Orphanet Journal of Rare Diseases

REVIEW

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Review of published 467 achondroplasia patients: clinical and mutational spectrum

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Abstract

Aim Achondroplasia is the most common of the skeletal dysplasias that cause fatal and disabling growth and developmental disorders in children, and is caused by a mutation in the fibroblast growth factor receptor, type 3 gene(*FGFR3*). This study aims to analyse the clinical characteristics and gene mutations of ACH to accurately determine whether a patient has ACH and to raise public awareness of the disease.

Methods The database of Pubmed, Cochrane Library, Wanfang and CNKI were searched with terms of "Achondroplasias" or "Skeleton-Skin-Brain Syndrome" or "Skeleton Skin Brain Syndrome" or "ACH" and "Receptor, Fibroblast Growth Factor, Type 3" or "*FGFR3*".

Results Finally, four hundred and sixty-seven patients with different *FGFR3* mutations were enrolled. Of the 138 patients with available gender information, 55(55/138, 40%) were female and 83(83/138, 60%) were male. Among the patients with available family history, 47(47/385, 12%) had a family history and 338(338/385, 88%) patients were sporadic. The age of the patients ranged from newborn babies to 36 years old. The mean age of their fathers was 37 ± 7 years (range 31–53 years). Patients came from 12 countries and 2 continents, with the majority being Asian (383/432, 89%), followed by European (49/432, 11%). Short stature with shortened arms and legs was found in 112(112/112) patients, the abnormalities of macrocephaly in 94(94/112) patients, frontal bossing in 89(89/112) patients, genu valgum in 64(64/112) patients and trident hand were found in 51(51/112) patients. The most common mutation was *p.Gly380Arg* of the *FGFR3* gene, which contained two different base changes, *c.1138G > A* and *c.1138G > C*. Ten rare pathogenic mutations were found, including *c.831A > C*, *c.1031C > G*, *c.1043C > G*, *c.375G > T*, *c.1133A > G*, *c.1130T > G*, *c.833A > G*, *c.649A > T*, *c.1180A > T* and *c.970_971insTCTCCT*.

Conclusion ACH was caused by *FGFR3* gene mutation, and *c.1138G > A* was the most common mutation type. This study demonstrates the feasibility of molecular genetic testing for the early detection of ACH in adolescents with short stature, trident hand, frontal bossing, macrocephaly and genu valgum.

Keywords Achondroplasia, *FGFR3*, Molecular study

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Introduction

Skeletal dysplasia has been a significant global public health problem. Achondroplasia(ACH, OMIM #100,800) is the most common skeletal dysplasia, its clinical and radiological phenotypes have been described for more than 50 years [1] and occurs in between one in 10,000 and one in 30,000 live births [2].

In 1994, Shiang [3] found that ACH has mutations in the transmembrane domain of the fibroblast growth factor receptor 3 (*FGFR3*) [3] and more than 98% of ACH cases carried the base conversion that changes G to A at position 1138 of cDNA in exon 10 of *FGFR3* gene, which changes the amino acid at position 380 of the *FGFR3* from glycine to arginine. Subsequently, in 1998, Wilkin DJ found that *FGFR3* mutations occur preferentially during spermatogenesis and that the risk of new point mutations increases with the paternal age increasing, while mutations always in paternal alleles in non-familial cases of achondroplasia [4].

The clinical features of achondroplasia are variable, including macrocephaly, brachydactyly, metaphyseal flaring and shortening of the pedicles [5]. The mean height of males was 132 cm and females was 123 cm, which was described by Alderborn in 1996 [5]. Despite the presence of the above clinical manifestations, ACH patients have a natural lifespan and intelligence [6].

The current strategy for identifying patients is to combine the clinical characteristics, imaging findings and molecular genetic testing. With the increasing application of gene sequencing technology, the diagnostic accuracy of ACH has been improved, but the awareness of ACH in public is not enough, which may easily lead to misdiagnosis and missed. Thus, the identification of patients with ACH is great help to give a good birth and good care as soon as possible and it is essential to recognize ACH patients. This study aims to analyse the clinical characteristics and gene mutations of ACH to accurately determine whether a patient has ACH and to raise public awareness of the disease.

Methods

Pubmed, Cochrane library, the China National Knowledge Infrastructure (CNKI), and Wanfang were searched from the date to 23 March 2023 without language restrictions. The search terms were "Achondroplasias" or "Skeleton-Skin-Brain Syndrome" or "Skeleton Skin Brain Syndrome" or "ACH" and "Receptor, Fibroblast Growth Factor, Type 3" or "*FGFR3*". Eligible studies met the following criteria: (1) published in English or Chinese; (2) the patients were diagnosed as ACH; (3) the patients confirmed the *FGFR3* mutations by gene diagnosis; and (4) the patients were postnatal.

The following clinical characteristics were studied: (1) gender; (2) country; (3) family history; (4) amino acid substitution and type of mutations in the *FRFR3* gene; (5) clinical characteristics. Flow chart of the systematic search process is showed in Fig. 1.

Results

Epidemiological characteristics and gene mutations in ACH

Eighty-seven studies including 467 individuals who met the criteria were enrolled. Among them, 432 patients

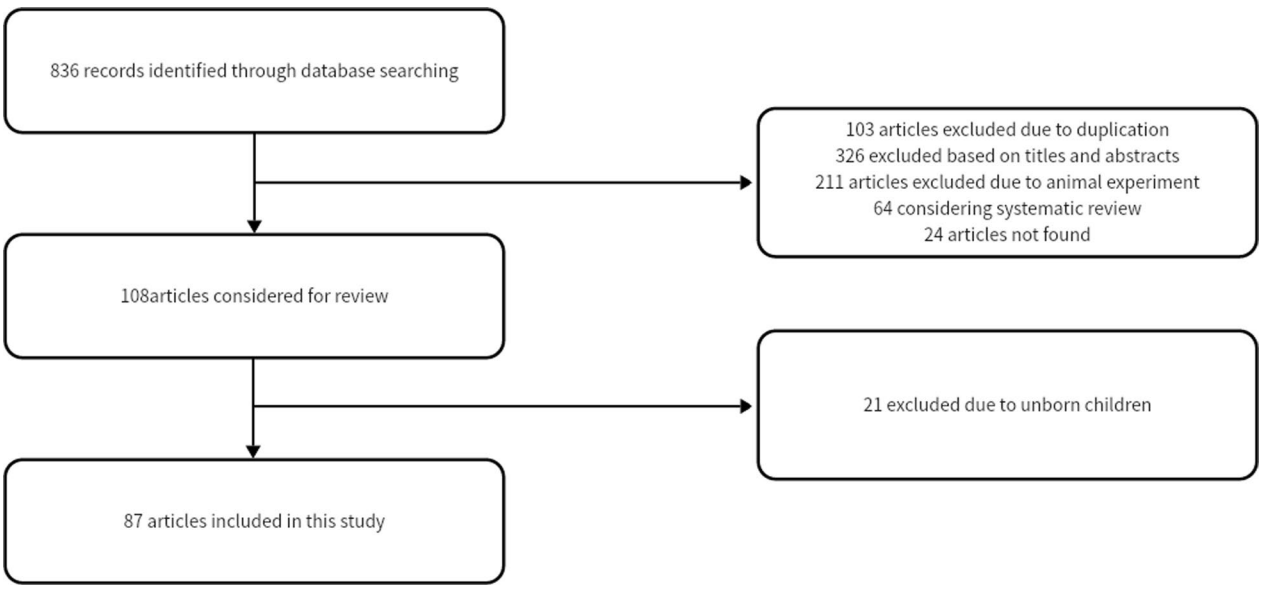

Fig. 1 Literature inclusion process

provided the country information. They came from 12 countries and 2 continents, with Asians making up the largest group (383/432, 89%) and Europeans making up 11% (49/432, 11%). Among the Asians, cases from China, Pakistan, Japan, Korea and India accounted for 72%, 11%, 7%, 7%, and 3%, respectively.

The amino acid substitutions and the percentage of mutations in *FGFR3* are listed in Table 1. The most common mutation was *p.Gly380Arg* and 421 patients provided detailed nucleotide changes, of which the proportion of *c.1138G>A* was higher than *c.1138G>C*, accounting for 97% (410/421, 97%), resulting in the same nucleotide changes, i.e. the glycine was replaced by an arginine. In addition, 6 patients carried the *c.649A>T* mutation, 4 patients carried the c.*1180A>T* mutation, 3 patients carried the *c.375G>T* mutation. The *c.1043C>G*, *c.1031C>G*, *c.833A>G* mutations were all carried by 2 patients, and the *c.831A>C* mutations were carried by one patient. Another specific mutation is *c.970_971insTCTCCT.*

Most of the patients had one mutation, but 2 patients had two mutations in *FGFR3* on the same allele. One patient carried the common *p.Gly380Arg* mutation and a novel *c.1130T>G* mutation [28], and another carried the *p.Gly380Arg* and *c.1133A>G* [19]. However, the above two novel mutations had not been reported as the direct pathogenic genes of ACH. Figure 2 shows the detailed information of the enrolled countries and mutation types.

Table 1 *FGFR3* mutations of ACH patients

References	cDNA	Nucleotide alteration	Protein	Percentage	allele frequencies
[5, 7–84]	c. 1138G>A or c. 1138G>C	glycine to arginine	p.Gly380Arg	95.5% (446/467)	4.79e-6 or 6.85e-7
[14, 89]	c.1031C>G	serine to cysteine	p.Ser344Cys	0.4% (2/467)	NA
[16, 72]	c. 375G>T	glycine to cysteine	p.Gly375Cys	0.6% (3/467)	1.20e-6
[47, 62]	c.833A>G	tyrosine to cysteine	p.Tyr278Cys	0.4% (2/467)	NA
[85]	c.831A>C	serine to cysteine	p.Ser279Cys	0.2% (1/467)	NA
[86]	c.970_971 ins TCTCCT	the insertion of Ser-Phe after position Leu324	p.L324delinsLSF	0.2% (1/467)	NA
[87, 88]	c.1043C>G	serine to cysteine	p.Ser348Cys	0.4% (2/467)	NA
[90, 92]	c.649A>T	serine to cysteine	p.Ser217Cys	1.3% (6/467)	NA
[91]	c.1180A>T	threonine to serine	p.Thr394Ser	0.9% (4/467)	NA

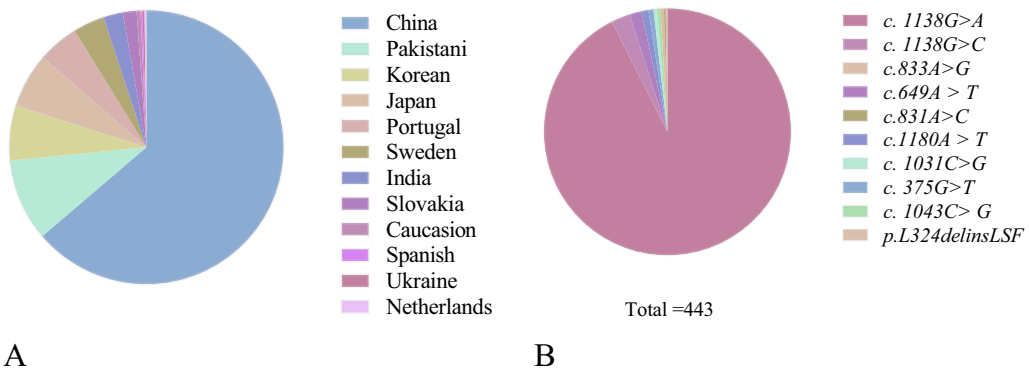

Fig. 2 **A** continent distribution radio of patients (%), **B** the percentage of different mutation sites (%)

Clinical characteristics of ACH

Of the 138 patients who provided the gender information, 83(83/138, 60%) were male and 55(55/138, 40%) were female. Of the 385 patients who provided family history information, 47(47/385, 12%) patients had a family history of ACH, 338(338/385, 88%) patients were sporadic.

The age of the patients ranged from newborn babies to 36 years old. Of the 11 and 10 patients who gave the age of their father and mother respectively. The average age of the fathers was 37 ± 7 years old (range from 31 to 53), of which 4(4/11, 36%) were older than 35 years old, and that of the mothers was 32 ± 5 years old (range from 23 to 39).

A total of 112 patients provided detailed clinical and radiological features, 112(112/112) had short stature with shortened arms and legs, 51(51/112) had the trident hand, 89(89/112) had frontal bossing, 94(94/112) had macrocephaly, 64(64/112) had genu valgum, 54(54/112) had narrowing of the interpediculate distance, 42(42/112) had kyphoscoliotic deformity, 42(42/112) had short femoral necks, 18(18/112) had metaphyseal flaring, 16(16/112) had square iliae and 16(16/112) had midface hypoplasia. Besides the aforementioned manifestations, eleven patients had a history of hydrocephalus found on magnetic resonance imaging. Figure 3 shows details of the clinical symptoms and the differences in the clinical presentation according to gender.

The boy with *c.1130T>G* and *c.1138G>A* in FGFR3 on the same allele had prolonged episodes of hypoxaemia with respiratory distress and shortness of breath, a chest CT showed pulmonary dysplasia, and a brain MRI showed a very narrow foramen magnum with additional compression of the cervical spine [28]. Similarly, a girl carrying *c.1133G>A* and *c.1138G>A* in FGFR3 showed more severe clinical and radiological characteristics than classic ACH patients, with respiratory distress, pulmonary hypoplasia, hydrocephalus and cervicomedullary compression [19].

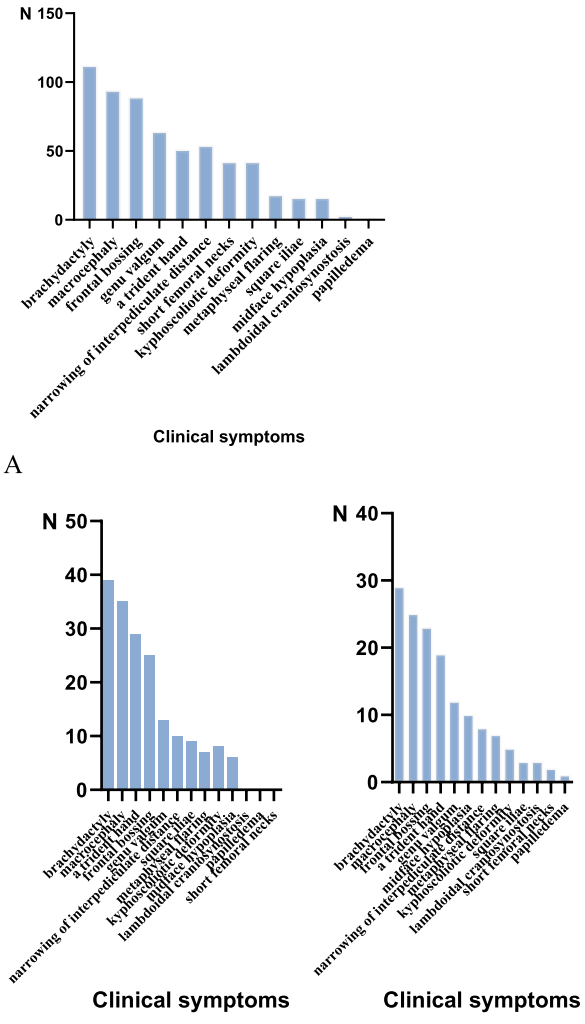

Fig. 3 **A** clinical symptoms(N:112), **B** clinical symptoms in male (N:39), **C** clinical symptoms in female (N:29)

Discussion

FGFR3 is located on the short arm of chromosome 4, 4p16.3, and is expressed in chondrocytes and mature osteobl*asts* [93]. The main forms of osteogenesis include intramembranous osteogenesis and endochondral osteogenesis, starting with the formation of chondrocytes from mesenchymal cells, followed by the formation of ossification centres from chondrocytes through proliferation and differentiation, and the gradual development of the diaphysis and epiphysis, with chondrocytes located in between promoting linear bone growth through proliferation and differentiation. The activation of *FGFR3* after birth inhibits the proliferation and hypertrophy of chondrocytes [94]. Mutations in *FGFR3* can activate tyrosine protein kinase activity, enhance negative regulatory function, inhibit chondrocyte proliferation, affect bone trabeculae formation, play a role in regulating chondrocyte proliferation and differentiation, and negatively regulate bone growth. In the HGMD database, we found that mutations in the *FGFR3* gene are associated with a variety of diseases, including hypochondroplasia, thanatophoric dysplasia, achondroplasia, craniosynostosis、lacrimo-auriculo-dento-digital syndrome, acanthosis nigricans, prostate cancer and wilms tumour, of which 28 mutations were identified for hypochondroplasia, 15 mutations for thanatophoric dysplasia and 11 mutations for ACH, as shown in Table 2.

Our study demonstrated that 338(338/385, 88%) patients with ACH were sporadic, which was a

Table 2 The number of mutations and types in *FGFR3* in HGMD database

Disease/phenotype	Number of mutations
Hypochondroplasia	28
Thanatophoric dysplasia	15
Achondroplasia	11
Craniosynostosis	4
Lacrimo-auriculo-dento-digital syndrome	2
Short stature ?	2
Skeletal dysplasia	2
Acanthosis nigricans	1
Achondroplasia ?	1
Achondroplasia with developmental delay & acanthosis nigricans	1
Achondroplasia with severe Platyspondyly	1
Camptodactyly, tall stature and hearing loss syndrome	1
Cleft lip and palate ?	1
Crouzon syndrome with acanthosis nigricans	1
Prostate cancer	1
Prostate cancer and additional primary cancers	1
Seborrhoeic keratosis ?	1
Short stature	1
Tall stature, lateral tibial deviation, scoliosis, hearing impairment, camptodactyly and arachnodactyly	1
Thanatophoric dysplasia, type 2	1
Wilms tumour	1

spontaneous mutation. Four hundred and twenty-one patients provided detailed *p.Gly380Arg* mutations in the *FGFR3* gene, and among them, four hundred and ten patients had *c.1138G>A* changes, which was consistent with the studies by Shiang in 1994 [3]. *c.831A>C*, *c.1031C>G*, *c.1043C>G*, *c.375G>T*, *c.1133A>G*, *c.1130T>G*, *c.833A>G*, *c.649A>T*, *c.1180A>T* and *c.970_971insTCTCCT* were ten rare pathogenic mutations. These mutations constitutively activate the *FGFR3* receptor, leading to abnormal membrane ossification, inhibit the growth and proliferation of chondrocytes, and finally hinder the extension of bone. In addition, we also found that there were two novel mutations that occurred simultaneously with the *p.Gly380Arg* mutation, *c.1130T>G* and *c.1133A>G*. But no related reports indicated that *c.1130T>G* and *c.1133A>G* were the direct cause of ACH, we did not know whether these mutations were pathogenic or not. Tadashi suggested that these mutations in the same gene may have an additive effect on the activated receptor of the *p.Gly380Arg* mutation and change the protein function, resulting in the severe phenotype of the disease [19].

ACH is an autosomal dominant genetic disorder and the risk of recurrence is associated with whether the parents themselves have ACH. The mean paternal age of the achondroplasia patients analyzed in this study was 37 ± 7 years old(range from 31 to 53), and four of them were over 35 years old. Wilkin analysed 40 families with sporadic ACH and found that the mutated allele was inherited exclusively from the father, suggesting that it affects DNA replication or repair during spermatogenesis [4].

Mutations in the *FGFR3* gene can also cause other types of skeletal dysplasia,, which need to be identified and classified from mild to severe: hypochondroplasia (HCH), achondroplasia, thanodermal dysplasia type I (TD I), severe achondroplasia with developmental delay and nigroschisis (SADDN), and thanodermal dysplasia type II (TD II). HCH is mainly caused by the *c.1620C>A* or *c.1651A>G* mutations, and patients usually present with mid-craniofacial deformities, limb deformities, and hand and foot deformities. In contrast, TD has more severe clinical manifestations than ACH, which can be divided into TD I and TD II. TD I is caused by the *c.742C>T*, *c.1111A>T* and *c.1118A>G* mutations in *FGFR3*, and TD II is mainly caused by the *c.1948A>G* mutation. SADDAN syndrome is a severe form of ACH associated with growth retardation and acanthosis nigricans caused by the *c.1949 A>T* mutation. In addition, previous studies have shown that skeletal abnormalities and growth disorders are associated with defects in the *SHOX* gene, such as Leri-Weill syndrome (LWD), Turner syndrome (TS) and idiopathic short stature (ISS). The *SHOX* gene is located at the end of the short arms of the X and Y sex chromosomes (Xp22.32 or Ypll.3) and was first identified in 1997 by Rao et al. [95]. Early detection of *SHOX* gene mutations and skeletal malformations is an important guideline for the diagnosis and management of dwarfism. Common clinical manifestations include short forearm and lower leg, cubitus valgus, Madelung deformity, high-arched palate and muscular hypertrophy [96]. In this study, we summarized the *FGFR3* mutation types of eighty-seven studies including 467 individuals and the clinical characteristics of 112 patients with ACH. Some common clinical characteristics of ACH were as follows: (1) short stature with shortened arms and legs (112/112); (2) trident hand (51/112); (3) frontal bossing (89/112); (4) macrocephaly (94/112); (5) genu valgum (64/112). The following radiological characteristics were common: (1) the narrowing of the interpediculate distance (54/112); (2) kyphoscoliotic deformity (42/112); (3) short femoral necks (42/112).

Based on the main clinical features (short stature, macrocephaly, frontal bossing, midface hypoplasia, genu valgum) and radiological features (square iliae, narrowing of interpediculate distance, kyphoscoliotic deformity, short femoral necks) can be diagnosed clinically in

most patients with ACH. In patients with clinical or radiological suspicion of ACH, it would be easy to determine the two most common pathogenic variants of the *FGFR3* mutation in the affected child by PCR. For children without mutations at common mutation sites or requiring differential diagnosis of ACH, whole-exon *FGFR3* sequencing should be used for detection. Prenatal screening programmes for ACH usually include chorionic villus sampling, amniocentesis and ultrasound. The realisation of early diagnosis and early treatment not only has a good therapeutic effect, but also reduces the burden of the disease and saves on the cost of medical care.

So far, there is no standardized treatment for ACH in the world. At present, the treatment of ACH mainly includes symptomatic treatment and surgical intervention. In this study, four patients were received growth hormone treatment, three of whom had an increase in height after six months, one with growth hormone 0.15 U/kg per day alone and two with growth hormone 2.5IU per day combined with L-thyroid hormone 12.5ug per day. Among them, two patients described the accurate figures of the increase, which were 8cm and 3.8 cm, respectively. Two patients received L-thyroxine while taking growth hormone, and all of them gained height growth. However, the sample data are too small to conclude whether L-thyroxine could promote the effect of growth hormone and we also could not get the right dose of growth hormone and the right treatment cycle. In 2005, Hertelt treated 35 pre-adolescent ACH children with recombinant human growth hormone (rhGH) 0.1 IU/kg or 0.2 IU/kg per day for 5 years, and found that the average growth rate increased significantly by 1.9/3.6 cm/year in the first year and 0.5/1.5 cm/year in the second year [97]. The short-term effect of rhGH on the height growth of ACH may be ideal. The growth of height and bone age of untreated ACH children are increasingly lagging behind that of children matched on age and sex [97]. Growth hormone is an important positive regulator of linear bone growth and promotes epiphyseal growth in children by stimulating hepatic production of insulin-like growth factor-1, which promotes chondrocyte growth and metabolism. One drug currently in development for the treatment of ACH is C-type natriuretic peptide (CNP), the overexpression of which in cartilage tissue is protective against chondrodysplasia [98], e.g. vasoretin. Binding of vosolide to NPR-B stimulates intracellular cyclic guanosine monophosphate (cGMP) production, which in turn inhibits the downstream signalling pathway of *FGFR3* and promotes chondrocyte proliferation, differentiation and endochondral bone formation and has been proved to restore normal bone growth in a mouse model of ACH. Several clinical trials have shown that the annual growth rate of patients with ACH has increased after treatment with the vosoritide, and no significant adverse effects were observed [99–101]. ACH can be treated surgically by limb lengthening, but high risk of postoperative complications still exists [102].

Our study has several limitations. First, in view of there were few articles that explicitly mentioned the country, the countries included in the article mainly included Asian countries such as China, Japan and Korea, but few countries in Europe and other continents. Second, 24 articles failed to find the full text and were excluded. Third, the included articles contained few treatment methods, so that we could not get the appropriate treatment scheme.

At present, there are obvious global differences in the clinical treatment of patients with achondroplasia. This variability leads to different results on the medical, functional and psychological consequences of achondroplasia. Exercise intolerance and exercise-induced fatigue are common symptoms in children with achondroplasia. The physical performance and the muscle strength of children with achondroplasia are weakened compared with that of general population [103]. The difference in body structure of ACH patients may lead directly or indirectly lead to the limitations in activity and participation, including interpersonal communication, physical performance and self-care. ACH is the most common bone dysplasia, which faces various medical and psychosocial challenges in life. We should promote the improvement and standardization of nursing methods, realize multidisciplinary management in the whole life cycle, and optimize its clinical outcome and life quality.

Acknowledgements
Not applicable.

Author contributions
XZZ performed the document retrieval, data extraction, data analysis, essay writing, and paper submission. SJ, RZ and SYG assisted in retrieving the document. QQS, KLW and YYS assisted in extracting and analysing the data. LL and JJD were corresponding author. All authors contributed to the article and approved the final manuscript.

Funding
This work was funded by the General Program of National Natural Science Foundation of China (82170824).

Availability of data and materials
All data extracted from the included studies are publicly available in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane (https://www.cochrane.org/), CNKI (https://www.cnki.net/) and WanFang (https://g.wanfangdata.com.cn/).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The review was conducted without any commercial or financial relationships that could be construed as potential conflicts of interest.

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Received: 11 August 2022 Accepted: 19 January 2024
Published online: 27 January 2024

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