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Rare Short Stature Disorders in Childhood: Future Implications for Treatment and Gene Therapy Options

Stefan Bittmann [a,b++*], Elisabeth Luchter [a] and Elena Moschüring-Alieva [a]

[a] Department of Pediatrics, Ped Mind Institute, Hindenburgring 4, D-48599 Gronau, Germany.
[b] School of Medicine, Shangluo Vocational and Technical College, Shangluo, 726000, Shaanxi, China.

Authors' contributions

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

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Review Article

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Abstract

Rare childhood short stature disorders such as Achondroplasia, Hypochondroplasia, ACAN syndrome, and Noonan Syndrome are primarily caused by specific genetic mutations that disrupt normal bone growth and development. Advances in molecular diagnostics have improved early detection, while emerging gene therapy approaches—including CRISPR-Cas9—offer promising future strategies to target the underlying genetic defects. The review aims to focus on rare genetically determined dwarfism syndromes, including conditions such as achondroplasia, hypochondroplasia, ACAN syndrome, and Noonan syndrome, with a focus on their underlying genetic causes, clinical features, and diagnostic approaches. The present review was conducted using secondary sources derived from existing academic literature, including peer-reviewed journal articles, books, and conference proceedings. Achondroplasia, the most common form of dwarfism, and hypochondroplasia are primarily caused by activating mutations in the FGFR3 gene, leading to impaired

[++]Honorary Professor (Hon.Prof.);
**Corresponding author: Email: stefanbittmann@gmx.de;*

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endochondral ossification. In contrast, ACAN mutations affect cartilage structure and growth plate function, while Noonan syndrome involves mutations in genes of the RAS/MAPK signaling pathway, such as PTPN11. Gene therapy, including genome editing technologies such as CRISPR-Cas9, offer a prospective avenue for causal treatment by targeting the underlying genetic defects. Early detection through advanced genetic screening, potentially even prenatally, may further enhance therapeutic outcomes. This review highlights the growing potential of gene-based interventions while emphasizing the need for continued research to translate these approaches into safe and effective clinical applications.

Keywords: Short stature; children; gene therapy; achondroplasia.

1. Introduction

Rare dwarfism syndromes are genetically determined disorders that often present with proportional or disproportional short stature, skeletal abnormalities, or facial dysmorphisms. Examples include achondroplasia, hypochondroplasia, ACAN syndrome, Noonan syndrome. Diagnosis is usually made through genetic testing. The causes are diverse, ranging from chromosomal aberrations to specific gene mutations, such as in idiopathic short stature. Many of these syndromes require specialized medical care, often by endocrinologists and geneticists. Some of these short stature syndromes are possible candidates for gene therapy options, which we discuss in detail in this review.

2. Achondroplasia

Achondroplasia is the most common form of genetically inherited dwarfism (Pahuja et al., 2026; Mei 2026). Affected individuals are characterized by significantly shortened arms and legs and a large head (Mei 2026, Hosny 2026, Horike 2026). The term achondrodysplasia was coined by the French physician Joseph Marie Jules Parrot in 1878. Achondroplasia is purely historical and does not explain the cause or manifestations of this disorder. Other designations, which are outdated and no longer in use, include chondrodystrophy, chondrodystrophia fetalis, Parrot syndrome, or Kaufmann syndrome (referring to the German pathologist Eduard Kaufmann). Achondroplasia is the most common genetically inherited form of dwarfism in most countries (Pahuja 2026, Mei 2026). It occurs with an incidence of 1 in 20,000 births (Pahuja et al., 2026; Mei 2026, Horike 2026). Therefore, like all types of dwarfism, it is considered a rare disease. Achondroplasia is a disorder of enchondral ossification, which is the bone growth that occurs in the growth plates of the long bones of the extremities and accounts for a significant portion of body height. This results in significantly shorter long bones, while other bones formed by desmal ossification, such as most trunk bones, are not affected. This leads to disproportionate dwarfism, where the trunk and head are relatively longer than the extremities.

In 1994, Le Merrer discovered that a mutation in the fibroblast growth factor receptor gene FGFR-3 is responsible for achondroplasia. This mutation is almost always an activating point mutation. In 96% of cases, there is a G(1138)A point mutation in the FGFR-3 gene, resulting in an amino acid exchange at position 380 of the protein, changing glycine to arginine (Gly380Arg) (Pahuja et al., 2026; Mei 2026; Sano 2026). In 3% of cases, a G(1138)C point mutation is found, which also leads to a glycine-to-arginine exchange. The FGF receptor 3 (FGFR3) is a cell membrane protein and a tyrosine kinase that is activated by phosphorylation (Ping 2026, Fava 2026, Bittmann 2025). FGFR3 is a negative regulator of chondrocyte proliferation and cell differentiation in the growth plates, and it also inhibits the synthesis of the extracellular cartilage matrix. An activating mutation of FGFR3 leads to increased inhibition of chondrocytes and reduced cartilage matrix formation, resulting in decreased ossification. Intracellular signal transduction from FGFR3 occurs through the STAT1 signaling pathway and the MAPK signaling pathway. Achondroplasia is inherited in an autosomal dominant manner, meaning it can only be passed on by individuals who are affected themselves. This is the case in about 20% of children born with achondroplasia. In the remaining approximately 80%, there is a de novo mutation in the FGFR3 gene, meaning dwarfism occurs independently of the parents' size. Embryos with a homozygous mutation (both the paternal and maternal variants of the gene are altered) are not viable and die shortly after birth or in utero. Treatment options include Vosoritide, a CNP analogon, Pan-FGFR3 inhibitors like infigratinib (Phase III) and highly selective FGFR3-tyrosine kinase inhibitors like TYRA-300 (dabogratinib) or LOXO-435 (vepugratinib) (Bittmann 2025). An ongoing phase 2 study reveals the efficacy, gain height and possible toxic side effects of TYRA-300 in a multicenter study and could be the future to “treat” achondroplasia patients in the future (Bittmann 2025). Due to its monogenetic origin and a point mutation achondroplasia could

be an optimal option to develop a one-time gene therapy approach for the future to cure the children with achondroplasia.

3. Hypochondroplasia

Hypochondroplasia (HCH) is a form of disproportionate dwarfism caused by a genetic mutation that slows down the growth of long bones. The symptoms are similar to achondroplasia but less pronounced. Hypochondroplasia is estimated to occur in one out of 30,000 newborns, making it a rare condition. The frequency is difficult to determine precisely because milder cases of hypochondroplasia are hard to distinguish from constitutional dwarfism. Individuals with hypochondroplasia have shortened arms and legs in proportion to the trunk, although this is less noticeable than in a chondroplasia. Other symptoms are similar to achondroplasia but milder. Hyperlordosis and leg deformities (usually bowlegs) are common. The hands are usually broad with short fingers. In many cases, the elbows are not fully extendable, but the knees and wrists can be hyperextended. Children may have mild muscle hypotonia in the early years, which usually does not significantly affect motor development. Adults with hypochondroplasia typically reach a height of 130 to 155 cm. Surgical correction may be necessary to address leg deformities. Children with hypochondroplasia may experience chronic middle ear infections due to the reduced skull base. In rare cases, infants with severely narrowed foramen magnum may require surgical enlargement to relieve pressure on the spinal cord, which can cause neurological deficits and apnea. Another rare complication is spinal canal stenosis in adults due to a narrowed spinal canal in conjunction with severe lordosis of the lumbar spine. In nearly 70% of patients diagnosed with hypochondroplasia based on symptoms, point mutations in the FGFR3 gene can be identified. For the remaining patients, it is assumed that there is another very similar form of dwarfism with an unknown cause. The FGFR3 gene is located on chromosome 4, gene locus 4p16.3. It regulates the growth of cartilage cells. Mutations in this gene inhibit cartilage development in growth plates, leading to slower growth of long bones responsible for lengthening. Hypochondroplasia is inherited in an autosomal dominant manner, meaning it can only be passed on by affected individuals themselves. In other cases, the mutation of the FGFR3 gene occurs spontaneously during embryo formation, independent of parental size. The most common point mutations are C(1659)A and C(1659)G, both resulting in an amino acid substitution in the FGFR3 protein at position 540 from asparagine to lysine. Children with hypochondroplasia are typically of normal size at birth, and their growth is only slightly disproportionate, making dwarfism less noticeable. Affected children gradually fall behind their peers in growth, with shortened arms and legs in proportion to the trunk and an unusual gait. Therefore, the diagnosis is usually made after learning to walk or even later. Diagnostic tests often involve ruling out other causes of dwarfism through blood tests and determining bone age by X-raying the left hand. The diagnosis of hypochondroplasia is based on growth patterns, additional X-rays of the legs and spine, and sometimes genetic analysis of the FGFR3 gene. Conditions to differentiate from include mild forms of mesomelic dysplasia, spondyloepimetaphyseal dysplasia, Léri-Weill dyschondrosteosis, pseudohypoparathyroidism, pseudopseudohypoparathyroidism, and Schmid-type metaphyseal chondrodysplasia.

4. Aggrecanopathies (ACAN)

ACAN gene mutations affect the Aggrecan gene, which is essential for cartilage formation (Pattani 2026, Trigui 2025). In humans, they lead to familial short stature, accelerated bone maturation, joint problems, and premature osteoarthritis (Trigui, 2025). The ACAN gene encodes the protein Aggrecan, which is responsible for the elasticity and function of cartilage in joints and growth plates (Pattani, 2026; Trigui, 2025). Mutations lead to skeletal dysplasias, such as spondyloepiphyseal dysplasia (Kimberley type), as well as idiopathic short stature. Affected individuals often show advanced bone maturation in childhood, leading to early growth cessation and reduced adult height (Pattani, 2026; Sentchordi-Montane et al., 2021, 2025; Farrell & Sura, 2024). Early osteoarthritis and osteochondritis dissecans are also common (Xu 2024, Ahmed et al., 2024, Renes 2024, Karatas, 2023; Huang, 2023; Ochoa, 2023).

5. Noonan Syndrome

Noonan syndrome is a genetic disorder characterized by a variety of genetic developmental abnormalities (Celik 2026). The resulting deformities can affect the external appearance as well as internal organs. *Congenital heart defects* are typical (Celik, 2026; Kim et al., 2026). Since the observable symptoms are very similar to those of Ullrich-Turner syndrome, Noonan syndrome is also referred to as "Pseudo-Turner syndrome" or "Male-Turner syndrome". However, unlike Ullrich-Turner syndrome, no chromosomal abnormalities are detectable. The term "Noonan syndrome" is named after the American pediatric cardiologist Jacqueline Noonan, who first described

the syndrome in 1963 and in detail in 1968. In half of the people with Noonan syndrome, mutations in the PTPN-11 gene, located on the long arm of chromosome 12, are present (Celik 2026, Cossettini 2026, Dauber 2025). This gene is responsible for a protein (SHP-2) that plays a central role in growth regulation and influences a variety of metabolic and growth processes (Kim et al., 2026; Um, 2025; Pescini, 2025). Many of these processes are regulated through the activation of the mitogen-activated protein kinase cascade (MAP kinase pathway). Other affected genes include the SOS1 and KRAS genes. Mutations in the protein kinase RAF1, which is at the top of the MAP kinase pathway, have also been found in Noonan patients. It is expected that additional responsible genes in the MAP kinase pathway will be identified for the remaining cases (Gazzin 2026, Roberts 2001/2025, Peng, 2025). Approximately 50% of cases are sporadic, meaning that parents of affected children are not carriers of Noonan syndrome themselves. In the remaining cases, Noonan syndrome is inherited, with the inheritance pattern of the gene mutation being autosomal dominant. This means that the likelihood of children inheriting the syndrome from an affected parent is 50%. Transmission usually occurs through the mother (3:1), as males with Noonan syndrome are usually infertile (Nazarie 2025, Coveney 2025, Perla 2025). Noonan syndrome is relatively common, with estimates of frequency ranging from 1:500 to 1:2500 (Celik 2026). In Germany, approximately 80,000 individuals are affected. The syndrome affects both genders equally and is the second most common genetic cause, after Down syndrome, that leads to the occurrence of a heart defect (Corso 2026, Peng 2025). The diverse manifestations of Noonan syndrome make clinical diagnosis challenging. Many of the milder cases may never be diagnosed. Molecular genetic testing of the PTPN-11 gene can now be used to confirm the suspected diagnosis. However, only about 50% have the sought-after mutation. The analysis of the gene in parents also allows for a better assessment of the risk for subsequent pregnancies. Prenatal diagnosis is also possible in cases of specific suspicion through prenatal diagnostics such as amniocentesis. Differential diagnoses include cherubism and other RASopathies such as cardio-facio-cutaneous syndrome, as well as Costello syndrome. Due to the misinformation on the affected gene, various symptoms and conditions are triggered. Not all features occur in all children and with increasing age, the symptoms become less pronounced. This makes a definitive diagnosis even more challenging. Many symptoms resemble those of Ullrich-Turner syndrome. These include short stature, which is less pronounced in Noonan syndrome, a low hairline at the neck, and occasionally pterygium colli or "webbed neck". Only symptomatic treatment of Noonan syndrome is possible, such as surgical correction of heart defects or pterygium, wearing glasses or hearing aids, speech therapy for speech disorders, or hormone therapy for short stature. There is currently no causal treatment for a cure. While the majority of individuals with Noonan syndrome have an average IQ, nearly 25% have mild cognitive impairment (IQ between 69 and 82). The most common learning difficulty in children with Noonan syndrome is difficulty in verbal reasoning. No specific behavioral pattern has been identified, although affected individuals often show signs of clumsiness, stubbornness, and irritability.

6. Discussion

Dwarfism, or short stature in humans, is a term used to describe a reduced body length growth that does not correspond to the average, and can be caused by a variety of congenital or acquired growth disorders. Approximately 100,000 people with dwarfism live in Germany, and around 10,000 in Austria. A significantly below-average growth in length is referred to as dwarfism in medicine. The former medical term "stunted growth" is no longer used due to its negative connotation. Similarly negatively connoted terms like "dwarf" or "midget" are sometimes used colloquially, although some affected individuals find them discriminatory. In adults, dwarfism means a height of under 150 cm (male) or 140 cm (female). Extreme dwarfism (previously referred to as dwarfism or nanosomia) results in a height of under 130 cm in adulthood. This definition may vary slightly from country to country. In medical terms, dwarfism in children is present when their height does not reach the third percentile of the growth curve for their age or falls more than two standard deviations below the mean, meaning that only 3% of peers are smaller. However, in most cases, this dwarfism does not have pathological significance, as healthy children can fall below these limits. Therefore, the child's growth development over time is more important. Their growth should follow the percentiles and not cross them downwards. There are about 450 different forms of dwarfism known, and the possible causes of dwarfism are very diverse. Some forms of dwarfism are established before birth (primary dwarfism), such as skeletal dysplasias or inadequate nutrition during pregnancy. Other forms of dwarfism develop later (secondary dwarfism), such as growth hormone deficiency or chronic illnesses. In diagnostics, it is more common to differentiate whether growth is proportionate or disproportionate, meaning there is an abnormal ratio between the head, trunk, and limbs. In familial dwarfism, the parents of the affected individual are also short, and the child's final height falls within the range expected based on the parents' height. Additionally, there are ethnic groups where the average height of men is below 150 cm, resulting in natural dwarfism. Constitutional delay of

growth involves delayed bone maturation and a delayed onset of puberty. It often occurs in families. Boys are twice as likely to be affected as girls. In these cases, normal height can be achieved, just with a delay. Individuals are very small at birth due to various factors during pregnancy. Most children can catch up on the growth delay, but some remain short-statured. In conditions like Turner syndrome, where individuals have only one functional sex chromosome, dwarfism is just one of many features. People with Down syndrome may also be short-statured at times. Syndromes like Noonan syndrome, Silver-Russell syndrome, or Prader-Willi syndrome are complex conditions where dwarfism is just one symptom among many. Skeletal dysplasias involve a general disorder of cartilage or bone growth. There are numerous skeletal dysplasias, most of which are associated with disproportionate dwarfism. The most common skeletal dysplasia and the most common form of dwarfism overall is achondroplasia. Other examples include spondyloepiphyseal dysplasia and diastrophic dysplasia. Malnutrition in children can lead to growth retardation. Growth delay can be caused by chronic illnesses like heart or liver diseases. Some growth disorders are due to hormonal imbalances like growth hormone deficiency, diabetes mellitus, or thyroid dysfunction. These disorders are usually treatable, allowing affected children to reach a normal final height. In phosphate diabetes, the body excretes too much phosphate, affecting bone growth and causing disproportionate dwarfism. Other metabolic disorders, such as protein or lipid metabolism disorders, can also cause dwarfism. Dwarfism can also have psychosocial causes, including psychosocial deprivation and depression.

Medical therapies that heavily burden the body, such as radiation therapy, chemotherapy, or high-dose glucocorticoid therapy, can also cause dwarfism.

Table 1. Different types of short stature disorders with Gene locus, Therapy to date and Future Perspectives

Type of Short stature disorder	Gene defect	Therapy to date	Future perspectives
Achondroplasia	Chromosome 4p16.3 „Gain of Function“-Point Mutation FGFR3 Gen Autosomal dominant	Vosoritide (Voxzogo) Surgical Interventions Neurosurgery	Gene therapy option CRISP Cas9-technology Selective FGFR3-inhibitors (TYRA-300, LOXO-435)
Hypochondroplasia	Chromosome 4p16.3 Gain of Function-Point Mutation FGFR3 Gene Autosomal dominant	Symptomatic	Vosoritide (Voxzogo)
Aggrecanopathies (ACAN)	Chromosome 15q26.1 ACAN gene Pathogenic variants are heterozygous	Symptomatic	None on short term
Noonan Syndrome	Chromosome 12q24.13 PTPN11-Gene (SOS1/RAF1/RIT1/KRAS/LZTR1/NRAS-gene) **Autosomal dominant**	Symptomatic (surgical correction of heart defects or pterygium, wearing glasses or hearing aids, speech therapy for speech disorders, or hormone therapy for short stature)	None on short term

7. Conclusion

Gene therapeutical options play an important in the treatment of short stature disorders as many years before and will become the future to cure rare genetic diseases. Especially in monogenetic diseases, like achondroplasia,

the future could be a cure of the disease by mutational repair on DNA/RNA level. Aware that the mutation and the change on DNA/RNA appears normally prenatally, future aspects of treatment must include prenatal whole genome sequencing with early detection of the early defect to cure it as early as possible by gene therapy options like CRISP Cas 9 technology, gene silencing or in special cases exone skipping methods. Despite many limitations in the field of gene therapy, difficulties to just repair the gene defect but not cut any other "healthy" regions on genetic level, is of upmost importance. Furthermore, to date, nobody knows exactly, at which time the gene therapy approach should be performed and how long the repair will then be prominent, or, if more than one approach is necessary to get the result you want over long time. A clear differentation must be made from *treating a child* and *curing a child*, and this means putting all efforts into the research of new gene therapy options in monogenetic short stature disorders in childhood.

Consent

It is not applicable.

Ethical Approval

It is not applicable.

Disclaimer (Artificial Intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

Competing Interests

Authors have declared that no competing interests exist.

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