Achondroplasia

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Short stature · Skeletal disorder · Sleep apnea · Endochondral ossification · Chondrocyte

14.1 Case Report

A pregnant woman was referred to the obstetrics department at a hospital because her doctor considered that her baby might have some congenital skeletal disorder. Echography of the fetus revealed that the fetal femur growth stopped at 27 weeks of gestational age and that the femur length was very short at 33 weeks (−6.7 SD). The chest of the fetus was hypoplastic. In contrast to her baby's short limbs and narrow chest, its head was large (+1.9 SD). Cephalopelvic disproportion was suspected. Therefore, her doctor chose to conduct a cesarean section.

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At 39 weeks of gestational age, a male baby was delivered by cesarean section. His Apgar scores were, respectively, 8 and 9 at 1 and 5 min. His mother (32 years old) and his father (39 years old) were non-consanguineous. Tachypnea and dyspnea were observed soon after birth. Therefore, mask bagging and oxygen supplementation were started. Physical examination showed a large head, depressed nasal bridge, and frontal bossing. His height was 46 cm (−1.4 SD). His weight was 2898 g (−0.23 SD). His head circumstance was 36.5 cm (2.3 SD), large for his stature. He had a narrow chest and short extremities. He also presented trident hand. Genitalia were of a normal male; testes were palpable in his scrotum.

Roentgenography at birth showed a small chest, hypoplasia of the iliac wing, and hypoplastic greater sciatic notches (Fig. 14.1a, b). Femurs, tibiae, humeri, ulnae, and radii were all short. The metaphyses of these bones were flared. Hydrocephalus was not identified by head CT analysis at 1 week after birth (Fig. 14.1c). The cranial base was hypoplastic (Fig. 14.1d). Foramen magnum was narrow, although compression of the cervical spinal cord was not observed. No abnormality was shown by blood examination or biochemical examination. Neonatal mass screening for congenital adrenal hyperplasia, congenital hypothyroidism, and congenital metabolic disorders all yielded negative results. Results of the physical and radiologi-

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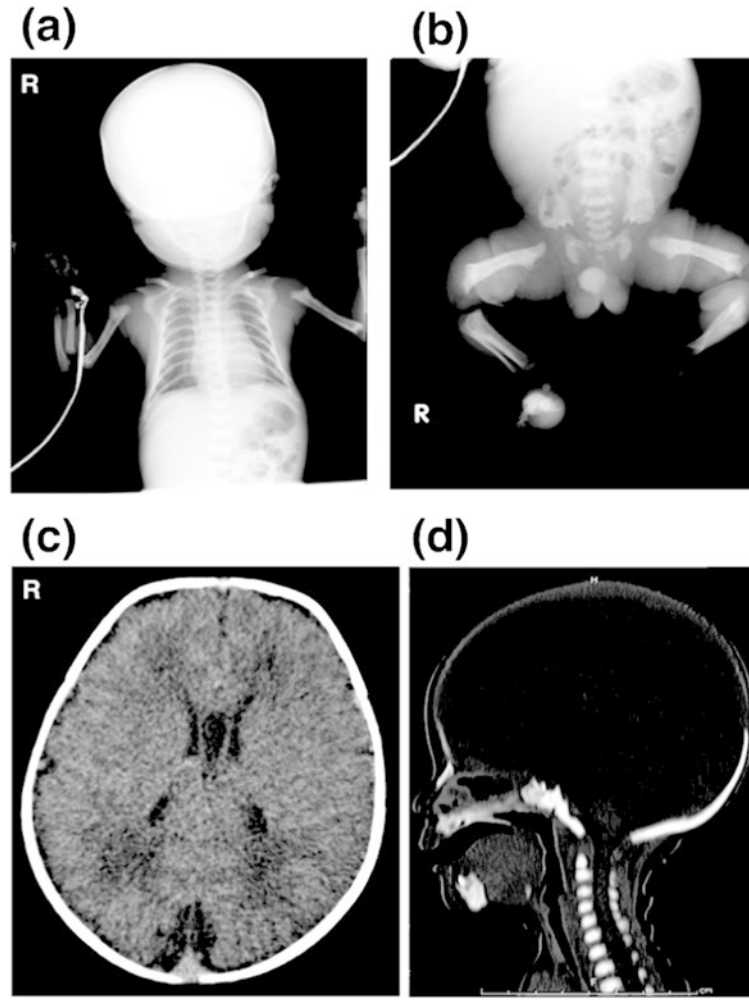

Fig. 14.1 Roentgenogram at birth (**a**, **b**) and head CT analysis at 1 week after birth (**c**, **d**). (**a**) Chest is narrow; metaphysis of the ulna and radius is flared. (**b**) Iliac wing and greater sciatic notches are hypoplastic. The femur is short and radiolucency of the femoral neck is apparent. Metaphyses in long bones of lower limbs are flared, as they are in upper limbs. (**c**) Hydrocephalus is not observed. (**d**) Foramen magnum was narrow. Cervicomedullary compression is not observed. The cranial base is hypoplastic

cal examinations described above led to his diagnosis as an achondroplasia patient.

Dyspnea improved gradually after 4 h. It was not observed again. Sucking of breast milk was not weak. He was discharged on hospital day 8. Achondroplasia results from genetic mutation of fibroblast growth factor receptor type 3 (*FGFR3*). Therefore, genetic analysis of *FGFR3* gene was conducted at 1 year of age; heterozygous nucleotide substitution of guanine at position 1138 to adenine was identified (Fig. 14.2). This substitution results in amino acid change from glycine at position 380 to arginine (p.Gly380Arg), a common genetic mutation in achondroplasia (Rousseau et al. 1994, Shiang et al. 1994, Bellus et al. 1995). His height growth after birth was stunted markedly (Fig. 14.3a), in contrast to his head growth: it gradually became larger for healthy infants. At 2 years of age, his head was large (52.5 cm: 2.0 SD) for his stature. Head MRI showed cervicomedullary compression (Fig. 14.4a). Decompression by laminectomy was necessary (Fig. 14.4b) at 2 years of age.

Because snoring and sleep apnea became severe from 2 years and 6 months old, polysomnography was conducted, which indicated obstructive sleep apnea (his apnea–hypopnea index was 34.2/h). An otolaryngologist resected adenoids and tonsils. At the time of his tonsillectomy, aeration tubes were inserted into both ears because of repeated otitis media.

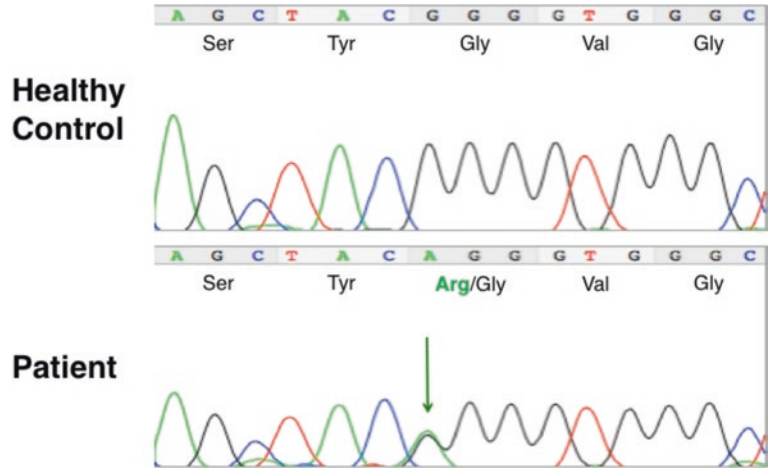

Fig. 14.2 Result of genetic analysis of *FGFR3* gene. In patient, heterozygous substitution of guanine to adenine is observed at nucleotide 1138 (arrow). This substitution results in amino acid change from glycine at 380 to arginine

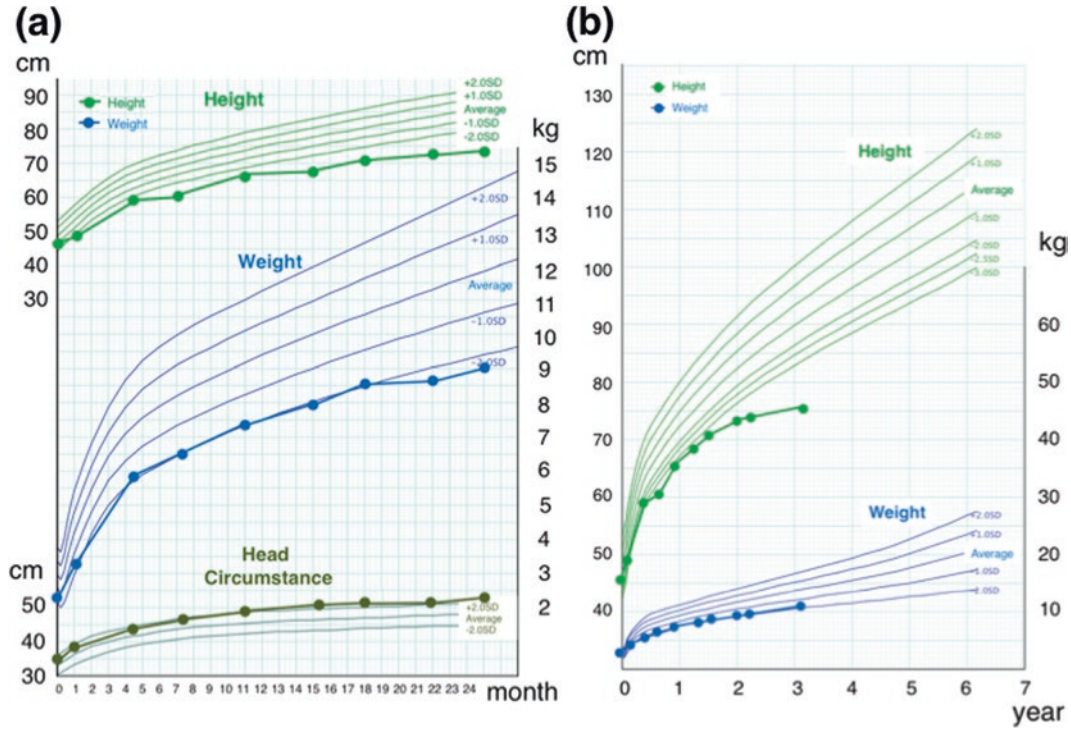

Fig. 14.3 Growth chart of patient. (**a**) Growth chart from birth to 2 years old. Height and weight growth are severely stunted while head circumstances are consistently large compared with the height and weight SD score. (**b**) Growth chart until 3 years old. Height growth is severely impaired after 3 years

His motor development before 3 years old was delayed: head control at 7 months, rolling over at 7 months, sitting alone at 12 months, standing alone at 20 months, and walking unaided at 24 months. In contrast to motor development, his neurological development was not delayed: he said one word at 11 months; he said two-word phrases at 24 months. At 3 years and 1 month old, his height was 75.8 cm (−5.2 SD). His arm span was 69.0 cm (Fig. 14.3b).

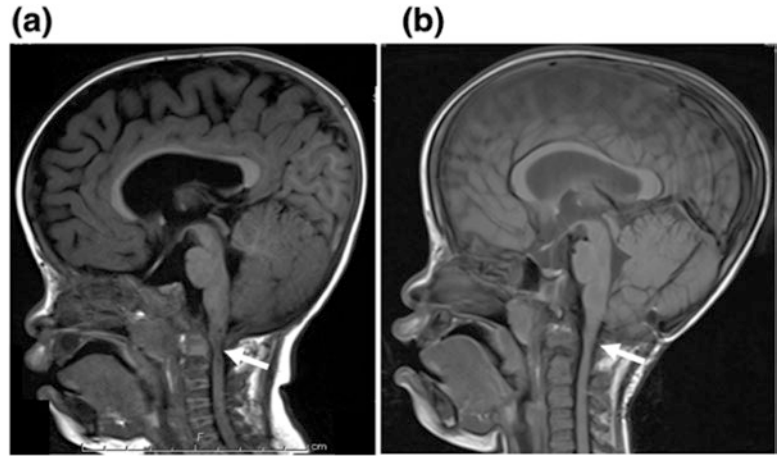

Fig. 14.4 Head MRI findings at 2 years old (T1-weighted images). (**a**) Before laminectomy. Cervicomedullary compression is observed at the foramen magnum (arrow). (**b**) After laminectomy. Compression is released (arrow).

14.2 Diagnosis

Achondroplasia, the most common congenital skeletal disorder, occurs with frequency of about 1 in 20,000. Most cases are sporadic, although some cases inherit an autosomal dominant trait. Its penetrance is 100%.

Diagnosis of achondroplasia is made mainly based on physical findings such as rhizomelic short stature, midface hypoplasia, and frontal bossing. The results of radiological examination are presented in Fig. 14.5. In some cases, diagnosis is made prenatally by ultrasound findings and 3D-CT analysis because shortening of long bones and macrocephaly are observed from the prenatal period, as in this patient.

FGFR3 gene analysis is helpful for the confirmation of clinical and radiological diagnosis because strong genotype–phenotype correlation is observed in FGFR3-related skeletal disorders described below. This patient was diagnosed as having achondroplasia from clinical findings and the heterozygous p.Gly380Arg mutation.

14.3 Biochemical and Molecular Perspectives

Bone is formed through two mechanisms: endochondral ossification and intramembranous ossification. Development of long bones such as the femur and humerus occurs through endochondral ossification. Endochondral ossification is a multistep process consisting of condensation of mesenchymal cells and proliferation of chondrocyte, differentiation to hypertrophic chondrocyte, apoptosis of hypertrophic chondrocyte, vascular invasion, and recruitment of osteoblasts. Chondrocytes in the growth plate are related to longitudinal bone growth (Fig. 14.6). These processes are regulated spatiotemporally by many hormones, growth factors, and transcription factors; expressions of chondrocyte-specific proteins also change according to the differentiation of chondrocytes. Abnormalities of these regulatory factors and chondrocyte-specific proteins produce various congenital skeletal disorders. During endochondral ossification, FGFR3 acts as "bone growth suppressor" by inhibiting chondrocyte proliferation and differentiation in the growth plate as explained below.

Fibroblast growth factor (FGF) has 22 isoforms, each of which exerts a different role through receptors of four types including FGFR3 (Brewer et al. 2016). The *FGFR3* gene is located on chromosome 4. Aside from bone, FGFR3 is expressed in various tissues such as the brain, skin, and testes. The FGFR3 molecule consists of an extracellular immunoglobulin-like domain and an intracellular tyrosine kinase domain. These two domains are connected by a transmembrane domain (Fig. 14.7). Ligand binding to FGFR3 at the extracellular domain causes dimerization of two FGFR3s and autophosphorylation at the intracellular tyrosine kinase domain, which results in subsequent signal transduction

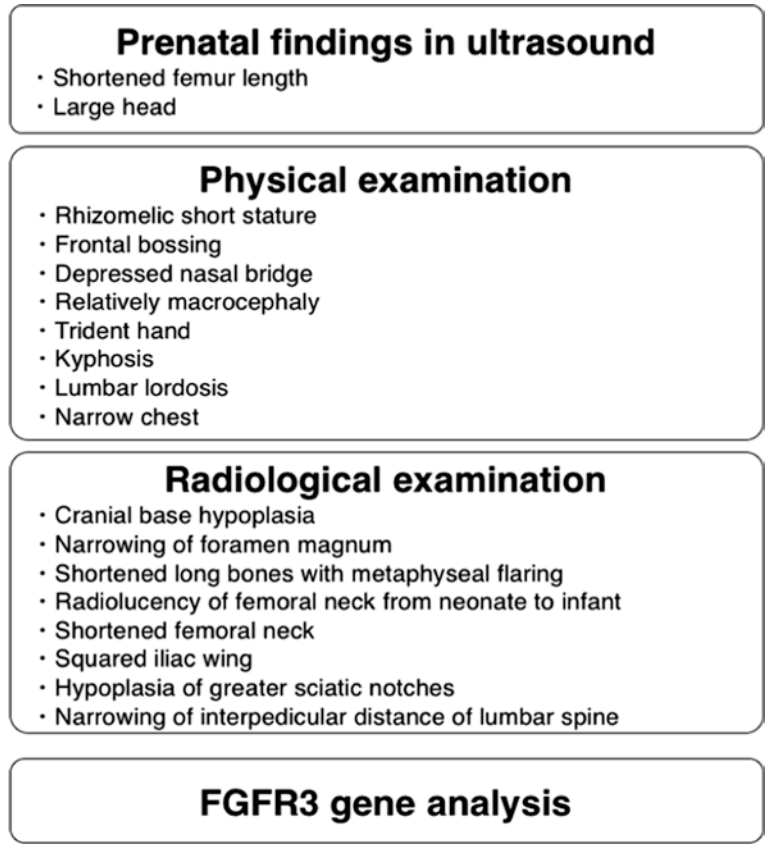

Fig. 14.5 Diagnostic procedure of achondroplasia. Diagnosis of achondroplasia is made based on the clinical and radiological information. *FGFR3* gene analysis is helpful to define the clinical diagnosis

(Horton et al. 2007). Among the FGFR3 downstream pathway, activation of signal transducer and activator of the transcription 1 (STAT1) pathway decreases chondrocyte proliferation. Mitogen-activated protein kinase (MAPK) pathways inhibit proliferation and terminal differentiation and matrix synthesis. By these functions, FGFR3 suppresses growth plate chondrocyte proliferation and differentiation and acts as a "bone growth suppressor" during the endochondral bone formation process. In fact, target deletion of FGFR3 in mouse shows overgrowth and expanded growth plate (Deng et al. 1996). Furthermore, in humans, loss-of-function mutation of FGFR3, p.Arg621His, results in CATSHL syndrome, of which the major feature includes **ca**mptodactyly, **t**all **s**tature, and **h**earing **l**oss in heterozygous state (Toydemir et al. 2006). Another mutation, p.Thr546Lys, reportedly causes tall stature, severe lateral tibial deviation, scoliosis, hearing impairment, camptodactyly, and arachnodactyly in a homozygous state (Makrythanasis et al. 2014). These two human disorders also support the fact that the function of FGFR3 is as a "bone growth suppressor."

In "nosology and classification of genetic skeletal disorders" which classifies 436 genetic skeletal disorders into 42 groups (Bonafe et al. 2015), FGFR3-related disorders group appears first of all. In this group, thanatophoric dysplasia (TD) type I and type II, **s**evere **a**chondroplasia with **d**evelopmental **d**elay and **a**canthosis **n**igricans (SADDAN), achondroplasia, hypochondroplasia, and CATSHL syndrome are involved. In other groups of this classification, some FGFR3-related disorders such as Crouzon-like craniosynostosis with acanthosis nigricans, craniosynostosis, Muenke type (craniosynostosis syndrome group), and lacrimo-auriculo-dento-digital syndrome (polydactyly-syndactyly-triphalangism group)

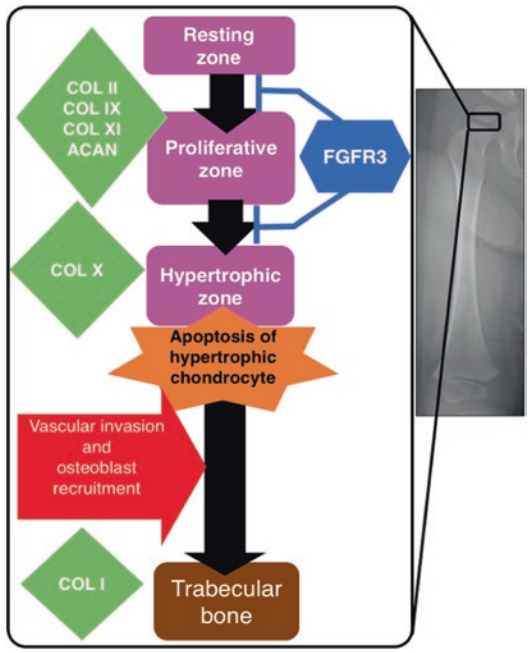

Fig. 14.6 Schematic representation of endochondral ossification in growth plate of femoral neck and action of FGFR3: *COL II* type II collagen, *COL IX* type IX collagen, *COL XI* type XI collagen, *ACAN* aggrecan, *COL X* type X collagen, *COL I* type I collagen

are involved. Each disorder shows some FGFR3 genotype–phenotype correlation (Fig. 14.7).

Actually, the p.Gly380Arg mutation in the transmembrane domain of *FGFR3* gene is found in more than 95% of achondroplasia patients. Other rare mutations such as p.Ser217Cys (Zhang et al. 2007), p.Ser279Cys (Heuertz et al. 2006), p.Ser344Cys (Takagi et al. 2015), p.Ser348Cys (Hasegawa et al. 2016), and p.Gly375Cys (Ikegawa et al. 1995) are also identified in achondroplasia patients. In p.Gly380Arg mutant FGFR3, constitutive activation of receptor occurs, producing excessive signal transduction that results in the inhibition of chondrocyte proliferation and differentiation through activation of STAT1. By activation of the ERK pathway, constitutive activation of FGFR3 also decreases chondrocyte matrix accumulation (Harada et al. 2009). This excessive signaling inhibits chondrocyte proliferation and differentiation severely and results in shortening of long bones and marked short stature. This mechanism is reproduced by a mouse model of achondroplasia (Naski et al. 1998). This mouse shows severely stunted growth and a narrow growth plate because of decreased proliferation and slowing of chondrocyte differentiation.

14.4 Clinical Features and Current Therapy of Achondroplasia

No fundamental treatment for patients with achondroplasia exists. Therapy is now designed to address the respective clinical symptoms such as short stature, neurosurgical complications, orthopedic complications, and otolaryngological complications.

Achondroplasia patients present extreme short stature because impairment of endochondral ossification causes growth disturbance of long bones. During childhood, height is about −5.0 SD. The absence of a growth spurt during puberty increases the difference from average height of healthy children. Adult height of Japanese achondroplasia patient with no treatment is about 130 cm in men (−7.0 SD) and 123 cm in women (−6.6 SD) (Tachibana et al. 1997). Not only legs but also arms become short, especially in the upper arms and femur. For that reason, achondroplasia is designated as "rhizomelic short stature" ("rhizomelic" means disproportion of the length of the proximal limbs). To treat short stature of achondroplasia, daily subcutaneous injection of recombinant human growth hormone (rhGH) was started in Japan. Short-term improvement of growth was observed (Tanaka et al. 1998), although it remains unknown how tall rhGH-treated achondroplasia patients will be as adults. Orthopedically, leg lengthening using external skeletal fixation devices such as an Ilizarov device has been conducted for the short stature treatment of achondroplasia. Infection, pain, and the long treatment duration are difficulties related to this procedure.

Impairment of endochondral ossification causes not only growth disturbance of long bones but also causes cranial base hypoplasia, which engenders hypoplasia of the foramen magnum in the occipital bone. One complication of achon-

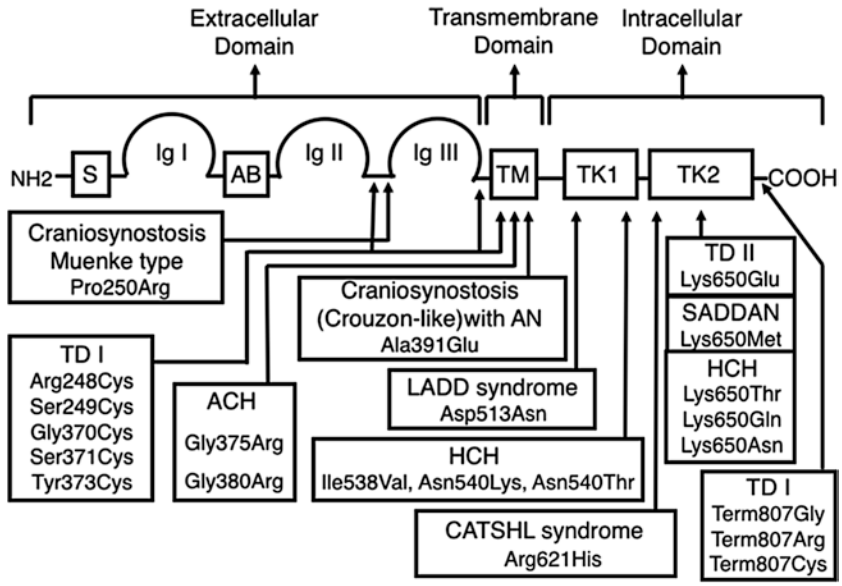

Fig. 14.7 Structural presentation of FGFR3 and representative FGFR3 mutations in FGFR3-related skeletal disorders: *NH2* amino terminal, *COOH* carboxy terminal, *S* signal sequence, *AB* acid box, *TM* transmembrane domain, *TK* tyrosine kinase domain, *Ig* immunoglobulin-like domain, *ACH* achondroplasia, *HCH* hypochondroplasia, *TD I* thanatophoric dysplasia type I, *TD II* thanatophoric dysplasia type II, *SADDAN* severe achondroplasia with developmental delay and acanthosis nigricans, *LADD* lacrimo-auriculo-dento-digital, *CATSHL* camptodactyly, tall stature, and hearing loss, *AN* acanthosis nigricans

droplasia is compression of the cervicomedullary junction caused by the foramen magnum stenosis. Cervicomedullary compression can cause sudden death and spastic paralysis. Therefore, cervicomedullary decompression by laminectomy for severe foramen magnum stenosis is necessary to release compression. Hydrocephalus is also observed occasionally in achondroplasia because narrowing of the craniocervical junction can engender increased intracranial venous pressure, which alters cerebrospinal fluid dynamics. A ventriculoperitoneal shunt is occasionally necessary for continuously worsening hydrocephalus.

Midface hypoplasia is a physical characteristic of achondroplasia. It frequently causes otolaryngological complications such as obstructive sleep apnea. Midface hypoplasia and physiological lymphoid tissue hyperplasia such as those of the tonsils and adenoids during childhood narrow the airway further. Severe airway obstruction engenders obstructive sleep apnea and subsequent life-threatening pulmonary hypertension. Narrowing of the airway also causes repetitive otitis media, which engenders persistent conductive hearing loss in adulthood if treated inappropriately.

Spinal canal stenosis can occur in achondroplasia patients from adolescence to adult because pedicles are short. The interpedicular distance is narrow compared with those of healthy subjects (Fig. 14.8a, b) and because kyphosis gradually becomes worse at the thoracolumbar junction (Fig. 14.8c, d). These orthopedic characteristics of achondroplasia engender spinal nerve compression (Fig. 14.8e), which causes bladder and rectal disturbance and intermittent claudication because of tenderness or numbness. Metaphyseal change in the femur, tibial bowing, change in bony alignment, and tendency of obesity in achondroplasia patients engender osteoarthritis of knee joints after adolescence.

Because of these various clinical features, achondroplasia patients should be managed by a multidisciplinary team from the fetal period to adulthood.

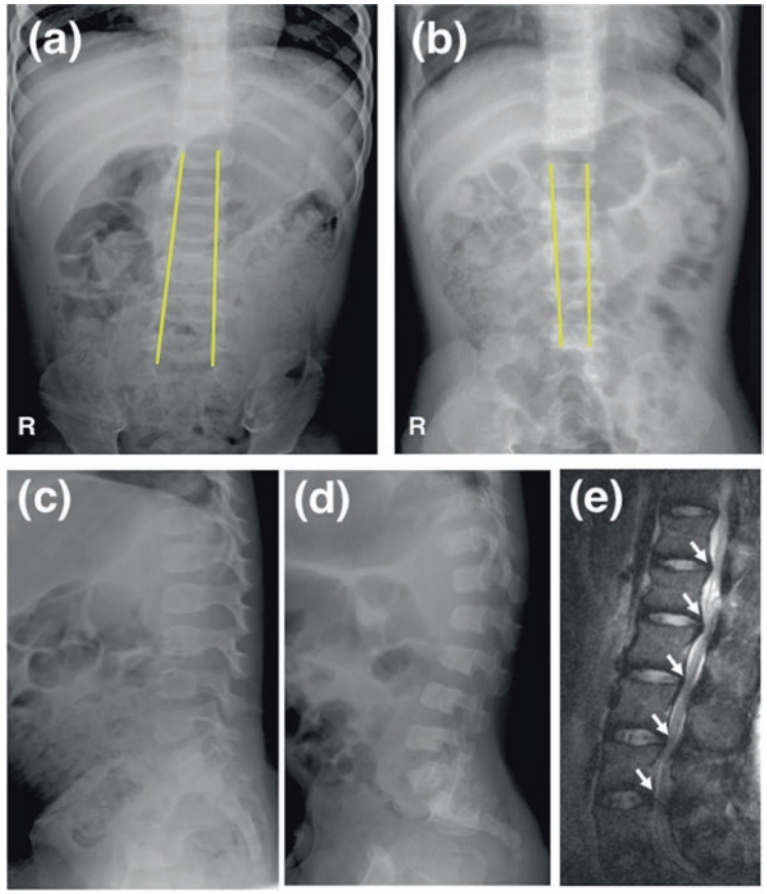

Fig. 14.8 Radiological finding of lumbar spine in a 3-year-old healthy subject (**a, c**) and 3-year-old girl with achondroplasia (**b**, **d**). Interpedicular distance (ID) of achondroplasia patient decreases from the upper to lower lumbar spine (**b**, yellow lines) in contrast to a healthy subject whose ID increases from upper to lower (**a**, yellow lines). In achondroplasia patients, pedicles are short (**d**) compared to those of healthy subject (**c**). Lordosis and gibbus might be readily apparent at the thoracolumbar and lumbosacral junction in achondroplasia patients (**d**) in contrast to healthy subject whose thoracolumbar and lumbosacral junctions are straight (**c**). (**e**) MR imaging of lumbar spine of adult patient with achondroplasia (T2-weighted image). Multiple lumbar hernias (arrow) are observed

14.5 Future Therapy Candidate of Achondroplasia

As explained above, patients with achondroplasia must cope with many complications, but no fundamental treatment exists. To find drug candidates to treat achondroplasia fundamentally, many trials are now underway.

C-type natriuretic peptide, CNP (coded by NPPC gene), belongs to the natriuretic peptide family to which atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) also belong. CNP acts through its receptor NPR2 (coded by NPR2 gene and also designated as NPRB), its second messenger cyclic GMP, and subsequent intracellular signaling. Because targeted ablation of CNP in mouse results in impaired longitudinal bone growth and severe short stature, CNP-NPR2 axis is found to be involved in endochondral ossification (Chusho et al. 2001). In humans, disorders by genetic mutation of NPR2 gene results not only in short stature but also in tall stature. Biallelic loss-of-function mutation of *NPR2* gene

results in acromesomelic dysplasia type Maroteaux (AMDM) (Bartels et al. 2004), which is characterized by extreme short stature, acromelia, and mesomelia. Mono-allelic loss-of-function mutation of *NPR2* gene results in idiopathic short stature with a family history (Vasques et al. 2013). In contrast to loss-of-function mutations of *NPR2* gene, gain-of-function mutation of *NPR2* gene results in epiphyseal chondrodysplasia, Miura type, which is characterized by extreme tall stature, scoliosis, and hallux valgus (Miura et al. 2014). These results show that CNP–NPR2 axis acts as a stimulator of endochondral ossification. Overexpression of CNP and CNP analog (Vosoritide: BMN 111) corrected the short stature phenotype of achondroplasia model mice (Yasoda et al. 2004, Lorget et al. 2012). A CNP analog is undergoing clinical trials for human patients with achondroplasia.

Statins, which inhibit the mevalonic acid pathway and which are used as lipid-lowering agents, recover the abnormal cartilage capacity of iPS cell from TD type I cell which could not generate normal cartilage and recover the skeletal phenotype of achondroplasia model mice (Yamashita et al. 2014).

Meclizine, an over-the-counter H1 receptor inhibitor, is used as an anti-motion sickness medication. By a drug repositioning strategy, this drug was found to facilitate chondrocyte proliferation and to recover extracellular matrix synthesis (Matsushita et al. 2013). As CNP and statins, meclizine also increases the longitudinal skeletal growth in achondroplasia model mice (Matsushita et al. 2015).

Through basic research, other drugs such as parathyroid hormone (Ueda et al. 2007, Xie et al. 2012), tyrosine kinase inhibitor (Jonquoy et al. 2012, Komla-Ebri et al. 2016), FGFR3-binding peptide (Jin et al. 2012), and soluble FGFR3(Garcia et al. 2013) were identified as candidate drugs for achondroplasia treatment.

End of Chapter Questions

1. What are the roles of fibroblast growth factors and their receptors in early human development?
2. What diseases, respectively, result from genetic mutations of *FGFR1*, *FGFR2*, and *FGFR4*?
3. What differences in clinical and radiological features are observed among achondroplasia, hypochondroplasia, and TD? Is there any correlation between clinical symptoms and the degree of receptor phosphorylation?
4. Except FGFR3, what factors are involved in the process of chondrocyte proliferation and differentiation in growth plate?
5. Is there any relation between parent age and achondroplasia?
6. In achondroplasia patients, are there any characteristics of motor and psychosocial development?
7. How do new drug candidates such as CNP, statin, and meclizine ameliorate the phenotype of achondroplasia model mice?

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