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

Alexandra Gkourogianni1, Emma Segerlund2, Sigrun Hallgrimsdottir2, Ola Nilsson1,3, Eva-Lena Stattin4

1. Division of Pediatric Endocrinology, Department of Women’s and Children’s Health, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; 2. Sunderbyn Hospital, Sunderbyn, Sweden; 3. Örebro University and University Hospital, Örebro, Sweden, 4. Department of Immunology, Genetics, and Pathology, Science for Life Laboratory, Uppsala University, Uppsala, Sweden

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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.

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

References

Alexandra Gkourogianni MD, PhD
Postdoctoral fellow

Karolinska Institutet & University Hospital
Growth & Cartilage Department
Solna, CMM L8:01, SE - 171 76 Stockholm, Sweden

E-mail: alexandra.gkourogianni@ki.se
Telephone: +46 70-215 01 16
Website: ki.se/en/people/alegko

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Poster presented at:

Growth and syndromes (to include Turner syndrome)
Alexandra Gkourogianni