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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Achondroplasia

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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