Journal of Clinical Pediatrics and Neonatology

Bittmann S, J Clin Pediatr Neonatol. 2025;5(1):16-18.

Commentary

Recent therapeutic progress to treat achondroplasia in children

Stefan Bittmann[1,2,*]

[1]Department of Pediatrics, Ped Mind Institute, Department of Pediatrics, Hindenburgring 4, D-48599 Gronau, Germany

[2]Professor (Hon. Prof.), Shangluo Vocational and Technical College, Shangluo, 726000, Shaanxi, China

*Author for correspondence: Email: stefanbittmann@gmx.de

Received date: July 03, 2025
Accepted date: September 19, 2025

Abstract

Achondroplasia is the most common form of genetically inherited dwarfism. Affected individuals are mainly characterized by severely shortened arms and legs and a large head. In 1878, the term achondrodysplasia was coined by the French physician Joseph Marie Jules Parrot. The term achondroplasia is purely historical and does not explain the cause or manifestations of this disorder. Achondroplasia is the most common form of genetically inherited dwarfism, occurring with an incidence of 1 in 20,000 births. Therefore, like all types of dwarfism, it is considered a rare disease. The diagnosis is made through genetic testing. Achondroplasia is the result of a point mutation in the fibroblast growth factor receptor gene *FGFR-3*. This mutation disrupts cartilage formation; the bone growth zone is prematurely ossified, leading to a restriction of length growth, especially in the arms and legs. This results in disproportionate dwarfism, where the trunk and head are relatively longer than the limbs. In 96% of cases, there is a G (1138) A point mutation in the *FGFR-3* gene, leading to an amino acid exchange at position 380 of the protein, changing glycine to arginine (Gly380Arg). In 3% of cases, a G (1138) C point mutation can be detected, which also results in a glycine-to-arginine exchange. Achondroplasia is inherited in an autosomal dominant manner, meaning it can only be passed on by individuals who are affected themselves. This is the case in about 20% of children born with achondroplasia. In the remaining approximately 80%, there is a *de novo* mutation in the *FGFR3* gene. Current research in achondroplasia is focused on developing therapies to reduce FGFR3 receptor overexpression and excessive signals and therefore inhibit chondrocyte formation to treat achondroplasia. This editorial focus on recent therapeutic progress to treat achondroplasia in children.

Introduction

In 1878, French physician Joseph Marie Jules Parrot coined the term achondrodysplasia, which is now considered a rare genetic disorder [1]. It is caused by a gain-of-function point mutation in the *FGFR-3* gene, leading to overexpression of the FGFR3 receptor pathway and inhibiting chondrocyte proliferation responsible for cartilage formation [1–4]. The specific mutation in the *FGFR3* gene that causes achondroplasia is a substitution of glycine with arginine at codon 380, disrupting normal bone formation and leading to disproportionate short stature [5–8]. Restricted growth, particularly in the arms and legs, leads to disproportionate short stature [5,6]. It affects about one in every 26,000–28,000 live births. Achondroplasia is the most common form of short stature, caused by a dominant *FGFR3* gain-of-function mutation that activates the FGFR3 and MAPK signaling cascade, inhibiting chondrocyte differentiation and growth plate activity [1,9,10]. This leads to complications like spinal stenosis and airway narrowing. Treatment recommendations aim to reduce morbidity and mortality, especially in infants and young children [6,11]. External symptoms include short upper arms and thighs, broad hands and feet, and a long trunk. Breathing and hearing issues are common due to chest size and narrow nasopharynx. Physical development may be delayed, but intelligence is not affected. Leg axis changes and spinal curvature may occur, with growth typically ending around 120–140 cm. Early gene mutation suspicion led to the discovery of achondroplasia. Fibroblast growth factor

receptor 3 is a receptor tyrosine kinase that binds fibroblast growth factors, regulating cell proliferation, differentiation, and migration. It plays a crucial role in bone ossification and cartilage remodeling. In achondroplasia, an overactive FGFR3 signaling pathway is present, affecting cell growth and differentiation. FGFR3 interacts with adapter proteins like GRB2 and Sos, forming complexes that link to the MAPK pathway. The activation of FGFR3 leads to phosphorylation of proteins like phospholipase C-γ, influencing cell signaling.

Therapeutic Drug Candidates

Vosoritide (BMN111) is a treatment for achondroplasia in patients over 2 years old with open epiphyses [9,12,13]. Marketed as Voxzogo, it comes in powder and solvent form for injection. Vosoritide acts as an agonist of NPR-B, promoting bone growth by inhibiting the MAPK pathway [5,14]. It is well-absorbed and metabolized via catabolic pathways [14]. The recommended dosage is weight-based to ensure consistent exposure. Common side effects include injection site reactions, vomiting, hypotension, dizziness, and syncope [9,13]. Vosoritide has minimal drug interactions due to its recombinant peptide nature. TransCon CNP is a modified form of CNP-38 attached to polyethylene glycol for sustained release in achondroplasia treatment. It offers continuous exposure to CNP, enhancing bone growth efficacy compared to intermittent exposure. Studies show it is well-tolerated with minimal cardiovascular effects.

The prolonged exposure to CNP with TransCon CNP reduces the risk of hypotension. Recifercept targets FGFGR3 to treat achondroplasia by downregulating specific signaling pathways, improving bone growth, skeletal development, skull proportions, and reproductive capacity [15–17]. It also shows promise in reducing atypical visceral obesity in achondroplasia. Further research is needed to understand its full efficacy and safety in humans. Vofatamab is a monoclonal antibody targeting FGFR3, studied for urothelial carcinoma treatment. It blocks FGF ligand attachment to inhibit cancer cell growth. While considered for achondroplasia, its large size may limit its effectiveness in dense extracellular matrices. Clinical trials are ongoing for urothelial neoplasms and multiple myeloma. Erdafitinib, an FGFR inhibitor, is effective in treating certain cancers by inhibiting FGFR subtypes and other tyrosine kinases. Approved by the FDA in 2019, it is used for metastatic or locally advanced urothelial carcinoma with specific gene mutations. Common side effects include stomatitis, diarrhea, abdominal pain, nausea, constipation, and dysgeusia. Recent publications in the New England Journal of Medicine and the Lancet shed light on oral infigratinib as a valuable milestone in the treatment of achondroplasia [2,5,6,9,11–13].

Therapeutic strategies aim to reduce excessive signals from the *FGFR3* gene, with potential treatments including C-Type Natriuretic Peptide (CNP), FGFR3-binding peptides, soluble FGFR3, meclizine, statin, and FGFR inhibitors [18]. Vosoritide, a stable form of CNP, has shown positive effects on growth in clinical trials. Targeting FGFR3 with Tyrosine Kinase Inhibitors (TKIs) is another potential strategy, although current inhibitors are not specific to FGFR3. Research is ongoing to develop more specific inhibitors for FGFR3 [13]. Treatment in childhood is crucial, but current therapies do not cure all symptoms associated with achondroplasia. The current treatments are life-long treatments without *curing* the patients with this rare disease in childhood.

Future research may focus on mutation repair methods to correct the gene defect, a point mutation on chromosome 4 in a one-time approach [13]. Point mutations, which are changes in the DNA that affect only a single base, can in principle be repaired, and there are various methods to try to do this [6, 7,10,11]. Repair possibilities include cellular repair mechanisms, where cells have built-in mechanisms to detect and repair DNA damage, including point mutations. These mechanisms can perform spontaneous repairs, but sometimes they are not sufficient to fix severe damage. For certain genetic diseases caused by point mutations, gene therapy may be considered. In this approach, the normal gene function is attempted to be restored by introducing an intact gene copy into the cells or directly repairing the faulty DNA. CRISPR/Cas technology is a relatively new method that allows for targeted modification of DNA and correction of point mutations. There are different approaches where either the faulty base is directly replaced or repaired with a template.

Repairing point mutations requires high precision to ensure that only the intended site is altered and no further damage occurs. From the point of efficacy, not all point mutations can be efficiently repaired with the available methods. Off-target effects are also important to evaluate, when using CRISPR/Cas, unintended changes can also occur at other locations in the genome. The applicability of the methods depends on various factors, such as the type of mutation, the affected tissue, and the underlying disease. In summary, it can be said that point mutations are in principle repairable, but the methods and their efficiency can vary.

Overall, further research should focus on mutation repair methods as early as possible, possibly as a *prenatal intrauterine one-time approach* in achondroplasia [19]. This could be the future to cure pediatric patients with achondroplasia. All other treatment options do not cure but treat the child, help to gain weight in a different degree with sometimes serious toxic side effects depending on the individual mechanism of action of the drug. Especially tyrosine kinase inhibitors should be more selective for FGFR3 signaling pathway, most often they inhibit other FGFR pathways with serious toxic side effects. Discovery of a potent FGFR2/3 Inhibitor to overcome mutation resistance and treat achondroplasia was published recently by a Chinese group of researchers and could be a valuable milestone to treat achondroplasia in childhood [20]. Another recently published interesting study is focused on CDK-8 inhibitors in achondroplasia model mice [21]. Further effective and selective drugs can be TYRA-300 and LOXO-435 as selective FGFR3-tyrosine kinase inhibitors [22–24]. Non-selective tyrosine kinase inhibitors like infigratinib, which include other inhibitory efficacy on other signaling pathways then the FGFR3 signaling pathway will have serious toxic side effects and are not the future for treatment in achondroplasia [7,10,22,25,26]. In conclusion, there are many different targets to *treat* achondroplasia on the one hand, of which a few shows toxic side effects beside the inhibition of the FGFR3-signaling pathway and, on the other hand, options to *cure* these children by pre-or postnatal one-time gene therapy approach. This must be the future.

Disclaimer

Author hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

Consent

As per international standards, parental written consent has been collected and preserved by the author.

Ethical Approval

As per international standards or university standards written ethical approval has been collected and preserved by the author.

Competing Interests

Author has declared that no competing interests exist.

References

1. Parrot J. Les malformations achondrodysplasiques. Bulletins de la Société d'anthropologie de Paris. 1878.
2. Hergenröther M, Palm K, Mohnike K, Witte K. Differences in gait parameters between children with achondroplasia and an age-matched control group of typically developed children in the age range of 6 to 12 years. PLoS One. 2025 Jun 18;20(6): e0326184.
3. Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet. 2007 Jul 14;370(9582):162–72.
4. Soğukpınar M, Demir GÜ, Utine GE, Gönç EN, Özön ZA, Şimşek-Kiper PÖ. Review of patients with achondroplasia: a single-center's experience with follow-up and associated morbidities. Eur J Pediatr. 2024 Sep;183(9):3819–29. doi: 10.1007/s00431-024-05643-y. Epub 2024 Jun 15. Erratum in: Eur J Pediatr. 2024 Sep;183(9):3831.
5. Kawabe T, Ichimura A, Yasue T, Li J, Ishikawa H, Kim GE, et al, Takeshima H. Phosphodiesterase 3 inhibitors boost bone outgrowth. Br J Pharmacol. 2025 Sep;182(18):4327–42.
6. Guillen-Navarro E, AlSayed M, Alves I, Ben-Omran T, Boero S, Cormier-Daire V, et al. Recommendations for management of infants and young children with achondroplasia: Does clinical practice align? Orphanet J Rare Dis. 2025 Mar 11;20(1):114.
7. Hoyer-Kuhn H. Oral Infigratinib in Children with Achondroplasia - Targeted Treatment. N Engl J Med. 2025 Feb 27;392(9):920–2.
8. Francomano CA. The genetic basis of dwarfism. N Engl J Med. 1995 Jan 5;332(1):58–9.
9. Cormier-Daire V, Edouard T, Isidor B, Mukherjee S, Pimenta JM, Rossi M, et al. Real-World Safety and Effectiveness of Vosoritide in Children with Achondroplasia: French Early Access Program. Horm Res Paediatr. 2025 Jan 25:1–9.
10. Savarirayan R, De Bergua JM, Arundel P, Salles JP, Saraff V, Delgado B, et al. Oral Infigratinib Therapy in Children with Achondroplasia. N Engl J Med. 2025 Feb 27;392(9):865–74.
11. Chen H, Zhang R, Jin M, Yang J, Chen L, Xie Y. Advances in the mechanism and therapies of achondroplasia. Genes Dis. 2024 Sep 24;12(4):101436.
12. Suzuki M, Sakamoto K, Sakurai Y, Saito H, Nakano S, Nishizaki N. Potential efficacy of vosoritide for foramen magnum stenosis in a patient with achondroplasia. Pediatrics International. 2025 Jan;67(1):e70106.
13. Ireland P, Carroll T, Pendlebury E, Weston E, Munns C. Functional Change in a Child With Achondroplasia Following 12 Months Treatment With Vosoritide-A Case Report. Am J Med Genet A. 2025 Jul;197(7):e64054.
14. Kitoh H. Vosoritide therapy in children with achondroplasia under 5 years of age. Transl Pediatr. 2024 Sep 30;13(9):1517–20.
15. Krejci P. C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia. N Engl J Med. 2019 Sep 26;381(13):1291.
16. Savarirayan R, Irving M, Day J. C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia. Reply. N Engl J Med. 2019 Sep 26;381(13):1291–2.
17. Savarirayan R, Hoover-Fong J, Yap P, Fredwall SO. New treatments for children with achondroplasia. Lancet Child Adolesc Health. 2024 Apr;8(4):301–10.
18. Sawamura K, Matsushita M, Esaki R, Mishima K, Kamiya Y, Ohno K, et al. Meclozine and growth hormone ameliorate bone length and quality in experimental models of achondroplasia. J Bone Miner Metab. 2025 Mar;43(2):74–85.
19. Vallin AL, Grévent D, Bessières B, Salomon LJ, Legeai-Mallet L, Cormier-Daire V, et al. Foetal achondroplasia: Prenatal diagnosis, outcome and perspectives. J Gynecol Obstet Hum Reprod. 2025 Feb;54(2):102891.
20. Fu D, Han T, Yang Z, Xia Y, Hu Z, Yang F, et al. Discovery of Potent FGFR2/3 Inhibitors to Overcome Mutation Resistance and Treat Achondroplasia. ACS Med Chem Lett. 2025 Jun 26;16(7):1428–34.
21. Sadamori K, Kubo T, Yoshida T, Yamamoto M, Shibata Y, Fukasawa K, et al. CDK8 inhibitor KY-065 rescues skeletal abnormalities in achondroplasia model mice. Biochim Biophys Acta Mol Basis Dis. 2025 Mar;1871(3):167626.
22. Bittmann S. Oral Infigratinib Therapy in Children with Achondroplasia. N Engl J Med. 2025 Jun 19;392(23):2387–8.
23. Hudkins RL, Allen E, Balcer A, Hoffman ID, Iyer S, Neal M, et al. Discovery of TYRA-300: First Oral Selective FGFR3 Inhibitor for the Treatment of Urothelial Cancers and Achondroplasia. J Med Chem. 2024 Sep 26;67(18):16737–56.
24. Starrett JH, Lemoine C, Guillo M, Fayad C, Kaci N, Neal M, et al. TYRA-300, an FGFR3-selective inhibitor, promotes bone growth in two FGFR3-driven models of chondrodysplasia. JCI Insight. 2025 Apr 3;10(9):e189307.
25. Savarirayan R, De Bergua JM, Arundel P, McDevitt H, Cormier-Daire V, Saraff V, et al. Infigratinib in children with achondroplasia: the PROPEL and PROPEL 2 studies. Ther Adv Musculoskelet Dis. 2022 Mar 21; 14:1759720X221084848.
26. Bittmann S. Editorial: Achondroplasia in Childhood: Treat or Cure? International Journal of Pediatrics and Child Health. 2025;13(2):1–2.