ACAN-relatert kortvoksthet

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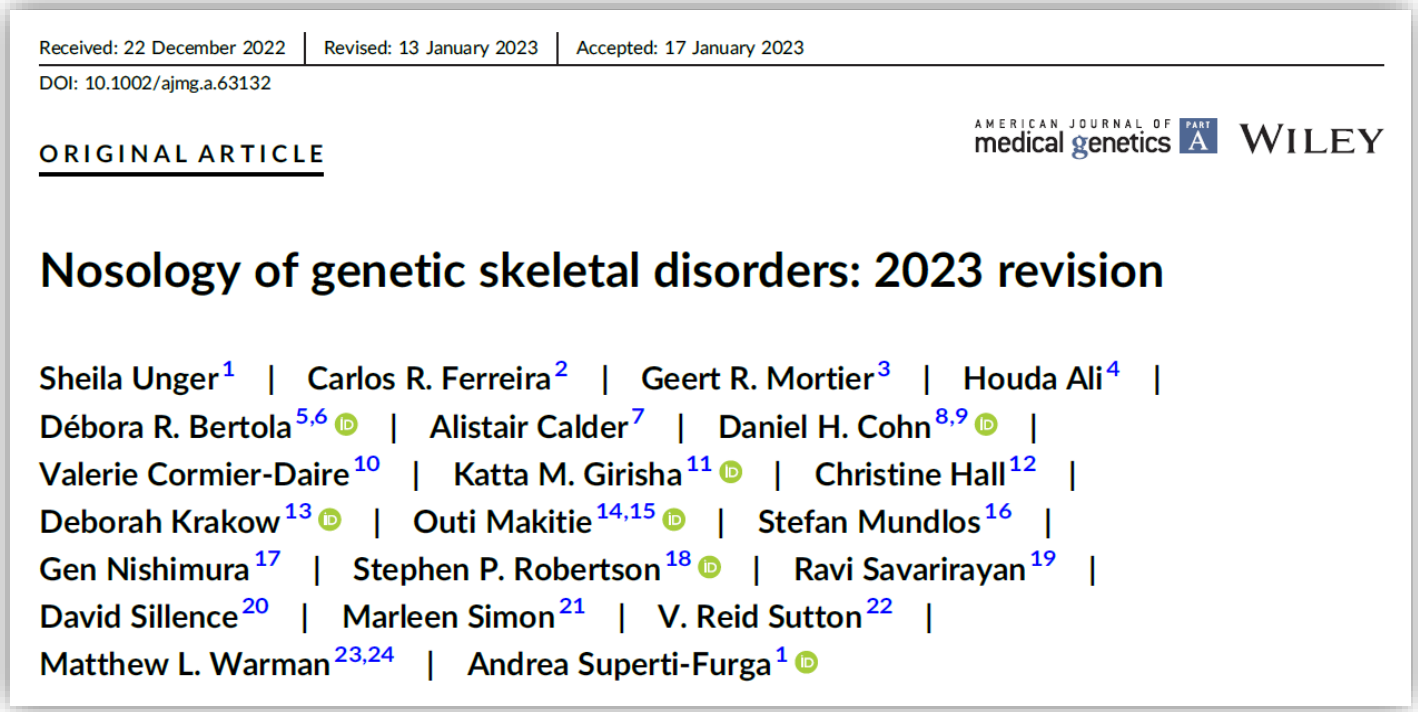
Mange ulike skjelettdysplasier



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ORIGINAL ARTICLE

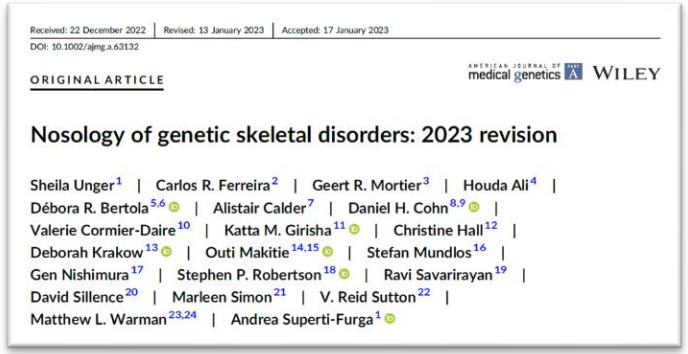
AMERICAN JOURNAL OF medical genetics PART A WILEY

Nosology of genetic skeletal disorders: 2023 revision

Sheila Unger[1] | Carlos R. Ferreira[2] | Geert R. Mortier[3] | Houda Ali[4] | Débora R. Bertola[5,6] | Alistair Calder[7] | Daniel H. Cohn[8,9] | Valerie Cormier-Daire[10] | Katta M. Girisha[11] | Christine Hall[12] | Deborah Krakow[13] | Outi Makitie[14,15] | Stefan Mundlos[16] | Gen Nishimura[17] | Stephen P. Robertson[18] | Ravi Savarirayan[19] | David Sillence[20] | Marleen Simon[21] | V. Reid Sutton[22] | Matthew L. Warman[23,24] | Andrea Superti-Furga[1]

- 771 skjelettdysplasier
- 552 ulike gener
- Klassifisert i 41 grupper

Gruppe 7: Proteoglycan core protein disorders



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Proteoglycan core proteins disorders				
Dyssegmental dysplasia, HSPG2-related	AR	*HSPG2*	224410, 224400	Variable severity; Includes both former Silverman-Handmaker and Rolland-Desbuquois types
Myotonic chondrodystrophy, HSPG2-related (Schwartz-Jampel syndrome)	AR	*HSPG2*	255800	Variable severity; includes previous Burton dysplasia
Spondylo-epiphyseal dysplasia, ACAN-related (dominant, Kimberley type)	AD	*ACAN*	608361	
Spondylo-epi-metaphyseal dysplasia, ACAN-related (recessive, aggrecan type)	AR	*ACAN*	612813	
Short stature with advanced bone age, ACAN-related	AD	*ACAN*	165800	Sometimes with osteochondritis dissecans; other cases short stature with no skeletal features and normal bone age

3 varianter beskrevet

- **Spondylo-epifyseal dysplasi (SED)**, ACAN-relatert, aut.dom, Kimberley type
- **Spondylo-epi-metafyseal dysplasia (SEMD)**, ACAN-relatert, aut rec.

- **ACAN-relatert kortvoksthet**, aut.dom – stor variasjon i denne gruppen
  - Noen med tidlig benmodning
  - Med og uten skjelettforandringer
  - Noen med en spesiell forandring i knærne - osteokondritis dissecans

Artikkel 2014

- **2014**: Nilsson et al
- Pas med ISS (idiopatisk short stature) = kortvoksthet uten kjent (genetisk) årsak
- **Fant at dette skyldtes en variant i *ACAN*-genet**
- Senere påvist mange varianter i flere studier

Short Stature, Accelerated Bone Maturation, and Early Growth Cessation Due to Heterozygous Aggrecan Mutations

Ola Nilsson,* Michael H. Guo,* Nancy Dunbar, Jadranka Popovic, Daniel Flynn, Christina Jacobsen, Julian C. Lui, Joel N. Hirschhorn, Jeffrey Baron, and Andrew Dauber

Program in Developmental Endocrinology and Genetics (O.N., J.C.L., J.B.), Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892; Center for Molecular Medicine and Pediatric Endocrinology Unit, Department of Women's and Children's Health (O.N.), Karolinska Institutet and Karolinska University Hospital, SE-171 76 Stockholm, Sweden; Program in Biological and Biomedical Sciences (M.H.G.), Harvard Medical School, Boston, Massachusetts 02115; Connecticut Children's Medical Center (N.D.), Hartford, Connecticut 06106; Children's Hospital of Pittsburgh (J.P., D.F.), University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15224; Division of Endocrinology (M.H.G., C.J., J.N.H., A.D.), Boston Children's Hospital, Boston, Massachusetts 02115; Department of Genetics (M.H.G., J.N.H.), Harvard Medical School, Boston, Massachusetts 02115; and Program in Medical and Population Genetics (J.N.H., A.D.), Broad Institute, Cambridge, Massachusetts 02142

Context: Many children with idiopathic short stature have a delayed bone age. Idiopathic short stature with advanced bone age is far less common.

Objective: The aim was to identify underlying genetic causes of short stature with advanced bone age.

Setting and Design: We used whole-exome sequencing to study three families with autosomal-dominant short stature, advanced bone age, and premature growth cessation.

Results: Affected individuals presented with short stature [adult heights −2.3 to −4.2 standard deviation scores (SDS)] with histories of early growth cessation or childhood short stature (height SDS −1.9 to −3.5 SDS), advancement of bone age, and normal endocrine evaluations. Whole-exome sequencing identified novel heterozygous variants in *ACAN*, which encodes aggrecan, a proteoglycan in the extracellular matrix of growth plate and other cartilaginous tissues. The variants were present in all affected, but in no unaffected, family members. In Family 1, a novel frameshift mutation in exon 3 (c.272delA) was identified, which is predicted to cause early truncation of the aggrecan protein. In Family 2, a base-pair substitution was found in a highly conserved location within a splice donor site (c.2026+1G>A), which is also likely to alter the amino acid sequence of a large portion of the protein. In Family 3, a missense variant (c.7064T>C) in exon 14 affects a highly conserved residue (L2355P) and is strongly predicted to perturb protein function.

Conclusions: Our study demonstrates that heterozygous mutations in *ACAN* can cause a mild skeletal dysplasia, which presents clinically as short stature with advanced bone age. The accelerating effect on skeletal maturation has not previously been noted in the few prior reports of human *ACAN* mutations. Our findings thus expand the spectrum of *ACAN* defects and provide a new molecular genetic etiology for the unusual child who presents with short stature and accelerated skeletal maturation. (*J Clin Endocrinol Metab* 99: E1510–E1518, 2014)

Artikkel

Gibson and Briggs *Orphanet Journal of Rare Diseases* (2016) 11:86
DOI 10.1186/s13023-016-0459-2

Orphanet Journal of Rare Diseases

REVIEW Open Access

The aggrecanopathies; an evolving phenotypic spectrum of human genetic skeletal diseases

Beth G. Gibson[1] and Michael D. Briggs[1,2*]

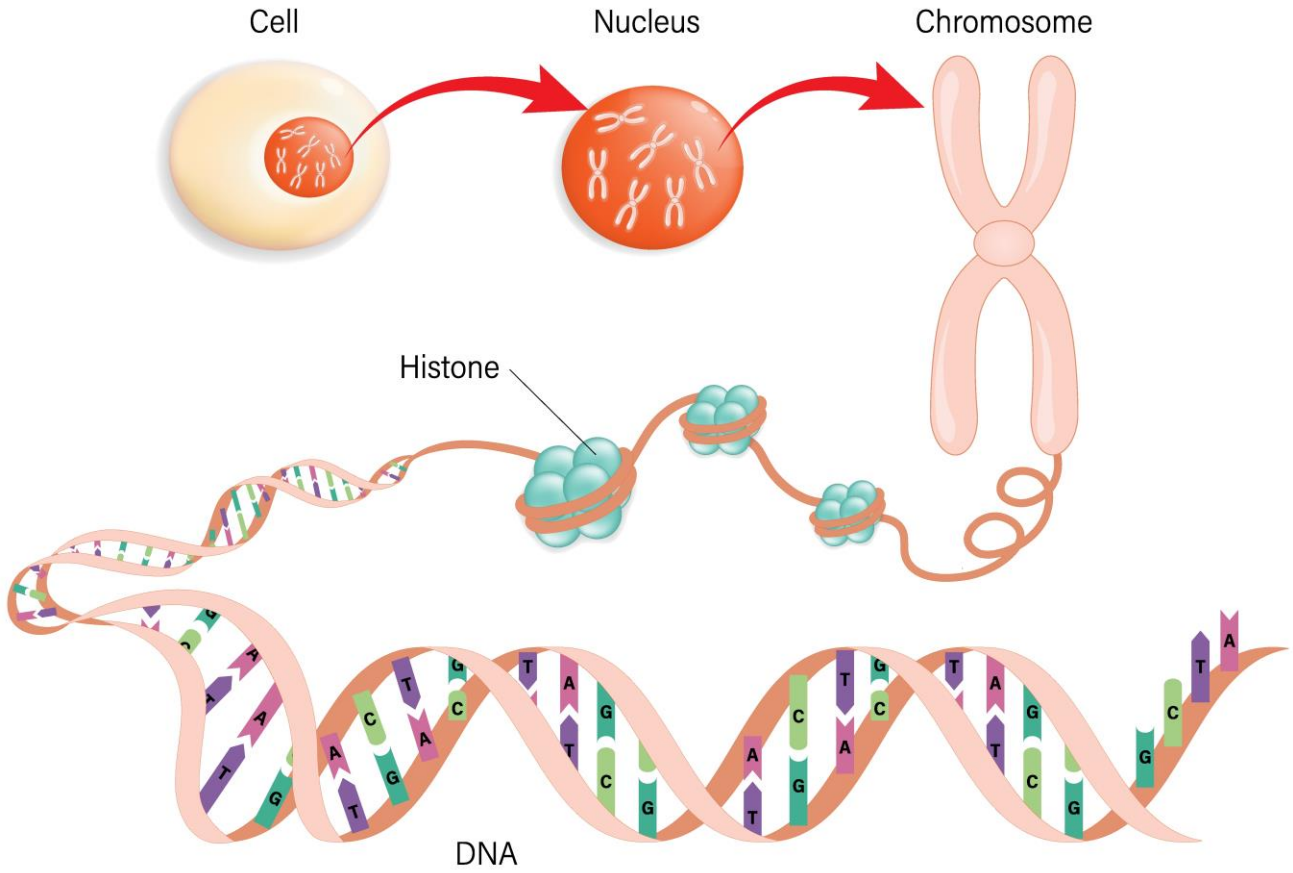
Abstract

The large chondroitin sulphated proteoglycan aggrecan (*ACAN*) is the most abundant non-collagenous protein in cartilage and is essential for its structure and function. Mutations in *ACAN* result in a broad phenotypic spectrum of non-lethal skeletal dysplasias including spondyloepimetaphyseal dysplasia, spondyloepiphyseal dysplasia, familial osteochondritis dissecans and various undefined short stature syndromes associated with accelerated bone maturation. However, very little is currently known about the disease pathways that underlie these aggrecanopathies, although they are likely to be a combination of haploinsufficiency and dominant-negative (neomorphic) mechanisms. This review discusses the known human and animal aggrecanopathies in the context of clinical presentation and potential disease mechanisms.

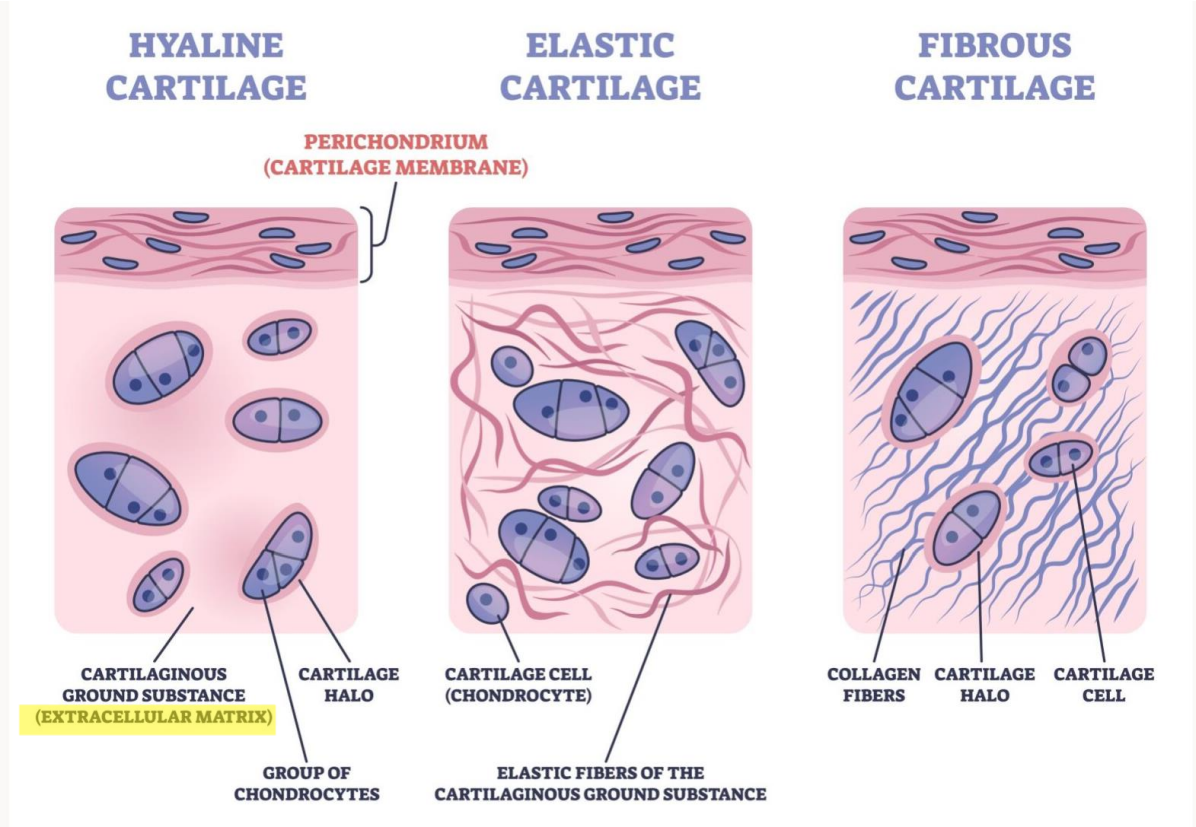
Keywords: Aggrecan, Osteochondritis dissecans, Chondrodysplasia, Cartilage, Skeletal dysplasia

Hva menes med ACAN-relatert?

- ***ACAN**:* gen som koder for Aggrecan
- **Aggrecan** er et proteoglycan
- Proteoglycan: viktig komponent i **ekstracellulær matrix** (det som er mellom bencellene) og **leddbrusk**

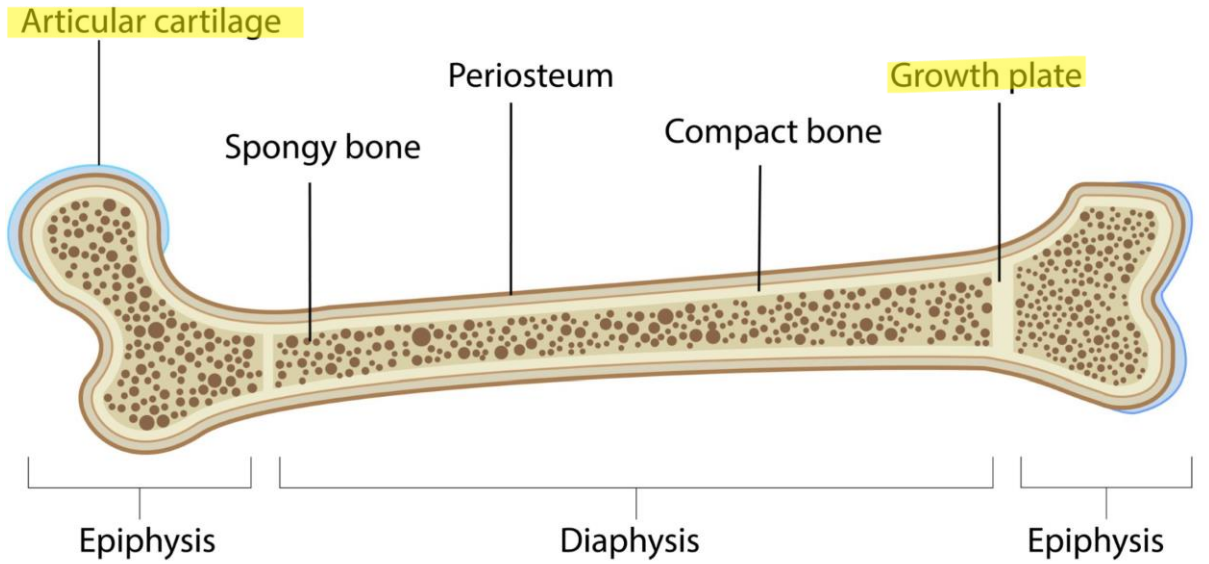


Vekstplaten i ben



Variant i ACAN-genet -> påvirker benvekst og leddbrusk

Proteoglycan gjør brusken slitesterk



ACAN-relatert kortvoksthet, kjennetegn

4 kjennetegn:

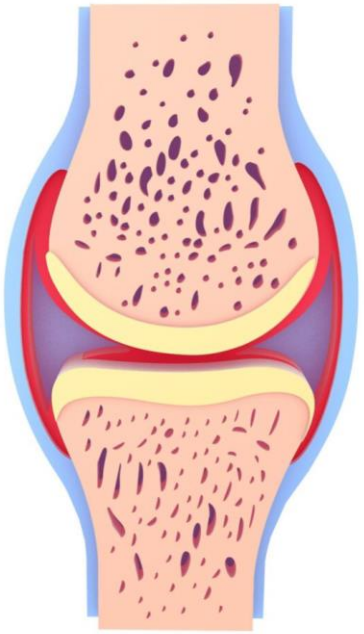
1. Moderat **kortvoksthet** (≈ -2,8 SD), tidlig vekststopp
   - Ikke så tydelig hos barn, mer hos voksne

2. Tidlig **artrose** (slitasje) i store ledd (spesielt knær):
   I en studie: >90% i minst ett ledd, 60% behov for kirurgi

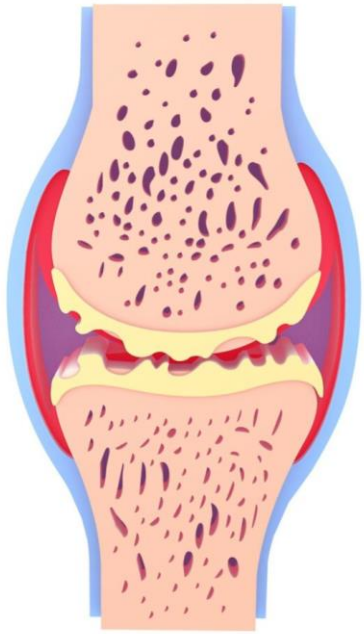
3. Økt forekomst av skiveutglidning og slitasje i **mellomvirvelskivene i ryggen**

4. Hos noen:
   - tidlig benmodning; ≈ +1,3 år (0 – 3,7 år)
   - Korte fingre/tomler
   - Mild påvirkning av ansiktsskjelett (stort hode, flatere nese)

Kjennetegn 2. Tidlig artrose – spesielt knær

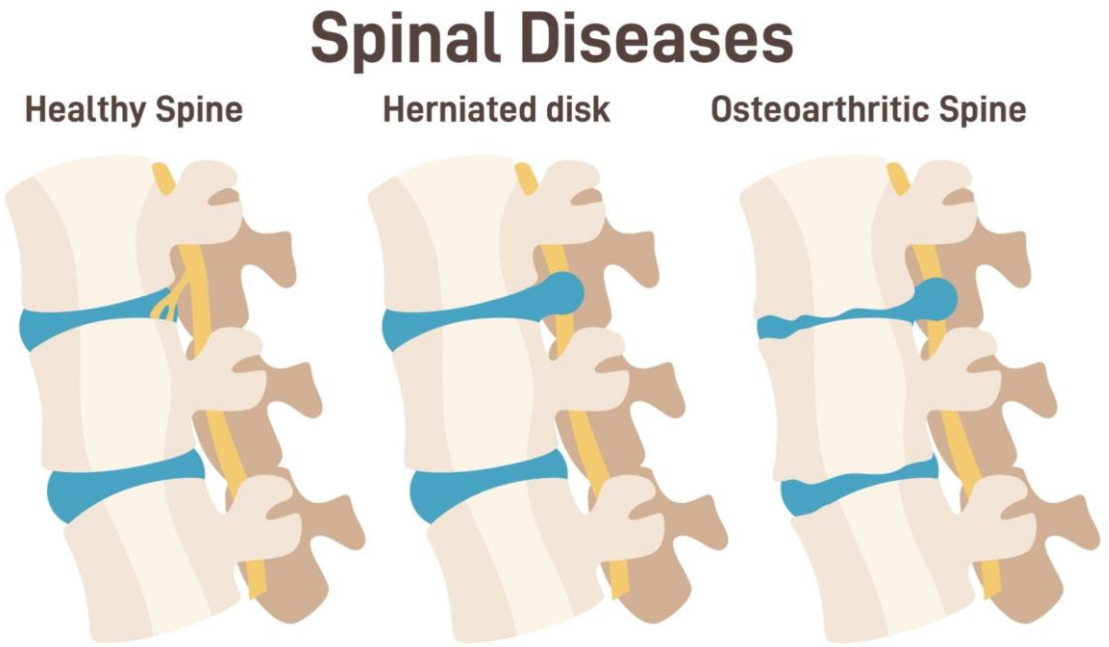


Normal leddbrusk



Artrose

Kjennetegn 3. Mellom-virvelskivene i ryggen påvirket



Behandling

- Ingen spesifikk behandling for ACAN-relatert kortvoksthet
- Behandlingen rettet mot symptomer

- Kliniske medikamentstudier i gang i USA
- Foreløpig små og i tidlig fase
  - **1. Veksthormon**
  - **2. Vosoritide**

1. Veksthormon

2022

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https://doi.org/10.1210/clinem/dgab904
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Clinical Research Article

Treatment of Short Stature in Aggrecan-deficient Patients With Recombinant Human Growth Hormone: 1-Year Response

Gajanthan Muthuvel,[1,*] Andrew Dauber,[2,3,*] Eirene Alexandrou,[4,5] Leah Tyzinski,[1] Melissa Andrew,[2] Vivian Hwa,[1,6] and Philippe Backeljauw[1,6]

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*Denotes joint first author

- liten studie, n=10
- Alder: gj.snitt 5,6 år (fra 2,4 til 9,7 år)
- Konklusjon: ga økt høydevekst
  - Fra ca 5.2 cm -> 8.3 cm på 1 år
- Mangler data på langtidseffekt

2. Vosoritide

- Utviklet for og testet på akondroplasi
- **Studier i gang på andre skjelettdiagnoser bl.a ACAN-relatert kortvoksthet**
- Ingen resultater ennå…

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For å kunne delta må du gi et informert samtykke for deg selv eller på vegne av ditt barn. Det kan du gjøre ved å gå inn på linken, eller scanne QR koden under. **Samtykke krever innlogging med BankID.** Vi trenger samtykke fra begge foresatte for å kunne registrere barnet i registeret.

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QR-kode:

[Norsk register for sjeldne, medfødte bensykdommer - Oslo universitetssykehus HF]