Clinical and Laboratory Features to Consider Genetic Evaluation among Children and Adolescents with Short Stature

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Conventional evaluation method for identifying the organic cause of short stature has a low detection rate. If an infant who is small for gestational age manifests postnatal growth deterioration, triangular face, relative macrocephaly, and protruding forehead, a genetic testing of *IGF2, H19, GRB10, MEST, CDKN1, CUL7, OBSL1*, and *CCDC9* should be considered to determine the presence of Silver–Russell syndrome and 3-M syndrome. If a short patient with prenatal growth failure also exhibits postnatal growth failure, microcephaly, low IGF-1 levels, sensorineural deafness, or impaired intellectual development, genetic testing of *IGF1* and *IGFALS* should be conducted. Furthermore, genetic testing of *GH1, GHRHR, HESX1, SOX3, PROP1, POU1F1,* and *LHX3* should be considered if patients with isolated growth hormone deficiency have short stature below -3 standard deviation score, barely detectable serum growth hormone concentration, and other deficiencies of anterior pituitary hormone. In short patients with height SDS < -3 and high growth hormone levels, genetic testing should be considered to identify *GHR* mutations. Lastly, when severe short patients (height z score < -3) exhibit high levels of prolactin and recurrent pulmonary infection, genetic testing should be conducted to identify *STAT5B* mutations.

Key words: Short stature, Small for gestational age, Growth hormone deficiency, Insulin like growth factor, Growth hormone insensitivity

REVIEW ARTICLE

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INTRODUCTION

Short stature (< 3rd percentile compared with the same sex and age) is one of the common reasons for visiting pediatric endocrinology. Its organic causes include renal failure, hypothyroidism, celiac disease, acid-base disorders, inflammatory bowel diseases, and impairment of thesomatotropin axis. However, in a previous study, the incidence of pathogenic causes of short stature was found in only 1.3% of 235 patients with short stature patients by the standard evaluation for identifying the above-mentioned underlying disease [1].

Also in a previous study, various monogenic causes of short stature were observed in a patient with idiopathic short stature, including short-stature homeo-box-containing gene, natriuretic peptide receptor 2 gene, natriuretic peptide precursor C gene, fibroblast growth factor receptor 3 gene, and aggrecan gene [2]. Early identification of monogenic short stature prevents further diagnostic work-up in patients and facilitates the evaluation of other medical comorbidities as well as the provision of genetic counseling to the family [3]. This article briefly reviews clinical and laboratory findings associated with monogenic short stature, including both the pre- and postnatal onsets of short stature.

CONSIDERATION OF GENETIC TESTING IN A PATIENT WITH PRENATAL ONSET OF SHORT STATURE

Factors known to inhibit intrauterine growth include congenital infections, smoking, placenta previa, and poor nutrition. However, a specific etiology is not identified in most infants that are small for gestational age (SGA) [3]. In a previous study, 80%–85% of idiopathic SGA infants exhibited rapid growth [4]. There are many underlying genetic conditions that result in pre- and postnatal growth restriction. Silver–Russell syndrome (SRS) is one of the common etiologies of SGA. SRS is mainly diagnosed based on clinical findings. According to the Netchine–Harbison scoring system, the presence of four of the following six criteria suggests SRS: low birth weight (≤ -2 standard deviation score for gestational age), postnatal growth restriction, relative macrocephaly at birth, prominent forehead, asymmetric body, feeding difficulties, and/or low body mass index [4]. Although molecular testing has a diagnostic yield of only around 60% [5] and a lack of positive molecular results cannot rule out SRS, it confirms the presence of the disease, particularly in children aged < 2 years, adolescents, and adult patients with less prominent signs and symptoms [6]. The most prevalent genetic cause is a hypomethylated imprinting region, including *IGF2* and *H19* genes, on the paternal allele of chromosome 11p15.5 [5], followed by uniparental disomy of chromosome 7. Methylation patterns could differ among leucocytes, buccal swabs, and skin fibroblasts [7,8]. The other candidate genes of SRS on chromosome 7 are *MEST* (7q32) and *GRB10* (7p12.1) [9,10]. Additional genetic testing includes a *CDKN1C* gain-of-function mutation and an *IGF2* loss-of-function mutation [11,12].

Another disorder with clinical features similar to SRS is 3-M syndrome. Patients with 3-M syndrome exhibit pre- and postnatal growth restriction, triangular faces, and normal head circumference [13]. Other features include normal intelligence, fleshy nasal tip, frontal bossing, and pointed chin, which become less pronounced as patient age [14]. The associated genes include *CUL7*, *OBSL1*, and *CCDC8*, which are inherited as a recessive condition [13]. Other disorders represented by severely restricted prenatal and postnatal growth with microcephaly are microcephalic osteodysplastic primordial dwarfism types I and II, Meier–Gorlin syndrome, and Seckel syndrome [15].

CONSIDERATION OF GENETIC TESTING IN A PATIENT WITH ISOLATED GROWTH HORMONE DEFICIENCY

Growth hormone (GH) conducts a critical role in human growth by itself or through the regulation of Insulin-like growth factor-1 (IGF-1) production. Isolated growth hormone deficiency (GHD) has an idiopathic cause [3]. In previous studies, genetic conditions associated with isolated GHD have been identified in 11%–34% of patients with isolated GHD. The candidate genes were *GH1*, *GHRHR*, *HESX1*, and *SOX3* [16,17].

Homozygous deletion, nonsense mutation, and compound heterozygous frameshift mutations of *GH1* induce GHD type 1A, the most severe form of isolated GHD. GHD type 1A is represented by severe postnatal growth deterioration, unverifiable serum GH, development of anti-GH antibodies, and autosomal recessive transmission. Conversely, GHD type 1B (less severe form) is induced by missense, nonsense, splice site, or frameshift mutations of *GH1* or *GHRHR*. It is represented by low but detectable serum GH concentrations and absence of anti-GH antibodies. Mutations within the first six nucleotides of intron 3 of *GH1* produce a shortened form of GH and induce type II GHD. The shortened GH has a dominant negative effect on GH receptor, which leads to reduced GH secretion and is possibly associated with multiple pituitary hormone deficiency (MPHD), including TSH, LH, and prolactin [3].

One of the important clinical features of children with isolated GHD with identified genetic causes was lower height SDS (-4.7 ± 1.6 vs. -3.4 ± 1.7) than those with unidentified genetic causes. However, no significant difference was observed in age at diagnosis, IGF-1 SDS, peak GH concentration after simulation test, and prevalence of anterior pituitary gland hypoplasia [17]. Further research on the criteria for conducting genetic testing in a patient with isolated GHD is warranted.

CONSIDERATION OF GENETIC TESTING IN A PATIENT WITH MPHD

PROP1

PROP1 antecedes and provokes the expression of *POU1F1*. It is also selectively expressed in the embryonic pituitary gland [18]. *PROP1* mutation is associated with MPHD, including GH, TSH, prolactin, LH, FSH, and ACTH deficiencies. However, physicians need to be cautious because panhypopituitarism may not be present from the beginning. The time of appearance and degree of hormone deficiencies vary significantly, particu-

larly for LH, FSH, and ACTH [19]. Thus, laboratory evaluation including FSH, LH, PRL, and ACTH levels in a patient with isolated GHD can help identify the patient at risk of developing panhypopituitarism. Another feature of MPHD is a small or normal-sized adenohypophysis. However, magnetic resonance imaging revealed pituitary hyperplasia in 33% of patients with multiple pituitary hormone deficiency. The pituitary enlargement exhibited a non-enhancing mass lesion located between the adenohypophysis and neurohypophysis [20].

POU1F1

POU1F1 is expressed in the developing pituitary gland and associated with the differentiation of cells responsible for the secretion of somatotropin, prolactin, and thyrotropin [21]. Patients with a POU1F1 mutation exhibit complete GH and prolactin deficiency during the first years of life. However, the extent and onset of TSH deficiency vary significantly. Furthermore, central hypothyroidism is common but does not occur in all patients with a POU1F1 mutation [22]. Radiologic findings of the pituitary gland include hypoplasia of adenohypophysis, normal infundibular stalk, and normally positioned neurohypophysis. However, normal-sized anterior lobes have been reported in rare cases [23]. Thus, genetic testing may be required in patients with GH and prolactin deficiencies, as well as TSH deficiency and structural abnormalities of the pituitary gland.

LHX3

LIM-homeobox 3 (MIM 600577) is expressed in the developing anterior pituitary gland and intermediate pituitary gland. It is important to determine all pituitary cell lineages, except corticotropes [24]. Patients with homozygous LHX3 loss-of-function mutations harbor GH, TSH, LH, FSH, and prolactin deficiencies. Other clinical features of associated abnormalities in patients with LHX3 mutations include a short neck with limited rotation as well as vertebral and skeletal problems.

GH insensitivity

Laron et al. reported GH insensitivity (GHI) earliest with the description of children with extremely short stature, the phenotype of hypopituitarism, and high level of serum GH [25]. GH derived from the pituitary gland stimulates IGF-I expression in both the hepatocytes and non-hepatic tissues [26]. In addition to the direct effect of GH on chondrocyte, GH also prompts longitudinal bone growth via the IGF-1-dependent mechanism. Binding of GH to cell surface homodimeric growth hormone receptor (GHR) activates cytosolic Janus kinase 2 (JAK2).

JAK2 phosphorylates the signal transducer and activator of transcription (STAT)-5b. Subsequently, tyrosyl-phosphorylated-STAT5b produces a homodimer and translocates to the nucleus, producing IGF-1, IGFBP3, and acid-labile subunit (ALS).

GHR mutations include missense, nonsense, and splice mutations [27,28]. The majority of patients with GHR mutations have homozygous or compound heterozygous mutations as well as autosomal recessive inheritance [29]. In a previous study, IGF-1 disruption reduced fetal growth in mice significantly [30]. Heterozygous GHR mutations cause a mild phenotype by dominant negative effect [31]. One of the characteristic findings suggesting GHI was severe short stature. The height SDS of a patient with GHI ranged from -3 to -10 SDS [32]. Even in Japanese sibling patients with a mild phenotype due to compound heterozygous mutations of GHR, the height SDSs were -3.0 and -3.5, respectively. Another clinical characteristic finding was elevated GH levels. In previous reports, the basal levels of GH were between 1.0 and 44 ng/mL. Furthermore, the peak GH concentrations after the stimulation test were between 23.8 and 48.1 ng/mL [33]. Thereafter, in patients with height SDS <-3 and high GH levels, genetic testing should be considered to identify GHR mutations.

STAT5B

Human STAT5B mutations cause severe postnatal growth restriction as STAT5b is critical for GH-induced production of IGF-I [34]. Clinical and laboratory characteristics are generally normal birth weight; severely restricted postnatal growth; unresponsiveness to GH replacement; elevated and stimulated basal GH concentrations, 0.13–17.7 ng/mL and 12.5–53.8 ng/mL, respectively; low IGF-I levels, absent to 38 ng/mL; and high prolactin levels, 13–169 μg/L [35-37]. Another important feature is immune dysfunction resulting in recurrent pulmonary infections and autoimmune disease [35]. Immune dysfunction includes lymphopenia and low regulatory T cells [38]. However, brain development is normal. The genetic mutations reported to date were autosomal recessive and homozygous, indicating that haploinsufficiency had a negligible effect on IGF-I expression [26]. Therefore, in patients with height SDS <-3, the presence of high prolactin levels and recurrent pulmonary infection indicate the need for genetic testing to identify STAT5B mutations.

IGF1

The clinical phenotypes of patients with homozygous IGF1 mutations include sensorineural deafness, severe deficit of in-

tellectual development, microcephaly, intrauterine growth retardation, and severe postnatal growth [39,40]. *In utero*, the development of the central nervous system appears to be associated with IGF-1 [24]. In previous reports, birth weight ranged from -5.4 to -1.2 SDS. IGF-1 levels were found to be very low [39,41,42], whereas IGFBP-3 and ALS levels were normal [41]. Heterozygous *IGF1* mutations may cause short stature through a dominant negative effect [42].

IGFALS

IGFALS mutations are characterized by GHI and IGF-1 and ALS deficiencies. *IGFALS* is located on chromosome 16p13.3 and encodes ALS by stimulating GH [43]. The clinical characteristics of patients with a homozygous IGFALS mutation included severe IGF-1, IGFBP3, and ALS deficiencies. However, relative mild growth failure and even a normal height were reported in some patients [44]. The known IGFALS mutations include missense and nonsense mutations, deletions, duplications, and insertions [45]. Patients with heterozygous IGFALS mutations exhibited approximately 1 SDS height loss compared with those with wild-type mutations [46].

IGF1R

IGF1R belongs to the insulin receptor family and is a transmembrane receptor; it binds IGF-1 and IGF-2. The *IGF1R* gene is located on chromosome 15q26.3 [26]. The clinical features of *IGF1R* mutations are impaired pre- and postnatal growth, small head circumference, developmental delay, micrognathia, and relatively high IGF-1 levels [47]. The signs and symptoms that suggest *IGF1R* mutation include small birth weight or length, postnatal growth failure, small head circumference, developmental delay and micrognathia, and relatively high IGF-1 levels [47]. The IGF-1 levels reported in previous literatures ranged from -2.78 to 2.9 SDS. The IGFBP3 levels were between -1.33 and +1.24 SDS [47-49]. A heterozygous mutation could result in a reduced amount of wild-type IGF1R protein and impaired postreceptor IGF-1 signaling [50].

CONCLUSION

Growth is a complex process involving various genetic factors both pre- and postnatally. Recent advancements in genetics have improved the molecular diagnosis for patients with short statures. Clinicians should be aware of the clinical characteristics of patients to consider genetic testing and use a broad-based genetic approach in children with short stature.

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