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# Recent Research in Achondroplasia in Childhood: A Special Focus on New Selective FGFR3 Tyrosine Kinase Inhibitors

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***Author's contribution***

*The sole author designed, analyzed, interpreted and prepared the manuscript.*

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***Letter to the Editor***

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Dear Editor,

Achondroplasia is the most common form of genetically inherited dwarfism. Affected individuals are characterized by significantly shortened arms and legs and a large head (Abraham et al., 2025, Jones et al., 2025, Nicolae et al., 2025). The term achondrodysplasia was coined by the French physician Joseph Marie Jules Parrot in 1878. The term achondroplasia is purely historical and does not explain the cause or manifestations of this disorder. Other designations, which are outdated and no longer in common use, include chondrodystrophy, chondrodystrophia fetalis, Parrot syndrome, or Kaufmann syndrome. Achondroplasia is the genetically inherited form of dwarfism in most countries. It occurs with an incidence of 1 in 20,000 births (Abraham et al., 2025, Jones et al., 2025, Nicolae et al., 2025).

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Therefore, like all types of dwarfism, it is considered a rare disease. Achondroplasia is a disorder of enchondral ossification, which is the bone growth that occurs in the growth plates of the long bones of the extremities and accounts for a significant portion of body height (Adedeji et al., 2025, Li and Xiong, 2025). This results in the long bones being significantly shorter, while other bones formed by diaphyseal ossification, such as most trunk bones, are not affected. This leads to disproportionate dwarfism, where the trunk and head are relatively longer than the extremities. In 1994, Le Merrer discovered that a mutation in the fibroblast growth factor receptor gene FGFR-3 is responsible for achondroplasia. This mutation is almost always a point mutation that is activating. In 96% of cases, a G (1138). A point mutation in the FGFR-3 gene is present, where glycine is replaced by arginine (Gly380Arg) (Dumitrascu et al., 2025, Merchant et al., 2025, Taylor-Miller and Savarirayan, 2024). In 3% of cases, a G (1138) C point mutation is found, which also leads to a glycine-to-arginine exchange. The FGF receptor 3 (FGFR3) is a cell membrane protein and a tyrosine kinase that is activated by phosphorylation. FGFR3 is a negative regulator of chondrocyte proliferation and cell differentiation in the growth plates, and it also inhibits the synthesis of the extracellular matrix of cartilage. An activating mutation of FGFR3 leads to increased inhibition of chondrocytes and reduced cartilage matrix formation, resulting in decreased ossification. Intracellular signal transduction from FGFR3 occurs through the STAT1 signaling pathway and the MAPK signaling pathway. Achondroplasia is inherited in an autosomal dominant manner, meaning it can only be passed on by individuals who are affected themselves (Savarirayan et al., 2024, Zhang et al., 2024). This is the case in about 20% of children born with achondroplasia. In the remaining approximately 80%, a de novo mutation in the FGFR3 gene is present, indicating that dwarfism occurs independently of the parents height. Embryos with a homozygous mutation are not viable and die shortly after birth or in utero.

Recent research on achondroplasia has included the development of the drug Voxzogo (Vosoritid), which promotes length growth, and the use of non-FGFR3-selective tyrosine kinase inhibitors, such as infigratinib, originally developed for cancer (Jones et al., 2025, Savarirayan et al., 2024, Onesimo et al., 2023). Further research focuses on identifying new mutations in the FGFR3 gene and investigating other potential benefits, such as expanding bone constrictions to prevent neurological problems. The discovery of new mutations in the FGFR3 gene contributes to the completion of the molecular patho-map of achondroplasia (Bilgeç et al., 2023, Merchant and Dauber, 2023, Ježová et al., 2023). Research is not only investigating length growth promotion but also focussing on the important FGFR-3 signaling pathway, which is primarily involved in achondroplasia (Legare, 2023, Bittmann, 2025). Recent research has f ocused on developing highly selective FGFR3 selective tyrosine kinase inhibitors like dabogratinib (TYRA-300) and Vepugratinib (LY3866288/LOXO-435) to treat children with achondroplasia more selectively with fewer toxic side effects by inhibiting further FGFR-signaling pathways beyond the FGFR3 signaling pathway (Bittmann, 2025, Chen, 2025).

Dabogratinib, also known as TYRA-300 or Compound 22, is produced by Tyra Biosciences. Dabogratinib is agnostic for FGFR-3 gatekeeper mutations. A multicenter, Phase II dose-escalation study is ongoing in children aged 3-10 years for 12 months (BEACH 301, NCT 06842355). Dabogratinib is an orally active FGFR-3 selective tyrosine kinase inhibitor with an IC-50 of 11 nMol in Ba/F3. The chemical structure is C25H24Cl2N603S. Further results are necessary to evaluate the efficacy of treating children with achondroplasia, as effectively controlling aberrant excessive signaling in FGFR3 signaling pathway can reduce toxic side effects by being highly selective for FGFR-3 (Bittmann, 2025, Chen, 2025).

The other interesting drug of ongoing research is vepugratinib (LY3866288/LOXO-435). In a phase III study (FORAGER2) in urothel cancer patients the focus of this medication is the sensitivity to the FGFR3-receptor. Further ongoing research and studies are closely necessary to evaluate the role of vepugratinib in achondroplasia in children. Gene therapeutic attempts are still in their infancy, despite of a clear understanding of one point mutation on chromosome 4, making pre- or postnatal gene therapeutic approaches ideally suited for curing the disease of achondroplasia in children.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## DISCLAIMER (ARTIFICIAL INTELLIGENCE)

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

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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