JIG Journal of Interdisciplinary Genomics

https://doi.org/10.22742/JIG.2026.8.2.36
Journal of Interdisciplinary Genomics 2026;8(2):36-44
eISSN 2671-6771

Genes Associated with Short Stature: An Update

Jung-Eun Moon

Department of Pediatrics, School of Medicine, Kyungpook National University, Kyungpook National University Children's Hospital, Daegu, Korea

Short stature is one of the most common reasons for referral to pediatric endocrinology clinics. In many children, no cause is identified, and they are classified as having idiopathic short stature (ISS). With recent advances in genetic testing, however, a growing number of these children are found to have monogenic defects. Linear growth is driven by chondrocyte proliferation, hypertrophy, and extracellular matrix production in the growth plate, and genetic variants that disrupt these processes impair growth. The affected mechanisms include endocrine signaling through the growth hormone (GH)–insulin-like growth factor I (IGF-I) axis; paracrine signaling and transcriptional regulation within the growth plate (*SHOX, FGFR3*, and *NPR2*); the cartilage extracellular matrix (*ACAN*); intracellular signaling (the RAS/MAPK pathway); fundamental cellular processes such as DNA replication and centrosome function; and genomic imprinting. Each mechanism is associated with a characteristic clinical pattern of birth size, body proportions, bone age, and biochemical findings. An accurate genetic diagnosis establishes the cause of growth failure, provides information on prognosis and associated risks, predicts the response to GH therapy, and enables genetic counseling. Mechanism-based therapies, such as C-type natriuretic peptide analogs for achondroplasia, are now entering clinical practice. In conclusion, the integration of clinical, biochemical, and genetic information according to the underlying cellular mechanisms is essential for the accurate diagnosis and management of children with short stature.

Key words: Body height, Growth plate, Growth disorders, Genetic testing

REVIEW ARTICLE

Received: October 6, 2026
Revised: October 20, 2026
Accepted: October 26, 2026

Correspondence to: Jung-Eun Moon, MD, PhD
Department of Pediatrics, School of Medicine, Kyungpook National University, Kyungpook National University Children's Hospital, 807 Hoguk-ro, Buk-gu, Daegu 41404, Korea
Tel: +82-53-200-5704
Fax: +82-53-425-6683
E-mail: subuya@knu.ac.kr

ORCID
https://orcid.org/0000-0001-9786-7898

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INTRODUCTION

Short stature is defined as a height more than 2 standard deviations (SD) below the mean for age and sex. It is one of the most common reasons for referral to pediatric endocrinologists [1]. Short stature has traditionally been classified according to its underlying etiology or clinical presentation, including growth hormone (GH) deficiency, chromosomal abnormalities, skeletal dysplasias, syndromic conditions, small for gestational age (SGA) without catch-up growth, and idiopathic short stature (ISS). However, the cause of growth failure remains unidentified in most children evaluated for short stature [2]. In this review, SGA refers to a birth weight and/or length below −2 SD for gestational age, whereas intrauterine growth restriction (IUGR) refers to a pathological process of restricted fetal growth; the two terms are therefore not used interchangeably [3].

Human height is a highly heritable trait. Common variants at hundreds of loci each exert a small effect, whereas rare variants in single genes can cause marked growth failure [1,4]. Next-generation sequencing, including gene panels and exome sequencing, has identified monogenic causes in a considerable proportion of children previously classified as having ISS or familial short stature [3,4]. However, the diagnostic yield depends strongly on the clinical phenotype. In a 2026 systematic review, the diagnostic yield of exome sequencing was 15.1% in isolated short stature and 50.8% in syndromic short stature [5]. These figures therefore cannot be applied uniformly to all children with ISS, and the yield is highest in

children with severe short stature, dysmorphic features, or skeletal abnormalities [5]. In the same year, the first international guideline on genetic testing in children with short stature was published [3].

A mechanism-based classification is now widely used. This approach places the growth plate chondrocyte at the center and classifies genetic defects according to where they disrupt chondrocyte function [1]. In this review, we summarize established genes and syndromes associated with short stature according to their underlying cellular mechanisms, together with recently implicated genes and the strengths and limitations of current genetic testing. Gene and variant nomenclature follows the Human Genome Variation Society (HGVS) recommendations, and variant terminology follows the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines.

GROWTH PLATE BIOLOGY

Linear growth occurs at the growth plate, a thin layer of cartilage located near the ends of long bones. The growth plate consists of three zones: the resting zone, the proliferative zone, and the hypertrophic zone [6]. Resting chondrocytes give rise to proliferative chondrocytes, which divide rapidly and form columns parallel to the long axis of the bone. These cells then enlarge into hypertrophic chondrocytes and secrete extracellular matrix. Finally, blood vessels and bone cells invade the hypertrophic zone, and the cartilage is remodeled into bone tissue [6].

Chondrocyte function is regulated at multiple levels. Endocrine factors include GH, insulin-like growth factor I (IGF-I), thyroid hormone, glucocorticoids, and sex steroids. Paracrine factors include C-type natriuretic peptide (CNP), fibroblast growth factors (FGFs), Indian hedgehog (IHH), parathyroid hormone-related protein (PTHrP), and bone morphogenetic proteins [1,6]. The cartilage extracellular matrix provides a structural and signaling environment for chondrocytes. In addition, intracellular processes common to all cells, such as DNA replication, cell cycle regulation, and centrosome function, are essential for chondrocyte proliferation. A defect at any of these levels can reduce growth plate output and cause short stature [1]. Clinical characteristics of short stature according to genetic defects are described in Table 1.

DEFECTS IN THE GH–IGF-I AXIS

GH secreted from the pituitary gland binds to the GH receptor (GHR) and activates the JAK2–STAT5B pathway. This induces hepatic and local IGF-I production. IGF-I circulates in a ternary complex with IGF-binding protein 3 (IGFBP-3) and the acid-labile subunit (ALS). IGF-I is released from this complex by proteases such as pregnancy-associated plasma protein A2 (PAPP-A2) and acts on chondrocytes through the IGF-I receptor (IGF1R) [1,2]. Defects at each step produce distinct biochemical profiles.

GH SYNTHESIS DEFECT: *GH1* VARIANTS (OMIM #262400, ISOLATED GH DEFICIENCY TYPE IA; OMIM #173100, ISOLATED GH DEFICIENCY TYPE II)

The *GH1* gene is located on chromosome 17q23. Isolated GH deficiency (IGHD) type IA is an autosomal recessive disorder caused by homozygous deletion of *GH1*. Affected children show severe growth failure from early infancy and may develop anti-GH antibodies during GH treatment. IGHD type II is inherited in an autosomal dominant manner and is mainly caused by splice-site variants that lead to skipping of exon 3. The resulting 17.5-kDa GH isoform exerts a dominant-negative effect on normal GH secretion [2]. Defects in pituitary transcription factors, such as *POU1F1* and *PROP1*, cause combined pituitary hormone deficiency, including GH deficiency [2].

Phillips et al. [7] first identified *GH1* gene deletions in patients with familial IGHD in 1981.

GH RECEPTOR DEFECT: *GHR* VARIANTS (OMIM #262500, LARON SYNDROME)

Laron syndrome is caused by homozygous or compound heterozygous variants in the *GHR* gene on chromosome 5p13. It is characterized by severe postnatal growth failure, midface hypoplasia, and truncal obesity. Serum GH levels are normal or elevated, whereas IGF-I, IGFBP-3, and ALS levels are markedly low. GH-binding protein is usually low or absent but may be normal when variants affect the transmembrane or intracellular domain [2,4]. Patients do not respond to GH therapy, and recombinant human IGF-I (rhIGF-I) is the treatment of choice.

Godowski et al. [8] first demonstrated a partial deletion of the *GHR* gene in patients with Laron syndrome in 1989.

Table 1. Clinical characteristics of short stature according to genetic defects

Gene	Cellular mechanism	Disorder	Inheritance	Birth size	Key clinical and biochemical clues	Growth-promoting therapy
GH1	GH synthesis	IGHD type IA, type II	AR (type IA); AD (type II)	Normal	Low stimulated GH, low IGF-I	GH effective
GHR	GH receptor	Laron syndrome	AR	Normal	Elevated GH, very low IGF-I and IGFBP-3	rhIGF-I
STAT5B	GH signal transduction	GH insensitivity with immune dysregulation	AR	Normal	Normal or elevated GH, low IGF-I, immune dysregulation, elevated prolactin	rhIGF-I
IGFALS	IGF-I complex stabilization	ALS deficiency	AR	Normal	Very low IGF-I and IGFBP-3, mild short stature	Limited GH response
PAPPA2	Release of IGF-I from IGFBPs	Short stature, Dauber-Argente type	AR	Normal	Elevated total IGF-I, IGFBP-3, and ALS; low free IGF-I	rhIGF-I (limited data)
IGF1	IGF-I production	IGF-I deficiency	AR	SGA	Microcephaly, hearing loss, intellectual disability	rhIGF-I
IGF1R	IGF-I receptor	IGF-I resistance	AD; rarely AR	SGA	Microcephaly, normal or elevated IGF-I	Partial GH response
SHOX	Chondrocyte transcriptional regulation	Léri-Weill dyschondrosteosis, ISS; Langer mesomelic dysplasia	Pseudoautosomal dominant (LWD, ISS); pseudoautosomal recessive (Langer)	Normal	Mesomelia, Madelung deformity	GH effective
FGFR3	Paracrine inhibition of chondrocytes	Achondroplasia, hypochondroplasia	AD (mostly *de novo*)	Normal	Rhizomelia, macrocephaly	Vosoritide (achondroplasia)
NPR2	CNP signaling	Acromesomelic dysplasia; SNSK	AR (acromesomelic dysplasia); AD (SNSK)	Normal	Short metacarpals, mild disproportion	Variable GH response
NPPC	CNP production	Autosomal dominant short stature	AD	Normal	Mild short stature, small hands	CNP analogs under investigation
IHH	IHH–PTHrP feedback loop	SNSK, brachydactyly type A1; acrocapitofemoral dysplasia	AD (SNSK, BDA1); AR (acrocapitofemoral dysplasia)	Normal	Mild disproportion, short middle phalanx of the fifth finger	GH (observational data)
ACAN	Cartilage extracellular matrix	Short stature with advanced bone age	AD	Normal or mildly reduced	Advanced bone age, early growth cessation, early-onset osteoarthritis	Some GH response
PTPN11	RAS/MAPK signaling	Noonan syndrome 1	AD	Normal	Characteristic facies, pulmonary valve stenosis, cardiomyopathy	GH effective
CUL7	Ubiquitin ligase, cell cycle	3-M syndrome 1	AR	SGA	Relative macrocephaly, normal intelligence, slender long bones	Poor GH response
ATR	DNA damage response	Seckel syndrome 1	AR	SGA	Severe microcephaly, intellectual disability	Poor GH response
PCNT	Centrosome function	MOPD II	AR	SGA	Microcephaly, cerebrovascular disease, insulin resistance	Poor GH response
ORC1 and others	DNA replication licensing	Meier-Gorlin syndrome	AR	SGA	Microtia, absent or hypoplastic patellae	Variable GH response
11p15 ICR1, UPD7	Genomic imprinting	Silver-Russell syndrome	Mostly sporadic	SGA	Relative macrocephaly at birth, body asymmetry, feeding difficulties	GH effective

AD, autosomal dominant; ALS, acid-labile subunit; AR, autosomal recessive; BDA1, brachydactyly type A1; CNP, C-type natriuretic peptide; GH, growth hormone; ICR1, imprinting control region 1; IGF-I, insulin-like growth factor I; IGFBP, IGF-binding protein; IGHD, isolated GH deficiency; IHH, Indian hedgehog; ISS, idiopathic short stature; LWD, Léri-Weill dyschondrosteosis; MAPK, mitogen-activated protein kinase; MOPD II, microcephalic osteodysplastic primordial dwarfism type II; PTHrP, parathyroid hormone-related protein; rhIGF-I, recombinant human IGF-I; SGA, small for gestational age; SNSK, short stature with nonspecific skeletal abnormalities; UPD7, maternal uniparental disomy of chromosome 7.

GH SIGNAL TRANSDUCTION DEFECT: *STAT5B* VARIANTS (OMIM #245590, GROWTH HORMONE INSENSITIVITY WITH IMMUNE DYSREGULATION)

STAT5B is the key intracellular mediator of GH-induced IGF-I transcription. Biallelic *STAT5B* variants on chromosome 17q21 cause severe postnatal growth failure with normal or elevated GH levels but low IGF-I, IGFBP-3, and ALS levels. Because STAT5B also mediates cytokine signaling, the condition is accompanied by immune dysregulation, including eczema, recurrent infections, lymphocytic interstitial pneumonia, and autoimmune disease. Elevated prolactin is another characteristic finding [9].

Kofoed et al. [9] first described a homozygous *STAT5B* variant in a patient with GH insensitivity in 2003.

IGF-I COMPLEX STABILIZATION DEFECT: *IGFALS* VARIANTS (OMIM #615961, ACID-LABILE SUBUNIT DEFICIENCY)

ALS stabilizes the IGF-I–IGFBP-3 ternary complex and prolongs the half-life of circulating IGF-I. Biallelic variants in the *IGFALS* gene on chromosome 16p13.3 cause marked reductions in serum IGF-I and IGFBP-3 that are disproportionately low relative to the degree of growth failure. Height is usually only mildly reduced, at approximately −2 to −3 SD, and delayed puberty and insulin resistance are common [10].

Domené et al. [10] first reported pathogenic *IGFALS* variants in 2004.

IGF-I BIOAVAILABILITY DEFECT: *PAPPA2* VARIANTS (OMIM #619489, SHORT STATURE, DAUBER-ARGENTE TYPE)

PAPP-A2 is a metalloproteinase that cleaves IGFBP-3 and IGFBP-5, releasing free IGF-I from the ternary complex. Homozygous loss-of-function variants in *PAPPA2* on chromosome 1q25 cause progressive growth failure, mild microcephaly, and thin long bones. The biochemical profile is distinctive: total IGF-I, IGFBP-3, IGFBP-5, and ALS levels are elevated, whereas free IGF-I is reduced [11].

Dauber et al. [11] first described this syndrome in two unrelated families in 2016.

IGF-I PRODUCTION DEFECT: *IGF1* VARIANTS (OMIM #608747, INSULIN-LIKE GROWTH FACTOR I DEFICIENCY)

Homozygous variants or deletions of the *IGF1* gene on chromosome 12q23 cause severe prenatal growth failure, resulting in SGA birth, and postnatal growth failure. Other features include microcephaly, sensorineural hearing loss, and intellectual disability. Serum IGF-I is undetectable or very low, but it may be elevated when the variant protein is biologically inactive [4].

Woods et al. [12] first reported a partial deletion of *IGF1* in a patient with severe prenatal and postnatal growth failure in 1996.

IGF-I RECEPTOR DEFECT: *IGF1R* VARIANTS (OMIM #270450, INSULIN-LIKE GROWTH FACTOR I RESISTANCE)

Most patients carry heterozygous variants in the *IGF1R* gene on chromosome 15q26, inherited in an autosomal dominant manner; biallelic variants cause a more severe phenotype. Patients are typically born SGA and present with postnatal growth failure and microcephaly. Serum IGF-I levels are normal or elevated, reflecting resistance at the receptor level [4,13].

Abuzzahab et al. [13] first identified pathogenic *IGF1R* variants in children with prenatal and postnatal growth failure in 2003.

DEFECTS IN PARACRINE SIGNALING AND TRANSCRIPTIONAL REGULATION IN THE GROWTH PLATE

Within the growth plate, chondrocyte proliferation and differentiation are regulated by local signaling networks. The FGFR3 pathway and the CNP–NPR2 pathway act in opposite directions on the mitogen-activated protein kinase (MAPK) cascade: FGFR3 signaling inhibits chondrocyte proliferation, whereas CNP–NPR2 signaling promotes it [1,6]. The transcription factor SHOX also regulates chondrocyte differentiation. These genes are now recognized as common monogenic causes of short stature [4].

TRANSCRIPTIONAL REGULATION DEFECT: *SHOX* DEFICIENCY (OMIM #127300, LÉRI-WEILL DYSCHONDROSTEOSIS; OMIM #300582, IDIOPATHIC FAMILIAL SHORT STATURE)

The *SHOX* gene is located in pseudoautosomal region 1

(PAR1) of the X and Y chromosomes (Xp22.33/Yp11.2). It encodes a homeobox transcription factor expressed in the limb growth plates. *SHOX* haploinsufficiency causes a spectrum of phenotypes, ranging from nonspecific short stature to Léri-Weill dyschondrosteosis, which is characterized by mesomelic limb shortening and Madelung deformity. Biallelic defects cause the more severe Langer mesomelic dysplasia. *SHOX* haploinsufficiency also accounts for a large part of the short stature in Turner syndrome [4]. Deletions of the gene or its downstream enhancers are more common than sequence variants. GH therapy is approved for *SHOX* deficiency.

Rao et al. [14] identified *SHOX* as the gene responsible for growth failure in ISS and Turner syndrome in 1997.

PARACRINE INHIBITION: *FGFR3* VARIANTS (OMIM #100800, ACHONDROPLASIA; OMIM #146000, HYPOCHONDROPLASIA)

The *FGFR3* gene on chromosome 4p16.3 encodes a negative regulator of chondrocyte proliferation and differentiation. Heterozygous gain-of-function variants constitutively activate FGFR3 and its downstream STAT1 and MAPK signaling. Achondroplasia, the most common skeletal dysplasia, is caused by the recurrent p.(Gly380Arg) variant (c.1138G>A or c.1138G>C) in nearly all patients, and most cases arise *de novo* [1]. It is characterized by rhizomelic short stature, macrocephaly, and midface hypoplasia. Hypochondroplasia has a milder phenotype and is frequently caused by the p.(Asn540Lys) variant. Vosoritide, a CNP analog that antagonizes FGFR3-mediated MAPK signaling, increased the annualized growth velocity by approximately 1.6 cm/year compared with placebo in a phase 3 trial [15].

Shiang et al. [16] identified pathogenic *FGFR3* variants as the cause of achondroplasia in 1994.

CNP SIGNALING DEFECT: *NPR2* VARIANTS (OMIM #602875, ACROMESOMELIC DYSPLASIA, MAROTEAUX TYPE; OMIM #616255, SHORT STATURE WITH NONSPECIFIC SKELETAL ABNORMALITIES)

The *NPR2* gene on chromosome 9p13.3 encodes natriuretic peptide receptor B, the receptor for CNP. Binding of CNP generates cyclic GMP, which promotes chondrocyte proliferation and hypertrophy. Biallelic loss-of-function variants cause acromesomelic dysplasia, Maroteaux type, a severe skeletal dysplasia with disproportionate short stature [17]. Heterozygous variants cause mild autosomal dominant short stature, sometimes accompanied by subtle skeletal findings such as short metacarpals.

Bartels et al. [17] first identified pathogenic *NPR2* variants in acromesomelic dysplasia in 2004. Subsequently, Vasques et al. [18] reported heterozygous *NPR2* variants in 6% of patients initially classified as having ISS.

NEWLY IMPLICATED GENES AND EXPANDING PHENOTYPES: *NPPC* AND *IHH*

The list of genes in the growth plate paracrine network continues to grow, and the phenotypes of known genes are expanding as genetic testing is applied to children with milder, nonsyndromic short stature. *NPPC*, located on chromosome 2q37.1, encodes CNP, the ligand of natriuretic peptide receptor B. Heterozygous loss-of-function *NPPC* variants cause autosomal dominant short stature, often with small hands, and thus represent the ligand-side counterpart of heterozygous *NPR2* defects. Because these children have reduced CNP signaling, CNP analogs originally developed for achondroplasia are now being evaluated for a broader range of growth disorders, including those involving the CNP–NPR2 pathway [19].

IHH encodes Indian hedgehog, which forms a negative feedback loop with PTHrP to regulate chondrocyte proliferation and hypertrophy [6]. Biallelic *IHH* variants cause acrocapitofemoral dysplasia, and heterozygous variants were classically associated with brachydactyly type A1. However, heterozygous *IHH* variants are now recognized as a relatively frequent cause of autosomal dominant short stature with nonspecific skeletal abnormalities, typically presenting as mildly disproportionate short stature with shortening of the middle phalanx of the fifth finger [3]. *IHH* is included among the genes with the strongest evidence of association with isolated short stature in the 2026 international guideline [3]. In a retrospective cohort of 19 children with heterozygous deleterious *IHH* variants treated with GH, 10 of whom reached adult height, GH therapy was associated with clinically meaningful height gains, and the response may differ according to variant class [20].

DEFECTS IN THE CARTILAGE EXTRACELLULAR MATRIX

The cartilage extracellular matrix is composed mainly of type II collagen and proteoglycans. It provides mechanical support and regulates the availability of growth factors to

chondrocytes. Severe matrix defects cause classic skeletal dysplasias, such as spondyloepiphyseal dysplasia (*COL2A1*), pseudoachondroplasia (*COMP*), and metaphyseal chondrodysplasia, Schmid type (*COL10A1*) [4]. Milder defects may present as apparently nonsyndromic short stature.

EXTRACELLULAR MATRIX DEFECT: *ACAN* VARIANTS (OMIM #165800, SHORT STATURE AND ADVANCED BONE AGE, WITH OR WITHOUT EARLY-ONSET OSTEOARTHRITIS AND/OR OSTEOCHONDRITIS DISSECANS)

The *ACAN* gene on chromosome 15q26.1 encodes aggrecan, the major proteoglycan of the growth plate and articular cartilage. Heterozygous variants cause autosomal dominant short stature. Unlike most children with ISS, affected children often have advanced bone age and early growth cessation, resulting in markedly reduced adult height [21]. Other features include mild midface hypoplasia, brachydactyly, early-onset osteoarthritis, and intervertebral disc disease. In a cohort of 103 individuals from 20 families, the median adult height was −2.8 SD, and bone age was advanced in most children [22]. Increased growth velocity was observed in some patients treated with GH [22].

Nilsson et al. [21] first identified heterozygous *ACAN* variants as a cause of short stature with advanced bone age in 2014.

DEFECTS IN INTRACELLULAR SIGNALING: RASOPATHIES RAS/MAPK SIGNALING DEFECT: *PTPN11* VARIANTS (OMIM #163950, NOONAN SYNDROME 1)

The RAS/MAPK pathway transmits signals from growth factor receptors and regulates cell proliferation and differentiation. Germline variants in genes of this pathway cause a group of disorders called RASopathies. Noonan syndrome is the most common of these, and short stature is one of its main features [4]. Noonan syndrome 1 is caused by heterozygous gain-of-function variants in the *PTPN11* gene on chromosome 12q24.13, which encodes the protein tyrosine phosphatase SHP-2. *PTPN11* variants account for approximately half of all patients [23]; other causative genes include *SOS1*, *RAF1*, *RIT1*, and *KRAS* [4]. Clinical features include characteristic facial features, pulmonary valve stenosis, hypertrophic cardiomyopathy, cryptorchidism, and bleeding tendency. Excessive RAS/MAPK activity impairs GH receptor signaling, resulting in a mild GH-resistant state with low IGF-I, and also directly inhibits growth plate chondrogenesis [4]. GH therapy is approved for Noonan syndrome.

Tartaglia et al. [23] identified pathogenic *PTPN11* variants as the cause of Noonan syndrome in 2001.

DEFECTS IN FUNDAMENTAL CELLULAR PROCESSES: PRIMORDIAL DWARFISM

Primordial dwarfism is a group of disorders characterized by severe prenatal and postnatal growth failure. These disorders are caused by defects in processes essential for all proliferating cells, such as protein degradation, the DNA damage response, centrosome function, and DNA replication licensing. Because the total number of cells is reduced, growth failure is usually proportionate and often accompanied by microcephaly. The response to GH therapy is generally poor [4].

UBIQUITIN LIGASE DEFECT: *CUL7* VARIANTS (OMIM #273750, 3-M SYNDROME 1)

3-M syndrome is an autosomal recessive disorder characterized by severe prenatal and postnatal growth failure, relative macrocephaly, a triangular face, and normal intelligence. Radiographs show slender long bones and tall vertebral bodies. Biallelic variants in *CUL7* on chromosome 6p21.1 account for most cases, and the remainder are caused by variants in *OBSL1* and *CCDC8*. CUL7 is a component of an E3 ubiquitin ligase complex, and the three proteins interact to regulate cell cycle progression and microtubule dynamics [4].

Huber et al. [24] identified pathogenic *CUL7* variants as the cause of 3-M syndrome in 2005.

DNA DAMAGE RESPONSE DEFECT: *ATR* VARIANTS (OMIM #210600, SECKEL SYNDROME 1)

Seckel syndrome is an autosomal recessive disorder characterized by severe prenatal growth failure resulting in SGA birth, postnatal growth failure, marked microcephaly, intellectual disability, and a characteristic beak-like nose. *ATR*, located on chromosome 3q23, encodes a key kinase of the DNA damage response that is activated by replication stress. Impaired ATR signaling disrupts cell cycle checkpoints and reduces cell proliferation during development.

O'Driscoll et al. [25] identified a splice-site variant in *ATR* in families with Seckel syndrome in 2003.

CENTROSOME DEFECT: *PCNT* VARIANTS (OMIM #210720, MICROCEPHALIC OSTEODYSPLASTIC PRIMORDIAL DWARFISM TYPE II)

Microcephalic osteodysplastic primordial dwarfism type II (MOPD II) is one of the most severe forms of human growth failure, with an adult height of approximately 100 cm. It is caused by biallelic loss-of-function variants in *PCNT* on chromosome 21q22.3, which encodes pericentrin, a centrosomal protein required for mitotic spindle formation. Other features include microcephaly, skeletal dysplasia, dental anomalies, insulin resistance, and cerebrovascular disease, including moyamoya disease and intracranial aneurysms, which require regular screening [26].

Rauch et al. [26] identified pathogenic *PCNT* variants as the cause of MOPD II in 2008.

DNA REPLICATION LICENSING DEFECT: *ORC1* AND OTHER PRE-REPLICATION COMPLEX GENE VARIANTS (OMIM #224690, MEIER-GORLIN SYNDROME 1)

Meier-Gorlin syndrome, also known as ear-patella-short stature syndrome, is an autosomal recessive disorder characterized by microtia, absent or hypoplastic patellae, and prenatal and postnatal growth failure. Intelligence is usually normal. The causative genes, *ORC1* (chromosome 1p32.3), *ORC4*, *ORC6*, *CDT1*, and *CDC6*, encode components of the pre-replication complex, which licenses DNA replication origins before S phase [27]. Impaired replication licensing delays cell cycle progression during periods of rapid growth.

Bicknell et al. [27] identified pathogenic variants in these five genes in patients with Meier-Gorlin syndrome in 2011.

EPIGENETIC DEFECTS: IMPRINTING DISORDERS IMPRINTING DEFECT: LOSS OF METHYLATION AT 11P15 AND MATERNAL UPD7 (OMIM #180860, SILVER-RUSSELL SYNDROME)

Genomic imprinting results in gene expression that depends on the parent of origin, and several imprinted genes regulate fetal growth. *IGF2*, a paternally expressed gene at 11p15.5, encodes a major fetal growth factor. Silver-Russell syndrome (SRS) is characterized by SGA birth, postnatal growth failure, relative macrocephaly at birth, a prominent forehead, body asymmetry, and feeding difficulties [28]. Loss of methylation at imprinting control region 1 (ICR1) on the paternal 11p15 allele is the most common cause and is found in 30%–60% of patients. This leads to biallelic expression of *H19* and reduced expression of *IGF2* [29]. Maternal uniparental disomy of chromosome 7 (UPD7) accounts for 5%–10% of cases. Rare monogenic causes include loss-of-function variants in *IGF2*, *HMGA2*, and *PLAG1* and gain-of-function variants in *CDKN1C* [29]. Temple syndrome, caused by 14q32 imprinting defects such as maternal UPD14, shows substantial phenotypic overlap with SRS [29]. The international consensus statement recommends clinical diagnosis using the Netchine-Harbison clinical scoring system, early nutritional support, and GH therapy [29].

Gicquel et al. [28] first identified 11p15 ICR1 hypomethylation in patients with SRS in 2005.

CLINICAL IMPLICATIONS

The cellular mechanism of a genetic defect manifests as a recognizable clinical pattern (Table 1). SGA birth with postnatal growth failure suggests a defect in IGF-I action, primordial dwarfism, or SRS. Disproportionate short stature suggests a growth plate defect, such as *SHOX*, *FGFR3*, *NPR2*, *IHH*, or *ACAN* variants, and a skeletal survey may be helpful [2]. Advanced bone age in a child with familial short stature suggests an *ACAN* variant [21]. The pattern of GH, IGF-I, IGFBP-3, and ALS levels helps distinguish defects along the GH–IGF-I axis [2].

The 2026 international guideline recommends genetic testing in a short child with any of the following: major malformations and/or neurodevelopmental disorders; a family history suggesting autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance, or a height SDS much lower than that of both parents; severe short stature (height <-3 SDS); microcephaly; absolute or relative macrocephaly; or body disproportion (sitting height/height or arm span/height outside ± 2.5 SDS) [3]. Genetic testing is also recommended for children with syndromic features or clinical or radiographic skeletal abnormalities [3].

When a specific diagnosis is suspected, targeted testing, such as 11p15 methylation analysis for SRS or *SHOX* deletion analysis, is efficient. When the phenotype is nonspecific, gene pan-

el or exome analysis combined with copy number analysis is recommended [3]. The diagnostic yield is higher in children with severe short stature or additional features [5]. A genetic diagnosis provides prognostic information, predicts the response to GH or other therapies, guides surveillance for associated complications, such as cardiac disease in Noonan syndrome or cerebrovascular disease in MOPD II, and enables genetic counseling for the patient's family [2,3].

The limitations of genetic testing should also be recognized. Exome sequencing analyzes only protein-coding regions, which constitute approximately 2% of the genome, and its sensitivity for copy number variants (CNVs), particularly small CNVs involving one or a few exons, is limited [3]. It cannot detect imprinting or methylation defects and may miss variants in deep intronic or regulatory regions, such as deletions of the *SHOX* downstream enhancers, as well as low-level mosaicism [3]. Therefore, chromosomal microarray or multiplex ligation-dependent probe amplification for CNVs and methylation-specific testing for imprinting disorders should be added when clinically indicated. A negative result does not exclude a genetic cause when clinical suspicion is strong, and periodic reanalysis of sequencing data is recommended [3]. In addition, variants should be classified according to the ACMG/AMP guidelines, and a variant of uncertain significance alone should not be used to establish a genetic diagnosis; segregation analysis and functional studies may help clarify its significance [3].

CONCLUSIONS

Short stature is a genetically heterogeneous condition, and many children previously classified as having ISS carry monogenic defects. These defects disrupt growth plate function at different levels, including the GH–IGF-I axis, paracrine signaling and transcriptional regulation, the cartilage extracellular matrix, intracellular signaling, fundamental cellular processes, and genomic imprinting. Each mechanism is associated with characteristic findings in birth size, body proportions, bone age, and biochemical profile. A mechanism-based approach helps clinicians select appropriate genetic tests and interpret their results, while recognizing the limitations of each testing method. An accurate genetic diagnosis guides individualized treatment, predicts the response to GH therapy, and enables surveillance for associated complications and genetic counseling. Mechanism-based therapies, such as CNP analogs, demonstrate how an understanding of growth plate biology can be translated into precision medicine for children with short stature.

NOTES

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Ethical statement

Not applicable. This review article did not involve human participants or animals.

Author contributions

Conceptualization, literature review, writing–original draft, and writing–review & editing: Moon JE.

Use of artificial intelligence

During the preparation of this manuscript, the author used Claude Opus 5.5 (Anthropic) to translate the author's Korean draft into English, to edit the language, and to format the manuscript according to the journal's instructions. The tool was not used to generate scientific content, create figures, or select references. The author reviewed and verified all content, including the references, and takes full responsibility for the content of the publication.

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