Tibia hemimelia in a patient with CHARGE syndrome

Aukema, Sietse M.; de Geus, Christa M.; Robben, Simon G.F.; van Kaam, Kim J.A.F.; Staal, Heleen M.; Witlox, Adhiambo M.; de la Haye, Nicole A.J.; Klaassens, Merel; Coumans, Audrey; Stegmann, Alexander P.A.

Published in:
American Journal of Medical Genetics, Part A

DOI:
10.1002/ajmg.a.62600

Publication date:
2022

Received: 27 September 2021 | Revised: 21 November 2021 | Accepted: 28 November 2021

DOI: 10.1002/ajmg.a.62600

AMERICAN JOURNAL OF medical genetics PART A WILEY

RESEARCH LETTER

Tibia hemimelia in a patient with CHARGE syndrome: A rare but recurrent phenomenon

Sietse M. Aukema[1] | Christa M. de Geus[2] | Simon G. F. Robben[3] | Kim J. A. F. van Kaam[1] | Heleen M. Staal[4] | Adhiambo M. Witlox[4] | Nicole A. J. de la Haye[5] | Merel Klaassens[5] | Audrey Coumans[6] | Alexander P. A. Stegmann[7] | Dror Paley[8] | Constance T. R. M. Stumpel[7]

[1]Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, The Netherlands

[2]Department of Clinical Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[3]Department of Radiology, Maastricht University Medical Center, Maastricht, The Netherlands

[4]Department of Orthopaedics, Maastricht University Medical Centre, Maastricht, The Netherlands

[5]Department of Pediatrics, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

[6]Department of Obstetrics and Gynaecology, Maastricht University Medical Center, Maastricht, The Netherlands

[7]Department of Clinical Genetics and GROW-School for Oncology & Developmental Biology, Maastricht University Medical Center+, Maastricht, The Netherlands

[8]Paley Orthopedic and Spine Institute, West Palm Beach, Florida, USA

Correspondence

Sietse M. Aukema, Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, the Netherlands.
Email: sietse.aukema@mumc.nl; smaukema@gmail.com

Constance T. R. M. Stumpel, Department of Clinical Genetics and GROW-School for Oncology & Developmental Biology, Maastricht University Medical Center+, Maastricht, The Netherlands.
Email: c.stumpel@outlook.com

To the Editor,

Tibia hemimelia, defined as the congenital partial or complete absence of the tibia, is a very rare lower limb deficiency and has an estimated worldwide incidence of only 1 in a million births (Chong & Paley, 2021; Paley, 2016; Stevenson, 2016; Taleb et al., 2019). Tibia hemimelia can be observed both unilateral and bilateral, isolated or with associated (lower)limb abnormalities, and is sporadic in the majority of the patients although familial occurrence has been described (Chong & Paley, 2021; Clinton & Birch, 2015; Kumar Sahoo et al., 2019; Matsuyama et al., 2003; Paley, 2016). Tibia hemimelia has been linked to or been described as part of several syndromes and associations (Chong & Paley, 2021; Paley, 2016) which include, among others, "tibia, hypoplasia or aplasia with polydactyly" (MIM#18874), "triphalangeal thumb with polysyndactyly" (MIM#174500), "trichorhinophalangeal syndrome type II/Langer-Giedion syndrome" (MIM#150230), VATER/VACTERL association (MIM%192350), split-hand/foot malformation syndrome with long bone deficiency (MIM% 119100) and Gollop–Wolfgang complex (MIM%228250). Although (minor) limb anomalies have been described in CHARGE syndrome (**C**oloboma, **H**eart defects, **A**tresia of the choanae, **R**etardation of growth and development, **G**enito-urinary and **E**ar abnormalities) syndrome in approximately 30%–40% of the patients (Brock et al., 2003; Legendre et al., 2017), tibia hemimelia has been described only occasionally (Alazami et al., 2008; Brock et al., 2003; Clinton & Birch, 2015; Gennery et al., 2008; Prasad et al., 1997; van de Laar et al., 2007). Whether tibia hemimelia is part of the phenotypic spectrum of CHARGE syndrome could be of diagnostic importance as subsequently the presence of tibia hemimelia should not automatically discard a possible diagnosis of CHARGE syndrome. This is especially the case at the beginning of diagnostic work-up when the presence or absence of hallmark characteristics of CHARGE syndrome has not been fully assessed yet.

On the neonatal intensive care unit, we saw a newborn girl with bilateral lower limb abnormalities (Table 1). The prenatal history reported bilateral clubfeet and an anomaly of the left lower leg. An amniocentesis was performed and copy number variant (CNV)-array analysis and QF-PCR (chromosomes 13, 18, and 21) were normal. Directly after birth, she developed respiratory distress likely because of choanal atresia and was intubated. Physical examination at the time of initial consultation showed a sedated newborn girl with mild facial dysmorphias including a right-sided external ear abnormality (left ear not assessable) and bilateral lower limb anomalies and clubfeet. As at

TABLE 1 Clinical and molecular characteristics

Age at diagnosis (years)	0
Sex	F
Molecular characteristics	
CHD7 mutation (c./p.)	c.4015C > T; p.(Arg1339*), heterozygous
Variant classification	Pathogenic
Detection method	Exome sequencing
Inheritance	de novo
Clinical classification	
Verloes classification	Typical CHARGE syndrome
Hale classification	CHARGE syndrome
Diagnostic hallmarks of CHARGE syndrome	
Coloboma[a,b]	No
Heart defect[c,d]	PDA
Choanal **A**tresia[a,b]	Yes, bilateral
Retardation growth/development[c,d]	No/NA
Genito-urinary abnormalities[d]	Bilateral cortical cysts, VUR Gr. III, unilateral hydronephrosis
Ear abnormalities[b,c]	
External	Minor (bilateral)
Middle	Middle ear pathology, Type-I, R > L
A-/hypoplasia semi-circular canals[a,b]	Yes
Other	
Other (potential) syndrome-related features	
Intellectual disability[c,d]	NA
Structural brain abnormalities[d]	No
Archincephaly and/or anosmia (N. I)	NA
Abnormalities cranial nerves VII–XII[c,d]	Hypoplasia N.VIII (R), aplasia (L)
Hypothalamo-hypophyseal dysfunction[c,d]	No
Esophageal abnormalities[c,d]	No anatomical malformation
Dysphagia/feeding difficulties[d]	Yes (MIC-KEY button, GERD, Nissen fundoplication, swallowing difficulties)
Other abnormalities	Thoracal/cervical spinal segmentation anomalies[e] Aberrant right subclavian artery (arteria lusoria)
Tibia hemimelia classification[e,f]	
Right	Yes
Jones	2
Weber	IIIb
Paley	4A
Left	Yes
Jones	1B
Weber	VIIa
Paley	4B
Other limb abnormalities[e]	Yes, club foot bilateral; foot, L: slightly hypoplastic digit I
Treatment	Bilateral amputation
Long-term outcome	NA

Abbreviations: F, female; GERD, gastroesophageal reflux disease; L, left; NA, not assessed/assessable; PDA, patent ductus arteriosus; R, right; VUR, vesicourethral reflux.
[a]Verloes major criterium.
[b]Hale major criterium.
[c]Verloes minor criterium.
[d]Hale minor criterium.
[e]Skeletal and limb anomalies are minor criterium in Hale classification.
[f]D. Paley was not involved in the orthopedic management of the patient.

the time of clinical consultation on the intensive care unit (i) no definitive syndromic diagnosis of CHARGE syndrome could be made as several clinical and radiologic investigations were still ongoing and (ii) the nature and extent of the limb anomalies was not fully elucidated, a clinical exome (virtual gene panel "Mendelian inherited diseases," 3671 genes) on the DNA of the proband and her parents was performed after written informed consent. Exome sequencing, data processing, and variant interpretation were performed as previously described (Arts et al., 2019). With exome sequencing a heterozygous, de novo, pathogenic variant in *CHD7* was identified: c.4015C > T, p.(Arg1339*), transcript NM_017780.3. Subsequent clinical and radiological investigations showed typical features of CHARGE syndrome (see Table 1 for a detailed overview). The clinical, molecular, and orthopedic characteristics are summarized in Table 1. The Jones, Weber, and Paley classifications (Paley, 2016) were 2/1B (right/left), IIIb/VIIa, and 4A/4B (Figure 1).

In the patient, bilateral tibia hemimelia was observed. The clinical and radiologic investigations, as well as the identified pathogenic *CHD7* mutation, are all in line with a diagnosis of typical CHARGE syndrome (Basson & van Ravenswaaij-Arts, 2015; Hale et al., 2016; Janssen et al., 2012; van Ravenswaaij-Arts & Martin, 2017; Verloes, 2005). Both CHARGE syndrome and tibia hemimelia are rare conditions with estimated frequencies of 0.1–1.2/10,000 and 1:1,000,000 respectively (Blake & Prasad, 2006; Paley, 2016). Several observations support that tibia hemimelia is indeed part of the limb anomaly spectrum in CHARGE syndrome (Alazami et al., 2008; van de Laar et al., 2007). First, CHARGE syndrome is much more frequently seen in patients with tibia hemimelia than expected by its incidence. In a large series of 117 consecutive patients with tibia hemimelia treated at the Paley Institute, three patients had a diagnosis of CHARGE syndrome corresponding to a frequency of 3%. Along the same lines, among 95 patients with tibia hemimelia published by Clinton and Birch (2015), 1 patient had CHARGE syndrome (1/95, 1%). From the CHARGE syndrome point-of-view, among 580 consecutive patients with a CHARGE syndrome phenotype seen at the national multidisciplinary CHARGE clinic at the University Medical Center Groningen, The Netherlands, 4 patients (including the patient in the present study) had unilateral or bilateral tibia hemimelia (4/580, 1%). Also in the series published by Brock et al. (2003), tibia hemimelia was observed in 1/172 patients (1%) with CHARGE syndrome. Second, with the used exome sequencing panel (3671 genes) no other (potential) causative single nucleotide variants or CNVs in genes—including *FGF8* (Basson, 2014)—associated with tibia hemimelia or other limb and developmental anomalies were identified (Basson, 2014; Petit et al., 2017; Tao et al., 2017).

In CHARGE syndrome, loss-of-function of *CHD7* has been proposed as the (main) responsible mechanism (Bouazoune & Kingston, 2012; Vissers et al., 2004). However, the exact mechanism(s) underlying and pathway(s) involved in tibia hemimelia in CHARGE syndrome are largely unknown at present. This may involve direct effects of altered CHD7 expression, modifier effects from variants in other genes and/or by epistatic interactions with (local) perturbation of expression of (downstream) transcription factors involved in limb formation in the developing limb (Basson, 2014; Basson & van Ravenswaaij-Arts, 2015; Browne et al., 2012; Petit et al., 2017; Riley et al., 2007; Schnetz et al., 2010; Yu et al., 2013).

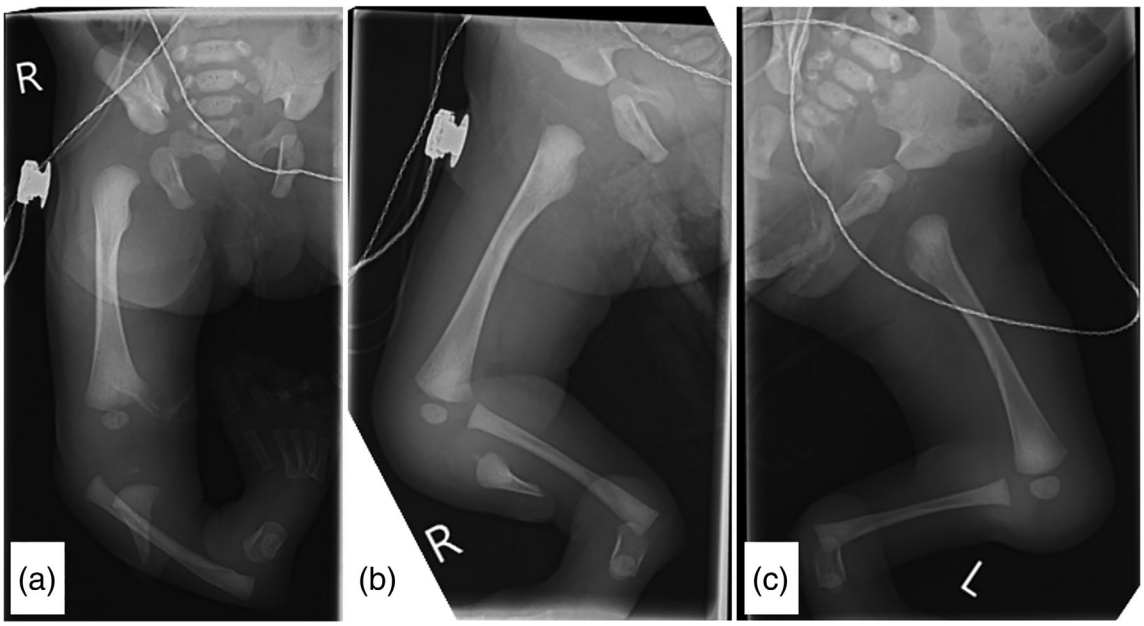

FIGURE 1 X-rays of the lower extremities of the patient. (a, b) The right hip and femur are normal. The proximal tibia is in normal position and appears slightly hypoplastic. The proximal tibia has a sharp tapering and the distal 2/3 is absent. The distal end of the tibia causes a soft tissue prominence. The hypertrophic fibula shows a clear varus deformity of the knee joint with apparent subluxation of the head. Ultrasound showed a normal aspect patella. (c) The left hip and femur are normal. In the lower leg, there is total aplasia of the tibia. The fibula appears normal but has a slightly hypertrophic impression. Ultrasound showed a normal aspect of the patella and a rudimentary tibial plateau

In conclusion, we describe a patient with typical characteristics of CHARGE syndrome with bilateral tibia hemimelia and provide estimates of the frequency of CHARGE syndrome among patients with tibia hemimelia and vice versa. The observations presented in our report together with those in previous publications (Alazami et al., 2008; van de Laar et al., 2007) indeed suggest that tibia hemimelia is part of the phenotypic spectrum. Major limb anomalies including tibia hemimelia in CHARGE syndrome should be further studied.

ACKNOWLEDGMENTS

The authors would like to thank the patient's parents for approving the publication of the data.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study design and manuscript writing: Sietse M. Aukema and Constance T. R. M. Stumpel. *Provision and/or interpretation of clinical, radiological and/or molecular data*: Christa M. de Geus, Simon G. F. Robben, Kim J. A. F. van Kaam, Heleen M. Staal, Adhiambo M. Witlox, Nicole A.J. de la Haye, Merel Klaassens, Audrey Coumans, Alexander P. A. Stegmann and Dror Paley.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Alexander P. A. Stegmann https://orcid.org/0000-0002-9736-7137

REFERENCES

Alazami, A. M., Alzahrani, F., & Alkuraya, F. S. (2008). Expanding the "E" in CHARGE. *American Journal of Medical Genetics. Part A*, *146A*(14), 1890–1892. https://doi.org/10.1002/ajmg.a.32376

Arts, P., Simons, A., AlZahrani, M. S., Yilmaz, E., AlIdrissi, E., van Aerde, K. J., Alenezi, N., AlGhamdi, H. A., AlJubab, H. A., Al-Hussaini, A. A., AlManjomi, F., Alsaad, A. B., Alsaleem, B., Andijani, A. A., Asery, A., Ballourah, W., Bleeker-Rovers, C. P., van Deuren, M., van der Flier, M., … Hoischen, A. (2019). Exome sequencing in routine diagnostics: A generic test for 254 patients with primary immunodeficiencies. *Genome Medicine*, *11*(1), 38. https://doi.org/10.1186/s13073-019-0649-3

Basson, M. A. (2014). Epistatic interactions between Chd7 and Fgf8 during cerebellar development: Implications for CHARGE syndrome. *Rare Diseases*, *2*, e28688. https://doi.org/10.4161/rdis.28688

Basson, M. A., & van Ravenswaaij-Arts, C. (2015). Functional insights into chromatin remodelling from studies on CHARGE syndrome. *Trends in Genetics*, *31*(10), 600–611. https://doi.org/10.1016/j.tig.2015.05.009

Blake, K. D., & Prasad, C. (2006). CHARGE syndrome. *Orphanet Journal of Rare Diseases*, *1*, 34. https://doi.org/10.1186/1750-1172-1-34

Bouazoune, K., & Kingston, R. E. (2012). Chromatin remodeling by the CHD7 protein is impaired by mutations that cause human developmental disorders. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(47), 19238–19243. https://doi.org/10.1073/pnas.1213825109

Brock, K. E., Mathiason, M. A., Rooney, B. L., & Williams, M. S. (2003). Quantitative analysis of limb anomalies in CHARGE syndrome: Correlation with diagnosis and characteristic CHARGE anomalies. *American Journal of Medical Genetics. Part A*, *123A*(1), 111–121.

Browne, M. L., Carter, T. C., Kay, D. M., Kuehn, D., Brody, L. C., Romitti, P. A., Liu, A., Caggana, M., Druschel, C. M., & Mills, J. L. (2012). Evaluation of genes involved in limb development, angiogenesis, and coagulation as risk factors for congenital limb deficiencies. *American Journal of Medical Genetics. Part A*, *158A*(10), 2463–2472. https://doi.org/10.1002/ajmg.a.35565

Chong, D. Y., & Paley, D. (2021). Deformity reconstruction surgery for tibial hemimelia. *Children (Basel, Switzerland)*, *8*(6), 461. https://doi.org/10.3390/children8060461

Clinton, R., & Birch, J. G. (2015). Congenital tibial deficiency: A 37-year experience at 1 institution. *Journal of Pediatric Orthopedics*, *35*(4), 385–390. https://doi.org/10.1097/BPO.0000000000000280

Gennery, A. R., Slatter, M. A., Rice, J., Hoefsloot, L. H., Barge, D., McLean-Tooke, A., Montgomery, T., Goodship, J. A., Burt, A. D., Flood, T. J., Abinun, M., Cant, A. J., & Johnson, D. (2008). Mutations in CHD7 in patients with CHARGE syndrome cause T-B + natural killer cell + severe combined immune deficiency and may cause Omenn-like syndrome. *Clinical and Experimental Immunology*, *153*(1), 75–80. https://doi.org/10.1111/j.1365-2249.2008.03681.x

Hale, C. L., Niederriter, A. N., Green, G. E., & Martin, D. M. (2016). Atypical phenotypes associated with pathogenic CHD7 variants and a proposal for broadening CHARGE syndrome clinical diagnostic criteria. *American Journal of Medical Genetics. Part A*, *170A*(2), 344–354. https://doi.org/10.1002/ajmg.a.37435

Janssen, N., Bergman, J. E. H., Swertz, M. A., Tranebjaerg, L., Lodahl, M., Schoots, J., Hofstra, R. M. W., van Ravenswaaij-Arts, C. M. A., & Hoefsloot, L. H. (2012). Mutation update on the CHD7 gene involved in CHARGE syndrome. *Human Mutation*, *33*(8), 1149–1160. https://doi.org/10.1002/humu.22086

Kumar Sahoo, P., Sahu, M. M., & Prasad Das, S. (2019). Clinical spectrum of congenital tibial hemimelia in 35 limbs of 24 patients: A single center observational study from India. *European Journal of Medical Genetics*, *62*(7), 103666. https://doi.org/10.1016/j.ejmg.2019.05.005

Legendre, M., Abadie, V., Attie-Bitach, T., Philip, N., Busa, T., Bonneau, D., Colin, E., Dollfus, H., Lacombe, D., Toutain, A., Blesson, S., Julia, S., Martin-Coignard, D., Genevieve, D., Leheup, B., Odent, S., Jouk, P.-S., Mercier, S., Faivre, L., … Gilbert-Dussardier, B. (2017). Phenotype and genotype analysis of a French cohort of 119 patients with CHARGE syndrome. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *175*(4), 417–430. https://doi.org/10.1002/ajmg.c.31591

Matsuyama, J., Mabuchi, A., Zhang, J., Iida, A., Ikeda, T., Kimizuka, M., & Ikegawa, S. (2003). A pair of sibs with tibial hemimelia born to phenotypically normal parents. *Journal of Human Genetics*, *48*(4), 173–176. https://doi.org/10.1007/s10038-003-0003-9

Paley, D. (2016). Tibial hemimelia: New classification and reconstructive options. *Journal of Children's Orthopaedics*, *10*(6), 529–555. https://doi.org/10.1007/s11832-016-0785-x

Petit, F., Sears, K. E., & Ahituv, N. (2017). Limb development: A paradigm of gene regulation. *Nature Reviews. Genetics*, *18*(4), 245–258. https://doi.org/10.1038/nrg.2016.167

Prasad, C., Quackenbush, E. J., Whiteman, D., & Korf, B. (1997). Limb anomalies in DiGeorge and CHARGE syndromes. *American Journal of Medical Genetics*, *68*(2), 179–181.

Riley, B. M., Mansilla, M. A., Ma, J., Daack-Hirsch, S., Maher, B. S., Raffensperger, L. M., Russo, E. T., Vieira, A. R., Dodé, C., Mohammadi, M., Marazita, M. L., & Murray, J. C. (2007). Impaired FGF signaling contributes to cleft lip and palate. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(11), 4512–4517. https://doi.org/10.1073/pnas.0607956104

Schnetz, M. P., Handoko, L., Akhtar-Zaidi, B., Bartels, C. F., Pereira, C. F., Fisher, A. G., Adams, D. J., Flicek, P., Crawford, G. E., Laframboise, T., Tesar, P., Wei, C.-L., & Scacheri, P. C. (2010). CHD7 targets active gene enhancer elements to modulate ES cell-specific gene expression. *PLoS Genetics*, *6*(7), e1001023. https://doi.org/10.1371/journal.pgen.1001023

Stevenson, R. E. (2016). Absence and hypoplasia of the tibia. In R. E. Stevenson, J. Hall, D. B. Everman, & B. Solomon (Eds.), *Human malformations and related anomalies* (3rd ed., pp. 53–54). Oxford: Oxford University Press.

Taleb, H., Afshar, A., Abdi Rad, I., Tabrizi, A., Ghazani, R. B., & Bateni, A. (2019). A high prevalence rate of tibia hemimelia in a subregion of West Azarbaijan, Iran. *Journal of Pediatric Genetics*, *8*(3), 137–141. https://doi.org/10.1055/s-0039-1692971

Tao, H., Kawakami, Y., Hui, C.-C., & Hopyan, S. (2017). The two domain hypothesis of limb prepattern and its relevance to congenital limb anomalies. *Wiley Interdisciplinary Reviews. Developmental Biology*, *6*(4). https://doi.org/10.1002/wdev.270

van de Laar, I., Dooijes, D., Hoefsloot, L., Simon, M., Hoogeboom, J., & Devriendt, K. (2007). Limb anomalies in patients with CHARGE syndrome: An expansion of the phenotype. *American Journal of Medical Genetics. Part A*, *143A*(22), 2712–2715. https://doi.org/10.1002/ajmg.a.32008

van Ravenswaaij-Arts, C., & Martin, D. M. (2017). New insights and advances in CHARGE syndrome: Diagnosis, etiologies, treatments, and research discoveries. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *175*(4), 397–406. https://doi.org/10.1002/ajmg.c.31592

Verloes, A. (2005). Updated diagnostic criteria for CHARGE syndrome: A proposal. *American Journal of Medical Genetics. Part A*, *133A*(3), 306–308. https://doi.org/10.1002/ajmg.a.30559

Vissers, L. E. L. M., van Ravenswaaij, C. M. A., Admiraal, R., Hurst, J. A., de Vries, B. B. A., Janssen, I. M., van der Vliet, W. A., Huys, E. H. L. P. G., de Jong, P. J., Hamel, B. C. J., Schoenmakers, E. F. P. M., Brunner, H. G., Veltman, J. A., & van Kessel, A. G. (2004). Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nature Genetics*, *36*(9), 955–957. https://doi.org/10.1038/ng1407

Yu, T., Meiners, L. C., Danielsen, K., Wong, M. T., Bowler, T., Reinberg, D., Scambler, P. J., van Ravenswaaij-Arts, C. M., & Basson, M. A. (2013). Deregulated FGF and homeotic gene expression underlies cerebellar vermis hypoplasia in CHARGE syndrome. *eLife*, *2*, e01305. https://doi.org/10.7554/eLife.01305

How to cite this article: Aukema, S. M., de Geus, C. M., Robben, S. G. F., van Kaam, K. J. A. F., Staal, H. M., Witlox, A. M., de la Haye, N. A. J., Klaassens, M., Coumans, A., Stegmann, A. P. A., Paley, D., & Stumpel, C. T. R. M. (2021). Tibia hemimelia in a patient with CHARGE syndrome: A rare but recurrent phenomenon. *American Journal of Medical Genetics Part A*, 1–5. https://doi.org/10.1002/ajmg.a.62600