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The Roles of Fibroblast Growth Factor Receptor 3 (FGFR3) in the Spectrum of Skeletal Dysplasia

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

The fibroblast growth factor receptor 3 (FGFR3) gene mutations were identified to be involved in the pathogenesis of most chondropathies. The FGFR3 gene encodes the FGFR3 receptor and is involved in the regulation of bone growth by limiting the ossification of long bones. Mutations of the FGFR3 gene result in abnormal cell proliferation and improper cartilage development. We aim to

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provide an overview of the roles of FGFR3 in skeletal dysplasia by highlighting the pathogenesis, clinical variants of skeletal dysplasia, diagnosis, and their management.
Achondroplasia is the most common form of chondropathies, occurring in approximately 1 in 20,000-30,000 live births, and it is the most common form of genetic dwarfism. In over 80% of cases of achondroplasia, the mutation is sporadic, and only 20% are inherited autosomal dominant. Achondroplasia results from a point mutation in the gene encoding the transmembrane portion of FGFR3. Two viable base substitutions are identified in achondroplasia, including a point mutation of guanine substituted for adenine (c.1138G>A); this is identified in approximately 98% of the affected individuals, and transversion of guanine to cytosine (c.1138G>C).
Hypochondroplasia is a milder form of chondropathies with an incidence between 1 in 33,000 and 1 in 47,000 live births. Missense mutations of FGFR3 (p.Asn540Lys) are isolated in tyrosine kinase domain I occurring in approximately 60% of cases, and missense mutation of FGFR3 (p.Lys650Asn) identified in the tyrosine kinase domain II of FGFR3. Thanatophoric dysplasia is the most lethal form of chondropathies, with neonatal fetal death secondary to pulmonary hypoplasia. In thanatophoric dysplasia, there is Lys650Met substitution in FGFR3 (Type I) with impairment of endochondral bone growth and a pathogenic variant of p.Lys650Glu substitution in FGFR3 (Type II). In addition, specific amino acid substitution in the FGFR3 gene (G380R) was identified to be associated with severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN).
The diagnosis of achondroplasias is routinely made from clinical presentations and radiological findings. FGFR3 molecular genetic testing is performed in children with atypical presentations. In addition, a pre-implantation genetic diagnosis should be available for parents pursuing in-vitro fertilization and embryo implantation procedures. Management of chondropathies includes symptomatic treatment with drugs, surgical intervention, and lifelong follow-up care. Different pharmacological options have been used, including those that directly block FGFR3 activation or regulate signalling pathways controlling chondrocyte proliferation and differentiation.

Keywords: Achondroplasia; chondropathy; hypochondroplasia; skeletal dysplasias; FGFR3.

1. INTRODUCTION

Chondropathies are disorders that affect cartilage formation, proliferation, and differentiation [1]. “Specific conditions in the spectrum include achondroplasia, costochondritis, relapsing polychondritis, spinal disc herniation, osteoarthritis, and cartilage tumors. The FGFR3 gene mutation is implicated in the etiopathogenesis of most chondropathies. Four known fibroblast growth factor receptors share similar structures and functions and play important roles in the regulation of cell proliferation, migration, differentiation, angiogenesis, wound healing, and embryogenesis. Notably, the FGFR3 protein regulates bone growth by limiting the ossification of the long bones” [1].

“Achondroplasia is the most common form of skeletal dysplasia, and its incidence is approximately 1 in 20,000-30,000 live births. The affected patients present with short stature, short limbs, macrocephaly, and characteristic facial features, including frontal bossing and midface hypoplasia. Sporadic cases of achondroplasia are associated with advanced paternal age, suggesting mutations occurring during spermatogenesis” [1]. “Hypochondroplasia is a milder form of chondropathies with an incidence between 1 in 33,000 to 47,000 live births. Thanatophoric dysplasia is the most lethal form of neonatal dwarfism, characterized by short stature, extremely short limbs, and extra folds of skin on the arms and legs. In addition, newborns with thanatophoric dysplasia usually die shortly after birth from respiratory distress secondary to pulmonary hypoplasia” [1,2].

1.1 Aims and Objectives

The aim of this review article is to provide an overview of the roles of FGFR3 in chondropathies by highlighting the pathogenesis, clinical variants, diagnosis, and management to improve the understanding of these clinical conditions.

2. METHODOLOGY

Original research and review articles were searched online. Search engines included Google Scholar, PubMed, Web of Science, and National Institute of Health. The keywords for the literature search were chondropathies, FGFR3,

skeletal dysplasia, achondroplasia, hypochondroplasia, and thanatophoric dysplasia. Manual searches were also conducted for articles related to the pool generated from the online search. From the reports generated, relevant sections were reviewed to understand the roles of FGFR3 in the skeletal dysplasia spectrum.

2.1 The Roles of FGFR3 in the Pathogenesis of Chondropathies

Achondroplasia, hypochondroplasia, and thanatophoric dysplasia arise from a similar genetic defect with different mutations in the FGFR3 gene. The mechanisms involved in the FGFR3 gene mutation are related to alterations in the DNA sequences coding for the protein. Thus, changes in the FGFR3 gene cause a broad spectrum of conditions, ranging from hypochondroplasia and achondroplasia to thanatophoric dysplasia. “In addition, the FGFR3 gene mutation is also involved in the pathogenesis of other subtypes of skeletal dysplasia, including severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), Crouzon syndrome with acanthosis nigricans, and Muenke craniosynostosis syndrome” [2,3].

2.1.1 Achondroplasia

“Achondroplasia results from a point mutation in the gene that codes for the transmembrane portion of fibroblast growth factor receptor 3 (FGFR3)” [4]. “FGFR3 is an essential FGF-binding tyrosine kinase receptor, and the human FGFR3 gene is located on chromosome 4q16.3. This gene is 15Kb, containing 19 exons and 18 introns” [5]. “An extracellular glycosylation ligand-binding domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase catalytic domain are all encoded by the FGFR3 gene” [5,6].

Typically, the FGFR3 protein functions as the brake for endochondral bone growth, occurring at the growth plates of the long bone. Alteration in the DNA sequence in this gene increases the ability of the FGFR3 protein to slow bone growth. Thus, this mutation results in a loss of function in FGFR3, leading to abnormal cell proliferation and improper cartilage development. This abnormal chondroid affects endochondral ossification and results in a decrease in linear bone growth. However, this pathologic process spares intramembranous ossification, which occurs in flat bones, including the skull, except the base of the skull, face, and clavicles.

“The FGFR3 gene mutation can be inherited or acquired during development, and achondroplastic patients are often born with severe skeletal malformations. In over 80% of cases, the condition occurs due to sporadic, or de novo, mutation. Thus a child with achondroplasia can be born to healthy parents with no family history of the disorder” [7]. “The remaining 20% of achondroplasia have one of their parents affected by the disease.

A mutation of FGFR3 in the hydrophobic transmembrane domain, a top genetic hot zone necessary for regulating cartilage development, was reported in patients with achondroplasia using a polymerase chain reaction combined with single strand conformation polymorphism (SSCP), and exon ten was identified to be the site of mutation and where the hydrophobic transmembrane domain is encoded. As a result of this mutation, the FGFR3 ability as a single-pass transmembrane receptor in regulating chondrocyte cell proliferation and cartilage formation is affected” [5,6].

“Two viable base substitutions due to a point mutation are identified, including a transition of guanine to adenine substitution (c.1138G>A), which occurs in approximately 98% of patients, and a transversion of guanine to cytosine (c.1138G>C) that are seen in about 1% of patient with achondroplasia. Both base substitutions convert glycine (Gly) to arginine (Arg) on the 380th amino acid leading to FGFR3 dysfunction. Thus, normal GGG codon change to AGG or CGG from base substitutions leading to glycine being replaced with arginine (p.Gly380Arg) in both situations and affecting the transmembrane domain of FGFR3. Swedish and Japanese research groups identified a third base mutation and found c.1123G→T in separate cases, but the mutation incidence is very low, about 1-2% of all mutations” [6].

“Deviant downstream signalling of ligand-receptor complex between FGF3 and FGFR3 results in the receptor's stimulation and dimerization with consequent stimulation of the target tyrosine kinase activity of the FGFR3, leading to autophosphorylation of the selected tyrosine residues in the cytoplasmic domain of the receptor. The fundamental activation of the receptor protein and a remarkable reduction in endochondral bone formation produce a genetic

mutation in FGFR3 (p.Gly380Arg) through escalation inhibition of chondrocyte proliferation and differentiation [5, 6, 8]. A gain-of-function mechanism of FGFR3 follows a quantitative cartilage and growth plate defect. FGFR3 signalling inhibits bone growth via the mitogen-activated protein kinase (MAPK) pathway and reduces chondrocyte proliferation via Stat1" [6].

2.1.2 Hypochondroplasia

"Although it remains unclear how FGFR3 mutations lead to the features of hypochondroplasia, researchers believe that these genetic changes cause the protein to be overly active. The overactive FGFR3 protein interferes with skeletal development and leads to disturbances in bone growth" [9]. It comparatively shares many phenotypic features with achondroplasia. Mutations in the FGFR3 gene are responsible for about 70% of cases of hypochondroplasia, and it is mostly de novo gene mutation in the FGFR3. "Missense mutation of the FGFR3 gene (p.Asn540Lys) isolated in tyrosine kinase domain I and occurs in approximately 60% of cases. Tyrosine kinase domain II of FGFR3 (p.Lys650Asn) in the extracellular domain is a less common missense mutation associated with this disorder. A study of the p.Asn540Lys mutation showed activation of ERK1/2 but not STAT1. In vitro analyses of the p.Lys650Asn mutation showed weak activation of the FGFR3 kinase domain" [8].

2.1.3 Thanatophoric dysplasia

"A mutation in the fibroblast growth factor receptor 3 (FGFR3) gene is also responsible for causing thanatophoric dysplasia" [10]. Two clinically distinct forms of short-limb dwarfism that are lethal in the perinatal period are identified in this disorder. Lys650Met substitution in FGFR3 is found in Type I thanatophoric dysplasia with impaired endochondral bone growth and a pathogenic variant of p.Lys650Glu substitution is a Type II form of thanatophoric dysplasia [6].

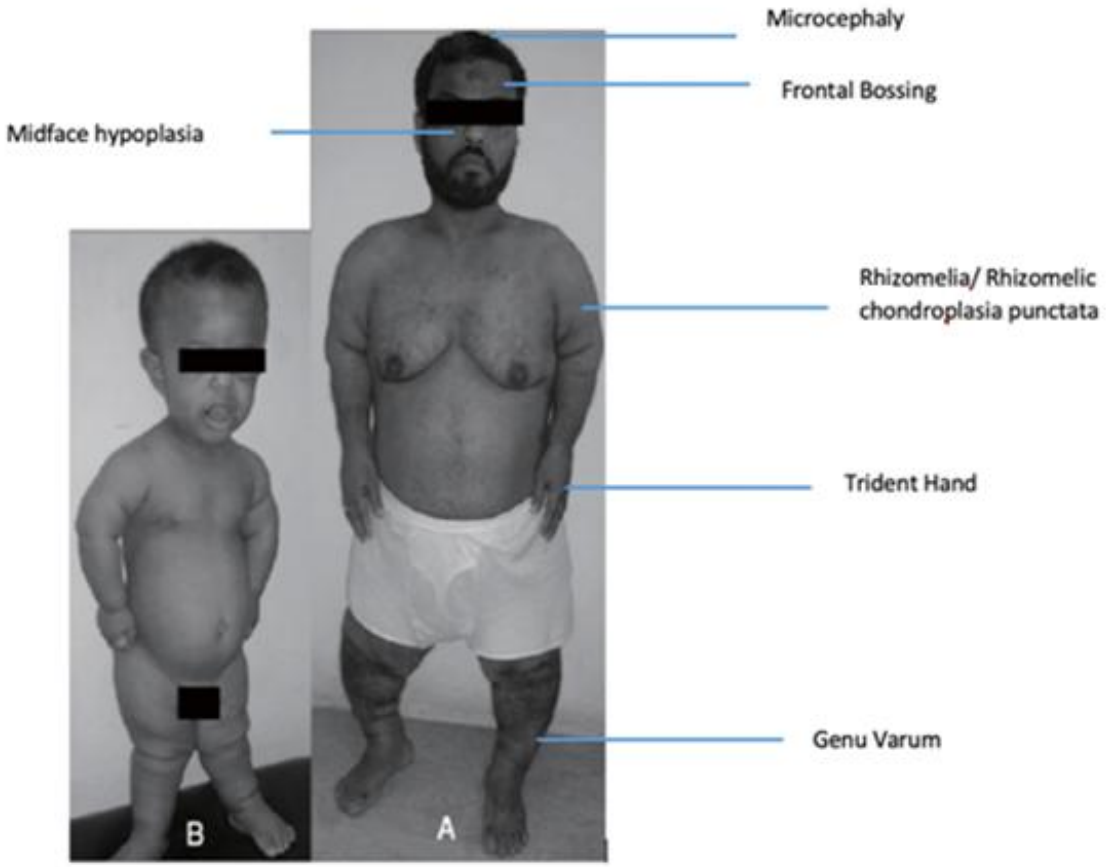

Fig. 1. Father and son with characteristics features of achondroplasia
Source: https://www.researchgate.net/journal/Egyptian-Journal-of-Medical-Human-Genetics-1110-8630V

2.2 Clinical Variants

2.2.1 Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans (SADDAN)

SADDAN is a dysplastic condition that arises from a different heterozygous mutation affecting the FGFR3 gene on chromosome 4p16. Specific amino acid substitutions in the FGFR3 gene (G380R) were identified to be associated with this disorder. The patient presents with extensive acanthosis nigricans starting early childhood, with or without neurological impairments. The skin changes in acanthosis nigricans are usually progressive and usually seen as a long-term complication rather than a specific clinical feature of SADDAN [11]. Impairment in endochondral bone growth is similar to what is observed in thanatophoric dysplasia, and Type I may also be seen in a patient with SADDAN. Apex posterior tibial and fibular bowing curved "ram's horn" deformities of the clavicles and femoral bowing are osseous deformities that may be seen in the disorder [9].

2.2.2 FGFR3 craniosynostosis syndrome

The distinguishing features can aid in the specific diagnosis of the different phenotypes [12]. FGFR3 Craniosynostosis Syndrome should be suspected in a patient with uni- or bi-coronal craniosynostosis or cloverleaf skull, with a characteristic facial feature and varying abnormal hand and foot findings. The clinical features may not be apparent in affected neonates or range from mild to severe, life-threatening presentations. The clinical features typically become more prominent with age, and diagnosis is usually based on clinical and radiologic findings in this disease. pathogenic FGFR1, FGFR2, or FGFR3.

2.3 Diagnosis

“FGFR3 molecular genetic testing should always be performed in children with atypical presentations. Over 350 skeletal dysplasia are known to cause short stature, most rare—Hypochondroplasia, and thanatophoric disorders present with rhizomelic dwarfism and lesser height disparity than achondroplasia” [13]. Most clinical presentations and radiological findings of skeletal dysplasias are very similar and tend to overlap. The affected patients may appear normal at birth. However, they tend to present with impaired linear growth, short limbs and trunk, and mild mental retardation in 10% of cases [7].

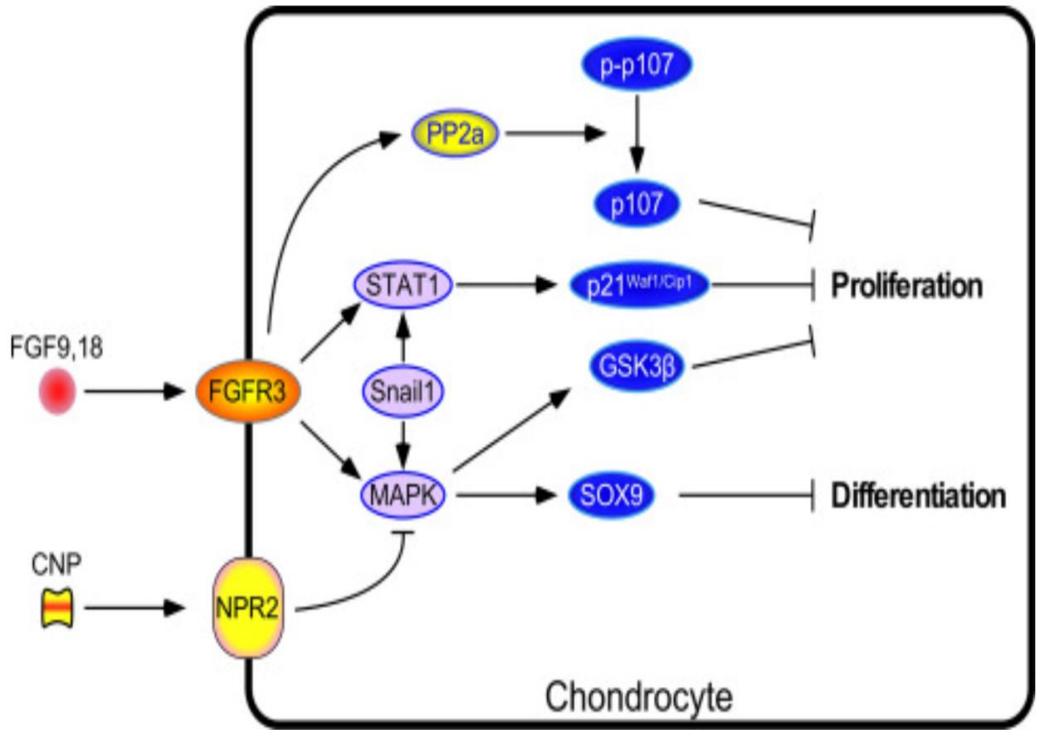

Fig. 2. Schematic of a cascade of genetic regulations and activities of FGFR3
Source: https://www.sciencedirect.com/topics/neuroscience/fibroblast-growth-factor-receptor-3

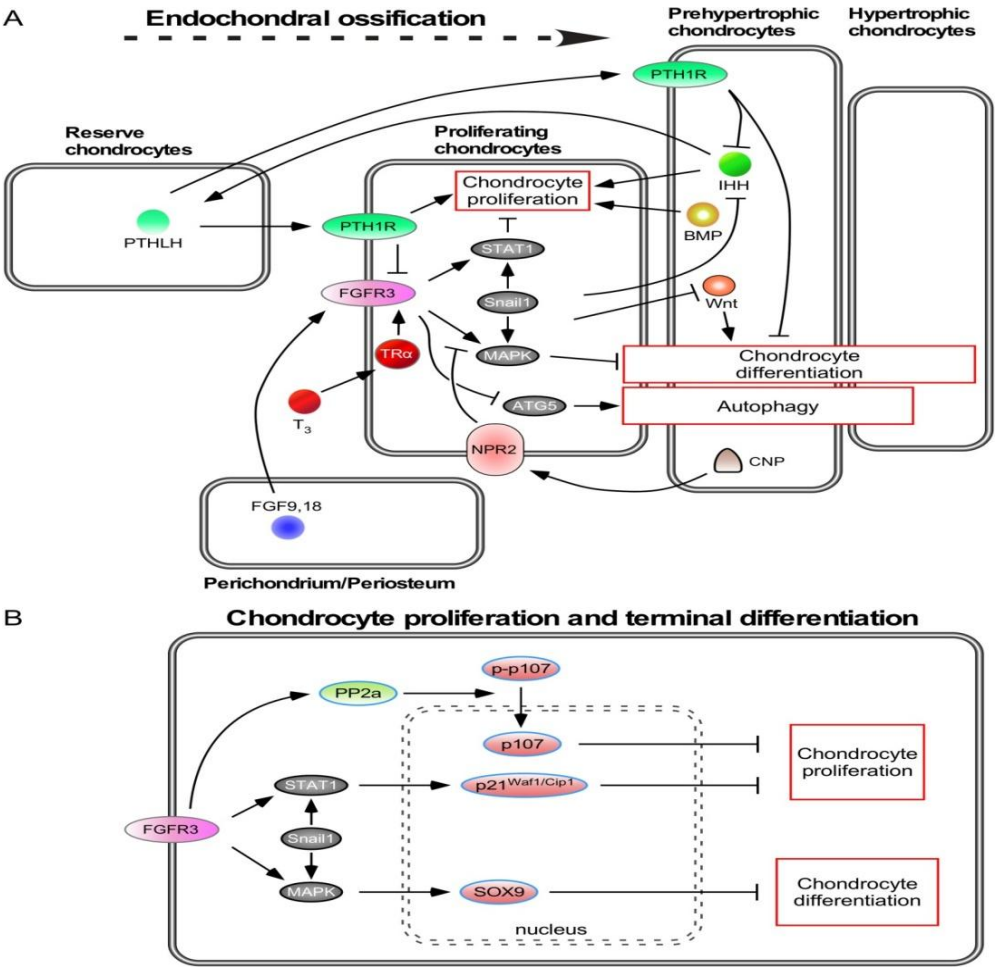

Fig. 3A and B. Schematic showing the genetic cascade in the pathogenesis of Achondroplasia (A) is Endochondral ossification and (B) chondrocyte proliferation and differentiation

Source: https://anatomypubs.onlinelibrary.wiley.com/doi/10.1002/dvdy.24479

Achondroplasias have been diagnosed routinely from clinical presentations, radiological findings, and genetic testing.

Congenital chondrodysplasias affect skeletal morphogenesis and growth with a low incidence of 3 to 6 cases per one million [3]. “Adult-onset diseases are associated with the pathology of articular joint cartilages of the long bone, such as rheumatoid arthritis and osteoarthritis. Osteoarthritis is the most common cartilage disorder affecting 32.5 million adult patients in the United States, compared to rheumatoid arthritis, which affects 0.24 to 1 percent of the population” [4,5].

“Prenatal diagnosis can be made on a routine second or third-trimester pregnancy ultrasound in a patient with shortened long bones. Non-invasive prenatal diagnosis using cell-free fetal DNA from maternal serum has been reported with high sensitivity and specificity” [7]. “In addition, a pre-implantation genetic diagnosis is available for parents pursuing in-vitro fertilization and embryo implantation procedures. The prenatal detection rate has recently improved significantly from 36% from 1991-1995 to 71% during 2011-2015” [14].

A contracted skull base, rhizomelic features of long bones, proximal femoral radiolucency, generalized metaphyseal "flaring" irregularities, inverted "V-shaped or chevron-shaped" distal femoral epiphyses, a "champagne-glass" shaped pelvis are more comprehensive than a deep pelvic outlet with a small sacro-sciatic notch and may be noticed on the skeletal survey. The radiographic features of narrowed interpedicular distances with short pedicles are usually found from L1-S1, vertebral body wedging is traditionally found at T12 or L1, and generalized posterior vertebral scalloping is unique to

achondroplasia. Signs and symptoms of corticomedullary myelopathy will be apparent if there is evidence of sleep apnoea [6].

"Hypochondroplasia is only diagnosed at birth if there is a prior family history" [9]. Most affected individuals present with a short stature as toddlers or young school-aged children. A false positive diagnosis of hypochondroplasia is often made because the disorder is considered common and associated radiologic findings are subtle.

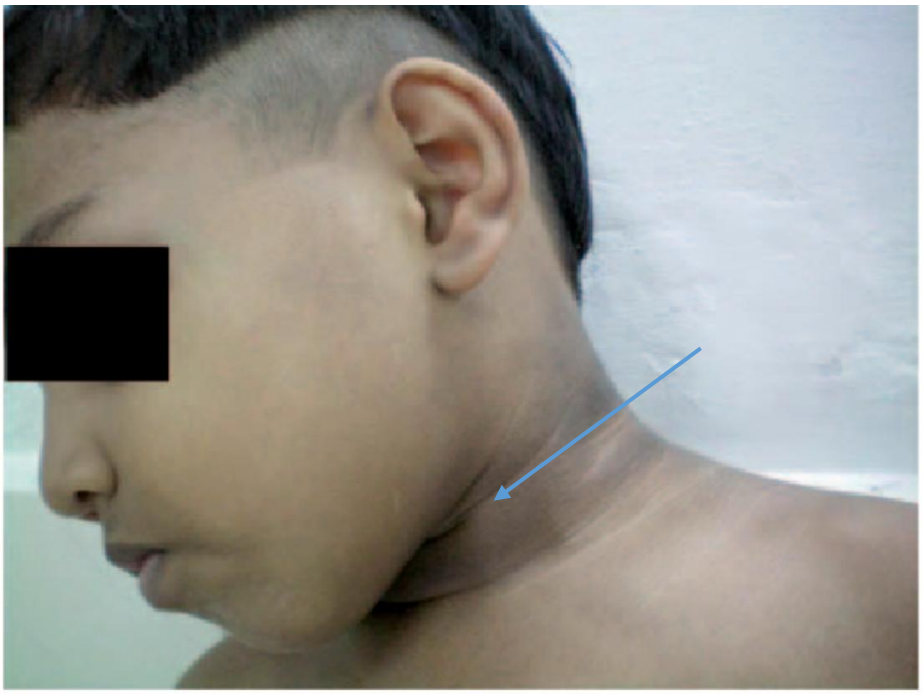

Fig. 4. Acanthosis Nigricans (blue arrow)
Source: https://www.semanticscholar.org/paper/SADDAN-syndrome.-Kumar-Shaikh/df00dd5070033d9b7367700e20e013b0a3da2387

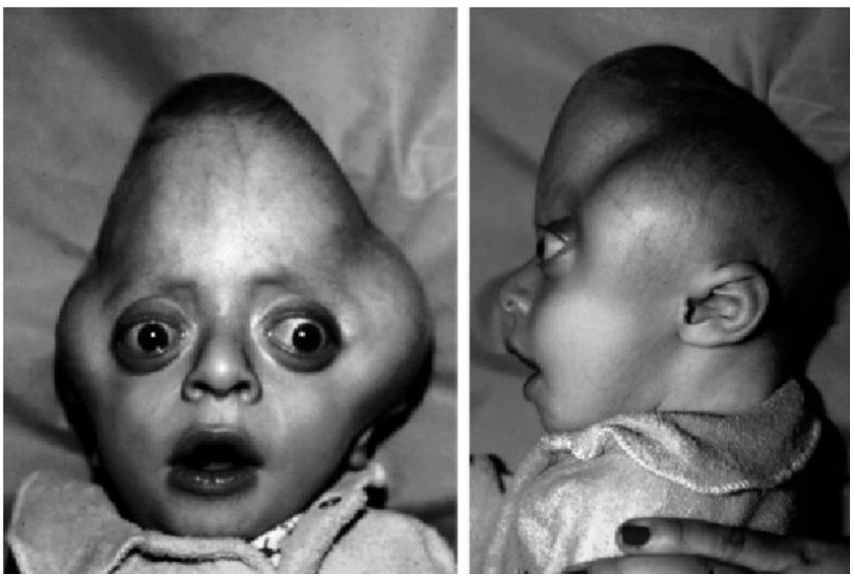

Fig. 5. Cloverleaf skull
Source: https://www.researchgate.net/figure/13-Cloverleaf-skull-deformity_fig8_289035218

"In the case of thanatophoric dysplasia, the condition is usually an incidental finding during a routine prenatal ultrasound with characteristic findings of shortened long bones, which can be visible as early as 14 weeks gestation" [15]. Two clinically distinct forms of short-limb dwarfism lethal in the perinatal period are known. In Type I, patients present with micromyelia with a bowed femur, and in Type II, patients present with micromyelia with a straight femur. "Typical clinical findings include cloverleaf skull deformity, infantile hypotonia, macrocephaly, frontal bossing, flat facies with ocular proptosis, ventriculomegaly, increased nuchal translucency, a narrow chest cavity with short ribs, and brachydactyly. Most infants with this disorder die due to respiratory insufficiency shortly following birth" [15].

Table 1. Types of thanatophoric dysplasia

Types	Differences	Similarities
I	Micromelia with the bowed femur	Cloverleaf skull deformity, infantile hypotonia, macrocephaly, brachydactyly
II	Micromelia with the straight femur	

2.4 Management

Achondroplasia has no known cure, but its complications can be managed symptomatically with drugs. In addition, surgical and nonsurgical strategies have been adopted to manage short stature with impaired linear growth, and management also includes lifelong follow-up care. Health problems commonly associated with achondroplasia include cervical medullary compression due to a reduced size of the foramen magnum and otitis media [16-19]. These complications must be treated to prevent cardiopulmonary failure, lumbar spinal compression, and hearing loss [20].

In addition, adenotonsillectomy, positive airway pressure support, and tracheostomy may be needed to address sleep apnea [20]. The first therapeutic strategy for treating achondroplasia includes using recombinant human growth hormone (r-hGH). Although, it is not recommended for all patients with achondroplasia, and parental concerns can influence the treatment [21]. The mechanism of action of recombinant human growth hormone is through its pro-anabolic properties by stimulating the growth of cartilage [5,6,22]. "Pharmacological interventions aimed to block FGFR3 activation or regulation of other signaling pathways by controlling the chondrocyte proliferation and differentiation" [23,24]. Recombinant human growth hormone is indicated for treating short stature in hypochondroplasia.

"Surgical intervention is a common therapy for proportional and disproportional dwarfism in achondroplasia and hypochondroplasia. Surgical limb lengthening classically uses the Ilizerov procedure in which long cortical bones are cut (osteotomy), external fixators are placed proximal and distal to the osteotomy, and distraction is applied gradually over many months to extend the bone length" [25]. "The average length gained is ~20.5 cm after multiple procedures applied to the femurs and tibias". [22,25]. "This surgical treatment allows functional gains and quality of life improvements. However, this procedure is painful and associated with complications that include infection, muscle contractures, and increased fracture risk" [26]. "Limb lengthening, involving the surgical breaking of a bone, fixation, and distraction during the healing process, remains controversial and is associated with a high risk" [25]. Before surgery, a pre-operative psychological assessment is required to evaluate the high risk of complications against the expected improvement of the short stature. Treatment for thoracolumbar kyphosis or genu varum is also necessary. Suboccipital decompression is used if the neurologic status is affected by spinal cord compression. In the future, combining surgical limb lengthening with pharmacological strategies could further improve outcomes. Developmental milestones are followed closely during early childhood so that cognitive impairments are addressed with special educational programs.

There is an increased incidence and prevalence of sporadic chondropathies especially Achondroplasia necessitating numerous clinical trials, among which is the use of C-type Natriuretic peptide analogues like Vosoritide in children with achondroplasia being explored [27-29].

3. CONCLUSION

Many studies have shown relationships between FGFR3 gene mutations and chondropathies. The mechanisms involved in the gene mutations are related to the alterations in the DNA sequences coding for the protein. The clinical manifestations of these disorders include impaired linear growth with short stature, short limbs, and trunk, while

clinical evaluations, radiological analysis, and genetic testing are required for diagnosis. In terms of management, pharmacological and surgical interventions are offered. Pharmacological interventions aim to directly block FGFR3 activation or regulate downstream signaling pathways involved in chondrocyte proliferation and differentiation. In patients with short stature and linear growth impairment, surgical limb lengthening is used to correct these abnormalities. In the future, the combination of pharmacological strategies and surgical interventions is bound to improve the clinical outcomes and quality of life of patients with chondropathies.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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