Combined achondroplasia and short stature homeobox-containing (SHOX) gene deletion in a Danish infant

Seiersen, Kasper V.; Henriksen, Tine B.; Andelius, Ted C. K.; Andreasen, Lotte; Diemer, Tue; Gudmundsdottir, Gudrun; Vogel, Ida; Gjørup, Vibike; Gregersen, Pernille A.

Published in:
European Journal of Medical Genetics

DOI (link to publication from Publisher):
10.1016/j.ejmg.2023.104894

Publication date:
2024

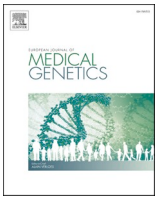
Document Version
Publisher's PDF, also known as Version of record

European Journal of Medical Genetics 67 (2024) 104894

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg



Combined achondroplasia and short stature homeobox-containing (*SHOX*) gene deletion in a Danish infant

Kasper V. Seiersen [a,b,*], Tine B. Henriksen [a,b], Ted C.K. Andelius [a], Lotte Andreasen [c], Tue Diemer [d], Gudrun Gudmundsdottir [e], Ida Vogel [b,c,f], Vibike Gjørup [g], Pernille A. Gregersen [b,c,h]

[a] Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Clinical Medicine, Health, Aarhus University, Aarhus, Denmark
[c] Department of Clinical Genetics, Aarhus University Hospital, Denmark
[d] Department of Clinical Genetics, Aalborg University Hospital, Aalborg, Denmark
[e] Department of Neurosurgery, Aarhus University Hospital, Denmark
[f] Center for Fetal Diagnostics, Aarhus University Hospital, Aarhus, Denmark
[g] Department of Gynaecology and Obstetrics, Aarhus University Hospital, Aarhus, Denmark
[h] Centre for Rare Diseases, Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark

ARTICLE INFO

Handling Editor: A. Verloes

Keywords:
Achondroplasia
Short stature homeobox protein
Infant
FGFR3
SHOX

ABSTRACT

Short stature or shortening of the limbs can be the result of a variety of genetic variants. Achondroplasia is the most common cause of disproportionate short stature and is caused by pathogenic variants in the fibroblast growth factor receptor 3 gene *(FGFR3)*.

Short stature homeobox (SHOX) deficiency is caused by loss or defects of the *SHOX* gene or its enhancer region. It is associated with a spectrum of phenotypes ranging from normal stature to Léri-Weill dyschondrosteosis characterized by mesomelia and short stature or the more severe Langer mesomelic dysplasia in case of biallelic SHOX deficiency.

Little is known about the interactions and phenotypic consequences of achondroplasia in combination with SHOX deficiency, as the literature on this subject is scarce, and no genetically confirmed clinical reports exist. We present the clinical findings in an infant girl with concurrent achondroplasia and SHOX deficiency. We conclude that the clinical findings in infancy are phenotypically compatible with achondroplasia, with no features of the SHOX deficiency evident. This may change over time, as some features of SHOX deficiency only become evident later in life.

1. Introduction

Achondroplasia is the most common cause of disproportionate short stature, occurring with a frequency of around 1/25,000–30,000 births (Pauli, 2019). Achondroplasia is a chondrodysplasia caused by heterozygosity for one of two recurring pathogenic missense variants in the fibroblast growth factor receptor 3 gene (*FGFR3*), most commonly NM_000142.5:c.1138G>A, resulting in a glycine to arginine substitution (Gly380Arg) (Bellus et al., 1995; Rousseau et al., 1994). The subsequent gene product results in gain of function of the FGFR3 protein, resulting in a constitutively active receptor which inhibits endochondral bone growth. The condition follows a pattern of autosomal dominant inheritance, but is most often a result of a *de novo* pathogenic variant (Webster et al., 1996). Achondroplasia is characterized by short stature, rhizomelia, and skeletal deformities (Pauli, 2019). Additionally, patients with achondroplasia have an increased risk of various medical complications (Pauli, 2019). Thus, there is a need for multidisciplinary expert care in order to ensure optimal management for better quality of life in patients with achondroplasia.

Pathogenic alterations in the short stature homeobox-containing gene (*SHOX*) is a common cause of short stature with an estimated population prevalence of 1/1000–2000 (Cicognani et al., 2010; Nicolosi

* Corresponding author.Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital , Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark.
E-mail address: kvs@clin.au.dk (K.V. Seiersen).

https://doi.org/10.1016/j.ejmg.2023.104894
Received 20 June 2023; Received in revised form 23 November 2023; Accepted 3 December 2023
Available online 7 December 2023

et al., 2010). *SHOX* is located on the pseudo-autosomal regions of the X and Y chromosome. The gene product is a transcription factor that regulates bone development, growth plates, and apoptosis (Marchini et al., 2016). SHOX deficiency disorders are most often a result of haploinsufficiency and follows a pattern of pseudo-autosomal dominant inheritance (Binder et al., 1993). *SHOX* is phenotypically related to height and heterozygous SHOX deficiency disorders results in phenotypes with varying degree of skeletal dysplasia ranging from average stature, isolated short stature, short stature with mesomelia to Léri-Weill dyschondrosteosis (LWD). SHOX deficiency disorders have a higher penetrance and increased severity in females (Binder et al., 1993).

To the author's knowledge, no genetically confirmed reports of achondroplasia in combination with SHOX deficiency confirmed by molecular genetic methods exist, and only few similar cases are available (Ross et al., 2003; Matczak et al., 2022; Cormier et al., 2017). Here we report the clinical findings in a newborn girl with combined achondroplasia and SHOX deficiency.

1.1. Clinical report

1.1.1. Patient history

We present a Danish newborn girl with achondroplasia and a *SHOX* deletion, the child of a mother with achondroplasia and a father with a *SHOX* deletion.

1.1.2. Genetic analyses and counselling

Due to achondroplasia and known c.1138G>A (Gly380Arg) *FGFR3* variant in the mother, prenatal genetic testing was carried out at 11 gestational weeks by chorionic villus sampling (CVS). Sanger sequencing showed heterozygosity for the c.1138G>A variant in *FGFR3*, inherited from the mother. The DNA from the chorionic villus sample was compared with DNA from the mother with no signs of maternal contamination.

An array comparative genomic hybridization (array CGH) analysis (Agilent 180 K oligo array) was performed on DNA from the chorionic villus sample as part of routine prenatal testing in CVS in addition to testing for achondroplasia. The analysis detected a 1.0 Mb partial deletion of Xp22.33 involving the *SHOX* region in the short arm pseudoautosomal region of chromosome X; arr [GRCh37] Xp22.33 (219609-1235388)×1 pat. No further genes were included in the deletion. The array CGH result was confirmed by multiplex ligation-dependent probe amplification analysis. The couple received genetic counselling about the achondroplasia result and the secondary finding of the *SHOX* deletion. The couple was counseled about the importance of parental analyses for the interpretation of the unexpected CVS result. If the *SHOX* deletion was found in the mother, who also had achondroplasia, we would assume there was little additional effect of the *SHOX* deletion, as she had a phenotype of classical achondroplasia. Array-CGH analyses were performed on parental samples, which revealed an identical *SHOX* deletion in the father's sample. The father was healthy and with a normal phenotype and no findings suggestive of SHOX deficiency disorders (Fig. 1A). Further, the pedigree was not indicative of any SHOX deficiency phenotype in his family members. We found no clinical reason for imaging of the father. International experts and the International Skeletal Dysplasia Society (ISDS) SKELDYS network were consulted, but the only known case was the one reported by Ross et al. (2003). Subsequent counselling of the family involved information on the great phenotypic variability in SHOX deficiency conditions, and the unpredictive phenotype in the child, but that we suspected achondroplasia would be the main phenotypic component.

1.1.3. Perinatal course

The girl was delivered at 37 weeks and 2 days gestation by planned caesarian section due to the risks associated with vaginal delivery in mothers with achondroplasia, including dystocia due to cephalopelvic disproportion, and spinal cord compression. Birthweight was 2620 g (−1.7 SD, according to achondroplasia specific growth charts), birth length 44 cm (−1.7 SD, according to achondroplasia specific growth charts), and head circumference at birth was 36 cm (−0.5 SD, according to achondroplasia specific growth charts) (Neumeyer and M.A.H.L). Apgar scores were 10 at 1, 5 and 10 min after birth. As retractions and grunting was observed at 30 min of age, oral suctioning was performed, and continuous positive air pressure was provided for approximately 7 h. The infant was discharged from the neonatal ward the following morning, and the family was discharged from the postnatal ward 2 days later. No other perinatal events of significance were recorded.

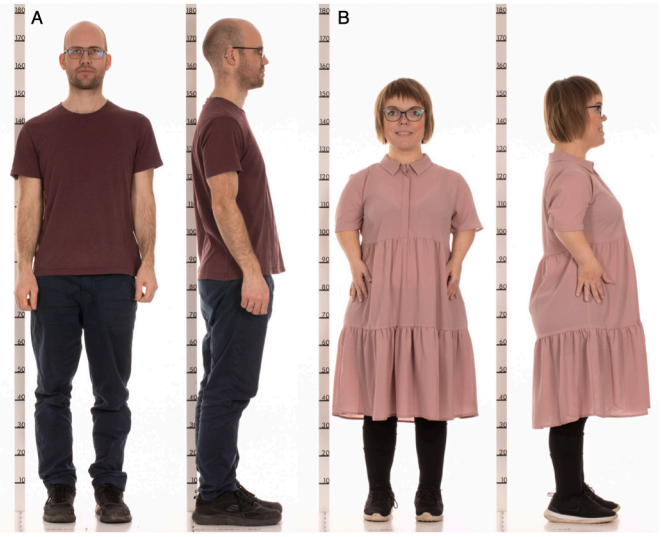


Fig. 1. Stature and phenotypic features of the parents. A: Father of average stature (height 173.8 cm, −1.1 SD according to standard growth charts (Tinggaard et al., 2014)) carrying the *SHOX* deletion. B: Mother with achondroplasia, only mildly short stature (height 152.4 cm, −2.7 SD according to standard growth charts (Tinggaard et al., 2014)) due to leg lengthening surgery (11.5 cm femoral lengthening, and 11 cm tibial lengthening), midface retrusion, rhizomelic shortening of the upper limbs, limitation of elbow extension, and trident hand configuration.

1.1.4. Clinical assessment

Clinical assessments were performed at 0, 22, 60, 120, 217 and 266 days of age and included measures of height, head circumference, and body weight (Table 1). Muscle tone, tendon reflexes, and facial features were also assessed. Upon examination, a large neurocranium was observed. Discrete frontal bossing was present along with classical facial features of achondroplasia including mild midfacial hypoplasia and a depressed nasal bridge. Upper and lower extremities had rhizomelic shortening (Fig. 2). Muscle tone, deep tendon reflexes, and infant reflexes were normal. No hypermobility of the hip joints was observed. Some hypermobility of the knees was present.

Table 1
Development of body measurements. Z-scores in parentheses, standard deviations from the mean of girls with achondroplasia (Neumeyer and M.A.H.L). Achondroplasia specific growth charts are utilized to explore potential interactions between achondroplasia and SHOX deletion.

Age in days	Body length in centimeters	Head circumference in centimeters	Body weight in grams
0	44 (−1.7)	36.0 (−0.5)	2620 (−1.7)
22	45.5 (−1.9)	36.2 (−1.9)	3025 (−1.6)
60	51 (−0.8)	39.5 (−1.2)	4280 (−0.3)
120	53 (−1.4)	42.5 (-0.8)	5400 (0.0)
217	59.0 (−0.4)	45.1 (−0.9)	6610 (+0.1)
266	60.0 (−0.7)	46.3 (−0.9)	7200 (+0.3)

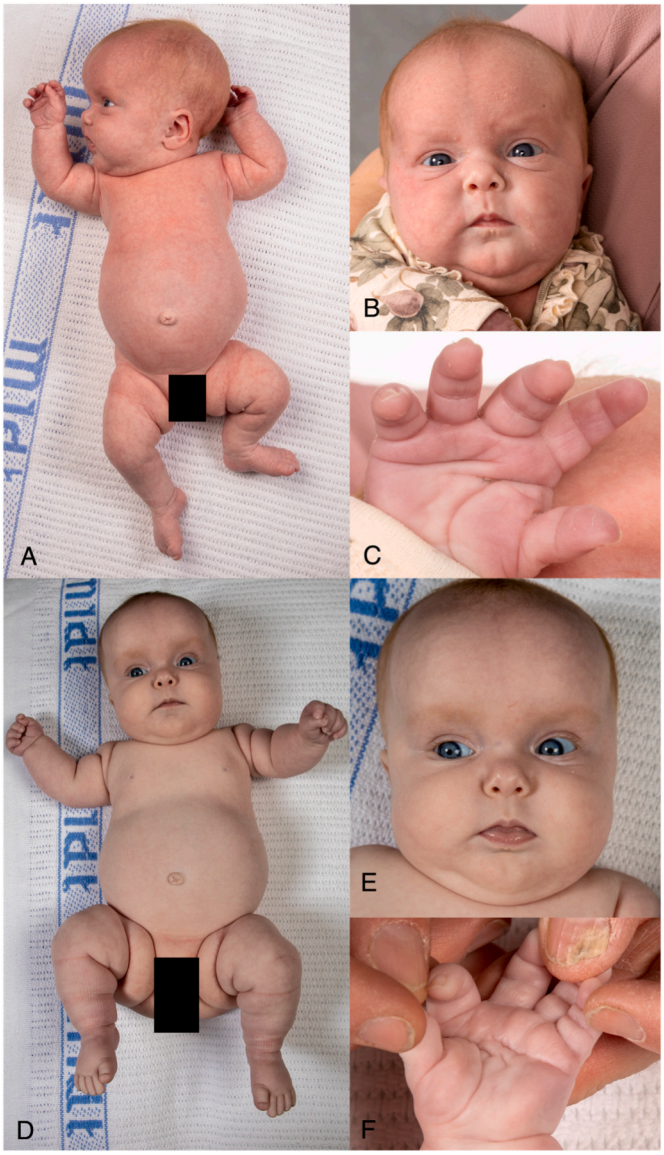


Fig. 2. Clinical features at 28 days of age (A, B, and C) and 120 days of age (D, E, and F). A + D: Rhizomelic shortening of the limbs, frontal bossing and a large neurocranium. B + E: Mild midfacial hypoplasia and depressed nasal bridge C + F: Short fingers and trident hand configuration.

1.1.5. Imaging

Magnetic resonance imaging (MRI) of the cranium and spine was performed under sleep (*feed-and-wrap*) at 30 days of age to evaluate the spinal cord due to the risk of compression at the craniocervical junction related to achondroplasia (Cheung et al., 2021; Irving et al., 2023). MRI showed reduction of space at the craniocervical junction with discrete spinal cord kinking. The space around the neural structures was deemed sufficient as there was adequate cerebrospinal fluid surrounding the spinal cord and there were no signs of compression of the brain stem or spinal cord.

2. Discussion

We describe a newborn girl with concurrent achondroplasia and SHOX deficiency confirmed by molecular genetic analysis. To our knowledge this is the first patient described to have both conditions confirmed by molecular genetic analysis. In the patient described, several phenotypic characteristics including rhizomelic limb shortening, midfacial hypoplasia, depressed nasal bridge, frontal bossing, craniocervical junction constriction, and trident hand configuration are present. The current findings are primarily compatible with the diagnosis of achondroplasia and at this point, no features of SHOX deficiency are observed. However, as certain features of SHOX deficiency, such as mesomelic limb shortening and Madelung deformity, usually only becomes evident at a later age, clinical follow-up will be required to confirm or dismiss features specific to SHOX deficiency (Binder et al., 1993).

Clinically speaking, achondroplasia and SHOX deficiency cause rhizomelic and mesomelic limb shortening, respectively. It is therefore reasonable to speculate that any additive effect may result in a more severe phenotype with regards to stature and limb length. Due to the highly variable expression seen in the heterozygous forms of SHOX deficiency, it is also possible that any additive effects of achondroplasia and SHOX deficiency would share this interindividual variability. Results found in vitro studies suggest that the *SHOX* gene product negatively regulates *FGFR3* expression, an effect predominantly observed in the distal limb bones (Decker et al., 2011). SHOX deficiency and subsequent reduced regulation of the constitutively active *FGFR3* gene product could lead to an additive effect on the length of the distal limb bones. Conversely, if the constitutive *FGFR3* activity already has a maximal or near-maximal effect in achondroplasia patients, the effect might be negligible.

Few reports of similar patients exist. Ross et al., report on a patient with genetically confirmed achondroplasia but without reporting a confirmed SHOX deficiency (Ross et al., 2003). SHOX deficiency of the patient was assumed as the father's phenotype seemed consistent with LMD, and thus, biallelic SHOX deficiency, although he only had genetically confirmed heterozygosity for SHOX deficiency. This prompted the authors to suspect the presence of an undetected variant of SHOX deficiency affecting both the patient and the father. The patient had phenotypical findings consistent with LWD/Madelung deformity (increased carrying angle, X-ray with carpal wedging, and radial bowing) (Ross et al., 2003). At the time of the report, the patient was 6.5 years of age, leaving the question on final stature unanswered. When compared to achondroplasia norms, the patient reported had a projected adult height similar to her mother with achondroplasia alone, prompting the authors to suggest a less than additive effect of this assumed double heterozygosity (Ross et al., 2003). Bioarcheological articles have reported cases of findings consistent with combined LWD and achondroplasia in human skeletal remains (Matczak et al., 2022; Cormier et al., 2017). In both cases, pronounced shortening of both proximal and distal limb bones were present, suggesting an additive effect on limb length. The diagnoses of these articles were based on anthropometric and pathological examinations. However, as little is known about the phenotype of combined SHOX deficiency and achondroplasia, and as genetic analyses could not be carried out, the validity of the diagnoses is uncertain (Matczak et al., 2022; Cormier et al., 2017).

As this is the first genetically confirmed case, and as some phenotypical features might not yet be fully developed, more knowledge is needed for optimal management of similar patients, especially when new medical therapies become available, as is the case for achondroplasia (Savarirayan et al., 2020, 2021, 2022; Chan et al., 2022). This is particularly true for combinations of skeletal dysplasia, as the one reported here, but also for rare skeletal dysplasias in general. Therefore, more patients, especially of older age, are needed to provide more knowledge on the clinical course and development of achondroplasia in combination with SHOX deficiency. Due to the relatively high estimated prevalence of SHOX deficiency in the general population, more cases are expected to exist among achondroplasia patients.

Consent

Oral or written Informed consent was obtained from the family prior to publication.

Funding sources

No funding was obtained to conduct this study.

CRediT authorship contribution statement

Kasper V. Seiersen: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Tine B. Henriksen:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Ted C.K. Andelius:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Lotte Andreasen:** Data curation, Writing – review & editing. **Tue Diemer:** Data curation, Writing – review & editing. **Gudrun Gudmundsdottir:** Data curation, Writing – review & editing. **Ida Vogel:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Vibike Gjørup:** Data curation, Writing – review & editing. **Pernille A. Gregersen:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Disclosure of conflict of interest

None.

Data availability

Data can be provided by the corresponding author upon reasonable request.

Acknowledgements

We warmly thank the family for participating in this study. Several authors of this publication are members of the European Reference Network for rare BONeDiseases. https://ernbond.eu/

References

Bellus, G.A., et al., 1995. Achondroplasia is defined by recurrent G380R mutations of FGFR3. Am. J. Hum. Genet. 56 (2), 368–373.

Binder, G., Rappold, G.A., 1993. SHOX deficiency disorders. In: Adam, M.P., et al. (Eds.), GeneReviews(®). University of Washington, Seattle (WA). Seattle Copyright © 1993-2023, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

Chan, M.L., et al., 2022. Pharmacokinetics and exposure-response of vosoritide in children with achondroplasia. Clin. Pharmacokinet. 61 (2), 263–280.

Cheung, M.S., et al., 2021. Achondroplasia foramen magnum score: screening infants for stenosis. Arch. Dis. Child. 106 (2), 180–184.

Cicognani, A., et al., 2010. The SHOX gene: a new indication for GH treatment. J. Endocrinol. Invest. 33 (6 Suppl. l), 15–18.

Cormier, A.A., Buikstra, J.E., Osterholtz, A., 2017. Overlapping genetic pathways in the skeletal dysplasias of a middle woodland individual: a case study. International Journal of Paleopathology 18, 98–107.

Decker, E., et al., 2011. FGFR3 is a target of the homeobox transcription factor SHOX in limb development. Hum. Mol. Genet. 20 (8), 1524–1535.

Irving, M., et al., 2023. European Achondroplasia Forum guiding principles for the detection and management of foramen magnum stenosis. Orphanet J. Rare Dis. 18 (1), 219.

Marchini, A., Ogata, T., Rappold, G.A., 2016. A track record on SHOX: from basic research to complex models and therapy. Endocr. Rev. 37 (4), 417–448.

Matczak, M.D., et al., 2022. Skeletal dysplasia of an adult male from medieval Łekno in Poland, Central Europe. Int. J. Osteoarchaeol. 32 (6), 1300–1309.

Neumeyer, L., M.A.H.L. Achondroplasia clinical charts. Version 2020. 2020 [cited 2023 26th of March]; Available from: https://www.achondroplasia-growthcharts.com/.

Nicolosi, A., Caruso-Nicoletti, M., 2010. Epidemiology of SHOX deficiency. J. Endocrinol. Invest. 33 (6 Suppl. l), 7–10.

Pauli, R.M., 2019. Achondroplasia: a comprehensive clinical review. Orphanet J. Rare Dis. 14 (1), 1.

Ross, J.L., et al., 2003. Mesomelic and rhizomelic short stature: the phenotype of combined Leri-Weill dyschondrosteosis and achondroplasia or hypochondroplasia. Am. J. Med. Genet. 116a (1), 61–65.

Rousseau, F., et al., 1994. Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. Nature 371 (6494), 252–254.

Savarirayan, R., et al., 2020. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. Lancet 396 (10252), 684–692.

Savarirayan, R., et al., 2021. Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study. Genet. Med. 23 (12), 2443–2447.

Savarirayan, R., et al., 2022. Literature review and expert opinion on the impact of achondroplasia on medical complications and health-related quality of life and expectations for long-term impact of vosoritide: a modified Delphi study. Orphanet J. Rare Dis. 17 (1), 224.

Tinggaard, J., et al., 2014. The 2014 Danish references from birth to 20 years for height, weight and body mass index. Acta Paediatr. 103 (2), 214–224.

Webster, M.K., Donoghue, D.J., 1996. Constitutive activation of fibroblast growth factor receptor 3 by the transmembrane domain point mutation found in achondroplasia. EMBO J. 15 (3), 520–527.