Traditionally, the growth hormone – insulin-like growth factor I (GH – IGF-I) axis is the most important signaling pathway in linear growth, and defects in this axis present as growth hormone deficiencies or IGF-I deficiencies. However, subtle changes in serum levels of GH or IGF-I, caused by gene mutations involved in the GH – IGF-I axis, can present as idiopathic short stature (ISS). This paper briefly discusses GHR and IGFALS. In addition, recent studies have shown that many factors, including paracrine signals, extracellular matrix, and intracellular mechanisms of chondrocytes, regulate the growth plate independent of the GH – IGF-I system. Rapid development of diagnostic technologies has enabled discovery of many genetic causes of ISS. This paper discusses 5 genes, SHOX, NPR2, NPPC, FGFR3, and ACAN, that may lead to better understanding of ISS.

Keywords: Idiopathic short stature, Growth plate, Gene sequencing

Introduction

When a child is very short, meaning that his or her height z-score is below -2.0, routine laboratory examinations are performed to identify chromosomal aberrations, growth hormone (GH) secretion disorders, or other hormonal or nutritional abnormalities. If these tests identify no reasons and the child had normal birth weight and height, the child is defined as having idiopathic short stature (ISS). Therefore, ISS is a diagnosis of exclusion and includes a diverse group of short stature. ISS also includes normal variants of short stature, such as familial short stature and constitutional delay of growth. These inclusions cause confusion in recognizing ISS as a disorder. There have been many attempts to classify ISS clinically; including familial or nonfamilial; bone age delay or not; pubertal delay or not. However, following the flow of GH secretion, GH action, production of insulin-like growth factor I (IGF-I), and IGF-I action, makes it easier to understand this complex disease.

Recently many genetic causes of ISS have been discovered because diagnostic technologies have developed rapidly; particularly those involving single nucleotide polymorphism array, array-comparative genomic hybridization, whole exome sequencing, genome-wide association studies, whole genome sequencing, RNA sequencing, and methylation assays. This review discusses recent studies centering on novel genetic causes of ISS that may provide better understanding of ISS.

Genetic causes of ISS

1. Traditional aspects of genetic causes in the GH – IGF-I axis

The GH – IGF-I axis is the most important signaling pathway in linear growth, and defects in this axis traditionally present as GH deficiencies or IGF-I deficiencies. However, some gene mutations involved in the GH – IGF-I axis may cause subtle changes of GH or IGF-I concentrations within the normal range.
1) **GHR**

The inactivating mutation of the GH receptor (GHR) gene, which causes complete insensitivity to GH and a very low IGF-I level, presents as Laron dwarfism. However, there is an area of overlap between ISS and GH insensitivity, which means that a mild defect of the GHR gene may cause ISS that presents as a lower serum IGF-I concentration, and a higher mean 12-hour serum GH concentration. In such ISS children, serum concentrations of GH binding protein, which is identical to the extracellular domain of the GHR, are low, suggesting that these children may have abnormalities in the GHR gene. Goddard et al. found a heterozygous mutation in the extracellular domain of the GHR gene in 4 of 14 ISS children with low levels of GH binding protein. Children with this GHR gene mutation had marginal growth responses to exogenous GH treatment, suggesting partial insensitivity to GH.

2) **IGFALS**

Growth failure can be caused not only by an absolute defect of the IGF-I, but also by a defect of the bioavailable IGF-I. Under normal conditions, about 80% of circulating IGF-I is in the form of ternary complex, which is composed of IGF-I, IGF binding protein-3 (IGFBP-3), and acid-labile subunit (ALS). This complex plays an important role in regulating the bioavailability of IGF-I by prolonging its half-life. Family studies of patients who have homozygous ALS gene mutations have shown that heterozygosity for an ALS defect may decrease stature and head circumference compared with those of noncarriers. Therefore, ALS abnormalities should be considered when circulating levels of IGF-I and IGFBP-3 are lower than those in the normal population.

2. **Novel insights of genetic causes beyond the GH – IGF-I axis**

Normal growth in children requires not only a normal GH – IGF-I axis but also normal local signals and environments within the epiphyseal growth plate. Recent studies have shown that many factors independent of the GH – IGF-I system regulate this growth plate, including paracrine signals, extracellular matrix, and intracellular mechanisms of chondrocytes. Phenotypic spectrums of these related genes exist. If homozygous mutations disrupt the functions of critical genes, patients usually present with skeletal dysplasia, enabling clinicians to recognize the disease easily. However, if the genes are less critical and their functions are impaired by heterozygous mutations, patients may present with ISS without syndromic features. The initial approach to these candidate genes was to compare data between carriers and noncarriers among the patient’s relatives. The following subsections summarize five genes, SHOX, NPR2, NPPC, FGFR3, and ACAN, found in ISS children.

1) **SHOX**

Short stature homeobox-containing gene, or SHOX, is located at pseudoautosomal region 1 (PAR1) of Xp22.33 and Yp11.2. SHOX protein is a transcriptional factor for chondrocyte differentiation. SHOX mutation causes a broad phenotypic spectrum with an apparent gene-dose effect. A homozygous mutation causes Langener mesomelic dysplasia (MIM# 249700), which presents as severe skeletal dysplasia, severely short stature, extreme shortening of the long bones in the arms and legs (mesomelia), and Madelung deformity. A heterozygous mutation causes Léri-Weill dyschondrosteosis (MIM# 127300) with milder skeletal dysplasia. Turner syndrome (MIM# 313000), skeletal dysplasia of Léri-Weill dyschondrosteosis phenotype presents when the defect in the X chromosome involves PAR1. A heterozygous aberration of the SHOX gene is responsible for 2%–15% (mean 3.8%) of ISS, depending on the study. ISS children with SHOX protein insufficiency may have body proportions that are either mildly affected or within the normal range. In addition, a heterozygous deletion of the downstream or upstream enhancer of the SHOX gene causes a phenotype similar to that caused by a defect of the SHOX gene itself.

2) **NPR2**

The NPR2 gene is located at 9p13 and encodes natriuretic peptide receptor B (NPR-B), which has high affinity for c-type natriuretic peptide (CNP), an important paracrine factor that acts as a positive regulator in the growth plate. When CNP binds to NPR-B, dimerization of the NPR-B activates the guanylyl cyclase in the cytosolic domain, and then, cGMP activates the type II cGMP-dependent protein kinase. This activation inhibits the MAPK pathway, which antagonizes the fibroblast growth factor receptor 3 (FGFR3) signaling. Therefore, CNP-NPR-B signaling increases the proliferation and differentiation of chondrocytes. A homozygous mutation causes acromesomorphic dysplasia, Maroteaux type (MIM# 602875) which is characterized by extremely short stature, short limbs, a severe skeletal dysplasia. A heterozygous mutation causes a phenotype similar to that caused by SHOX haploinsufficiency with mesomelia, except for the absence of Madelung deformity. Recent studies have suggested that 2%–3% of ISS cases have a heterozygous loss-of-function mutation of the NPR2 gene, either with or without abnormal body proportions. Wang et al. reported a prevalence of 13.6% in familial cases, suggesting that such variants frequently explain patients with nonsyndromic familial ISS.

3) **NPPC**

The NPPC gene is located at 2q37 and encodes CNP, which is a ligand for NPR-B, as described above. NPR2 variants have been widely reported in ISS children, but to date no NPPC mutation has been reported in human. Recently, Hisado-Oliva et al. identified 2 heterozygous NPPC mutations in 2 families with proportionate short stature and small hands, which was the first report. This finding strengthens the evidence for clinical trials of CNP analog treatment in short stature.
4) FGFR3

The FGFR3 gene is located at 4p16.3, and paracrine signaling of FGF – FGFR3 is well known as a negative regulator of growth plate chondrogenesis. Its gain of function mutation affects the growth plate through various cellular processes, including decreasing proliferation in the proliferative zone, accelerating the onset of hypertrophic differentiation, decreasing the size of the hypertrophic chondrocytes, and decreasing matrix production. Therefore, activating mutation of the FGFR3 gene results in inhibited long bone growth with skeletal dysplasia. The wide range of phenotype includes hypochondroplasia (MIM# 146000), achondroplasia (MIM# 100800), thanatophoric dysplasia (MIM# 187600), and a lethal skeletal dysplasia with very short limbs and underdeveloped ribs. Several studies have failed to find a relationship between FGFR3 and ISS, but one recent report identified an activating mutation of FGFR3 that caused proportionate familial short stature. Therefore, if short stature is transmitted in an autosomal dominant pattern, FGFR3 should be considered as a cause of ISS.

5) ACAN

Aggrecan is the most abundant proteoglycan of growth plate cartilage and is crucial for their structure and function. The ACAN gene, which encodes aggrecan, is located at 15q26.1, and its mutation leads to aggrecan deficiency, abnormal structure of the cartilage extracellular matrix, decreasing chondrocyte proliferation, and accelerating hypertrophic chondrocyte differentiation. A homozygous mutation causes spondyloepimetaphyseal dysplasia aggrecan type (MIM# 612813), which presents as severe skeletal dysplasia, extremely short stature, brachydactyly, and severe midface hypoplasia. A heterozygous mutation causes milder skeletal dysplasia, associated with adult height z-scores of -2.0 to -4.0, which is called spondyloepiphyseal dysplasia Kimberley type (MIM# 608361). As aggrecan is important to the articular cartilage, osteochondritis dissecans (MIM# 165800) and early-onset osteoarthritis occurs. A heterozygous mutation of ACAN was found in ISS children who have no evident radiographic skeletal dysplasia. Their statures were disproportionate or proportionate, and some of them had advanced bone age, which led to early cessation of growth. A case of ISS with novel heterozygous mutation with early-onset multiple disc herniation has also been reported. Compared to the prevalences of SHOX and NPR2, the prevalence of gene variants of ACAN is not widely known, however, Hu et al. reported 1.4% of non-syndromic short stature patients and 2.5% of familial short stature patients.

Conclusions

Recent diagnostic technologies for gene hunting have enabled finding more causative genes associated with short stature. This paper discussed two genes involved in the GH – IGF-I axis and five genes beyond the GH – IGF-I axis. This paper discussed two genes involved in the GH – IGF-I axis and five genes beyond the GH – IGF-I axis (Table 1). Subtle changes in serum levels of GH binding protein, IGF-I, and IGFBP-3 may provide information to enable better approaches to screening genes associated with the GH – IGF-I axis. In addition, mild but specific phenotypes, including those involving body proportion or skeletal dysplasia features, may provide many clues that will aid in accessing involved genes within the growth plate. There are many candidate genes, and screening for all of them would require prohibitive investments of time and money. Therefore, more specific clues are needed about which genes to target.

Conflict of interest

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

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