

Review

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Advances in research on and diagnosis and treatment of achondroplasia in China

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Summary

Achondroplasia is a rare autosomal dominant genetic disease. Research on achondroplasia in China, however, has received little emphasis. Around 80-90% of cases of neonatal achondroplasia result from mutations in fibroblast growth factor receptor 3 (*FGFR3*) according to polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP). Recently, genetic research on achondroplasia in China made a major breakthrough by revealing two novel mutations located on the *FGFR3* gene, thus helping to complete the pathological molecular map of achondroplasia. There are still, however, unknown aspects of the diagnosis and treatment of achondroplasia. This review will summarize advances in research on and the clinical diagnosis and treatment of achondroplasia in China.

Keywords: Rare diseases, gene mutation, chondrodystrophia fetalis, chondrodystrophic dwarfism

1. Introduction

Achondroplasia (MIM: 100800) is an autosomal dominant genetic disease that is also known as chondrodystrophia fetalis or chondrodystrophic dwarfism. Features of achondroplasia are distinctively identifiable. Patients have a large head with frontal bossing, midface hypoplasia, short limbs, trident hands, and muscular hypotonia. Commonly, these patients have recurrent ear infections, delayed motor milestones, and eventually develop bowed legs; luckily, patients with achondroplasia generally have normal intelligence (1). Ain *et al.* (2) found that 95% of six-month-old newborns with achondroplasia have the deformities mentioned earlier, and these defects progress with age. The body size of adult patients with achondroplasia is relatively small, with an average height of 131 cm for men and 124 cm for women and an average weight of 55 kg for men and 46 kg for women (3). X-rays have clearly shown that achondroplastic patients exhibit developmental

disorders including an underdeveloped skull base/facial bones, small facial bones, an enlarged head, a prominent forehead, bullet-shaped vertebral bodies, shorter anteroposterior diameter of the spinal canals, thicker long bones as well as metaphyseal flaring (4,5). Additionally, a third of patients with achondroplasia may develop spinal stenosis and thoracolumbar kyphosis (6,7). Leg and lower back pain are reported in half of adult patients, revealing the first signs of spinal stenosis. These symptoms may appear early and can be mediated by treatment with anti-inflammatory drugs, such as periradicular corticosteroid injections for lumbar radiculopathy. A number of associated factors are considered to play an aggravating role and have to be minimized through adequate physiotherapy to prevent lumbar lordosis and/or prevention of excess weight.

Achondroplasia is a rare disease worldwide but it has a 100% rate of expression. According to statistics from western research institutes, achondroplasia has a global incidence about 1/77,000-1/15,000 (8). 80-90% of newborns with this condition have a sporadic case caused by mutation, and 10-20% of newborns with this condition have a familial/genetic form. Fibroblast growth factor receptor 3 (*FGFR3*) is currently known to be the only gene that causes achondroplasia, mutations in this gene lead to an abnormal protein (9-13).

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The understanding of and research on achondroplasia started later in China than in Europe and the United States. From the 1980s to 1990s, nearly 60 clinical cases were reported around the country (14). Since then, there have been no exact statistical data on the incidence of achondroplasia in China. As a result, there is a low level of medical evidence and a lack of experience diagnosing this disease. Therefore, this review aims to summarize advances in research on and clinical diagnosis and treatment of achondroplasia in China.

2. Genetic aspects of achondroplasia

2.1. Mutations of *FGFR3* are associated with achondroplasia

Achondroplasia is a rare autosomal dominant disorder. *FGFR3* is currently known to be the only gene that causes achondroplasia. *FGFR3* is one of the key FGF binding tyrosine kinase receptors and is highly conserved in both humans and mice. The human *FGFR3* gene is located on chromosome 4q16.3 (15). Research has shown that *FGFR3* is expressed in different tissues including cartilage, the brain, kidneys, and the intestine in different stages of development (16). *FGFR3* is a single-pass transmembrane receptor and is involved in regulating cartilage and varied aspects of long bone development, including chondrocyte proliferation and cartilage matrix calcification. The *FGFR3* gene is 15 Kb and contains 19 exons and 18 introns. Numerous functional domains are encoded by the *FGFR3* gene, including an extracellular glycosylation ligand-binding domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase catalytic domain (17). In 1994, Shiang *et al.* (18) first reported a mutation of *FGFR3* in the hydrophobic transmembrane domain in patients with achondroplasia according to polymerase chain reaction (PCR) combined with single-strand conformation polymorphism (SSCP). The study by Shiang *et al.* indicated that the hydrophobic transmembrane domain may be the key genetic hot zone essential to regulating cartilage development. A study by Perez-Custro *et al.* (19) confirmed the location of the

mutation at exon 10, which encodes the hydrophobic transmembrane domain.

Genetically, around 99% of achondroplasia cases are caused by the c.1138G→A and c.1138G→C mutations. Both mutations convert glycine (Gly) into arginine (Arg) on the 380th amino acid, leading to dysfunctional proteins (20). In 1995, Swedish and Japanese research groups found a third base mutation – c.1123G→T – in individual cases and one family, but the incidence of this mutation is very low (about 1-2% of all mutations) (21,22). Recently, Prinos *et al.* reported another novel mutation, Gly to Glu on the 346th amino acid (23) (Table 1).

FGFR3 mutations generate deficient proteins that affect chondrocyte proliferation and calcification and hinder cartilage growth and development. In *FGFR3* knock-out mice, cartilage and long bones grow but the growth of other bones is delayed, indicating that *FGFR3* inhibits bone growth by limiting chondrocyte proliferation and that it acts as a negative regulator of bone growth (24). In brief, *FGFR3* mutations reduce chondrocyte proliferation and limit the growth of cartilage and long bones, thereby resulting in an external phenotype of achondroplasia.

Aberrant downstream signaling of ligand-receptor interaction of FGF3 and *FGFR3* is also another key factor affecting achondroplasia (25). Binding of FGF ligands to *FGFR3* leads to activation and dimerization of the receptor and can sequentially activate target tyrosine kinase of *FGFR3*, leading to autophosphorylation of selected tyrosine residues in the cytoplasmic domain of the receptor (26). A recent study showed that *FGFR3* signaling inhibits bone growth *via* the MAPK pathway and reduces chondrocyte proliferation *via* Stat1 (27). Another study recently noted a complex pattern of spatial regulation of FGFs and FGFRs (especially FGF2 and FGF4) (28), and detailed aspects of this regulatory mechanism must be explored.

2.2. *FGFR3* mutations in the Chinese achondroplastic population

In 1994, Shiang *et al.* (18) confirmed that *FGFR3* was

Table 1. *FGFR3* mutations responsible for achondroplasia

Mutation	Location	Result of mutation	Mutation rate	Type
c.1138G → A	380thExon10	Gly → Arg	≥ 95%	missense
c.1138G → C	380thExon10	Gly → Arg	3-4%	missense
c.1123G → T	375thExon10	Gly → Cys	1-2%	missense
c.1037G → A	364thExon9	Gly → Glu	No data	missense
c.1180A → T*	394thExon10	Thr → Ser	No data	missense
c.649A → T*	217thExon5	Ser → Cys	No data	missense

* new mutation found in the Chinese population.

the gene responsible for achondroplasia for the first time. At about the same time, Bellus *et al.* (29) reported a prenatal gene diagnosis of an achondroplastic patient through a villi biopsy, opening up a new area of genetic analysis of *FGFR3* mutations in achondroplasia. In China, research on achondroplasia started only in 2005 when Ma *et al.* (30) analyzed the profiles of Chinese patients with achondroplasia for the first time. They used PCR-SSCP to analyze cord blood for *FGFR3* mutations in order to diagnose patients with achondroplasia, providing a potential way to detect or even predict achondroplasia clinically. The same group later (30) identified *FGFR3* as a gene responsible for achondroplasia in the Chinese population and they detected the c.1138G→A mutation in Chinese patients. Further investigations have corroborated the finding that most *FGFR3* mutations in the Chinese population are the c.1138G→A mutation; only a handful of studies have noted the c.1138G→C mutation (31).

Recently, research on achondroplasia in China has made great progress. Zhu *et al.* (32) analyzed probands and families with a history of achondroplasia and found no mutations at the 1138 and 1123 sites, suggesting that a new mutation site may be involved in this pedigree. Further investigation revealed a new mutation, c.1180 A→T at exon 10 (the 394th amino acid), in this pedigree. Using linkage analysis and direct DNA sequence, a study by Zhang *et al.* found that there was a c.649 A→T transition at exon 5 of the *FGFR3* gene in Chinese patients with achondroplasia (33). Since it was not present in other normal family members, their finding indicated that this mutation is also pathogenic for achondroplasia. This is the first identified mutation in the Ig II loop of the *FGFR3* gene outside exon 10.

3. Diagnosis of achondroplasia in China

Aging may also play a promoting role in modulating the prevalence of achondroplasia in patients with de-novo gene mutation (34), necessitating the development of a precise method of diagnosing the condition in the prenatal stage. To date, several routine methods to diagnose achondroplasia, including ultrasound diagnosis and genetic examination, have been proposed. These methods are quick, efficient, and accurate. In recent years, advanced methods of diagnosing achondroplasia have also been explored. One is the use of high resolution melting (HRM), a new, rapid, and inexpensive method of molecular detection to screen for genetic mutations. He *et al.* (35) identified 12 cases, including 10 sporadic cases and 2 cases, in a family with achondroplasia using both HRM analysis and restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR). Of those cases, 11 involved the c.1138G→A heterozygous mutation while 1 involved the c.1138G→C heterozygous mutation. This finding implies that HRM analysis can

provide an improved approach over RFLP-PCR in terms of detecting *FGFR3* mutations in patients with achondroplasia.

Denaturing high performance liquid chromatography (DHPLC) is another common method to diagnose achondroplasia in the Chinese population. DHPLC involved the separation and analysis of nucleotide fragments to detect changes in the DNA sequence using a column. In accordance with the melting characteristics of heteroduplex DNA with homologous double-stranded DNA and the fact that heteroduplex DNA has a shorter retention time than homoduplex DNA in the column, the heteroduplex DNA is eluted first, and bimodal or multimodal distributions then yield certain elution curves (36). Zhu *et al.* (37) detected the pathogenic mutation of *FGFR3* in three families with achondroplasia by DHPLC, restriction enzyme (SfcI and MspI) digestion analysis, and sequencing analysis. They found that all of these methods were able to detect mutations of the *FGFR3* gene although DHPLC is faster, easier, and more sensitive, making it ideal for prenatal genetic diagnosis of patients with achondroplasia.

Achondroplasia can be diagnosed effectively and accurately using the methods mentioned. However, many medical facilities usually combine these methods to confirm a diagnosis of achondroplasia in order to ensure the reliability of the clinical diagnosis and avoid misdiagnosis by a single method.

4. Treatment of achondroplasia in China

4.1. Hormone therapy

To date, there are many treatments for achondroplasia (Table 2). In Western countries, growth hormone (GH) therapy has been widely used to lessen the clinical complications of achondroplasia (38,39). In China, GH therapy is also a therapeutic option for most patients with achondroplasia. After treatment, some patients improve by becoming taller while others do not, suggesting a patient-specific response to GH therapy. Additionally, the high cost of GH limits the choice of this therapy. For a long time, there have been differing views on the adverse reactions to growth hormone treatment (30). A recent follow-up study of patients after 5 years of GH therapy found that GH improved height without any adverse effects on trunk-leg disproportion (40).

In addition to GH, a recent study showed that systemic intermittent injection of parathyroid hormone (PTH) may significantly alleviate retarded skeletal development in achondroplastic mice (41). In this model, the bone length of the humerus and tibia was extended compared to the bone length in wild-type mice. Furthermore, research has also shown that PTH treatment can alleviate osteopenia and improve bone

Table 2. Current treatment of achondroplasia in China and the West

China	Western countries
Growth hormone (GH)	1. Growth hormone (GH)
Double leg lengthening surgery	2. Osteotomy 3. Spinal canal decompression
peptide P3	1. Systemic intermittent PTH (1-34) 2. Selective inhibition of FGFR3 tyrosine kinase 3. C-type natriuretic peptide 4. Blocking antibodies to interfere with binding of FGF ligands to FGFR3

structure in achondroplastic mice. At the molecular level, increased PTH-related peptide (PTHrP) expression and down-regulated FGFR3 expression may be responsible for the benefits of PTH in terms of bone growth in achondroplasia, but PTH therapy has not been approved for routine clinical use.

4.2. Surgical therapy

Surgical therapy is the most effective treatment option for achondroplasia. In Western countries, a surgical procedure such as osteotomy is often proposed when genu varum is present and persists during childhood. Osteotomy is a preferred surgical treatment for thoracolumbar kyphosis and lumbar stenosis in patients with achondroplasia (42). The early experience with surgical limb-lengthening procedures resulted in a high incidence of complications such as pain and infections (38), but more advanced procedures have recently resulted in a significant increase in patient height over a 24-month period (43).

Spinal canal decompression is one of the most common surgical strategies to treat spinal stenosis in patients with achondroplasia, and it can reduce symptoms of lumbar stenosis (6). However, the great risk of neurological injury has discouraged the use of this procedure. The angles and diameters of thoracic and lumbar pedicles of patients with achondroplasia and those of healthy people have been determined despite anatomical differences. Recent studies on the management of spinal disorders in patients with achondroplasia have demonstrated the safety and efficacy of spinal instrumentation (44,45).

Double leg lengthening surgery has been proposed as an alternative to treat the Chinese achondroplasia population by restoring the normal ratio of the trunk and lower limbs through extension of the lower limbs (46). After surgery, the tibia and femur are extended an average of 10 cm. Since patients with achondroplasia have lower limbs that need to be considerably extended,

age is a concern when performing this surgery. Postoperatively, the lower limbs need to be used soon to enhance new bone formation and should be closely monitored for 1-2 years as the epiphyseal plates close.

4.3. Other potential therapies

In addition to the methods mentioned earlier, several alternative treatments have recently been proposed to counteract the effects of overactive FGFR3 on endochondral bone formation. One practical example would be use of selective inhibitors of FGFR3 tyrosine kinase, such as imatinib (47). Furthermore, the administration of C-type natriuretic peptide (CNP) has also been proposed. Over-expression of CNP in mouse chondrocytes alleviated achondroplasia *via* the MAPK-dependent pathway (48,49). In addition, a treatment using blocking antibodies to interfere with FGF-FGFR3 interaction could be another option to treat patients with achondroplasia (50). A novel inhibitory peptide for FGFR3 signaling – peptide P3 – was recently identified by a Chinese group (51). Peptide P3 exhibits a high binding specificity to the extracellular domain of FGFR3, inhibiting tyrosine kinase activity. It thus may act as a potential therapeutic agent for FGFR3-related skeletal dysplasia.

5. Conclusion

Achondroplasia is a rare autosomal dominant genetic disease that affects many patients in China. Recently, genetic research on achondroplasia in China has made great progress. In China, the condition is being studied and diagnosed *via* ultrasound, a genetic examination, HRM, and DHPLC and treated *via* GH therapy, double leg lengthening surgery, and peptide P3. However, the study of achondroplasia is still in its infancy and its pathogenesis is unclear, resulting in a lack of effective treatments. As molecular genetic techniques develop, the pathogenesis of this condition will be studied and more effective treatments are anticipated for patients with achondroplasia in China.

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