Paediatric growth patterns and their impact on health: Achondroplasia in focus

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A conversation between:

Dr Andrew Dauber
Children's National Hospital
Washington, DC, USA

Dr Nadia Merchant
Children's National Hospital
Washington, DC, USA

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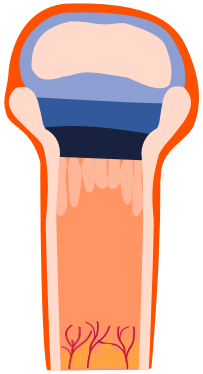
Bone growth: Understanding normal and abnormal physiology

Dr Andrew Dauber

Children's National Hospital,
Washington, DC, USA

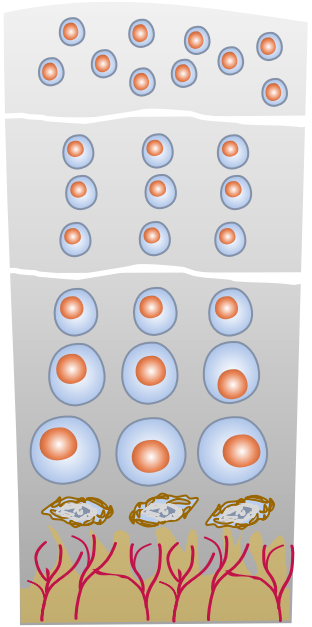
Co-regulatory role of FGFR3 and NPR2 in osteogenesis

Osteogenesis at the growth plate:[1,2]

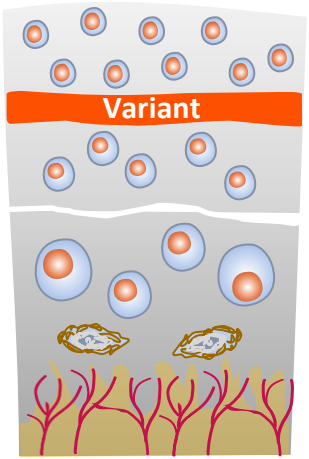


- **Resting zone** — Matrix production
- **Proliferative zone** — Mitosis
- **Hypertrophic zone** — Growth and terminal differentiation
- **Calcification zone**
- **Ossification zone**

Typical growth[1,2]



Dysregulated osteogenesis at the growth plate in achondroplasia[1–3]



- Resting chondrocytes
- Limited chondrocyte production
- Fewer chondrocytes mature and grow
- Impaired endochondral ossification

FGFR3, fibroblast growth factor receptor-3; NPR2, natriuretic peptide receptor-2.

1. Ciszewski P. Available at: https://bit.ly/3x1Or0C (accessed 08 June 2022); 2. Ornitz DM, Legeai-Mallet L. *Dev Dyn*. 2017;246:291–309;
3. Krejci P, et al. *J Cell Sci.* 2005;118:5089–100.

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Co-regulatory role of FGFR3 and NPR2 in osteogenesis

FGFR3[2–5]

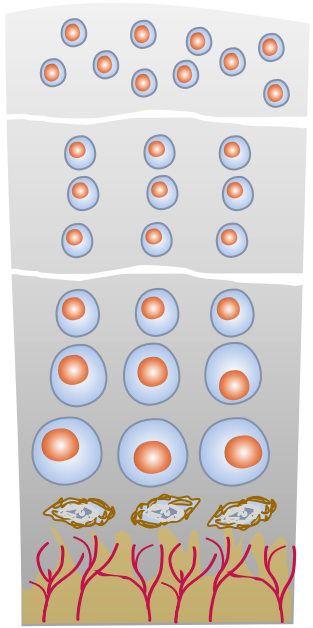
Negatively regulates endochondral bone growth

Suppresses chondrocyte proliferation & terminal differentiation

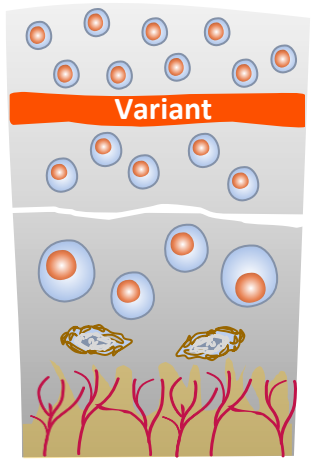
CNP/NPR2[3,4]

Opposes downstream signalling effects of FGFR3

Typical growth[1,2]



Achondroplasia[1,2]



FGFR3 variants[2–5]

Cause excess signal activation

Dysregulate chondrocyte proliferation & differentiation

Inhibit endochondral bone growth

NPR2 variants[6]

Reported in short stature conditions (AMDM and ISS)

Figures from published schematics.[1,2] AMDM, acromesomelic dysplasia, Maroteaux type; CNP, C-natriuretic peptide; FGFR3, fibroblast growth factor receptor-3; ISS, idiopathic short stature; NPR-2, natriuretic peptide receptor-2.

1. Ciszewski P. Available at: https://bit.ly/3x1Or0C (accessed 08 June 2022);
2. Krejci P, et al. *J Cell Sci*. 2005;118:5089–100; 3. Klag KA, Horton WA. *Hum Mol Genet*. 2016;25:R2–8; 4. Ornitz DM, Legeai-Mallet L. *Dev Dyn*. 2017;246:291–309;
5. Marzin P, Cormier-Daire V. *Ther Adv Endocrinol Metab*. 2020;11:2042018820904016; 6. Wang SR, et al. *Hum Mutat*. 2015;36:474–81.

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FGFR3 variants and phenotypic severity

Achondroplasia encompasses a family of skeletal dysplasias caused by FGFR3 variants[1–4]

Gain-of-function variants activate FGFR3, with an association between phenotype and degree of FGFR3 overactivation[2]

Hypochondroplasia[1–4]

Less-marked form of achondroplasia

'Mild' limb-to-trunk disproportion, often overlooked in infancy

Achondroplasia[1–4]

Most common short skeletal dysplasia

Short limbs, macrocephaly, frontal bossing, midface hypoplasia

Features evolve, becoming more pronounced over time

Thanatophoric dysplasia (types I and II)[1,2,4]

Type I: curved femora
Type II: straight femora; cloverleaf skull

Respiratory distress due to pulmonary hypoplasia, often fatal

Dysregulated and disproportionate bone growth underpins clinical features and medical complications

FGFR3, fibroblast growth factor receptor-3.

1. Pauli RM, et al. *Orphanet J Rare Dis*. 2019;14:1; 2. Xue Y, et al. *Mol Genet Genomic Med*. 2014;2:497–503; 3. Sabir AH, et al. *Am J Med Genet*. 2021;185A:73–82; 4. Wrobel W, et al. *Int J Mol Sci.* 2021;22:5573.

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Detecting and assessing achondroplasia to tailor care: Growth charts and assessment criteria

Dr Andrew Dauber

Children's National Hospital,
Washington, DC, USA

International Achondroplasia Consensus Statement

2022 Statement

Improve and harmonize care to optimize clinical outcomes and maximize QoL for people living with achondroplasia

Detection and diagnosis

Clinical and radiographic hallmarks enable accurate diagnosis in most cases

Genetic testing provides confirmation when clinical signs limited (incl. prenatally)

FGFR3 p.Gly380Arg (c.1138G>A) variant present in ~99% of cases

Assessment and monitoring

Regularly monitor growth and development:
incl. head circumference, height, weight and height-to-weight ratio

Developmental milestones differ:
use standardized syndrome-specific screening tools and growth charts

Investigate delays in milestone attainment

Multisystem manifestations require comprehensive and ongoing assessment

FGFR3, fibroblast growth factor receptor 3; QoL, quality of life.

Savarirayan R, et al. *Nat Rev Endocrinol*. 2022;18:173–89.

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Growth charts, assessment and tailored care

Appropriate age-stratified, syndrome-specific charts and tools should be used to meaningfully assess developmental milestone attainment

Achondroplasia-specific growth charts have been developed to tailor care[1–7]

International Achondroplasia Consensus Statement Group 2022[1]

CDC/WHO recommended anthropometrics:[8–10]

- Segmental lengths (upper arm, lower leg)
- Head circumference
- Crown–rump length
- Sitting height
- Arm span

Recommendation 26.

Provide parents with specific charts and a growth-parameters register (height, weight, head circumference)

Recommendation 44.

Monitor growth longitudinally at each medical check-up using achondroplasia-specific height, weight and head circumference growth charts

CDC, Center for Disease Control and Prevention (US); WHO, World Health Organization.

1. Savarirayan R, et al. *Nat Rev Endocrinol*. 2022;18:173–89; 2. Neumeyer L ,et al. *Am J Med Genet.* 2021;185A:401–12; 3. Hoover-Fong J, et al. *Am J Med Genet.* 2020;145:e20201010; 4. Del Pino, M.et al. *Am J Med Genet A* .2018;176:896–906; 5. Tofts L, et al. *Am J Med Genet A.* 2017;173:2189–200; 6. Merker A, et al. *Am J Med Genet A.* 2018;176:1723–34; 7. Merker A, et al. *Am J Med Genet A.* 2018;176:1819–29; 8. Fryar CD, et al. *Vital Health Stat 3.* 2021;(46):2021; 9. CDC. Growth charts. Available at: bit.ly/3PJbupH (accessed 08 June 2022); 10. WHO. Child growth standards. Available at bit.ly/3wUcdM1 (accessed 08 June 2022).

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Preorthograde motor movement strategies

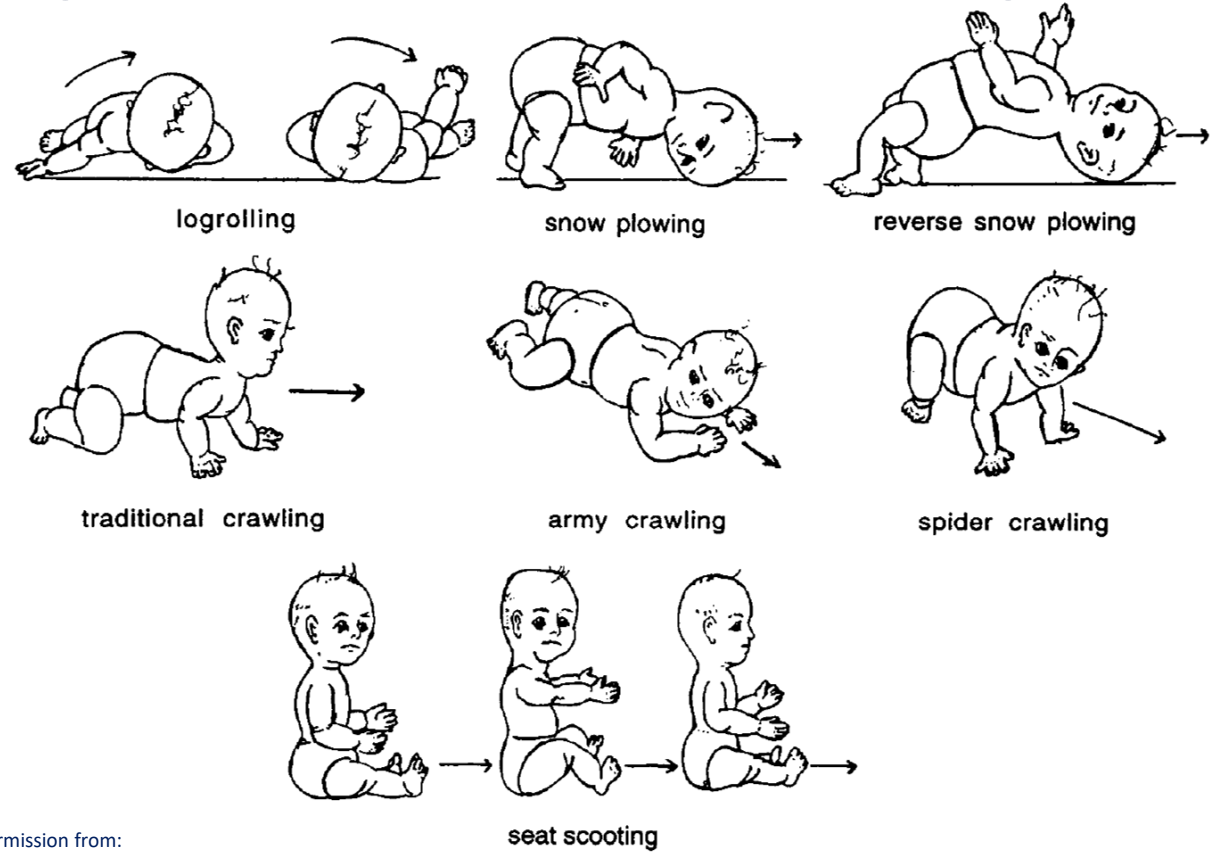

Figure reproduced with permission from:
Pauli R, et al. *Orphanet J Rare Dis*. 2019;14:1 (under the terms of the Creative Commons license available at bit.ly/PauliRM-CC-License; accessed 10 June 2022).

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Individualizing clinical management in achondroplasia: The potential role of emerging targeted therapies

Dr Andrew Dauber

Children's National Hospital,
Washington, DC, USA

Multidisciplinary management needs in achondroplasia

Specialty referrals[1]

- Ear, nose and throat
- Genetic counselling and family planning
- Neurology
- Nutrition and dietetics
- Physical therapy
- Respiratory and sleep medicine

Surgery[1]

- Spine
- Extremities:
  - Genu varum
  - Limb lengthening
- Orthodontics/maxillofacial surgery

Pharmacotherapies[1,2]

- Targeting pathophysiology
- Promoting growth
- Pain relief
- Anaesthesia

Whole-health needs[1]

- Psychosocial support
- Family perspectives
- Pain management

1. Savarirayan R, et al. *Nat Rev Endocrinol.* 2022;18:173–89; 2. Hoover-Fong J, et al. *Pediatrics.* 2020;145:e20201010.

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Therapies targeting achondroplasia pathophysiology

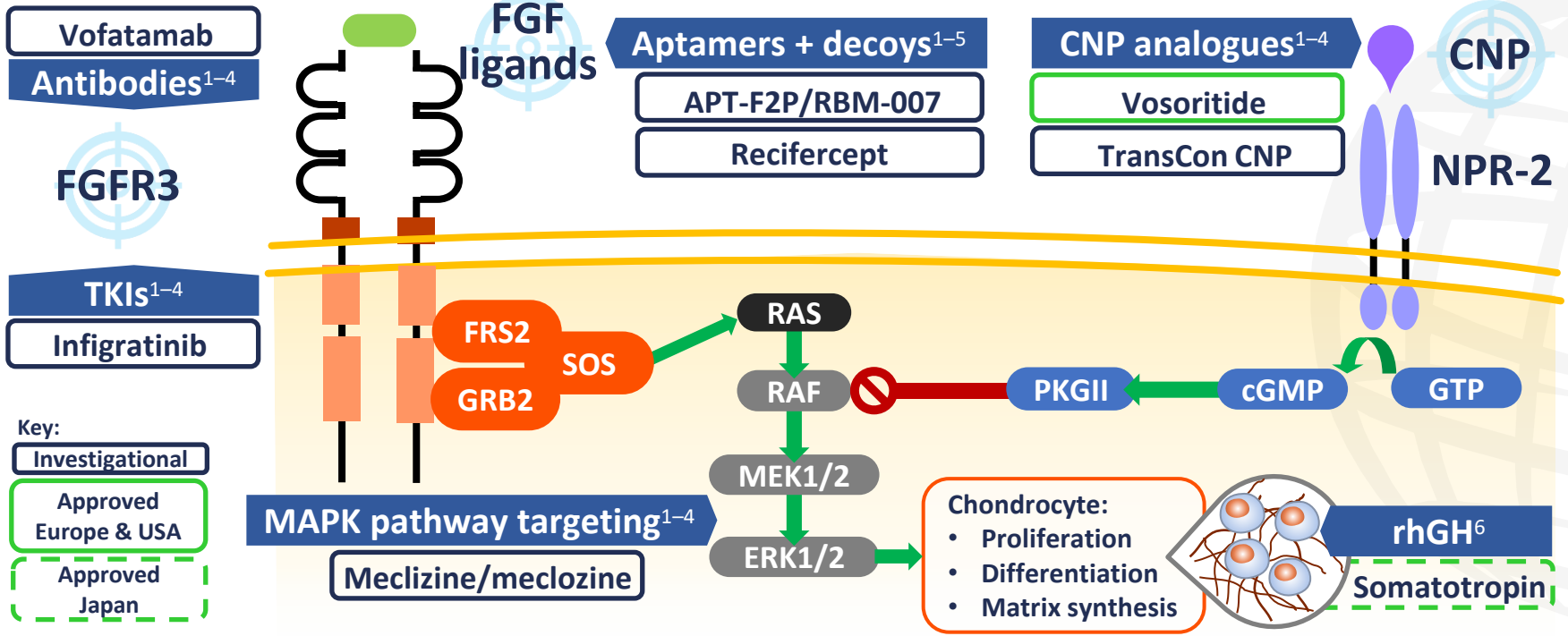

Figure adapted from published schematics.[1–3] Vosoritide is EMA and FDA approved in the European Union and United States, respectively.
Current indications searchable at: EMA: https://www.ema.europa.eu/en; FDA: https://www.accessdata.fda.gov/scripts/cder/daf/ (both accessed 13 June 2022). rhGH is approved in Japan.[6]
CNP, C-natriuretic peptide; FGF, fibroblast growth factor; FGFR3, FGF receptor-3; MAPK, mitogen-activated protein kinase; NPR-2, natriuretic peptide receptor-2; PK, pharmacokinetics; rhGH, recombinant human growth hormone; TKI, tyrosine kinase inhibitor.
1. Klag KA, Horton WA. *Hum Mol Genet.* 2016;25:R2–8; 2. Högler W, Ward LM. *Wien Med Wochenschr.* 2020;170:104–11; 3. Legeai-Mallet L, Savarirayan R. *Bone.* 2020;141:115579; 4. Wrobel W, et al. *Int J Mol Sci.* 2021;22:5573; 5. Jin L, et al. *Mol Ther.* 2016;24:1974–86; 6. Tanaka T. *Clin Ped Endocrinol.* 2022;31:1–9.

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