



ACHONDROPLASIA

Height is a metric—health is the focus^{1,2}

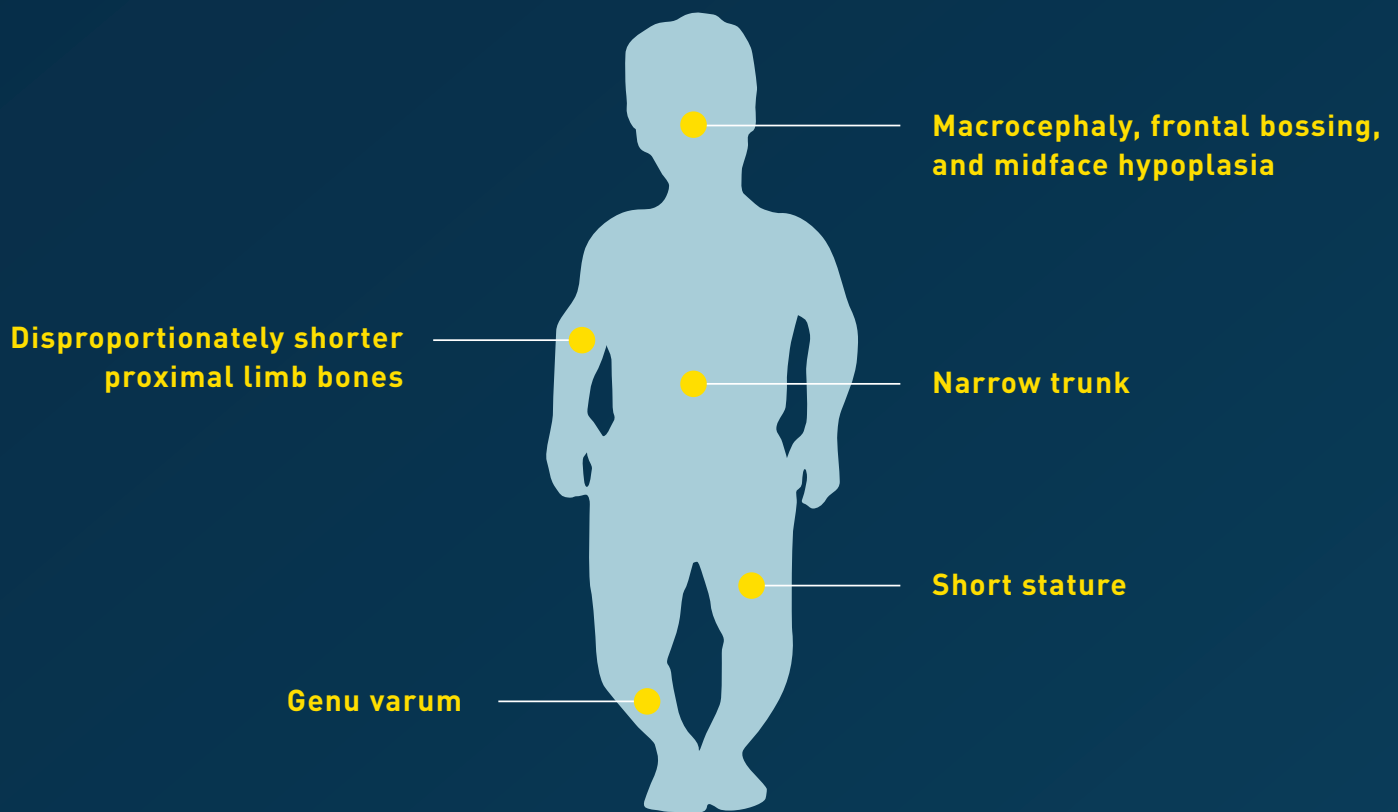
Find out how early and consistent
growth assessments can help create
a comprehensive care plan²

B:OMARIN[®]

1 IN 25,000 PEOPLE EACH YEAR ARE BORN WITH ACHONDROPLASIA^{3,4}

Achondroplasia, characterized by impaired endochondral bone growth, is the most common type of skeletal dysplasia, accounting for about 90% of disproportionate short stature.^{5,6}

PHYSICAL CHARACTERISTICS^{1,2,6}



ACHONDROPLASIA IS CAUSED BY A GAIN-OF-FUNCTION MUTATION IN THE FIBROBLAST GROWTH FACTOR RECEPTOR 3 (FGFR3) GENE AND HAS A DISTINCT PHYSICAL PRESENTATION.⁶

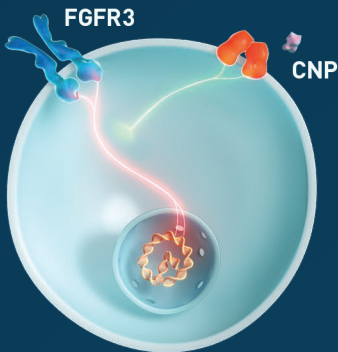
IMBALANCE BETWEEN FGFR3 AND CNP SIGNALING PATHWAYS IMPAIRS BONE GROWTH⁷

Endochondral bone growth—the replacement of cartilage by bone—is primarily regulated by 2 processes⁸:

- Signaling from **fibroblast growth factor receptor 3 (FGFR3)**, which slows linear bone growth⁹
- Counter-signaling from the **C-type natriuretic peptide (CNP) pathway**, which promotes bone growth⁹

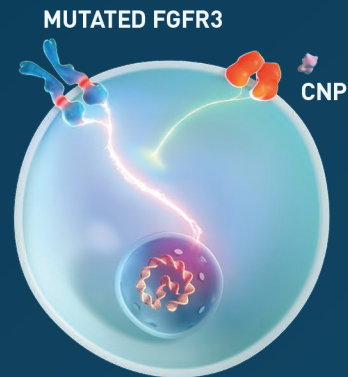
Average Stature

The CNP pathway blocks the signal from FGFR3, resulting in typical bone growth.^{9,10}

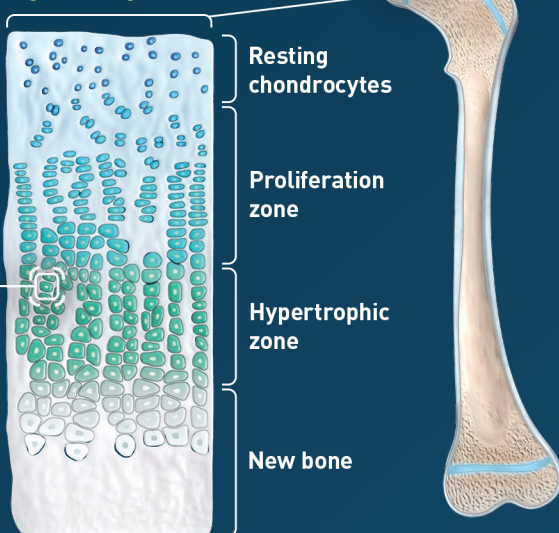


Achondroplasia

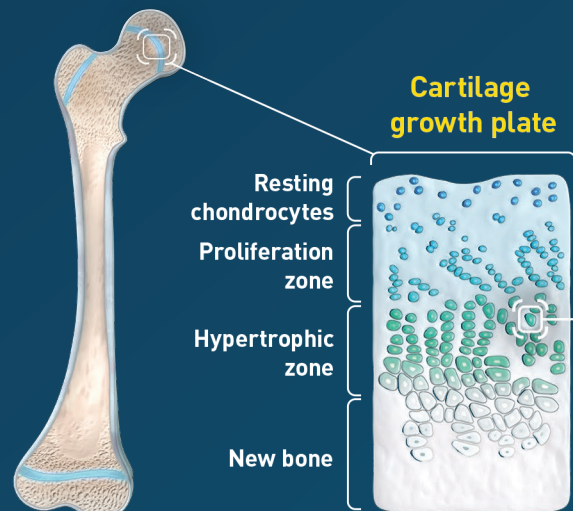
Overactive FGFR3 signaling overwhelms the CNP pathway, resulting in impaired bone growth.^{9,10}



Cartilage growth plate



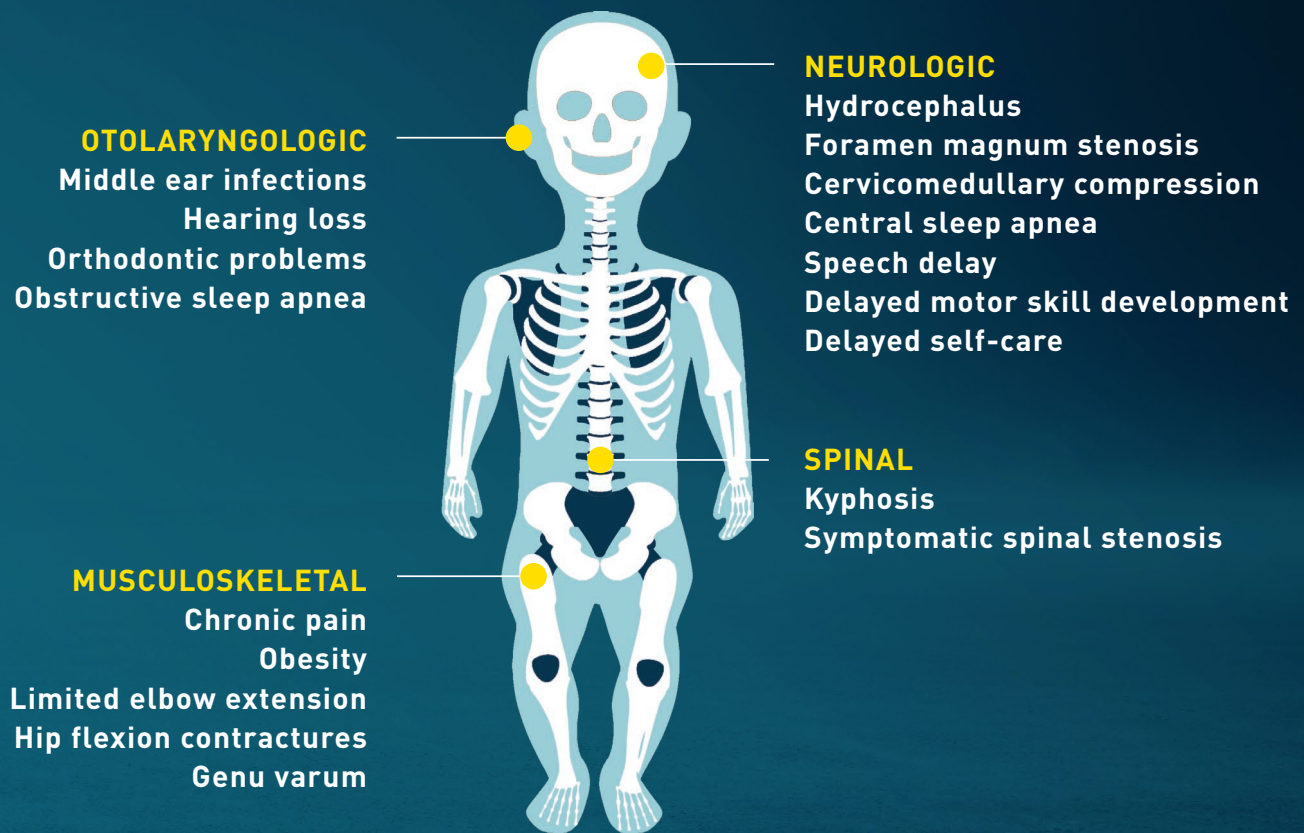
Cartilage growth plate



SERIOUS, MULTISYSTEMIC COMPLICATIONS CAN RESULT FROM IMPAIRED BONE GROWTH IN ACHONDROPLASIA¹

Impaired endochondral bone growth leads to more than just short stature—progressive neurologic, orthopedic, respiratory, and physical development complications can have long-term health implications for people who have achondroplasia.^{1,2}

POTENTIALLY AFFECTED SYSTEMS ACROSS LIFESPAN^{10,11}



**10X
HIGHER**

rate of deaths expected
from heart disease (ages 25-35)
than the general population³

**10YR
REDUCTION**

in median life expectancy
compared with
general population³

A COMPREHENSIVE CARE PLAN BEGINS WITH REGULAR GROWTH MONITORING⁹

Because achondroplasia is often diagnosed during infancy and can lead to progressive complications, early intervention can play an important role in managing its long-term impact. Achondroplasia-specific assessment of key growth measurements, which can include growth velocity, body segment proportions, weight, and occipital-frontal circumference, can enable timely intervention.^{1,6,9,12}

Examples of growth measurements that can help include^{12,13}:



Growth velocity



Upper to lower body proportion



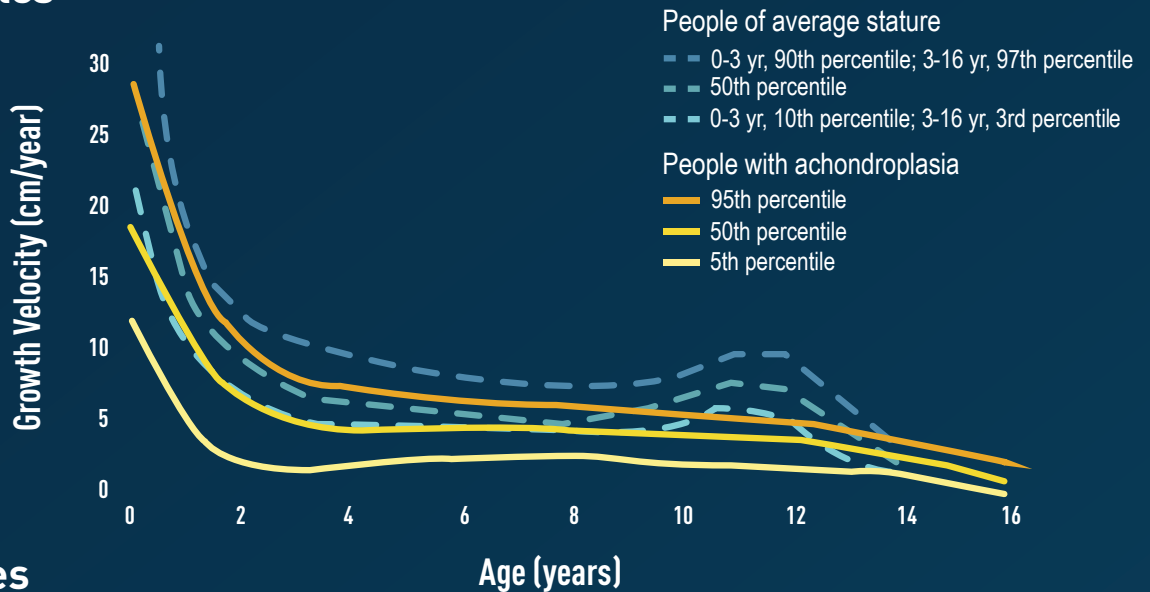
Occipital-frontal circumference

Height is a metric—health is the focus^{1,2}

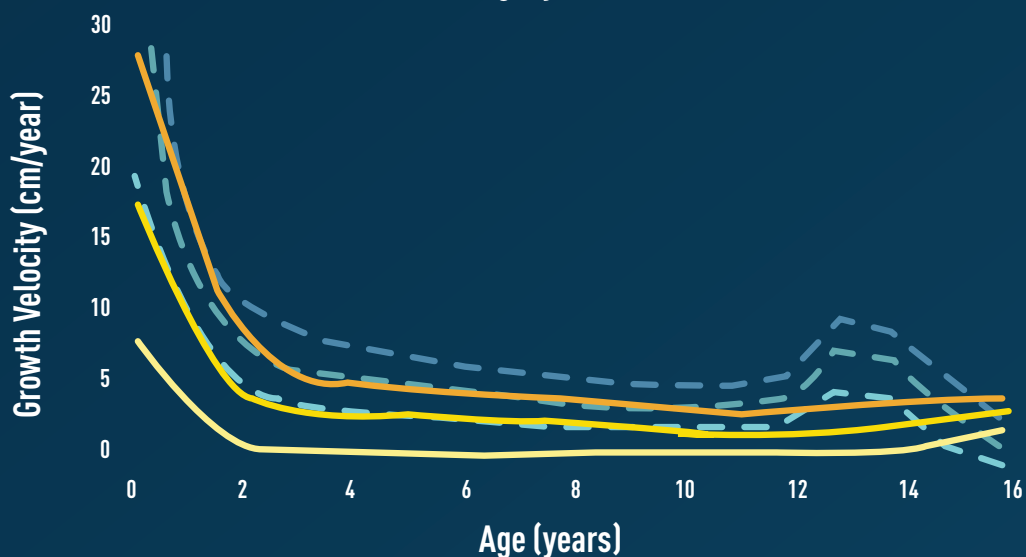
ANNUALIZED GROWTH VELOCITY IS A PROXY FOR ENDOCHONDRAL BONE GROWTH¹³

Children with achondroplasia have significantly reduced growth velocity—they experience slower linear growth from infancy and may not have a pubertal linear growth spurt.¹³

Females



Males

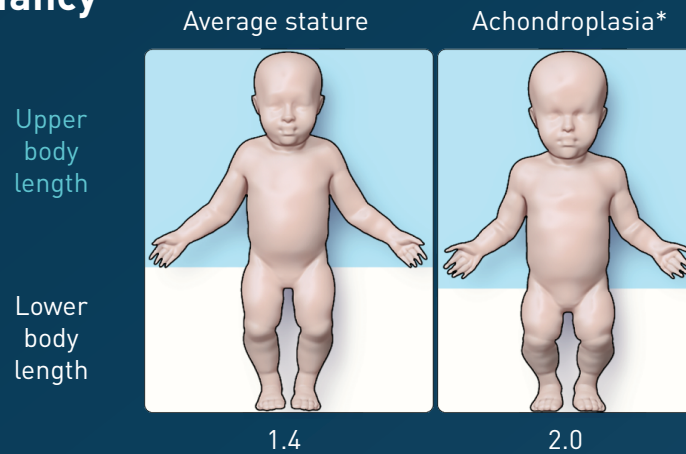


PEOPLE WITH ACHONDROPLASIA HAVE FINAL ADULT HEIGHTS THAT ARE
6-7 STANDARD DEVIATIONS BELOW THE GENERAL POPULATION MEAN.⁶

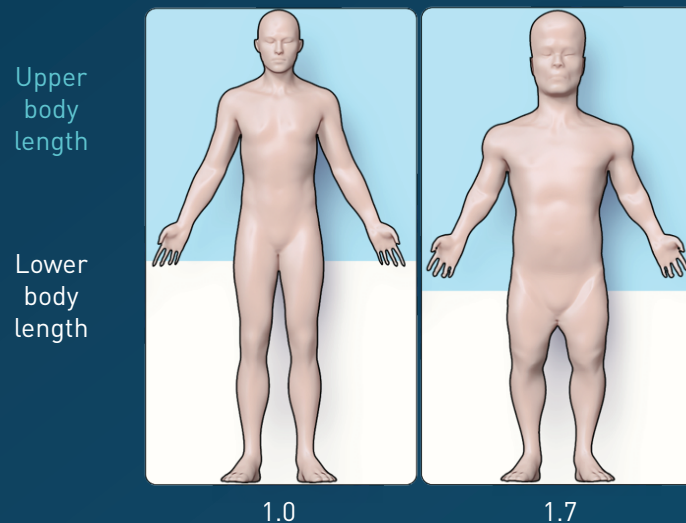
BODY SEGMENT DISPROPORTIONALITY IS AN IMPORTANT PHYSICAL MARKER OF ACHONDROPLASIA¹³

As average stature children grow into adulthood, their upper and lower body lengths become proportional. However, children with achondroplasia have a higher upper to lower body segment ratio at infancy, which continues into adulthood.^{13,14}

Infancy



From 10 years old to adulthood



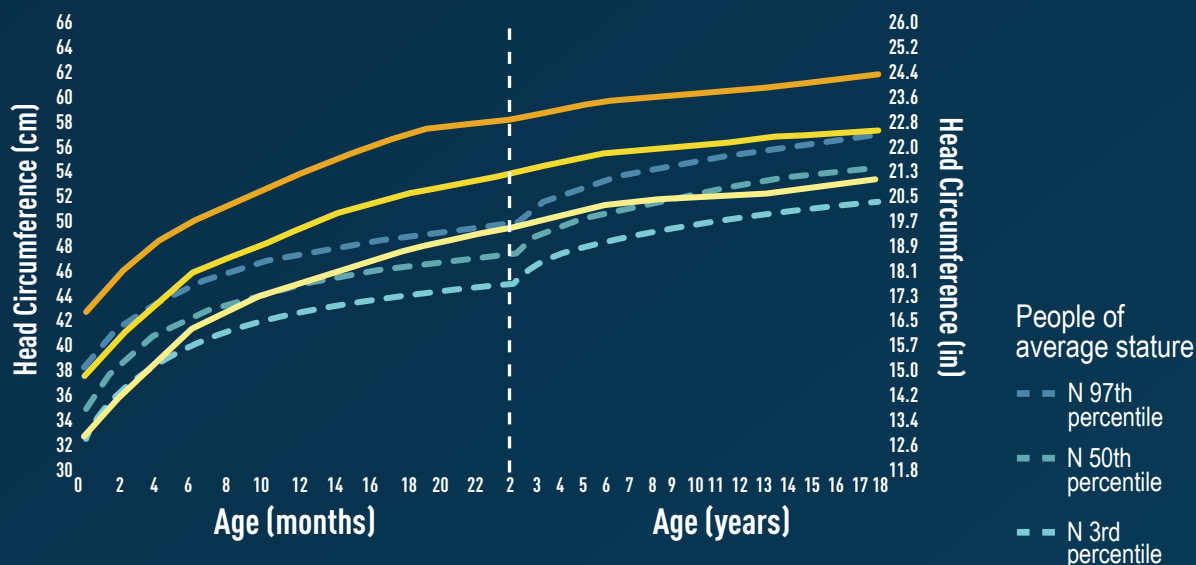
PEOPLE WITH ACHONDROPLASIA HAVE A 1.7:1 RATIO OF UPPER TO LOWER BODY LENGTH AT SKELETAL MATURITY.¹⁴

*These ratios represent the 50th percentile of children with achondroplasia.

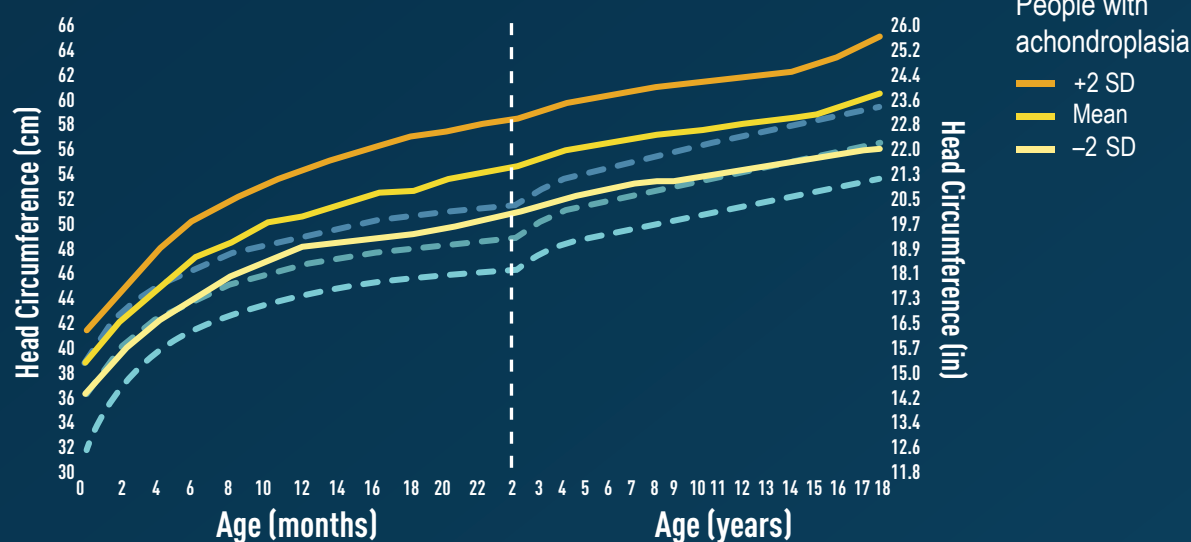
OCCIPITAL-FRONTAL CIRCUMFERENCE CAN HELP IDENTIFY POTENTIAL NEUROLOGIC COMPLICATIONS¹

Close monitoring of the occipital-frontal circumference (OFC) using achondroplasia-specific growth charts can help identify potential neurologic complications.^{1,2}

Females



Males



CHILDREN WITH ACHONDROPLASIA WHO EXPERIENCE A RAPID INCREASE IN HEAD SIZE OR SYMPTOMS OF INCREASED INTRACRANIAL PRESSURE MAY NEED TO BE REFERRED TO A PEDIATRIC NEUROLOGIST.¹

CAREGIVERS CAN HELP IDENTIFY COMPLICATIONS EARLY

Discussing the signs of potential complications with parents and caregivers of people with achondroplasia can help ensure timely identification and management.



Sleep disordered breathing

Affects >50% of people with achondroplasia¹²



Dental issues

Including misaligned teeth, a narrow palate, open bite, or underbite¹⁷



Genu varum (tibial bowing)

Bowing of legs can affect walking and running¹⁵



Obesity

Can lead to heart disease^{18,19}



Symptomatic spinal stenosis

Can lead to leg weakness, incontinence, and chronic pain, especially in the back^{16,17}



Functional challenges

Associated with the complications caused by achondroplasia can affect mobility, independence, and daily activities^{19,20}



Pain

Especially back pain, which can result in loss of mobility¹⁷



Foramen magnum stenosis

May be associated with compression of the lower brain stem and higher mortality²¹⁻²³



Recurrent otitis media

Ear infections can affect up to 70% of people with achondroplasia⁶



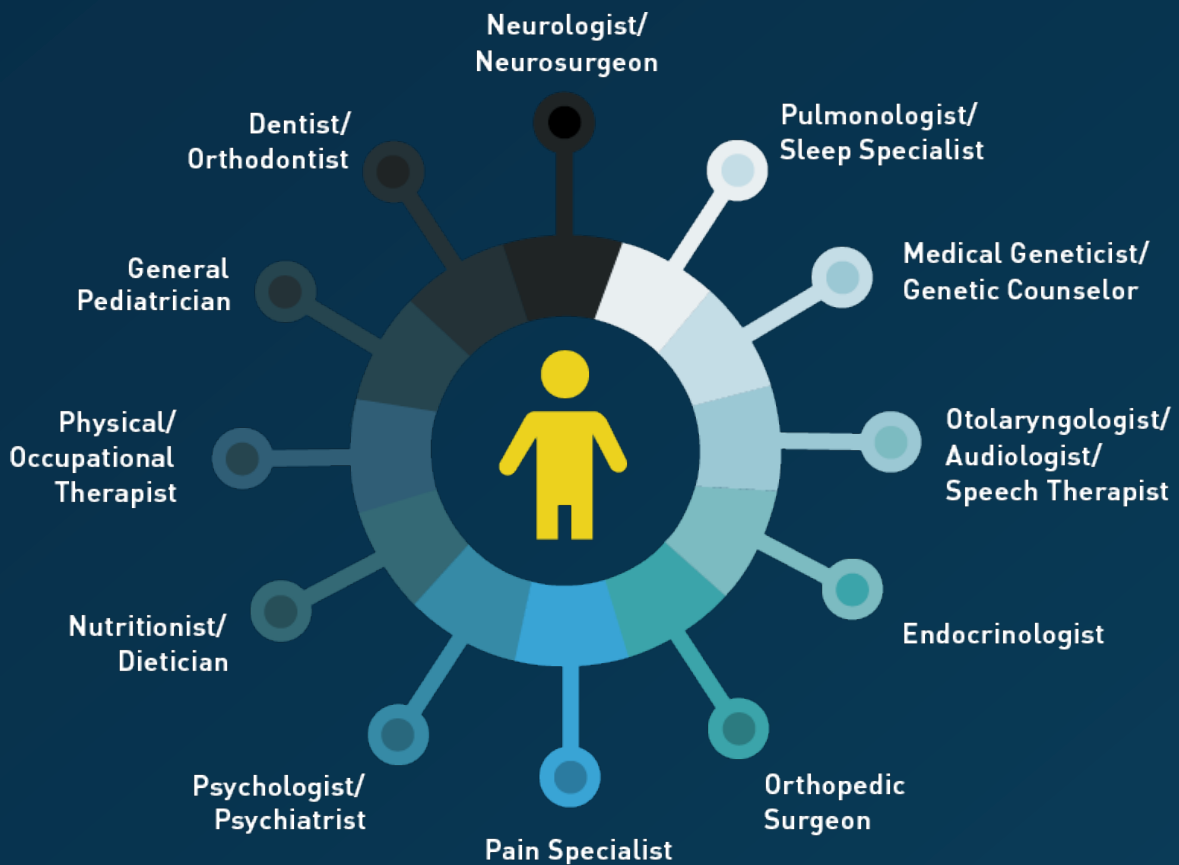
Psychosocial impact

Negative appraisal of one's own stature could lead to poor self-esteem²⁴

CAREGIVERS CAN VISIT [ACHONDROPLASIA.COM](https://achondroplasia.com) TO LEARN MORE ABOUT
THE SIGNS OF COMPLICATIONS RELATED TO ACHONDROPLASIA.

A COMMUNITY OF HEALTHCARE PROVIDERS SUPPORT PARENTS AND CAREGIVERS²

The multisystemic challenges of achondroplasia require a multidisciplinary team. Coordinated care is needed to provide optimal results for patients and to support their parents and caregivers.^{2,6,12,17,25}



VISIT HCP.ACHONDROPLASIA.COM TO STAY IN THE KNOW
ABOUT NEW DEVELOPMENTS.

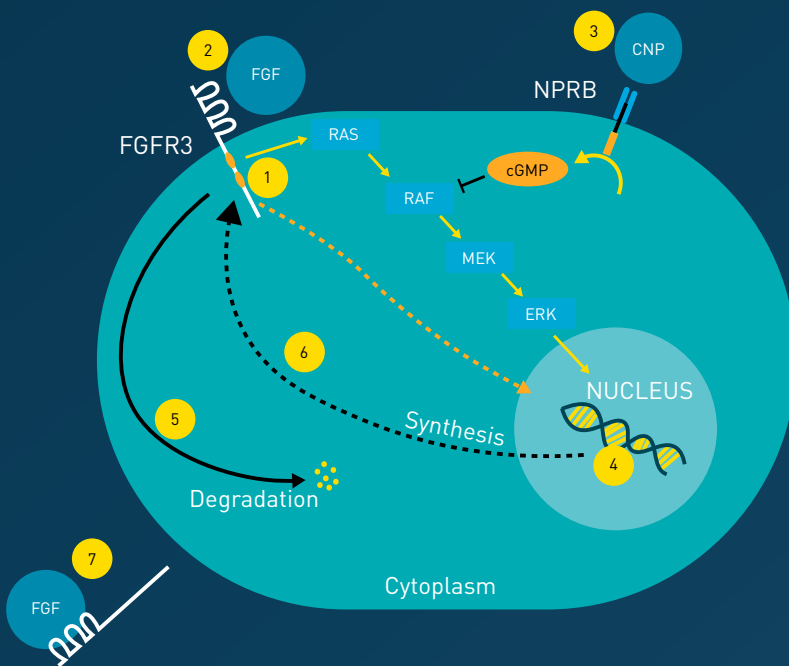


VIEW IN 3D

Hold the camera app on your
phone over the QR code.

RESEARCH INTO ACHONDROPLASIA IS ONGOING²⁶

Current treatments do not address the underlying cause of achondroplasia and is limited to the management of complications. Different approaches targeting FGFR3 overactivity and the CNP pathway are under investigation. However, none of these approaches have been determined to be safe or effective or approved for use.^{9,10,25-27}



- 1 Chemical inhibitors to reduce FGFR3 tyrosine kinase activity
- 2 Antibodies to block FGFR3 activation
- 3 Exogenous CNP to enhance CNP-mediated antagonism of downstream signals
- 4 RNA interference (RNAi) to reduce FGFR3 production
- 5 Heat shock protein 90 (Hsp90) inhibitors to induce degradation of activated FGFR3
- 6 Agents to disrupt direct nuclear signaling of FGFR3
- 7 Soluble FGFR3 decoys to prevent cellular FGF binding

NO THERAPIES FOR ACHONDROPLASIA HAVE BEEN APPROVED FOR USE OR DETERMINED TO BE SAFE OR EFFECTIVE.

HEIGHT IS A METRIC—HEALTH IS THE FOCUS^{1,2}



1 in 25,000 people

each year are born with achondroplasia, which is characterized by impaired endochondral bone growth^{3,6}



Regular growth assessments

using achondroplasia-specific growth charts can help identify potential complications^{11,12}



Serious complications

that affect multiple physiological systems can result from impaired bone growth in achondroplasia^{1,2}



Research on targeted pharmacologic approaches

to achondroplasia is ongoing^{25,26}



SIGN UP FOR UPDATES

Hold the camera app on your phone over the QR code.



QUESTIONS

Email us at:
medinfo@bmrn.com

References: 1. Ireland PJ, Pacey V, Zankl A, Edwards P, Johnston LM, Savarirayan R. Optimal management of complications associated with achondroplasia. *Appl Clin Genet*. 2014;7:117-125. 2. Hoover-Fong J, Scott CI, Jones MC; AAP Committee on Genetics. Health supervision for people with achondroplasia. *Pediatrics*. 2020;145(6):e20201010. 3. Wynn J, King TM, Gambello MJ, Waller DK, Hecht JT. Mortality in achondroplasia study: a 42-year follow-up. *Am J Med Genet A*. 2007;143A(21):2502-2511. 4. McDonald EJ, De Jesus O. Achondroplasia. NCBI Bookshelf. Accessed April 7, 2021. 5. Waller DK, Correa A, Vo TM, et al. The population-based prevalence of achondroplasia and thanatophoric dysplasia in selected regions of the US. *Am J Med Genet A*. 2008;146A(18):2385-2389. 6. Pauli RM. Achondroplasia: a comprehensive clinical review. *Orphanet J Rare Dis*. 2019;14(1):1. 7. Vasques GA, Arnhold IJP, Jorge AAL. Role of the natriuretic peptide system in normal growth and growth disorders. *Horm Res Paediatr*. 2014;82(4):222-229. 8. Berendsen AD, Olsen BR. Bone development. *Bone*. 2015;80:14-18. 9. Horton WA, Hall JG, Hecht JT. Achondroplasia. *Lancet*. 2007;370(9582):162-172. 10. Laederich MB, Horton WA. Achondroplasia: pathogenesis and implications for future treatment. *Curr Opin Pediatr*. 2010;22(4):516-523. 11. Ireland PJ, McGill J, Zankl A, et al. Functional performance in young Australian children with achondroplasia. *Dev Med Child Neurol*. 2011;53(10):944-950. 12. Unger S, Bonafé L, Gouze E. Current care and investigational therapies in achondroplasia. *Curr Osteoporos Rep*. 2017;15(2):53-60. 13. Hoover-Fong JE, Schulze KJ, McGready J, Barnes H, Scott CI. Age-appropriate body mass index in children with achondroplasia: interpretation in relation to indexes of height. *Am J Clin Nutr*. 2008;88(2):364-371. 14. Chitbule SK, Dutt V, Madhuri V. Limb lengthening in achondroplasia. *Indian J Orthop*. 2016;50(4):397-405. 15. Shirley ED, Ain MC. Achondroplasia: manifestations and treatment. *J Am Acad Orthop Surg*. 2009;17(4):231-241. 16. Ain MC, Abdullah MA, Ting BL, et al. Progression of low back and lower extremity pain in a cohort of patients with achondroplasia. *J Neurosurg Spine*. 2010;13(3):335-340. 17. Hunter AG, Bankier A, Rogers JG, Sillence D, Scott CI Jr. Medical complications of achondroplasia: a multicentre patient review. *J Med Genet*. 1998;35(9):705-712. 18. Hecht JT, Hood OJ, Schwartz RJ, Hennessey JC, Bernhardt BA, Horton WA. Obesity in achondroplasia. *Am J Med Genet*. 1988;31(3):597-602. 19. Fredwall SO, Maanum G, Johansen H, Snekkevik H, Savarirayan R, Lidal IB. Current knowledge of medical complications in adults with achondroplasia: a scoping review. *Clin Genet*. 2020;97(1):179-197. 20. Alade Y, Tunkel D, Schulze K, et al. Cross-sectional assessment of pain and physical function in skeletal dysplasia patients. *Clin Genet*. 2013;84(3):237-243. 21. Hecht JT, Francomano CA, Horton WA, Annegers JF. Mortality in achondroplasia. *Am J Hum Genet*. 1987;41(3):454-464. 22. Hecht JT, Horton WA, Reid CS, Pyeritz RE, Chakraborty R. Growth of the foramen magnum in achondroplasia. *Am J Med Genet*. 1989;32(4):528-535. 23. Hecht JT, Bodensteiner JB, Butler IJ. Neurologic manifestations of achondroplasia. *Handb Clin Neurol*. 2014;119:551-563. 24. Nishimura N, Hanaki K. Psychosocial profiles of children with achondroplasia in terms of their short stature-related stress: a nationwide survey in Japan. *J Clin Nurs*. 2014;23(21-22):3045-3056. 25. Wright MJ, Irving MD. Clinical management of achondroplasia. *Arch Dis Child*. 2012;97(2):129-134. 26. Högl W, Ward LM. New developments in the management of achondroplasia. *Wien Med Wochenschr*. 2020;170(5-6):104-111. 27. Laederich MB, Degnin CR, Lunstrum GP, Holden P, Horton WA. Fibroblast growth factor receptor 3 (FGFR3) is a strong heat shock protein 90 (Hsp90) client: implications for therapeutic manipulation. *J Biol Chem*. 2011;286(22):19597-19604.

B:OMARIN®