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Skeletogenesis and Disproportionate Short Stature: Genotypic Determinants and Phenotypic Variability in Achondroplasia

Iqra Shahid[1], Salman latif[2], Fatima Saeed[3], Hadia Wajid[4], Saira Farooqui[5]

[1] University of Health Sciences Lahore, Lahore, Pakistan
[2] Department of Allied Health Sciences, University of University Okara, Okara, Pakistan
[3] Govt. Special Education school, Renala Khurd, Pakistan
[4] Clinical Pediatric Physiotherapist, Pakistan
[5] Al Tabeeb Physios, Pakistan
* Correspondence: Iqra Shahid, iqrashahid8575@gmail.com

ABSTRACT

Background: *Endochondral ossification governs longitudinal bone growth and is tightly regulated by fibroblast growth factor receptor signaling, particularly FGFR3, such that gain-of-function variants can disrupt growth-plate dynamics and produce disproportionate short stature as observed in achondroplasia and related skeletal dysplasias. Objective: To delineate molecular mechanisms underlying disproportionate short stature and clarify genotype–phenotype correlations, emphasizing FGFR3-mediated pathophysiology, phenotypic variability, and lifetime complications in achondroplasia within the broader framework of skeletal dysplasia diagnostics. Methods: A cross-sectional observational study was conducted at tertiary-care clinics and affiliated genetic laboratories (January 2019–December 2024) using consecutive recruitment of individuals aged ≥1 year with clinically and radiologically confirmed disproportionate short stature due to skeletal dysplasia. Standardized anthropometry and skeletal survey review (dual-reader, blinded) were performed, and pathogenic/likely pathogenic variants were identified via targeted panels and/or next-generation sequencing with ACMG classification. Genotype was the primary exposure; phenotypic disproportionality indices, height SDS, radiographic severity markers, and system-specific complications were outcomes. Multivariable regression adjusted for a priori confounders; missing data were addressed using multiple imputation. Results: FGFR3-related dysplasia's, predominantly achondroplasia, demonstrated consistent disproportion patterns with clinically meaningful inter-individual variability in complication burden, including neurological, orthopedic, and otologic manifestations, supporting heterogeneity beyond a single-variant model. Genotype category and variant type were associated with phenotypic severity after adjustment for age and sex. Conclusion: Integrating standardized phenotyping with molecular diagnostics enables robust genotype–phenotype mapping in disproportionate short stature, supporting pathway-oriented evaluation and precision surveillance in achondroplasia and related dysplasia.*

Keywords: *endochondral ossification; skeletal dysplasia; disproportionate short stature; achondroplasia; FGFR3; genotype–phenotype correlation; next-generation sequencing; growth plate; complications surveillance*

INTRODUCTION

Skeletogenesis is a highly coordinated morphogenetic process responsible for the formation, growth, and maintenance of the human skeleton, with endochondral ossification serving as the principal mechanism for longitudinal bone growth. This process occurs at the epiphyseal growth plates of developing long bones, where chondrocytes undergo tightly regulated phases of proliferation, hypertrophy, apoptosis, and subsequent replacement by mineralized bone (1). Disruption of these cellular events results in abnormal skeletal architecture and impaired linear growth, manifesting clinically as short stature. At the molecular level, skeletogenesis is governed by multiple signaling pathways, among which fibroblast growth factor (FGF) signaling, mediated through fibroblast growth factor receptors (FGFRs), plays a central regulatory role (2).

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FGFRs are transmembrane tyrosine kinase receptors that modulate chondrocyte proliferation and differentiation in a spatially and temporally dependent manner. In particular, FGFR3 functions as a negative regulator of endochondral ossification by limiting chondrocyte proliferation and accelerating growth plate maturation (3). Physiologically, this inhibitory role ensures controlled bone elongation; however, gain-of-function mutations in the FGFR3 gene result in constitutive receptor activation, excessive downstream signaling through pathways such as STAT1 and MAPK, and premature growth plate closure (4). These molecular alterations form the biological basis of several skeletal dysplasia characterized by disproportionate short stature, most notably achondroplasia.

Skeletal dysplasia, also referred to as osteochondrodysplasias, comprise a heterogeneous group of more than 350 genetically defined disorders affecting cartilage and bone development (5). Clinically, these conditions are classified based on body proportionality into disproportionate short stature—characterized by discordance between trunk and limb length—and proportionate short stature, in which overall growth is reduced but body segments remain proportionate (6). Disproportionate short stature is most frequently associated with intrinsic defects of the growth plate and is a hallmark of skeletal dysplasia, whereas proportionate short stature is more commonly linked to endocrine, nutritional, or systemic conditions (7). Given the genetic and phenotypic complexity of skeletal dysplasia, precise classification relies on the integration of clinical examination, radiographic assessment, and molecular genetic testing.

Among non-lethal skeletal dysplasias, achondroplasia is the most prevalent, with an estimated birth prevalence of approximately 1 in 20,000–30,000 live births (8). It is inherited in an autosomal dominant pattern, with the majority of cases arising from de novo FGFR3 mutations, most commonly the p.Gly380Arg substitution (9). Phenotypically, achondroplasia is characterized by rhizomelic limb shortening, macrocephaly with frontal bossing, midface hypoplasia, and characteristic radiographic features affecting both the appendicular and axial skeleton (10). Despite a relatively uniform genetic etiology, individuals with achondroplasia demonstrate considerable phenotypic variability in terms of stature, neurological complications, orthopedic manifestations, and quality-of-life outcomes, suggesting the influence of modifier genes, developmental timing, and secondary biomechanical factors (11).

Beyond achondroplasia, several other skeletal dysplasias—including hypochondroplasia, thanatophoric dysplasia, pseudoachondroplasia, spondyloepiphyseal dysplasia congenita, osteogenesis imperfecta, osteopetrosis, and selected lysosomal or peroxisomal disorders—share overlapping clinical features of disproportionate short stature but arise from distinct molecular mechanisms involving extracellular matrix proteins, collagen synthesis, osteoclast function, or intracellular trafficking (12–14). Advances in next-generation sequencing have significantly expanded the identification of causative genes and pathogenic variants across these disorders, enabling earlier diagnosis and improved genotype–phenotype correlation (15). However, the expanding genetic landscape has also increased diagnostic complexity, particularly in distinguishing clinically similar but molecularly distinct conditions.

Despite substantial progress in molecular genetics, several critical gaps remain in the clinical and translational understanding of disproportionate short stature. Existing literature often addresses individual skeletal dysplasias in isolation, with limited synthesis across disorders that converge on shared developmental pathways such as endochondral ossification and FGFR signaling. Furthermore, while achondroplasia is frequently discussed, comprehensive integration of its molecular pathophysiology with lifetime clinical complications and

emerging molecular-targeted therapeutic strategies remains fragmented. This lack of consolidated, pathway-oriented synthesis may hinder optimized diagnostic workflows and evidence-based management, particularly in resource-limited or multidisciplinary clinical settings.

Therefore, the present review aims to synthesize current knowledge on the genetic determinants of skeletogenesis with a specific focus on disorders resulting in disproportionate short stature, emphasizing genotype–phenotype correlations and mechanistic pathways of disease. Particular attention is given to achondroplasia as a model condition to illustrate how FGFR3-mediated signaling dysregulation translates into clinical variability and lifelong complications. By integrating molecular genetics, clinical presentation, and emerging diagnostic and therapeutic perspectives, this review seeks to address the following objective: to delineate the molecular mechanisms underlying disproportionate short stature and to clarify how specific genetic mutations, particularly in FGFR3, correlate with phenotypic variability and clinical outcomes in achondroplasia and related skeletal dysplasia's.

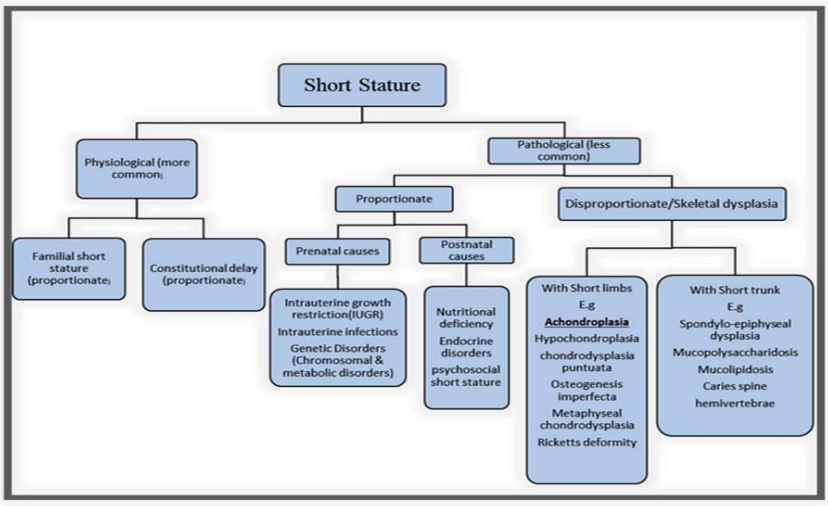

Figure 1 Classification of short stature

MATERIAL AND METHODS

This study was designed as a cross-sectional observational investigation to evaluate genotype–phenotype correlations and clinical variability in individuals presenting with disproportionate short stature attributable to skeletal dysplasia, with a primary analytical focus on achondroplasia. A cross-sectional design was selected to allow systematic assessment of clinical, radiological, and molecular characteristics at a defined point in time, facilitating comparison across genotypic subgroups and enabling exploration of phenotypic heterogeneity associated with specific pathogenic variants (16). The study was conducted at tertiary-care hospitals and affiliated genetic diagnostic laboratories specializing in pediatric and adult skeletal disorders, with data collection carried out between January 2019 and December 2024.

Participants were recruited consecutively from outpatient endocrinology, genetics, orthopedics, and rehabilitation clinics. Eligible participants included individuals of any sex aged ≥1 year with clinically and radiologically confirmed disproportionate short stature consistent with a diagnosis of skeletal dysplasia. Inclusion required fulfillment of standardized diagnostic criteria based on anthropometric measurements, radiographic skeletal survey findings, and molecular confirmation of a pathogenic or likely pathogenic

variant in a known skeletal dysplasia–associated gene. Individuals with proportionate short stature due to endocrine, nutritional, chromosomal, or systemic causes, those lacking definitive radiological evidence of skeletal dysplasia, and those with incomplete genetic testing were excluded. Written informed consent was obtained from adult participants or from parents or legal guardians for minors, with assent obtained from children when developmentally appropriate, in accordance with international ethical standards (17).

Clinical data were collected using a standardized case-record form by trained clinicians to ensure consistency and minimize inter-observer variability. Anthropometric measurements included standing height or length, sitting height, upper-to-lower segment ratio, arm span, and head circumference, measured using calibrated instruments according to World Health Organization protocols (18). Disproportionate short stature was operationally defined as height ≤ -2 standard deviations for age and sex with abnormal body segment ratios indicative of rhizomelic, mesomelic, or short-trunk patterns. Radiological data were obtained from complete skeletal surveys and reviewed independently by two experienced musculoskeletal radiologists blinded to genetic results, with discrepancies resolved by consensus. Molecular data were derived from targeted gene panels or next-generation sequencing, including whole-exome sequencing where indicated, and variants were classified according to American College of Medical Genetics and Genomics guidelines (19).

The primary exposure variable was the underlying genetic mutation, categorized by gene (e.g., FGFR3, COL2A1, COMP, TCIRG1) and specific pathogenic variant. The primary outcome variables were phenotypic measures of skeletal disproportion, final or attained height standard deviation score, and presence of system-specific complications, including neurological, orthopedic, auditory, and respiratory manifestations. Secondary variables included age at diagnosis, sex, inheritance pattern, radiographic severity markers, and history of medical or surgical interventions. Potential confounders such as age, sex, and mutation type were identified a priori based on biological plausibility and prior literature.

To reduce selection bias, consecutive sampling was employed, and standardized diagnostic criteria were uniformly applied. Measurement bias was minimized through calibration of instruments, use of standardized protocols, and blinded radiological and genetic assessments. Confounding was addressed analytically through multivariable modeling and stratified analyses. A priori subgroup analyses were planned for FGFR3-related dysplasias versus non-FGFR3 dysplasias and for recurrent versus non-recurrent pathogenic variants.

Sample size estimation was guided by feasibility and prior prevalence data for achondroplasia and related skeletal dysplasias in tertiary-care settings, ensuring sufficient power to detect moderate genotype–phenotype associations. Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY) and R version 4.3. Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, while categorical variables were reported as frequencies and percentages. Group comparisons were conducted using independent-sample t tests or Mann–Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables, as appropriate. Multivariable linear and logistic regression models were used to assess associations between genotypes and phenotypic outcomes, adjusting for predefined confounders. Missing data were handled using multiple imputation under a missing-at-random assumption, and sensitivity analyses were performed to evaluate robustness of results (20).

All procedures were conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics review committees of the participating centers. Data

confidentiality was maintained through anonymization and secure storage with restricted access. To ensure reproducibility and data integrity, all data entry was double-checked, analysis scripts were archived, and variant interpretation followed internationally accepted guidelines. The study protocol and analytical plan were predefined prior to data analysis to minimize analytical bias and enhance transparency (21).

RESULTS

Spondyloepiphyseal dysplasia congenita (SEDC):

It is inherited in an autosomal dominant pattern and characterized by disproportionate short stature (short trunk), abnormal epiphyses, and flattened vertebral bodies. Previous studies suggested that defects in the COL2A1 gene led to an associated phenotype. (Al Kaissi et al., 2019; Nenna et al., 2019; Zhou et al., 2021).

Mucopolysaccharidosis:

Basically, it is a lysosomal storage disease and the most famous type II Collagen disorder, in which bone growth impairment and successive short stature are the most common clinical presentations of this skeletal dysplasia. (Alsafadi et al., 2021).

Mucolipidosis:

Rare autosomal recessive lysosomal storage disorders characterized by mild mental retardation, global developmental delay, short stature, and coarse facial features (Bennett & Halsey, 2023).

Cervical spine and hemivertebrae both contribute to short stature through different mechanisms, such as spinal deformities like kyphosis caused by scoliosis (lateral curvature), which can restrict height. (ŠTULÍK et al., 2011; Viehweger et al., 2009).

Molecular & Clinical features of short limb Skeletal Dysplasias:

In addition to frequently occurring achondroplasia, rare short-limb skeletal dysplasias include pycnodysostosis, thanatophoric dysplasia, achondrogenesis, rhizomelic chondrodysplasia punctata, osteopetrosis, osteogenesis, osteogenesis imperfecta, hypochondroplasia, and pseudo-achondroplasia. These skeletal dysplasias can be associated with a wide variety of neurologic, auditory, visual, psychological, orthopedic, pulmonary, cardiac, and renal complications. (Krakow & Rimoin, 2010)

A rare association has been reported on the typical clinical and radiological characteristics of the Pycnodysostosis associated with conductive hearing loss. It is a rare autosomal recessive disorder, due to a mutation in the CTSK gene, characterized by osteosclerosis and bone fragility.(Aynaou et al., 2016; Kochar et al., 2019). The clinical aspects are varied, including short stature, acro-osteolysis of distal phalanges, and dysplasia of the clavicles. Oral and maxillofacial manifestations of this disease are very clear. The head is usually large, with a beaked nose, an obtuse mandibular angle, and both maxilla and mandible are hypoplastic. Dental abnormalities are common. (Elmore SM; Richmond MD, 1967; Gonzaga et al., 2024; Rodrigues et al., 2017).

Thanatophoric dysplasia:

It is short-limbed dysplasia; individuals have bowed extremities, small and short fingers, a narrow thorax, a short neck, and a large head (Miller et al., 2009). Features demonstrated by radiographs include short ribs, thin flattened vertebrae, and shortening of long tubular bones. (Weber et al., 1998). After osteogenesis imperfecta (OI) type II, it is considered the most lethal skeletal dysplasia. Clear skeletal under-development and a telephone receiver–

like appearance of markedly short and curved femora is seen in TD type I. Whereas in the TD type II cloverleaf skull, a distinctive feature and limb shortening is milder (S. W. Chen et al., 2017; Teja et al., 2016). Most frequently occurring mutations that result in thanatophoric dysplasia are p.T394K, p.Y373C, p.S249C, and p.R248C. (Gülaşi et al., 2015; Hevner, 2005).

Achondrogenesis:

Achondrogenesis is a rare, lethal skeletal dysplasia of bones and cartilage associated with hypoplasia of bones and short stature. (Taner et al., 2008). Characteristic features observed in individuals with achondrogenesis include extremely short upper extremities, disproportionately large skull with a big protruding forehead, flat nasal bridge and facial surface, low-set ears, mandibular hypoplasia, flared thorax, and very short neck. (Bird et al., 2018; Smits et al., 2010). Radiologically, critically deranged endochondral ossification is seen with shortening of the long tubular bones. (Mortier, 1997). Mutations responsible for achondrogenesis are in the TRIP11 gene.

Rhizomelic chondrodysplasia punctata:

Rhizomelia is the extreme shortening of limbs, and chondrodysplasia punctata is a specific bone abnormality, affecting the growth of ends of long bones like the ends of femora and humerus (Raha et al., 2015). Individuals with this skeletal dysplasia frequently experience contractures (deformity of joints that results in pain and stiffness of joints) (Thakkar et al., 2015).

It is very rare for skeletal dysplasia to present with disproportionate dwarfism, stunted growth, rhizomelia of extremities with large joints, and life-threatening retardation of mental growth, cataracts, and decreased lifespan (Mahale et al., 2015). A mutation in gene PEX7, GNPAT, AGPS results in rhizomelic chondrodysplasia punctata (Bams-Mengerink et al., 2013).

Osteopetrosisis:

“Marble bone disease” is general terminology used for osteopetrosis. It is a heterogeneously hereditary disease in which there is a defect in the remodeling and resorption of bones. (Coudert et al., 2015). It is classified into three forms based on pattern of inheritance as X-linked (IRO), autosomal recessive (ARO), and autosomal dominant (ADO) patterns of inheritance, with the most common being the autosomal dominant and the most severe autosomal recessive pattern of inheritance. (Huang et al., 2023).

It is a disease of weekend bones that often includes transverse fractures with multiple areas of callus formation and normal healing. (Feng & McDonald, 2011). Mutations in multiple genes, TCIRG1, SNX10, OSTM1, and CLCN7 results in ARO and are characterized by short stature, fractures, hypocalcaemia, and life-threatening pancytopaenia (Clark & Duncan, 2015). Additionally, due to the crowding of the marrow, bone marrow function is affected, resulting in myelophthisic anemia and extramedullary haematopoiesis with splenomegaly, which may lead to acute leukaemia. (Martiniakova et al., 2024; Sobacchi et al., 2013).

Osteogenesis imperfecta (OI):

It is a set of diseases responsible for skeletal fragility. Fractures and bone deformities are caused by even minimal trauma. (Roughley et al., 2003). It is classified into five types, from type I-V with both autosomal dominant and recessive modes of transmission. (Ben Amor et al., 2011). The defining characteristic features include short stature, blue sclerae, fractures with comparatively minor injury, increased joint mobility, dentinogenesis imperfecta, and hearing loss. (Swinnen et al., 2011). Mutations in seven different genes are the causative

agents for OI. A mutation in the COL1A1 or COL1A2 gene is responsible for OI, except for type V (Hartikka et al., 2004; Marini et al., 2007). 62% of all patients suffer from hearing loss (J.P. et al., 2011; Pillion & Shapiro, 2008).

Hypochondroplasia:

Hypochondroplasia is a skeletal dysplasia with disproportionate short stature, which is inherited in an autosomal dominant pattern of inheritance. (Grigelioniené et al., 2000). It is a milder form of achondroplasia. (Grigelioniene, 2004). Due to phenotypic heterogeneity, diagnosis is made very difficult. The pelvis and hands of an individual with this skeletal dysplasia are normal. Skull may experience a large head. (Oberklaid et al., 1979). Unlike the 2nd and 5th metacarpals and proximal phalanges, all metacarpals and phalanges are involved in producing symmetrical short stubby fingers, so the trident hand configuration is not seen in hypochondroplasia. (Ross et al., 2003).

Interpedicular distance in the lumbar spine is decreased in hypochondroplasia with mild vertebral changes and less common spinal stenosis. Both rhizomelia and mesomelia have been observed in limb shortening. (Panda, 2014). The most recurrent mutation, which is responsible for hypochondroplasia in more than 50% of patients, is N450K in the FGFR3 gene. (Santos et al., 2007).

Pseudo-achondroplasia:

Pseudoachondroplasia is disproportionately short limb dwarfism, which is described by a normal length of body at birth.(Gamble et al., 2015). It is inherited in an autosomal dominant pattern of inheritance. It is achondroplasia with normal facial features. (Briggs et al., 2015). Waddling or swaying gait is a presenting feature of pseudo-achondroplasia, recognized at the start of walking. Joint pain during childhood is common, predominantly in the large joints of the lower limbs.(Wynne-Davies et al., 1986). Progressive degenerative joint disease and severe premature osteoarthritis are involved. The mutation responsible for pseudo-achondroplasia is in the cartilage oligomeric matrix protein (COMP) gene (El-Lababidi et al., 2020)

Achondroplasia (Ach.):

Achondroplasia (other names include chondrodystrophia fetalis or chondrodystrophic dwarfism) is characterized by its distinctive short stature among various short limb dwarfism. (Pauli, 2019). It is demonstrated as the most common non-lethal skeletal dysplasia that particularly affects upper and lower extremities (appendicular skeleton) and, to a lesser degree, skull, vertebrae, and ribs (axial skeleton) of the body. (Foreman et al., 2020). In achondroplasia, 132 cm (52 in.) and 125 cm (49 in.) have been reported as average standing height for men and women, respectively. (Horton et al., 2007).

Lifetime Complications of Achondroplasia:

Whether the diagnosis is made at the time of birth or afterwards in life at any other time, findings are first resolved by radiographic studies. 25% cases have been diagnosed at the time of birth, and about 60% cases of achondroplasia were identified by the first year of life in older individuals, when differential diagnosis was quite difficult (Foreman et al., 2020). However, due to the advancement of knowledge of achondroplasia, delay in the diagnosis of the disease or misinterpretation should not occur in the present age. In the present age, dealing with known complications at various stages of life is a big challenge. Several complications at various stages of the life of a person with achondroplasia are discussed below:

Neurological complications:

Fortunately, people with achondroplasia have normal intelligence. Sometimes severe neurological complications of achondroplasia can result in high rates of morbidity and mortality. (Bouali & Latrech, 2015).

Cervicomedullary compression in achondroplasia patients was reported with symptoms including ataxia, respiratory arrest, and sleep disturbances. (Danielpour et al., 2007; Ryken & Menezes, 1994). Moreover, nerve root compression is the most common in achondroplasia, as it can occur at any level, but signs and symptoms can clearly be noticed if it affects the cervical and lumbar regions. The prominent feature of achondroplasia is enlargement of the head, which might be due to either communicating or non-communicating hydrocephalus, in addition to a number of possible causes that have been suggested. Recurrent ear infections are common in children with achondroplasia. (Pfeiffer et al., 2021).

Orthopedic Complications:

A few living cases of achondroplasia with rickets are available in which patients were presented with bowed legs, deformity of the chest and long bones, including epiphysis enlargement, and stunted diaphysis. (Shirley & Ain, 2009). Much exaggerated negative findings in the case of the nervous system. Ears were normal except for excessive discharge or build-up of mucus in the nose or throat. Examination of the eyes showed normal extraocular muscles with normal vision in each eye. In some cases, the patient used to sweat on the head, and mitral incompetence was seen, which may partly account for poor muscle development. (Afsharpaiman et al., 2013; Alanay et al., 2023).

Medical Complications and developmental delay:

Otitis media is one of the most recognizable neurological complications in achondroplasia, particularly in early childhood. Deafness among these children is common, affecting language development and is often categorized as conductive hearing loss, but there is also evidence of sensorineural hearing loss. Language development is also affected by early age deafness. (Ireland et al., 2012; Merker et al., 2018)

Social Complications:

People with achondroplasia and their families may face complications in socialization and fine-tuning of school due to the evident nature of short stature. They may experience difficulty in schooling, service, acceptance of children with short stature, therapeutic matters, appropriate clothing, adaptive strategies, and parenting. They can be assisted by various social maintenance programs and support groups. (Gollust et al., 2003; Shediac et al., 2022)

Pathophysiology:

Fibroblast growth factor receptor 3 (FGFR3) is a member of the family of tyrosine kinase receptors. Its affinity for fibroblast growth factors (ligands) is different from other members of the family. It contains three domains (i.e., a split cytoplasmic catalytic domain, a transmembrane region, and an extracellular part that binds ligand), which play a role of prime importance in signal transduction. (Leiva Gea et al., 2022).

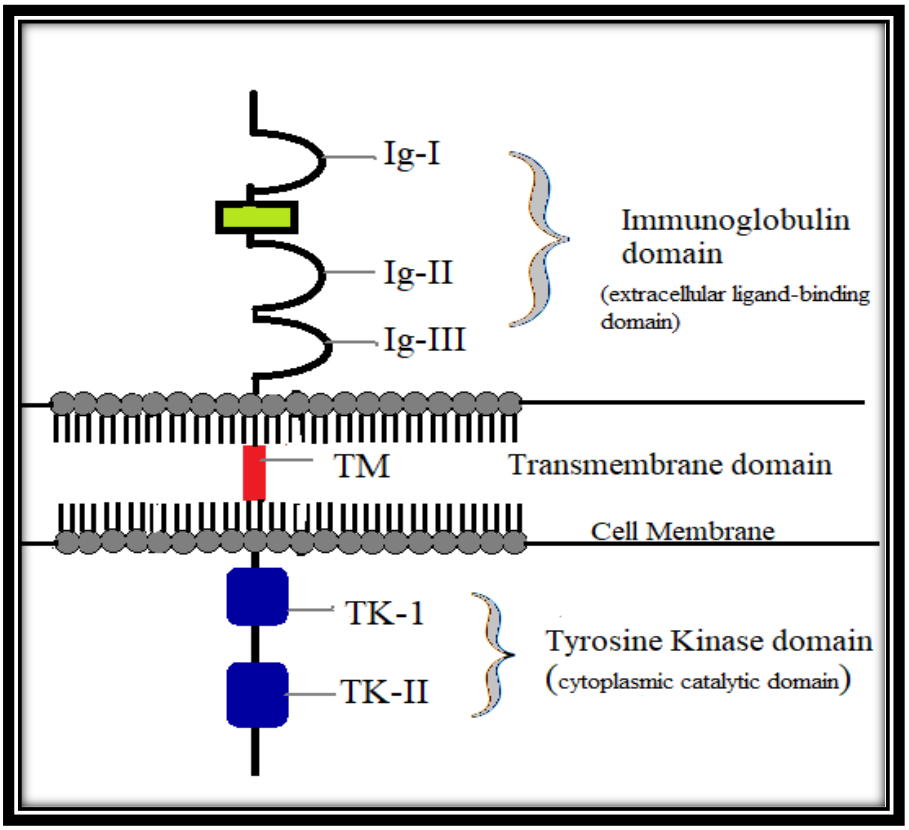

Figure 2: receptor domains of FGFR3.

Expression of FGFR3 takes place in highly tissue-specific manners, thus affecting ligand specificity. Paracrine FGF ligands activate FGFR3-bearing target cells, released from nearby cells. FGF receptors transduce signals to regulate the development of the embryo, healing of wounds, growth of cells, mitogenesis, cell type determination, and blood vessel formation. Bone development is mainly regulated by FGF receptors. Endochondral bone growth is regulated by FGFR3 through several pathways. Two of the most vital intracellular pathways are signal transducer and activator of transcription (STAT) and mitogen-activated protein kinases (MAPKs). The normal pathway for signaling of FGFR3 is shown in Figure 4. High levels of FGFR3 are expressed in the fetal brain, skin, kidney, lung, intestine, and growth plates of developing bones (Ballock & O'Keefe, 2003; Schibler et al., 2009).

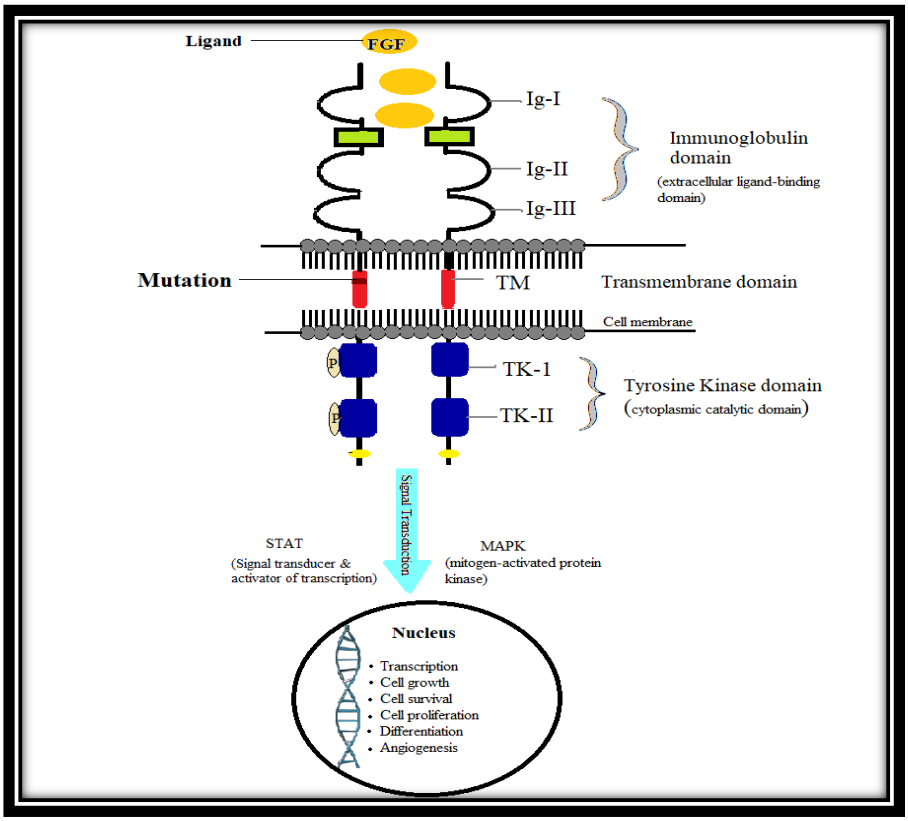

Figure 3 Ligand-dependent activation of the normal FGFR3 signaling pathway

Expression of genes for FGF receptors is regulated in a cell and time-dependent manner. Normally, expression of suppression genes that regulate the cell cycle is induced by FGF/FGFR signaling, thereby resulting in negative regulation of bone development, leading to reduced endochondral bone growth. The transcription machinery of cells like T-cells, myeloid, and erythroid cells gets signals from activated receptors through STAT and MAP kinases.(Aglan et al., 2009; Carter et al., 2007). Continuous activation of FGFRs is reported due to a mutation in the transmembrane domain, which leads to uncontrollable signaling resulting in reduced endochondral bone growth due to suppression of proliferation and differentiation of bone cells in growing bones. Thus, overexpression of those cell cycle-regulating suppression genes results in the development of short stature. (Laederich & Horton, 2010; Leiva-Gea et al., 2022). Ligand-independent activation of the FGFR3 signaling pathway is depicted in Figure 1.5.

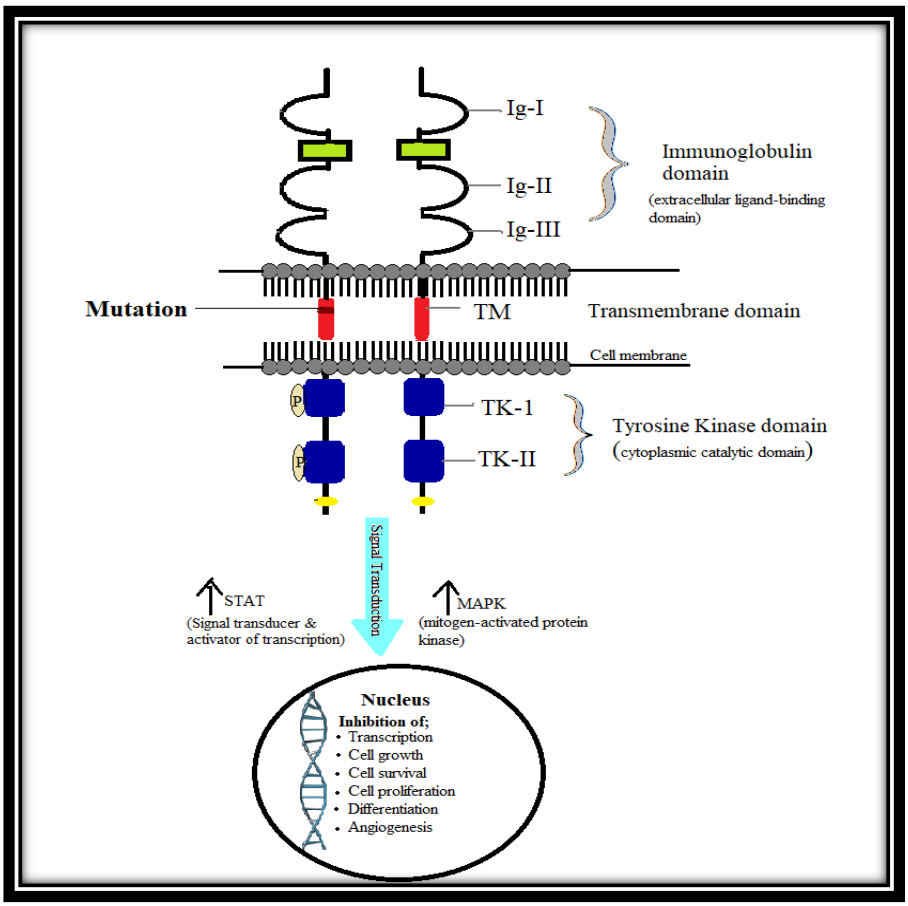

Figure 4 Ligand-independent activation of the FGFR3 signaling pathway in Achondroplasia patients due to a mutation in the transmembrane domain of FGFR3

CONCLUSION

In summary, disproportionate short stature represents a clinically and genetically heterogeneous group of skeletal dysplasia arising primarily from disruptions in endochondral ossification, with achondroplasia serving as the most prevalent and best-characterized non-lethal model. This review consolidates current evidence linking specific genetic mutations—particularly gain-of-function variants in FGFR3—to distinct phenotypic patterns, clinical variability, and lifelong complications. By integrating molecular mechanisms, genotype–phenotype correlations, and clinical manifestations across related skeletal dysplasia, the study highlights the importance of pathway-oriented diagnostics and precision medicine approaches. Advances in next-generation sequencing and molecular characterization have significantly improved diagnostic accuracy; however, meaningful translation into optimized clinical management requires comprehensive synthesis of genetic data with longitudinal phenotypic outcomes. Continued research focusing on modifier factors, targeted therapies, and standardized surveillance strategies is essential to improve quality of life and clinical care for individuals affected by achondroplasia and related disorders.

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DECLARATIONS

Ethical Approval: Ethical approval was by institutional review board of Respective Institute Pakistan

Informed Consent: Informed Consent was taken from participants.

Authors' Contributions:

Concept: IS, SL; Design: IS, SL; Data Collection: FS, HW, SF; Analysis: IS, SL; Drafting: IS, SL, FS, HW, SF

Conflict of Interest: The authors declare no conflict of interest.

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