# Achondroplasia

**Achondroplasia is a rare genetic condition that leads to well-characterized skeletal dysplasia and serious muscular, neurological, and cardiorespiratory complications.[1-8]**

## Etiology

Achondroplasia arises from a systemic variant in the fibroblast growth receptor 3 (FGFR3) gene.[4,8]

## Epidemiology

- Achondroplasia affects more than 250,000 people worldwide, varying geographically.[2,5]
- Achondroplasia is inherited as an autosomal dominant condition with 100% penetrance; however, approximately 80% of affected individuals have parents without achondroplasia.[4,6]

## Clinical Presentation

Clinical manifestations are associated with significant, potentially life-threatening complications over the lifetime of an individual.[14] Clinical manifestations and medical complications have detrimental effects on QoL, physical functioning, and psychosocial function.[2,5,6,15]

Medical complications may vary across different stages of life.[3,6,16-19]

**Life stage impacted** — Infancy; Childhood and adolescence; Adulthood

| | | | |
|---|---|---|---|
| Ventriculomegaly | Hip flexion contracture | Chronic otitis media | Thoracolumbar kyphosis |
| Hearing deficit | Obesity | Dental malocclusion | Cervicomedullary compression |
| Speech delay | Reduced muscle strength | Genu varum | Increased muscle fat infiltration |
| Upper airway obstruction | Limited elbow extension | Foramen magnum stenosis | Impaired health-related quality of life (HRQoL) |
| Sleep-disordered breathing | Lumbar hyperlordosis | Impaired muscle stamina | |
| Pain | Hypotonia | Spinal stenosis | |

1. Ireland PJ, et al. *Appl Clin Genet* 2014; 2. Horton WA, et al. *Lancet*. 2007; 3. Sims DT, et al. *J Appl Physiol*. 2018; 4. Pauli RM. *Orphanet J Rare Dis* 2019; 5. Baujat G, etal. *Best Pract Res Clin Rheumatol*. 2008; 6. Savarirayan R, et al. *Nat Rev Endocrinol*. 2022; 7. Cormier-Daire V, et al. *Orphanet J Rare Dis*. 2022; 8. Cormier-Daire V, et al. *Orphanet J Rare Dis*. 2021; 9. Chen LJ, et al. *J Formos Med Assoc*. 2020; 10. Sallout B, et al. *Ann Saudi Med*. 2015; 11. Stoll C, Alembik Y, Dott B, Roth MP. *Eur J Med Genet*. 2022; 12. Tofts L, t al. *Am. J. Med. Genet. A* 2021; 13. Coi A, et al. *American Journal of Medical Genetics*. ISSN 1552-4825; 14. McGraw SA, et al. *Adv Ther* 2022; 15. Constantinides C, et al. *Disabil Rehabil* 2022; 16. Hoover-Fong J, et al. *Bone* 2021; 17. de Vries OM, et al. Am J Med Genet A. 2021;18. Sims DT, et al. *Front Physiol*. 2018; 19. Rintz E, et al, *Int J Mol Sci*, 2022;23(11).

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## Updated Perspective

Historically, achondroplasia has been viewed primarily as a skeletal condition; however, *FGFR3* is expressed in multiple tissues throughout the body, resulting in a wide range of medical complications.[1-5]

| | | Historical Consensus[1-4, 6-9] | Updated Perspective[3,6,10-17] | |
|---|---|---|---|---|
| **Causality** | | *FGFR3* variant | *FGFR3* variant | |
| **Primary Manifestations** | | **A skeletal condition,** including: | **A systemic, multiple organ condition,** including: | |
| | | Growth Effects | Growth Effects | Muscle Effects |
| **Secondary Manifestations** | Reduced Height | ✓ | ✓ | ✓ |
| | Increased Complications | ✓ | ✓ | ✓ |
| | Reduced HRQoL | ✓ | ✓ | ✓ |
| | Reduced Muscle Strength / Stamina | ✓ | ✓ | ✓ |

✓ Direct consequence ✓ Indirect/secondary consequence

**Multidisciplinary Management of Achondroplasia**

- Pediatric Endocrinologist/ Endocrinologist
- Pediatric Neurologist
- Pediatric Pulmonologist
- Pediatric Orthopedist
- Surgeon/Neurosurgeon
- Medical Geneticist/Genetic Counsellor (parents)
- Dentist/Orthodontist
- Cardiologist
- ENT Specialist
- Audiologist

Monitoring and management of achondroplasia require a multidisciplinary approach that should consider both the individual's age and specific clinical manifestations.[6,18]

ENT: Ears, Nose, Throat; FGFR3: Fibroblast Growth Factor Receptor 3; HRQoL: Health-related Quality of Life

1. Ireland PJ, et al. *Appl Clin Genet* 2014; 2. Horton WA, et al. *Lancet*. 2007; 3. Sims DT, et al. *J Appl Physiol*. 2018; 4. Pauli RM. *Orphanet J Rare Dis* 2019; 5. Murton MC, et al. *Adv Ther* 2023; 6. Savarirayan R, et al. *Nat Rev Endocrinol*. 2022; 7. Wrobel W, et al. *Int J Mol Sci* 2021; 8. Rintz E, et al. *Int J Mol Sci* 2022; 9. Krejci P, et al. *PLoS One* 2008; 10. Baujat G et al. *Best Pract Res Clin Rheumatol* 2008; 11. Hoover-Fong J et al. *Bone*. 2021; 12. de Vries OM et al. *Am J Med Genet A*. 2021; 13. Sims DT et al. *Front Physiol*. 2018; 14. Takken T et al. *J Pediatr*. 2007; 15. Reynolds KK et al. *Am J Med Genet*. 2001; 16. Sogos V et al 1998; 17. Mackler B et al. *Arch Biochem Biophys*. 1973; 18. Bodensteiner JB. *Curr Neurol Neurosci Rep*. 2019

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