/6	NR	1/6	NR	NR	1/6	NR
Current study	32 (14/18) 14 fams	4/13	-4.3/-1.86 -5.4/-1.79	5/13	5/13	4/13	3/13	12/13	11/13	NR	3/13	5/13	3/13	6/6	3/14	1/14
SUMMARY	164 (59/105)	11/40	-4.7/-0.6	30/45	9/40	4/13	22/30	19/28	19/38	8/16	7/27	5/13	3/13	27/74	20/45	10/30

- Premature termination codons potentially resulting in truncated proteins or haploinsufficiency through nonsense mediated mRNA degradation

- Dominant-negative (neo-morphic) missense mutations that disrupt cartilage structure and function

- Expands the clinical and molecular spectrum of heterozygous *ACAN* mutations.

- Strong candidate in patients with short stature and minor skeletal defects and not only those with advanced bone age and osteoarticular complications.

- Hand, knee and hip anomalies should be carefully observed as they can be indicative of aggrecanopathies.

Spanish ACAN study

- Lucía Sentchordi-Montané, Miriam Aza-Carmona, Sara Benito-Sanz, Ana Barreda-Bonis, María Consuelo Sánchez-Garre, Pablo Prieto-Matos, Pablo Ruiz-Ocaña, Alfonso Lechuga-Sancho, Atilano Carcavilla-Urquí, Inés Mulero-Collantes, Gabriel A. Martos Moreno, Ángela del Pozo, Elena Vallespín, Amaka Offiah, Manuel Parrón-Pajares, Sergio B. de Sousa, Purificación Ros-Pérez, Isabel González-Casado, Karen E. Heath

Dysplasia research group

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- *NGS y Arrays:* Elena Vallespin, Vicky F. Montaño, Maria Palomares, Julian Nevado
- *Genética Clínica y prenatal:* Fernando Santos, Sixto García-Miñaur, Pablo Lapunzina, Elena Mansilla, Fe Santiago
- *Bioinformática:* Ángela del Pozo, Kristina Ibañez, Juan Carlos Silla, Mario Solís

Skeletal dysplasia multidisciplinary unit (UMDE), Hospital La Paz

- Fernando Santos (coordinador), Ana Coral Barreda y Isabel González, Rima Regojo, Gaspar González, Manuel Parrón, Eugenia Antolín, Marta Cabrera