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Abstracts

Contents

[101. Fat Infiltration in the Thigh Muscles is Associated With Symptomatic Spinal Stenosis and Reduced Physical Functioning in Adults With Achondroplasia 2](#_Toc135926604)

[102. The Impact of Cervical Medullary Decompression on Height in Children with Achondroplasia 3](#_Toc135926605)

[103. Vosoritide Treatment in Achondroplasia Children: Therapeutic Education and Impact on Multidisciplinary Team 4](#_Toc135926606)

[105. Observational Study of Fetal Foramen Magnum Stenosis and Thoracolumbar Kyphosis in Achondroplasia 5](#_Toc135926607)

[106. Point Of Care Ultrasound Role in Foramen Magnum Stenosis Early Diagnosis 7](#_Toc135926608)

[107. Coronal Plane Knee Joint Motion and Loading in Achondroplasia During Walking and Running Assessed with Biomechanical Motion Capture Technology 9](#_Toc135926609)

[108. Growth Modulation via 8-plates in Children with Achondroplasia Compared to Children with Idiopathic Frontal Knee Axis Malalignments 11](#_Toc135926610)

[109. Agreement Between X-ray and Frontal Plane Knee Alignment in Achondroplasia and Patients with Idiopathic Axial Deformity 13](#_Toc135926611)

[110. The European Registries for Rare Bone and Mineral Conditions (EuRR-Bone): Using a Core Registry to Collect Outcomes on Achondroplasia 15](#_Toc135926612)

[111. The Genetic Intersection of Normal Range Facial Shape and Achondroplasia 16](#_Toc135926614)

# 101. Fat Infiltration in the Thigh Muscles is Associated With Symptomatic Spinal Stenosis and Reduced Physical Functioning in Adults With Achondroplasia

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TRS National Resource Centre for Rare Disorders

**Background:** Symptomatic spinal stenosis is a prevalent complication in adults with achondroplasia. Increased muscle fat infiltration (MFI) and reduced thigh muscle volumes have also been reported, but the pathophysiology is poorly understood. We explored whether the increased MFI and reduced thigh muscle volumes were associated with the presence of symptomatic spinal stenosis and physical functioning.

**Methods:** MFI and thigh muscle volumes were assessed by MRI in 40 adults with achondroplasia, and compared to 80 average-statured controls, matched for BMI, gender, and age. In achondroplasia participants, the six-minute walk-test (6MWT), the 30-second sit-to-stand test (30sSTS), and a questionnaire (the IPAQ) assessed physical functioning.

**Results:** Symptomatic spinal stenosis was present in 25 of the participants (the stenosis group), while 15 did not have stenosis (the non-stenosis group). In the stenosis group, 84% (21/25) had undergone at least one spinal decompression surgery. The stenosis group had significantly higher MFI than the non-stenosis group, with an age-, gender and BMI-adjusted difference in total MFI of 3.3 percentage points (pp) (95% confidence interval [CI] 0.04 to 6.3 pp; p=0.03). Compared to matched controls, the mean age-adjusted difference was 3.3 pp (95% CI 1.7 to 4.9 pp; p<0.01). The non-stenosis group had MFI similar to controls (age-adjusted difference -0.9 pp, 95% CI -3.4 to 1.8 pp; p=0.51). MFI was strongly correlated with the 6MWT (r= -0.81, -0.83, and -0.86; all p-values <0.01), and moderately correlated with the 30sSTS (r= -0.56, -0.57, and -0.59; all p-values <0.01). There were no significant differences in muscle volumes or physical activity level between the stenosis group and the non-stenosis group.

**Conclusion:** In this cohort of Norwegian adults with achondroplasia, increased MFI in the thigh muscles was associated with the presence of symptomatic spinal stenosis, reduced functional walking capacity, and reduced lower limb muscle strength. The increased thigh MFI observed in participants with achondroplasia with spinal stenosis is consistent with the accumulation of MFI in the thigh muscles observed in patients in the general population following a spinal cord injury. Further studies are needed to determine the causality between spinal stenosis and the accumulation of thigh MFI, including the optimal timing of surgical intervention. We have demonstrated that MRI might serve as an objective muscle biomarker in future achondroplasia studies, in addition to functional outcome measures. The method could potentially aid in optimizing the timing of spinal decompression surgery and in planning of post-surgery rehabilitation.

**Disclosures of Interest:** J. Linge: stockholder and employee in AMRA Medical AB, O.D. Leinhard: stockholder and employee in AMRA Medical AB, M. Petterson: employee in AMRA Medical AB, P. Widholm: stockholder and employee in AMRA Medical AB

# 102. The Impact of Cervical Medullary Decompression on Height in Children with Achondroplasia

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**Background:** Foramen magnum stenosis (FMS) is a life-threatening complication in children with achondroplasia (ACH) which may require cervicomedullary decompression (CMD). There is no evidence on the impact of FMS and CMD on growth in children with ACH.

**Aim:** To evaluate the impact of FSM and CMD surgery on anthropometric measurements in children with ACH.

**Methods:** Sixty patients with ACH (30 females -F-, 30 males-M-) were evaluated between 4-6 yrs of age. Height SDS (H-SDS), weight SDS (W-SDS) and body mass index (BMI) SDS (BMI-SDS) were calculated according to Merker et al (ref.1).

**Results:** Thirty-six children (60%; 19 F, 17 M) underwent CMD, n= 19 (31,7%; 11 F, 8 M) within the first yr (mean 0.62±0.20 yrs) and n= 17 after the age of 1 yr (mean 2.01±1.23 yrs). Mean age at anthropometric evaluation was 5.2± 0.4 yrs. H-SDS of patients with CMD was significantly lower (-0.57±1.05 vs 0.03±1.01, P=0.03) and even lowest when CMD occurred after 1 yr of age (-0.8±1,01 vs 0,10±1.21, P=0.02). Furthermore, H-SDS was more affected in males than F (-0.98±1.07 vs -0.22±0.88, P=0.03). There were no significant differences in W-SDS and BMI-SDS except in patients without FMS. In the latter group of patients, F had significantly higher BMI-SDS than M (0.28±1.16 vs -0.60±0.87, P=0.04).

**Conclusions:** H-SDS evaluated at the age of 5 years is more affected in children with ACH who underwent CMD. Furthermore, height appears to be influenced by age at the time of surgery. Our data suggest that FMS and/or CMD surgery may have a negative impact on height growth in children with ACH and that early initiation of medical therapy is desirable in these children.

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**Disclosures of Interest:** M. Maghnie: Research grants, Merck Serono, Pfizer; Lecture fees, Novo Nordisk, Sandoz, Merck Serono, Pfizer, Ascendis, BioMarin; Advisory boards, Novo Nordisk, Sandoz, Pfizer, Merck Serono, BioMarin, Ferring

# 103. Vosoritide Treatment in Achondroplasia Children: Therapeutic Education and Impact on Multidisciplinary Team

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**Background:** Vosoritide (Voxzogo®) is a medicine developed to improve growth in children with achondroplasia. In Portugal and following EMA’s approval (above 2 years), *Infarmed* approved its use in the context of an Early Access Program (*Programa de Acesso Precoce*) in December 2021, being the first commercially available medicine for achondroplasia.

On the top of the necessary complex multidisciplinary care in achondroplasia children, the introduction of this medication had a significant impact on the dynamics of the multidisciplinary team, especially at the role of the nurse.

**Aim:** We describe here how this process has been happening within the multidisciplinary Bone Dysplasia team at Pediatric Hospital in Coimbra, Portugal, where treatments started in January 2022. By February 2023, we have 24th children with achondroplasia on treatment (age range 2-14 years), and expect to have additional 6 children in the next 3 months.

Given that this is a recent and orphan drug, with faster approval times and smaller number of patients included in clinical trials, a close follow-up is needed. Our team adapted the protocol previously put in place in other countries, namely France, which includes a detailed anthropometric evaluation but also bone age and blood collections, in order to monitor the effectiveness and safety of the treatment.

The teaching and training of parents in the preparation and administration of subcutaneous medication are carried out by the reference nurses, in hospital context, followed by nursing visits to reinforce teaching and medication training (1 to 2 visits depending on the parents' needs). Usually at least the second dose of medication is also given by the parents in hospital context (outpatient clinic) with the support and supervision of the reference nurses.

Parents receive a starter kit with all the information available about the treatment and also the team contacts (phone and email) to support and clarify any doubts they may have at home.

**Methods:** In between nursing visits, nurses maintain contact with parents in order to understand adherence to treatment and any difficulties that can be discussed with the team.

The reference nurses carry out the detailed anthropometric assessment on the first day of medication intake, at 6 months of treatment, at 12 months and then annually. Especially attention was given to this aspect, as we need to try measure small differences in height. We also aim to explore possible impact in disproportion, where the clinical trials were not conclusive. The same two nurses, who had been trained previously on clinical trials context, do all the measurements in a systematic homogenous approach and using the same calibrated equipment. In these visits, other complementary diagnostic exams are carried out, such as electrocardiogram, blood collection and determination of bone age, according to the developed protocol.

These educator’s nurses maintain throughout the course of the treatment the oversight of the therapeutic regime at home, review of procedures, clarification of doubts and review of child/family records.

Regarding adherence, only one family has made a pause on treatment (and multidisciplinary follow-up) after significant family/social problems. These issues do need to be taken into account. A consultation with the team’s social service professional is always included in our routine practice.

**Conclusion:** Overall, the introduction of Vosoritide treatment in routine care brought a significant amount of additional work to our team, especially for the nurses, but the overall experience has been very positive.

**Disclosure of Interest:** C. Gomes: BioMarin funded the participation in this meeting, M.J. Pais: BioMarin funded the participation in this meeting, I. Silva: BioMarin funded the participation in this meeting, S.B. Sousa: BioMarin funded the participation in this meeting, A. Mirante: BioMarin funded the participation in this meeting.

# 105. Observational Study of Fetal Foramen Magnum Stenosis and Thoracolumbar Kyphosis in Achondroplasia

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**Objectives**

Achondroplasia is the most common form of dwarfism. Recent advances in the development of gene targeted novel therapies is broadening the scope of treatment options for those affected. It is reasonable to theorise that earlier administration of gene targeted therapeutic interventions will result in a more favourable outcome. Fetal development of the foramen magnum and thoracolumbar spine in achondroplasia is not well understood. This study aims to address that by observing the natural history of the development of these structures using MR imaging and motion correction 3D reconstruction. An attempt is also made to devise a method of quantifying the changes seen.

**Methods**

10 pregnant women (31-37 weeks gestation) whose fetuses have achondroplasia were included in the study. Fetal head and whole body MRI scans were performed.  To resolve out-of-plane motion, 3D reconstructed images were produced using slice to volume reconstruction. With this data, we devised a method of fetal foramen magnum measurement using 3D MPR viewer software to orientate the images into standard planes. Inter-observer variability was determined by statistical analysis of measurements.  The foramen magnum was interpreted using the achondroplasia foramen magnum stenosis (AFMS) severity scoring system. Cases were followed up and AFMS scores also determined postnatally.

**Results**

We were able to visualise the relevant anatomy in fetuses with achondroplasia to determine the presence of foramen magnum stenosis. Reconstructed body MRI images were reviewed to assess the presence of thoracolumbar kyphosis.

The foramen magnum measurement system devised had an average inter-observer variability of 7.2%. Relevant to the requirement of earlier therapeutic intervention, foramen magnum stenosis was detected in 6 out of 10 fetuses. Of these six babies, one went on to develop grade 3 foramen magnum stenosis and is currently on the waiting list for decompression surgery. Four of the six developed severe grade 4 stenosis, all going on to have decompression surgery.

The remaining four out of 10 fetuses showed no sign of foramen magnum stenosis on antenatal images. Two of these babies when born developed foramen magnum stenosis AFMS2 and AFMS3 which resolved or remained stable on follow-up scans with no intervention. At the time of writing, the youngest two postnatal scans are still pending.

**Conclusion**

These results suggest that foramen magnum stenosis is detectable antenatally in Achondroplasia with features seen in 60% of our cohort, all of which progressed to AFMS3 or AFMS4. Antenatal detection of foramen magnum stenosis may be indicative of more aggressive progression postnatally and an early postnatal screening MRI scan is recommended.

Our initial observations demonstrate that complications of achondroplasia initiate in the fetus. Expanding on this knowledge will provide tangible measures for the consideration of early interventional therapy.

**Disclosure of Interests:** M. Irving: Received honoraria for consultancy services from: BioMarin, QED Therapeutics, Pfizer/Therachon, Sanofi, Ascendis, Alexion, Kyowa Kirin, Innoskel

# 106. Point Of Care Ultrasound Role in Foramen Magnum Stenosis Early Diagnosis

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**Background:** Foramen magnum stenosis (FMS) is a frequent complication in achondroplasia. (1)

During the first year of life, foramen magnum is smaller and with a diminished growth rate. (2)

International Consensus Statement 2022 suggests clinical monitoring for FMS at least in the first 3 years. If the child has no symptoms, it’s recommended to screen with cranio-cerebral-cervical magnetic resonance imaging (MRI) in the first 3-6 months of life, and subsequently in an if-needed basis. (3)

As MRI access is onerous and with delay, health care professionals may deal with the possibility of FMS in the absence of symptoms.

Rehabilitation may be limited by the fear of iatrogeny.

Having an accessible and manageable imaging tool would be important, namely Point of Care Ultrasound (POCUS).

**Methods:** Review of the evidence on FM ultrasound imaging in new-borns and infants.

Development of a POCUS FMS screening.

**Results:** POCUS is disseminated in several medical specialities. (4)

Studies demonstrate its usefulness and ease with which an adequate level of structure identification is achieved, after proper training. (5)

US performed via the FM is better at detecting new-born and infant anomalies in posterior fossa structures than via the anterior fontanelle. (6) Its use in morphometric measurements of the brainstem has been attested. (7)

Proposed POCUS protocol to perform regular evaluations in the first year of life:

Static and dynamic visualization of craniocervical structures. (8)

Visualization of the patency of the subarachnoid space at the plane of foramen magnum on static evaluation. (9)

Examination technique:

-A sectorial or micro convex probe is used for the examination of the craniocervical junction with a frequency of 7.5 MHz.

-Static evaluation: The patient in a lateral decubitus; the neck in a slightly flex position (15º).

A) In the sagittal section, at the level of the craniocervical junction, observe: the basion and opistion (consider abnormal if protuberant into the vertebral canal); the spinal cord, the subarachnoid space.

-Dynamic evaluation of above A), with </=50º flexion and </=30ºextension of the neck. (10)

Proposed POCUS FMS score:

|  |  |
| --- | --- |
| ITEM | SCORE (0= NORMAL; 1= ABNORMAL) |
| Static evaluation |  |
| Basion and Opistion |  |
| Patency of subarachnoid space at FM level |  |
| Dynamic evaluation |  |
| 50 degrees of flexion 🡪 narrowing of the ventral subarachnoid space < 40% and a widening of the dorsal subarachnoid space of <80% (compared with the neutral position, 0 degrees). |  |
| 30 degrees of extension🡪 increase in the diameter of the ventral subarachnoid space <10%; the dorsal subarachnoid space reduced <20%. |  |
| MRI evaluation if: | Total score =/> 2 |

**Conclusions:** POCUS FMS screening might bring a breakthrough filling in the gaps on the current guidelines.

The possibility to further deepen this issue and to find partners willing to evaluate the correlation of the proposed protocol to clinical and MRI findings, in a multicentre prospective study, is our proposition to the EAF on the 2023 meeting.

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**Acknowledgements:** A. Soudo, Hospital de Dona Estefânia - Centro Hospitalar de Lisboa Central

**Disclosures of Interest:** M. Pires: I thank BioMarin for the possibility of attending EAF 2023

# 107. Coronal Plane Knee Joint Motion and Loading in Achondroplasia During Walking and Running Assessed with Biomechanical Motion Capture Technology

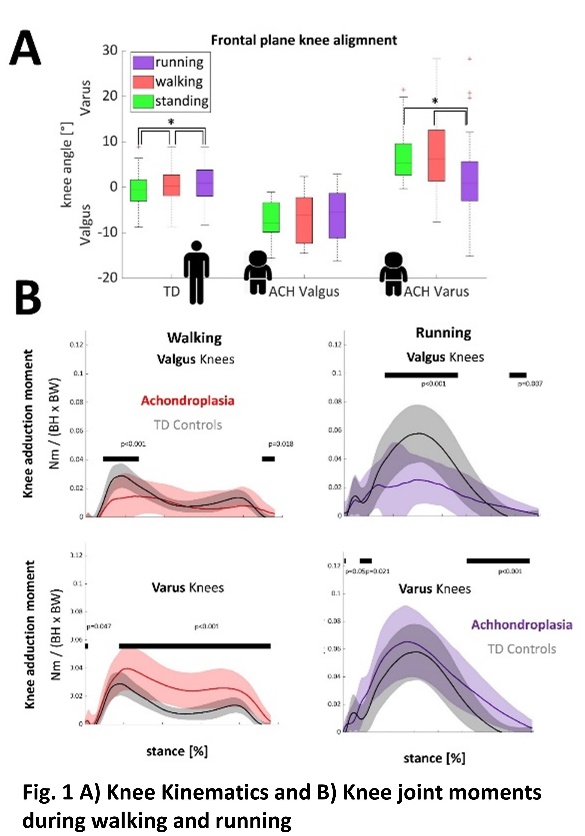
M. Hösl, F. Aififi, A. Thamm, F. Wagner, S. Marx, S. Nader

Schoen Clinic Vogtareuth

**Background:** Motion capturing is frequently used in idiopathic axial deformities to inform about pathology and treatment effects [1]. Yet, to date, few biomechanical studies of gait in Achondroplasia [ACH] with limited sample size [3-5] exist. They provided inconsistent reports about knee malalignments and overloadings [3 vs. 5]. The current research question was: How does walking and running affect frontal knee angles as well as joint moments in ACH and controls?

**Methods:** 23 patients with ACH (age: 11.8±4.0 y., height: 112+16cm) and 25 typically developing controls (age: 10.1±3.9 y., height 140+21cm) were analyzed during standing, walking and running using 3D motion capturing (Vicon Nexus, AMTI force plates). To quantify static leg alignment quiet standing was measured. Concerning ambulation, we extracted the mean frontal knee angle during single support phase while walking or running. Knee joint moments were calculated and bodyweight x height normalized [7]. A 2-way mixed ANOVA with condition [standing, walking, running] and group [ACH vs. controls], as well as [Statistical Parametric Mapping](https://www.fil.ion.ucl.ac.uk/spm/) was used to compare knee angles and joint moments. In addition, we predicted the knee alignment values during ambulation from standing values.

**Results:** ACH-knees were categorized according to the median alignment of controls into Valgus [N=20 legs] or Varus [N=26 legs]. During gait, the median in ACH Valgus was -7.9° [-38.0 to -1.1°] and 5.4° [-0.3 to 21.5] in ACH Varus and in controls 0.5° [-8.7, 8.9]. Controls showed consistently more varus from standing to running (P<0.001). Apart from group and condition effects (P<0.001, Fig. 1), a sign. interaction was found for Varus knee angles (P<0.01), with less varus during running than walking (P≤0.002). Yet, the increased valgus persisted (P= 0.838). During walking, peak knee moments (Fig. 1B) for Valgus knees during 1st half of stance were shifted by -35% while the moments in varus knees nearly doubled in the 2nd half stance (both P<0.01). During running, these overloadings were less pronounced in varus knees, while for Valgus knees the shift was more pronounced (Fig. 1B). When predicting knee motion during running from standing, the root mean square deviation was 2° for control knees, and 2.9° and 5.6° for ACH Valgus and Varus knees, respectively.

****

**Conclusions:** During ambulation, knees in ACH featured aberrant alignments and moments. On average varus knees decreased their overloadings during running, partly by reducing the extent of varus, amongst others compensated with excessive frontal thorax lean. In the past, manual goniometry or distances between the knees, mid-tibiae or malleoli or visual assessments were recommended [8,9], as well as observation of a knee thrust with weight bearing. Notably, in the current study, considerable uncertainty was noted in ACH when trying to predict knee motion during dynamics task, likely affected by joint laxity. Muscular effort for stabilization may contribute to early fatigue. Also knee pain in adults with ACH has been reported [10]. In normal stature, joint moments are predictive for pain [11] and for contact forces within the knee [2,6]. Thus, 3D gait analysis may provide an objective, meaningful instrument in ACH.

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# 108. Growth Modulation via 8-plates in Children with Achondroplasia Compared to Children with Idiopathic Frontal Knee Axis Malalignments

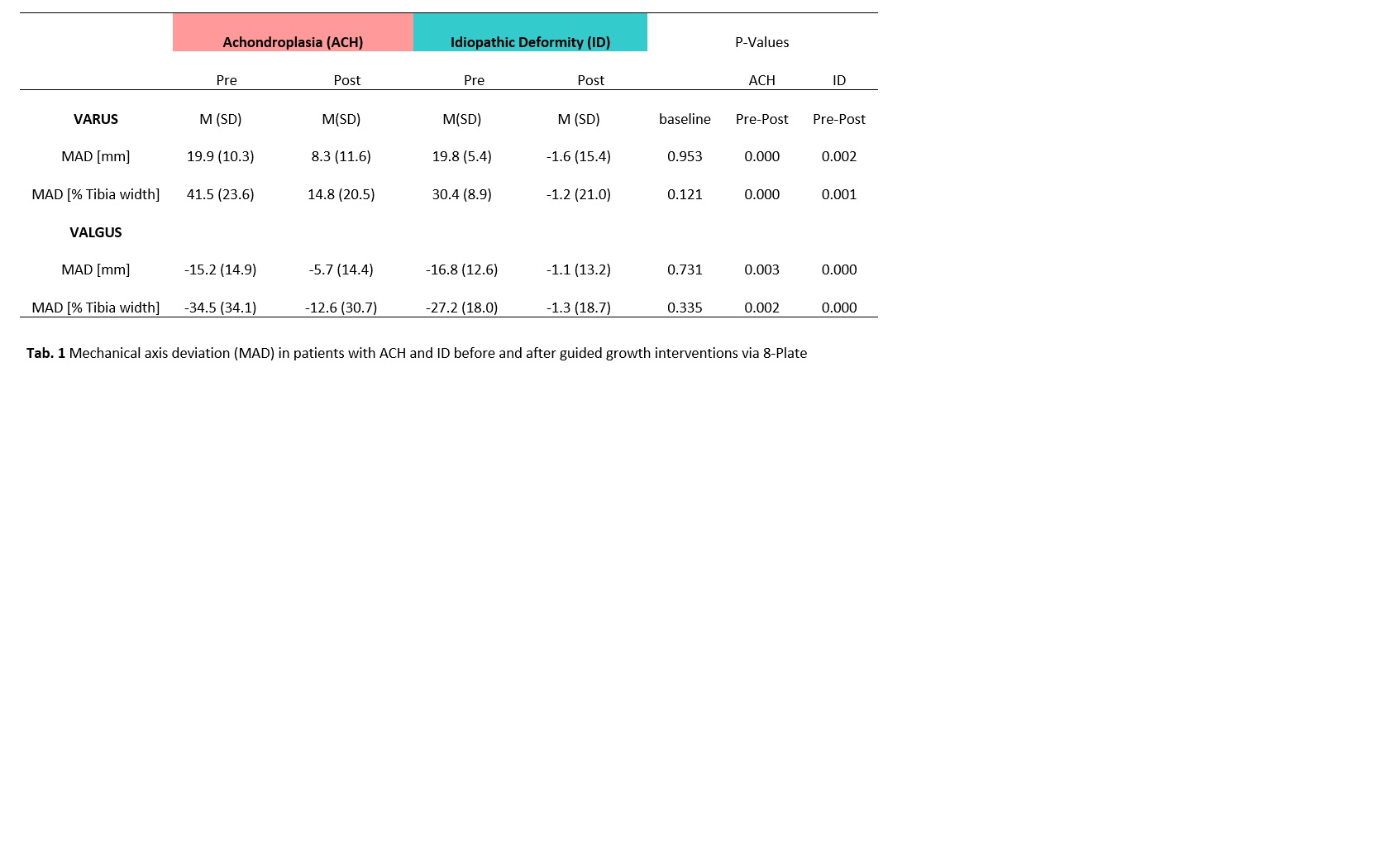
M. Hösl, F. Aififi, A. Thamm, F. Wagner, S. Marx, S. Nader

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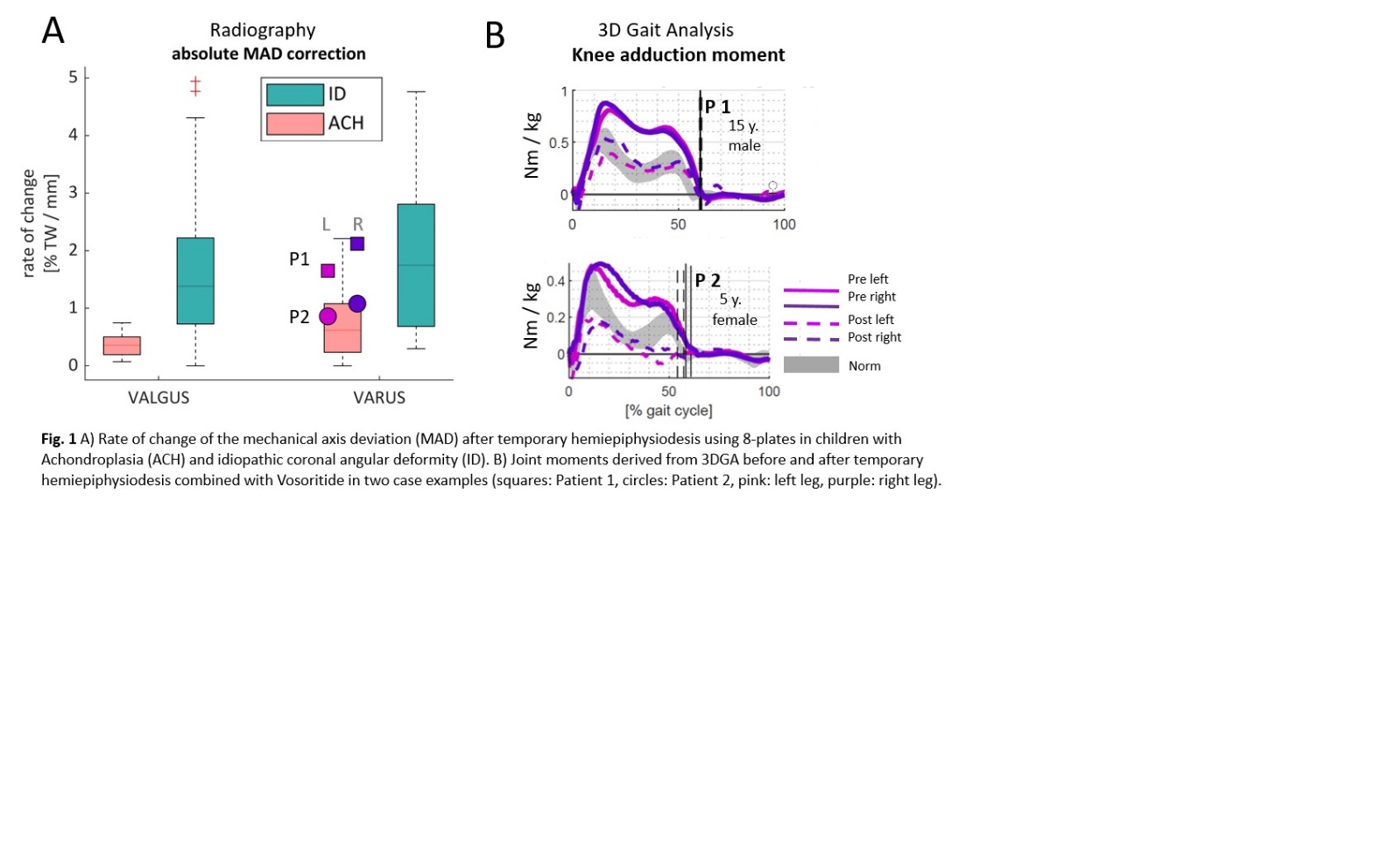
**Background:** Along with disproportional short extremities, coronal knee malalignments are hallmarks in Achondroplasia (ACH) and, in severe deformities, orthopedically treated by hemiepiphysiodesis [1]. This is known as guided growth, a surgical technique using diverging screws to function like a hinge at the growth plate to gradually correct limb malalignment in skeletally immature patients. Our aim was to compare the efficacy of growth modulation in ACH compared to idiopathic knee deformity (ID).

**Methods:** 20 patients with ACH (8 Valgus/31 Varus knees) and 29 with ID (55 Valgus/2 Varus knees) were retrospectively included. All underwent hemiepiphysiodesis using 8-Plates® (ACH: 29 tibial/25 femoral; ID: 36 tibial/28 femoral). Main outcome was the mechanical axis deviation (MAD) from radiographs before surgery and at plate removal. Further, the correction rate was defined as MAD change per month. 2 additional patients with ACH (1 male, 15 y. old; 1 female, 5 y. old, both with varus malalignments) served as case reports. Their hemiepiphysiodesis coincided with Vosoritide (VOXZOGO®) treatment. Their rate of MAD correction was compared to the average of the former population. Both also underwent 3D gait analysis via motion capturing (VICON Nexus, AMTI Force plates) prior to implantation and plate removal to investigate joint kinematics and kinetics.

**Results**



For ID, implant duration in valgus was 13.4±7.9 months, in varus: 11.7±4.6 months. For ACH, assessed correction interval was longer (valgus: 27.4±7.2 months, varus: 21.8±13.7 months, both P<0.001). Absolute and normalized MAD showed significant improvements in both cohorts and for valgus and varus knees (Tab. 1). Rate of correction (Fig. 1A) was slower in ACH (both P<0.001. There was on average 1.22 mm and 1.25 mm less MAD correction per month in valgus and varus knees in ACH than ID (both P≤ 0.0025). Concerning the 2 cases with combined treatment, rate of correction was 0.86-2.12 mm/month (Fig. 1), which was on average 1.25 [0.35-2.35] standard deviations above the mean correction speed. Next to the static bony alignment, the increased frontal plane joint moments (Fig. 1B) could be considerably reduced towards reference values of healthy controls.



**Conclusions:** Regardless of limited growth, children with ACH benefitted from 8-Plates® by reducing mechanical axis pathology. The 2 preliminary case-reports show that Vosoritide might accelerate deformity correction when orthopedically guiding axial deformities. It potentially also corrects knee overloading during ambulation. This might offer larger correction in severe deformities and the chance to intervene in older patients with less remaining growth, which usually show lower success of hemiepiphysiodesis [2] e.g. patients who are seen too late by orthopaedic specialists and may need to be recommended for more invasive osteotomies [3]. The slight over-correction in patient 2, warrants for a fairly close monitoring when combining guided growth and growth enhancing drugs. Notably though, such over-correction is also regularly done in prevention of rebound-phenomenon in ID, which describes a gradual reoccurrence of deformity [4].

As in ID, growth modulation by 8-Plates® is effective in ACH for valgus and varus knees , however with slower speed of correction and longer duration of treatment. In the future, a RCT to investigate guided growth and growth enhancing drugs would be promising. As the goal of guided growth is the prevention of joint overloading, a biomechanical monitoring via 3D gait analysis appears crucial when assessing its functional impact [5].

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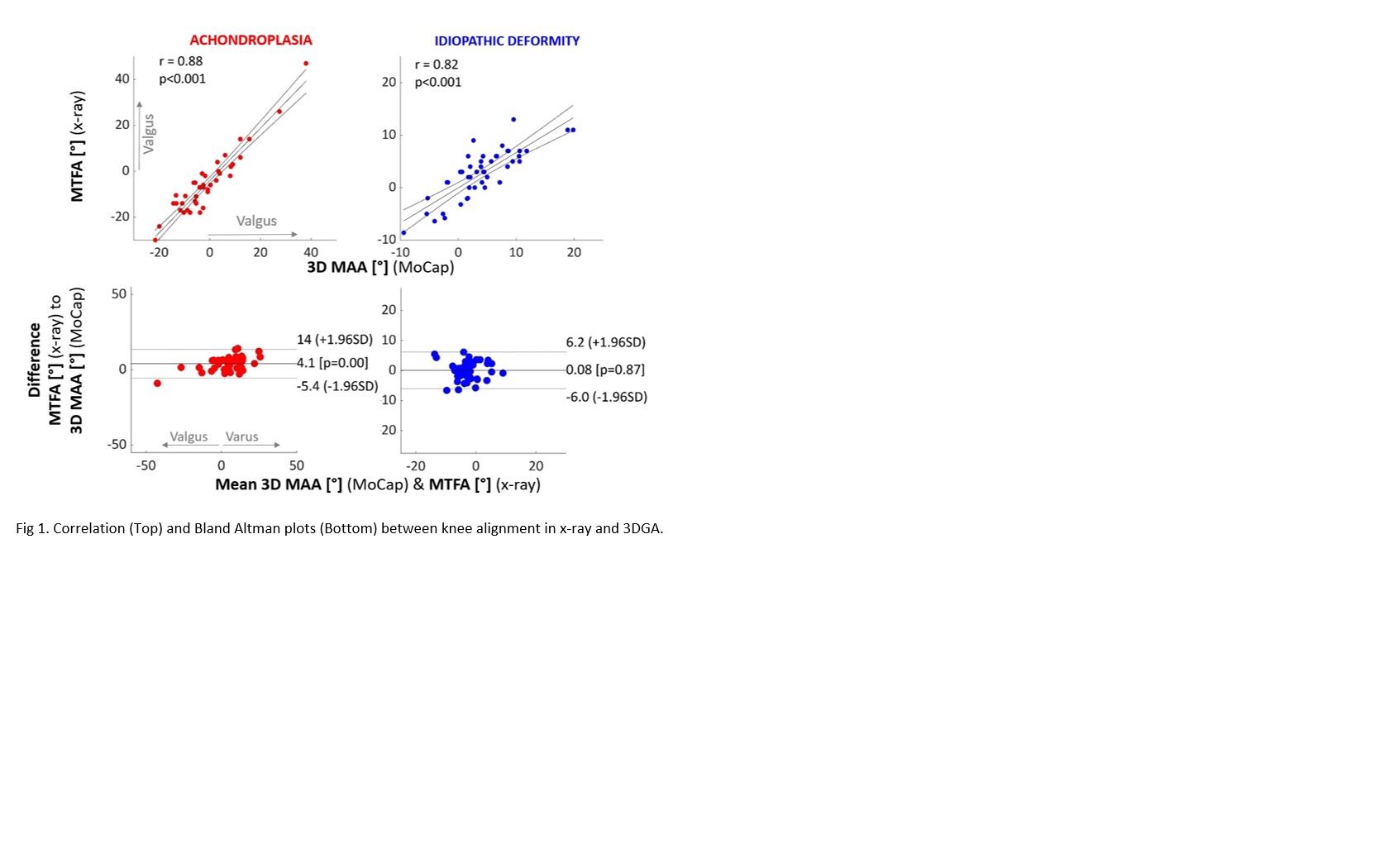
# 109. Agreement Between X-ray and Frontal Plane Knee Alignment in Achondroplasia and Patients with Idiopathic Axial Deformity

A. Thamm, M. Hösl, F. Aififi, F. Wagner, S. Marx, S. Nader

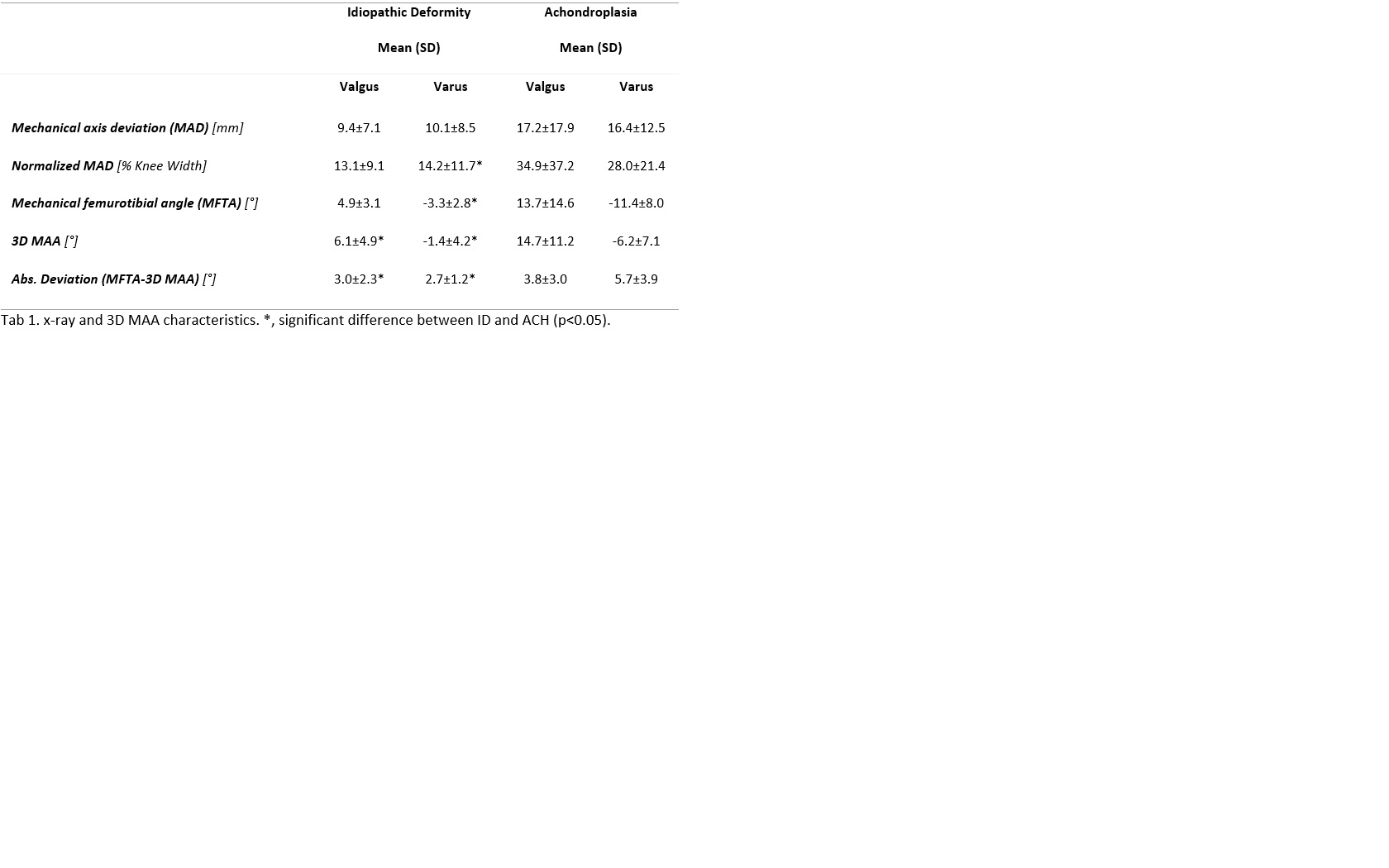
Schoen Clinic Vogtareuth

**Background:** Knee malalignments are common in Achondroplasia (ACH) [1]. In paediatric orthopaedics, standing radiographs usually assess the degree of deformity. In idiopathic deformities (ID), the agreement between the radiological mechanical femurotibial angle (MFTA) and motion capture data is high [2], while up to now no correlations have been reported in ACH [3]. Our aim was to compare knee malalignment in ACH to ID and investigate if motion capturing can predict radiological pathology also in ACH.

**Methods:** We retrospectively included 20 patients with ACH (31 varus, 9 valgus knees, age: 12±3 y., height: 113±15cm) and 23 ID patients (11 varus, 35 valgus knees, age: 13±2 y., height: 159±12cm). Both received a long-leg standing x-ray and a 3D gait analysis (3DGA) (VICON Nexus) within 3 months as part of their standard of care. From the static standing trial of 3DGA, we extracted the frontal plane knee mechanical axis angle (3D MAA). From the x-ray, we extracted the MFTA and the mechanical axis deviation (MAD). All x-ray values were compared between ACH and ID. The relationship and agreement between techniques was determined via correlations and Bland Altman analysis and compared between ACH and ID.



**Results:** MAA from 3DGA and MFTA from x-ray were highly correlated in ID and in ACH (r=.82, p<.001; r=.88, p<.001, respectively) (Fig.1). The MFTA malalignment was more pronounced in ACH for varus (P<.001) but not for valgus (p=.057). Absolute MAD was not significantly different between groups, but there was a main effect when normalized to knee width for larger MAD in ACH compared to ID (Tab. 1). Comparing MFTA and 3D MAA, the agreement was significantly smaller in varus knees in ACH compared to ID (p<.001) but not in valgus knees (p=.482). Bland Altman analysis indicated an over prediction of knee malalignment towards valgus in ACH (4.1°, p<.001). BMI, age or height were no further confounding factors in ACH.



**Conclusion:** Overall, the knee malalignment was more pronounced in magnitude in ACH. Agreement between frontal knee malalignment from radiography and 3DGA was high in ACH and ID. The deviation between x-ray and motion capturing in ID was similar to other reports [2] but was larger in ACH compared to ID. A bias towards valgus in ACH was noted. This might likely be related to the location of the hip joint centre being placed to laterally in ACH. The conventional biomechanical gait model uses anthropometric relations of patients with normal stature and leg length as a predictor to calculate the medio-lateral position of the hip joint centre. Patients with ACH might yet feature distinctive pelvic geometry . Therefore, developing a disease specific biomechanical model for ACH may further improve the accuracy of 3DGA evaluations by accounting for altered pelvic and hip joint geometry [4].

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# 110. The European Registries for Rare Bone and Mineral Conditions (EuRR-Bone): Using a Core Registry to Collect Outcomes on Achondroplasia

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**Introduction**: Disease registries describe the natural history, estimate the impact of living with a condition and evaluate the effects of procedures and treatment. EuRR-Bone, created in collaboration with the European Reference Network on Rare Bone Conditions (ERN-BOND), collects data on rare bone and mineral conditions using a Core Registry. This platform gathers a set of Common Data Elements and condition-specific outcomes through clinician and patient participation.

**Methods**: The EuRR-Bone Working Group on achondroplasia is a multidisciplinary team composed of healthcare professionals and patient representatives. This Working Group has reached consensus on a diagnosis-specific dataset and issued recommendations on the use of Patient-Reported Outcome Measures (PROMs) in patients with achondroplasia. Built within the Core Registry platform, this module is open February 2022 to contributors (ERN and non-ERN members) to register new and existing cases of achondroplasia.

**Results**: The final dataset included 80 Clinician-Reported Outcomes (CROs) covering domains such as family history, anthropometry, achondroplasia developmental score, monitoring, medical therapy including the documentation of adverse events, surgery and other therapies. Two Patient-Reported Outcomes (PROs) were included: educational attainment and employment status. Additionally, the Working Group recommended the use of the Brief Pain Inventory - Short Form (BPI-SF) in this group of patients. The BPI-SF is available and validated in multiple languages and provides 2 main scores, a pain severity score and a pain interference score. Furthermore, the BPI-SF inquires about painful areas using a body map and the use of pain relief medication.

To date, 113 patients with achondroplasia have been entered into the Core Registry by 4 centres in 3 European countries. The median age was 46 years (range 1-86). Of 113 cases, 4 (3.5%) were within the age range 0-9, 8 (7%) within 10-18 years and 101 (89%) >18 years of age. Of 113 cases, 108 (96%) were under active follow-up and a diagnosis-specific outcome has been completed for 3 of them.

**Conclusion**: The use of a Core Data set in combination with a disease-specific dataset developed by healthcare providers and patient representatives, can provide insight on the natural history and clinical outcomes of rare diseases such as Achondroplasia.

**Acknowledgements:** authors of this abstract might be affiliated to the European Reference Network on Rare Bone Disease (ERN BOND) as HCP members or patient advocates.

# 111. The Genetic Intersection of Normal Range Facial Shape and Achondroplasia

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**Background/Objectives:** Human facial shape is a complex phenotype that is largely genetically determined, whose development involves a series of highly coordinated embryonic events. Naturally occurring mutations that disturb facial development can cause craniofacial dysmorphism. This provides a unique window into the genetics underlying facial variation*.* In this work, we introduce a novel syndrome-informed facial phenotyping method to identify genomic loci associated with facial variation along a syndromic axis using achondroplasia as an example.

**Methods:** We compared 3D facial scans from 8,246 healthy European-ancestry individuals and 48 achondroplasia patients to calculate an achondroplasia endophenotypic score. In our healthy control sample, we performed a multivariate GWAS of these scores using canonical correlation analysis and observed 35 independent genetic loci that reached genome-wide significance (p<5x10-8).

**Results:** Gene ontology analysis showed significant enrichment of genes involved in skeletal development, particularly chondrocyte differentiation and cartilage development. Compared to a GWAS of normal facial variation in the same cohort, this enrichment was specific to our study. Furthermore, by applying these genes to a multivariate genotype-phenotype model in mice, we recovered an achondroplasia-like phenotype, even without the *Fgfr3* mutation that is associated with achondroplasia.

**Conclusion:** In summary, we identified a polygenic basis for normal facial variation along the achondroplasia trait axis and found an enrichment for developmental processes that are key in achondroplasia pathophysiology. This suggests that both complex and Mendelian genetic variation act on the same biologically determined axes of facial variation, providing novel insights into the genetic intersection of complex traits and Mendelian disorders.