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New developments in the genetic diagnosis of short stature

Youn Hee Jee[1], **Jeffrey Baron**[1], **Ola Nilsson**[2,3]

[1]Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, United States

[2]Karolinska Institutet, Department of Women's and Children's Health, Stockholm, Sweden

[3]Örebro University, Department of Medical Sciences, Örebro, Sweden

Abstract

Purpose of review—Genome wide approaches including genome-wide association studies as well as exome and genome sequencing represent powerful new approaches that have improved our ability to identify genetic causes of human disorders. The purpose of this review is to describe recent advances in the genetic causes of short stature.

Recent findings—In addition to *SHOX* deficiency which is one of the most common causes of isolated short stature, *PAPPA2, ACAN* (aggrecan), *NPPC* (C-natriuretic peptide, CNP), *NPR2* (CNP receptor), *PTPN11* (and other rasopathies), *FBN1, IHH* and *BMP2* have been identified in isolated growth disorders with or without other mild skeletal findings. In addition, novel genetic causes of syndromic short stature have been discovered, including pathogenic variants in *BRCA1, DONSON, AMMECR1, NFIX, SLC25A24, and FN1.*

Summary—Isolated growth disorders are often monogenic. Specific genetic causes typically have specific biochemical and/or phenotype characteristics which are diagnostically helpful. Identification of additional subjects with a specific genetic cause of short stature often leads to a broadening of the known clinical spectrum for that condition. The identification of novel genetic causes of short stature has provided important insights into the underlying molecular mechanisms of growth failure.

Keywords

Short stature; genetic cause; exome sequencing; genome-wide association study

Introduction

Childhood growth is the result of chondrogenesis at the growth plates which are located at the ends of long tubular bones and vertebrae [1]. The growth plate is composed of 3 distinct layers in which chondrocytes undergo proliferation and differentiation in a spatially and temporally regulated manner in order to produce new cartilage and direct growth in

Correspondence: Youn Hee Jee, M.D., PDEGEN, NICHD, NIH, 10 Center Drive, Building 10 Clinical Research Center, Room 1-3330, Bethesda, Maryland 20892, USA, tel 001-301-435-5312; jeeyh@mail.nih.gov.

Conflicts of interest

YHJ & J.B. have nothing to disclose.

primarily one dimension [2]. Defects in the regulation of growth plate chondrogenesis cause primary growth defects presenting as isolated short stature or in severe form, skeletal dysplasias or syndromic short stature [3]. If the defect causes increased chondrogenesis, it could cause overgrowth syndromes and present as tall stature. Currently, children with growth disorders are evaluated to exclude nutritional, hormonal (growth hormone, IGF-1, thyroid hormone, glucocorticoid, sex steroids), inflammatory, other systemic disorders, skeletal dysplasias and other syndromes affecting growth. Even if negative, a genetic cause may still be suspected and trigger further genetic evaluations. Previously recognized genetic defects in isolated short stature include paracrine regulatory systems (for example, CNP, BMPs, FGFs, PTHrP), extracellular matrix (for example, aggrecan, collagen II and X, fibrillin, metalloproteinases) or intracellular proteins (for example, RUNX2, SOX9, SHOX, RAS proteins)[3]. However, these known genetic defects may be estimated to explain 25–40 % of children with isolated short stature if their screening evaluation for short stature is negative [4] indicating that many of genetic causes of isolated short stature remain to be discovered [4].

Adult height, the accumulated result of childhood growth, is highly heritable [5]. Genome-wide association (GWA) studies have identified more than 500 loci associated with human height [6]. An additional 83 rare and low-frequency variants have been identified within coding sequence [5]. Among them, 22 genes were identified in both studies [5]. Interestingly, but not surprisingly, many of the genes identified, e.g. *ACAN, FBN1, NPPC, NPR2, PAPPA2* have important functions in growth plate chondrogenesis and have been implicated in childhood growth disorders. Another approach to identify genes important for growth is to identify copy number variants (CNVs) associated with anthropometric traits. Copy number variants have recently been reported to be associated with body size including height in a large population study [7].

The rapidly developing knowledge of the genetic causes of growth disorders will directly expand our understanding of the molecular mechanisms of childhood growth. In this review, we will focus on the most recent genetic findings in monogenic isolated short stature and newly discovered genes of syndromic short stature.

Monogenic causes of isolated short stature

In the last 20 years, identification of monogenic conditions in the large group of children with isolated short stature has underscored that it is a heterogeneous condition with many different etiologies, many of which are genetic. Mutations in the genes listed below have been reported in patients and families with isolated short stature. Despite the use of advanced genetic approaches, most recent findings (listed below) expand the clinical phenotype of previously identified genetic growth disorders, rather than discovering new growth genes.

Mutations in GH-IGF-1 axis have been well documented and may occur at multiple levels of the axis. However, genetic defect in the axis is not a common cause of short stature. In addition to the genes that are involved in growth hormone production (GH1), its receptor (GHR), the downstream signaling (STAT5B) or the effector IGF-1 and its receptor (IGF1R), other genes that participate the axis have also been discovered. PAPPA2 is an enzyme that

cleaves IGFBP-3 and IGFBP-5 and increases IGF-I bioactivity. Therefore, loss-of-function mutations in *PAPPA2* decrease biologically active IGF-1 causing short stature [8]. A recent association study identifying rare genetic variants with larger effect sizes (up to 2 cm) than common variants detected height-increasing variants in *STC2* [5]. STC2 normally inhibits PAPPA which, in turn, cleaves IGFBP-4 to increase bioactive IGF-1. However, the identified variants impaired *STC2* mediated inhibition of PAPPA resulting in increased proteolytic cleavage of IGFBP-4 [5]. Decreased IGFBP-4 presumably results in increasing levels of bioactive IGF-1, likely explaining the growth-promoting effects of the identified variants [5]. Conversely, overexpression of *Stc2* in mice results in decreased growth [9]. Presumably, genetic variants causing increased activity of STC2 would cause short stature by decreasing the amount of bioavailable IGF-1.

Mutations in aggrecan (*ACAN*) cause short stature often with an advanced bone age. Since the mutations in multiple families with isolated short stature were described [10], several studies have reported additional patients with mutations in *ACAN*, confirming the original findings and also expanding the reported phenotypic spectrum [11]. Patients with *ACAN* mutations can have proportionate or disproportionate short stature, bone age which is often but not always advanced, and brachydactyly. Affected family members, particularly adults, may have early-onset osteoarthritis or osteochondritis or intervertebral disc disease [11–12]. Hauer el al analyzed 428 families of mostly European descent who presented with short stature and found that 1.4% of families had potential disease-causing mutations in *ACAN* [13]. Van Der Steen's et al studied 29 children who were born SGA with no or incomplete catch-up growth and advanced bone age and found that 4 out of 29 (14%) children had a heterozygous mutation in *ACAN* [14]. Although the functional studies were not performed to prove the alteration of protein function, the clinical presentations were consistent with the reported patients with *ACAN* mutations and the mutations co-segregated with the phenotype in the affected family members [14]. Most *ACAN* mutation cases were inherited in an autosomal dominant fashion but a *de novo* mutation has also been reported in a sporadic case [15]. Interestingly, a family who had a balanced reciprocal translocation which disrupted *ACAN* at the break point also presented with proportionate short stature with other typical symptoms of abnormal aggrecan [16]. The exact prevalence of the *ACAN* mutations in the group of children with isolated short stature is not known, but 1–5% may be a reasonable estimation given the published studies [13–14]. The *ACAN* gene is large having 7,296 nucleotides in the coding region. Considering the high frequency of non-disease-causing changes (polymorphism) found in *ACAN*, the type of variant, its frequency in the general population, the predicted effect of the variant on the protein, the phenotype of affected family members as well as the co-segregation of the variant in the larger family need to be carefully evaluated, especially for novel missense variants, before the diagnosis is made.

SHOX haploinsufficiency may be one of the most common genetic causes of isolated short stature and has been reported in 2–15% of children with "idiopathic short stature" [17]. SHOX deficiency should be considered if the family history shows an autosomal dominant inheritance pattern of disproportionate short stature (increased sitting height index or increased upper to lower body segment ratio), short 4th metacarpal bones and/or Madelung

deformity. Recently, Ramachandrappa et al reported that SHOX haploinsufficiency may be detected during routine antenatal ultrasound as early as 19-weeks of gestation [18]. However, it did not seem that antenatal presentation of SHOX haploinsufficiency was indicative of severe postnatal growth restriction [18].

Mutations in RAS-MAPK signaling proteins, such as *PTPN11*, *SOS1*, *RAF*, *KRAS*, *BRAS*, and *NRAS* are also relatively common causes of isolated short stature [19]. They often have some of the characteristic facial features which include widely spaced eyes and low-set ears in 80%, and short stature in 70%. Another common feature is pulmonary stenosis in about 50% emphasizing the importance of early recognition and correct diagnosis [19]. Interestingly, in patients with *PTPN11* mutations, the production of IGF-1 appear to be decreased which may explain that Noonan syndrome patients commonly respond well to growth hormone treatment [20–21].

Mutations in NPPC (Natriuretic Peptide type C, CNP) and **its receptor NPR2** have also been reported to be a cause of isolated short stature in children. Hisado-Oliva et al screened 697 patient/families with disproportionate or proportionate short stature and identified the first reported families with heterozygous mutations in *NPPC* (which encodes CNP) causing autosomal dominant short stature [22]. The affected family members also had small hands and mild facial abnormalities [22]. In a study by Shuhaibar et al., FGF and CNP signaling interactions were explored using a mouse model with an *Npr2* protein that cannot be dephosphorylated and a live tissue imaging system [23]. They found that lack of NPR2 dephosphorylation caused increased growth whereas FGF stimulation induced dephosphorylation and inactivation of NPR2, lowering cyclic GMP production and thus altering growth plate chondrogenesis [23] identifying NPR2 dephosphorylation as a novel molecular mechanism involved in growth regulation.

Mutations in *FBN1* usually present as syndromic tall (Marfan syndrome) or short stature, as in Weill-Marchesani syndrome 2, acromicric dysplasia, and geleophysic dysplasia. However, some patients may have only mild syndromic features and may thus present as isolated short stature [24]. It is well known that *FBN1* mutations in Marfan syndrome can cause aortic aneurysm or dissection, but it is important to be aware that the heterozygous *FBN1* mutations that cause short stature, especially in patients with Weill-Marchesani syndrome 2 and geleophysic dysplasia, also have been associated with various cardiac valve issues or aortic aneurysm [24]. How mutations in the same gene can cause opposite effects on growth but similar cardiac findings remain to be clarified [25]. The distinctive phenotype caused by *FBN1* mutations is described in Table 1.

Mutations in IHH in the heterozygous state cause brachydactyly type A1 which presents with variably short or rudimentary middle phalanges of all digits as well as short stature. The middle phalanges are occasionally fused with distal phalanges [26] and proximal phalanges of the thumbs and big toes may be also short [26]. IHH, along with PTH-related peptide (PTHrP), is a an important regulator of chondrocyte proliferation and hypertrophy forming a PTHrP-IHH negative feedback loop in the growth plate. Recently, a study of copy number variations involving the regulatory region of IHH was conducted and revealed 9 enhancers in digits, growth plates, and skulls [27] and the copy-number variations of the IHH locus

involving conserved noncoding elements were found to cause syndactyly and craniosynostosis in human. Vasques *et al.* reported IHH mutations as a cause of short stature with non-specific skeletal findings in families with mildly disproportionate short stature (severe to mild short stature) with an autosomal dominant inheritance pattern [28]. There was variable brachydactyly and often shortening of the middle phalanx of the fifth finger. For these children, growth hormone accelerated height gain [28]. This report expands the phenotypic spectrum of *IHH* mutations and demonstrates that they may present as short stature with only subtle skeletal findings emphasizing the importance of careful clinical and radiological evaluations of children with growth failure.

Mutations in *BMPR1B, GDF5* and duplications in a *BMP2* enhancer region have been known to cause brachydactyly type A2, which presents with hypoplasia or aplasia of the middle phalanx of the index finger and sometimes also the 5th finger as well as variable short stature. Interestingly, duplications of a downstream BMP2 regulatory element [29] have been identified in families with this condition. Recently, Tan et al reported heterozygous *BMP2* variants which caused short stature with craniofacial (midface hypoplasia, short nose, anteverted nares and long philtrum) and phalangeal abnormalities (not necessarily brachydactyly) with or without congenital heart disease [30]. In the growth plate, BMPs induces Runx2, a key regulator of chondrocyte differentiation, and promote proliferation and differentiation of growth plate chondrocytes [31–33].

Monogenic causes that may present with isolated growth disorders are summarized in Table 1.

Rare syndromic short stature can also present clinically as isolated short stature if the other features of the syndrome are mild or even absent in an individual patient. This situation may especially occur when the patient presents with poor growth during infancy and early childhood since some syndromic features may be less obvious at an early age. For example, in a recent report of two siblings with *BRF1* mutations, the younger sibling showed abnormal growth but reportedly lacked syndromic features at presentation and only later developed these features [34]. Another example is 3-M syndrome which is a rare syndromic growth disorder due to mutations in *CUL7*, *OBSL1*, or *CCDC8* that usually presents with extreme short stature, skeletal dysplasia, and facial abnormalities. Interestingly, Liao L et al report 2 siblings with a previously reported pathogenic *CCDC8* variant but only mild short stature (height −2.2 to −2.7 SDS) and subtle facial abnormalities [35].

Novel genetic causes of syndromic short stature

Recent studies of rare forms of syndromic short stature have revealed mutations in several different genes not previously recognized to cause syndromic short stature.

Biallelic loss-of-function mutation in *BRCA1*

BRCA1 is a tumor suppressor gene. Heterozygous germline mutations confer a high risk of breast and ovarian cancers in women. Freire et al reported a biallelic loss-of-function mutation in *BRCA1* in a patient who presented with microcephaly, short stature,

developmental delay, dysmorphic facial features and cancer predisposition which mimic Fanconi anemia [36]. Interestingly, the previously reported patients with compound heterozygous mutations in *BRCA1* also had short stature suggesting that *BRCA1* has an important role in growth plate chondrogenesis [36].

Biallelic loss-of-mutation in *DONSON*

The gene *DONSON* is important for DNA replication and genome stability by stabilizing forks during genome replication. Reynolds et al reported mutations in *DONSON* in 29 patients with microcephalic dwarfism [37]. The patients also showed decreased cerebral cortical size with less gyral folding, fifth finger clinodactyly, syndactyly, brachydactyly, hypoplasia of carpal or phalangeal bones, radial head dislocation and mild intellectual disability [37]. The mechanism by which mutations in *DONSON* affects growth plate chondrocyte function is not known but might involve a direct effect on the rapidly replicating cells of the proliferative zone chondrocytes.

X-linked loss-of-function in *AMMECR1*

Moyses-Oliveira et al reported that mutations in *AMMECR1* causes short stature, cardiac (arrhythmia) and skeletal abnormalities, and hearing loss in five unrelated subjects [38]. Patients also had prominent forehead, flat face, malar flattening, and midface hypoplasia. The biological function of *AMMECR1* is unknown, but it codes for a protein which has a putative nuclear localization signal and may therefore encode a factor that regulates transcription [39–40].

Microduplication encompassing *NFIX*

Loss-of-function mutations in *NFIX* have been known to cause Malan (also called Sotos syndrome type 2) or Marshall-Smith syndrome which is an overgrowth syndrome with macrocephaly, developmental delay, facial dysmorphism (long narrow face, prominent forehead) and advanced bone age [41]. Interestingly, Trimouille et al reported 9 patients who exhibited short stature and small head circumference, which are the reverse of Sotos syndrome-2 phenotypic features as well as variable intellectual disability [42]. All patients had microduplications encompassing *NFIX*. The function of NFIX is not known but NFIX was found to be highly expressed in the pre-hypertrophic zone of the growth plate, and *Nfix* knock-out mice showed kyphosis, delayed endochondral ossification and reduction of trabecular bone formation. Therefore, it was speculated that *NFIX* is likely a negative regulator of endochondral ossification [43].

Monoallelic mutations in *SLC25A24*

Ehmke et al reported coronal craniosynostosis and severe midface hypoplasia, body and facial hypertrichosis, microphthalmia, short stature, and short distal phalanges in 5 unrelated patients [44–45]. SLC25A24, a solute carrier 25 family member, encodes a calcium-binding mitochondrial carrier protein. SLC25A24 plays a role in maintaining optimal adenine nucleotide levels in the mitochondrial matrix by regulating the exchange of ATP-Mg and phosphate between the cytosol and mitochondria. Mutations in SLC25A24 cause impaired

mitochondrial ATP synthesis and consequently affected energy metabolism [44–45]. The role of SLC25A24 in growth plate chondrocytes has not been investigated.

Monoallelic mutations in *FN1*

Spondylometaphyseal dysplasias (SMDs) compose a diverse group of skeletal dysplasias characterized by short stature, growth-plate irregularities, and vertebral anomalies [46]. Lee et al identified *FN1* mutations in SMD patients with radiological appearance of metaphyseal "corner fractures" and showed that the mutations affected the secretion of the encoded protein fibronectin. Fibronectin is a glycoprotein secreted by osteoblasts, chondrocytes and mesenchymal cells and act as a regulator of extracellular matrix assembly and is also important for cell-matrix interactions and thus important for normal chondrogenesis [46].

Monoallelic mutations in *PUF60*

Low et al reported 12 unrelated patients with mutations in *PUF60* who presented with short stature, facial abnormalities (micrognathia, a thin upper lip, long philtrum, narrow almond-shaped palpebral fissures, and facial hypertrichosis), spinal segmentation anomalies, congenital heart disease, ocular coloboma, hand anomalies and kidney abnormalities [47]. *PUF60* regulates RNA splicing and transcription [47], but the exact biological function and its role in growth plate chondrogenesis remain to be elucidated.

Conclusion

The recent advances in genetic growth disorders reviewed in this paper further demonstrate that the genetic causes of short stature are highly heterogeneous and may cause a wide phenotypic spectrum ranging from mild and isolated short stature to severe and syndromic short stature. A detailed family history, careful physical exam to identify distinctive clinical features including body proportions, facial dysmorphism, scoliosis or other skeletal findings, and laboratory and radiological evaluation including bone age are all crucial to the evaluation of children with growth failure. Improved genetic diagnosis may directly benefit the patient by allowing management and counseling specific for the disorder. In addition, identifying novel genetic causing growth disorders may reveal novel therapeutic targets and may thus, in the long-term, lead to novel treatment approaches directly targeted to the underlying pathogenic mechanisms of growth failure.

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Key points

- Isolated growth disorders are heterogeneous and often monogenic. When monogenic, they can appear sporadic or familial, showing a Mendelian inheritance pattern. For example, pathogenic genetic variants have been identified in *PAPPA2*, *ACAN* (aggrecan), *NPPC* (C-natriuretic peptide, CNP), *NPR2* (CNP receptor), *PTPN11* (and other rasopathies), *FBN1*, *IHH* and *BMP2.* However, many genetic causes of isolated short stature sill remain unknown.
- New genetic causes of syndromic short stature were recently identified in *BRCA1, DONSON, AMMECR1, NFIX, SLC25A24, and FN1.* The mechanisms by which they affect growth plate chondrogenesis needs further investigation.
- Identifying the genetic causes of isolated growth failure and syndromic short stature is critical to understand the pathogenesis of these conditions and may guide the evaluation and management and accelerate the development of novel strategies to treat growth disorders.

Table 1.

Monogenic causes that may present with isolated growth disorders

Gene	Function	Mechanism of isolated growth disorders (name of growth disorders)	Clinical phenotype
PAPPA2	cleaves IGFBP-3 and IGFBP-5 to increase IGF-I bioactivity	Loss-of-function mutations in *PAPPA2* decrease biologically active IGF-1	AGA[α], small chins, mild microcephaly long fingers and toes, elevated IGF-I and IGFBP-3, bone age = chronological age, possibly low bone mineral density[8]
ACAN	proteoglycan extracellular matrix in growth plate	Not known	AGA/SGA[β], frontal bossing, midface hypoplasia, flat nasal bridge, anteverted ears, brachydactyly, bone age > chronological age[γ], with/without early-onset osteoarthritis, with/without osteochondritis dissecans, with/without intervertebral disc disease[10–15]
SHOX	Not known	Not known (SHOX haploinsufficiency, Léri-Weill dyschondrosteosis)	AGA, disproportionate body proportion (decreased arm span and increased sitting to standing height ratio), short 4th me metacarpal bones, Madelung deformities[17–18]
PTPN11 and other rasopathy genes	Ras signaling regulator	Gain of function mutation increases ras signaling and suppress the production of IGF-1 (Noonan or Noonan-like syndrome)	AGA, down-slanted eyes, widely spaced eyes, low-set ears, low set posterior hairline, webbed neck, pulmonary stenosis, hypertrophic cardiomyopathy, scoliosis, undescended testes, coagulopathy, learning disability, renal anomalies, skin pigmentation lesions[19]
NPPC	C-natriuretic peptide; Regulator of ras signaling	Dysregulation of ras signaling	Hypertelorism, bone age = chronological age, small hands and feet, short 4th metacarpal, mild facial hypoplasia[22]
NPR2	Receptor for CNP	Dysregulation of ras signaling (Miura type-epiphyseal chondrodysplasia)	High-arched palate, mesomelic shortening of limbs, cubitus valgus, muscular hypertrophy, bone age < chronological age, short 4th metacarpal bone, cone shaped epiphysis, short 5th digit[23]
FBN1	Formation of microfibril	Disruption of microfibril formation which alters TGF-β signaling (Weill-Marchesani syndrome 2, acromicric dysplasia, and geleophysic dysplasia)	AGA/SGA, round face, thickened skin, coarse facial features, bulbous nose, joint stiffness, brachydactyly, disproportionate short stature, various cardiac valve problems, aortic aneurysm, bone age < chronological age[24–25]
IHH	PTHrP-IHH feedback loop	Dysregulation of chondrocyte hypertrophy (brachydactyly type A1)	AGA/SGA, short or rudimentary middle phalanges of some or all digits, disproportionate short stature[26–28]
BMP2	A key regulator of chondrocyte proliferation and differentiation	Dysregulation of chondrocyte hypertrophy (brachydactyly type A2)	AGA, hypoplasia or aplasia of the middle phalanx of the index finger, other phalangeal abnormalities, midface hypoplasia, short nose, anteverted nares and long philtrum, with/without congenital heart disease[29–30]

α: AGA, appropriate for gestational age

β: SGA, small for gestational age

γ: Advanced bone age is observed in most of patients with mutations in *ACAN*.