Clinical and radiological manifestations in a large Swedish family with a pathogenic heterozygous *ACAN* variant

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Objective

Heterozygous mutations in the aggrecan gene (*ACAN*) are associated with idiopathic short stature, with or without advanced bone age (BA), osteochondritis dissecans (OCD) and early onset of severe osteoarthritis (OA). Variable features also include midface hypoplasia, brachydactyly, short thumbs and intervertebral disc (ID) degenerative disease.

Patients & Methods

All included individuals belong to a five generation Swedish family with short stature (Fig 1), OCD, and early onset OA (MIM#165800), caused by a pathogenic sequence variant, p.V2303M, in the C-type lectin domain of *ACAN.*

We reviewed 173 radiographs in 22 individuals (8F:14M) (Fig 2) 2 computed tomography & 5 magnetic resonance imaging.

Results

In the group of **children** (n=6; age ≤15 years; 3F:3M) (Fig 3&4)

- 6 had moderately advanced BA (range: 6-17.5 months)
- 4 had subtle defects of the distal radial growth plate
- 3 males had OCD in the knees & 1 of them also presented OCD of the hip, scoliosis and Schmorl`s nodes of ID

■ Operations

One male patient went through derotation osteotomy in both hips and later a proximal tibia osteotomy and distal fibula osteotomy

Among 16 **adult** patients (age ≥15 years 5F:11M) (Fig 5)

- 16 had OCD
- 13 developed early onset (>40y) OA
- 4 had radiological manifestations of the spine

■ Operations

8 adult patients (3F:5M) have been operated

- 4 patients had hip replacement (1F:3M;3bilateral;1unilateral)
- 5 knee arthroplasties (2F:3M; 3bilateral; 2unilateral)
  5 patients had tibia osteotomy
  1 had combined tibia and fibula osteotomy

Brachydactyly

No pediatric or adult patient presented brachydactyly.

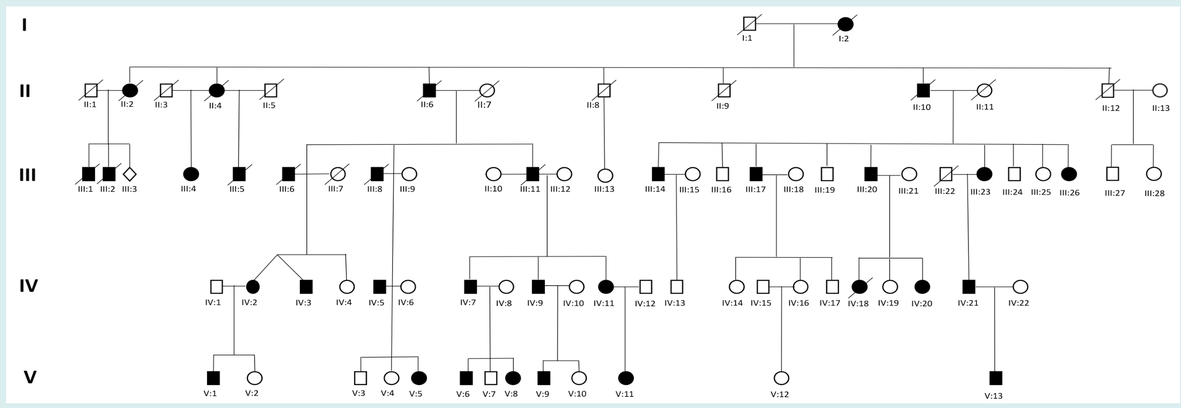

Fig 1. *ACAN* 5 generations pedigree

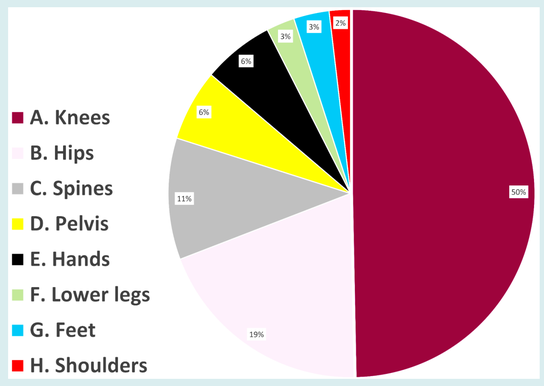

Fig 2. *ACAN* patients radiographs

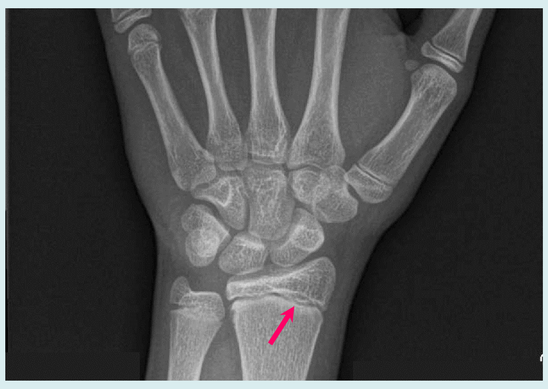

Fig 4. Subtle defects of the distal radial growth plate in *ACAN* patient

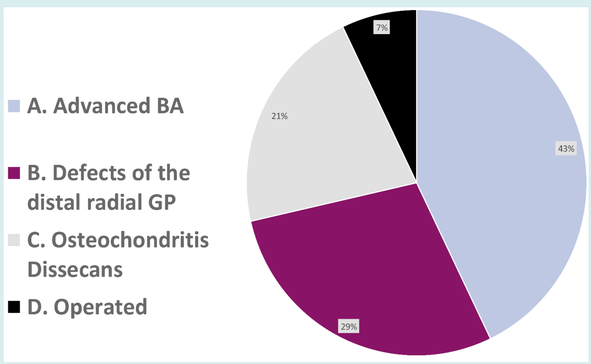

Fig 3. *ACAN* children

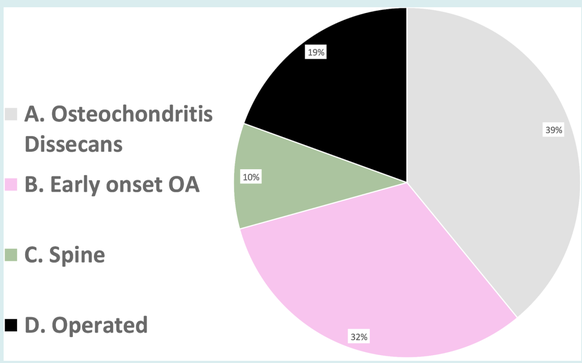

Fig 5. *ACAN* adults

Conclusions

- The pathogenic heterozygous p.V2303M variant in the *ACAN* gene causes mildly disproportionate short stature with early-onset OA and intervertebral disc degeneration often requiring multiple orthopedic interventions
- Radiologic findings, included moderately advanced BA, OCD in knees, hips, and elbows as well as OA in 13 individuals
- Further studies are needed to identify preventive measures that may slow the progression of OA and intervertebral disc disease and to determine the role of rhGH to improve final height

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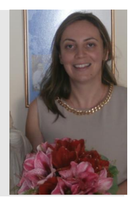

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Growth and syndromes (to include Turner syndrome)
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