Idiopathic short stature: will genetics influence the choice between GH and IGF-I therapy?

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Abstract

Background: Idiopathic short stature (ISS) includes a range of conditions. Some are caused by defects in the GH–IGF-I axis. ISS is an approved indication for GH therapy in the USA and a similar approval in Europe may be imminent. Genetic analysis for single-gene defects has made enormous contributions to understanding the physiology of growth regulation. Can this type of investigation help in predicting growth responses to GH or IGF-I therapy?

Methods: The rationale for choice of GH or IGF-I therapy in ISS is reviewed. Many ISS patients have low IGF-I, but most can generate IGF-I levels in response to short-term GH administration. Some GH resistance seems to be present. Mutation analysis in several cohorts of GHIS and ISS patients is reviewed.

Results: Low IGF-I levels suggest either unrecognised GH deficiency or GH resistance. In classical GHIS patients, there was a positive relationship between IGFBP-3 levels and height SDS. No relationship exists between mutations and phenotype. There is a wide variability of phenotype in patients carrying identical mutations. Heterozygous GH receptor (GHR) mutations were present in 5% of ISS patients and their role in causing growth defects is questionable. Exceptions are dominant negative mutations that have been shown to disturb growth.

Conclusions: Analysis for single-gene defects does not give sensitive predictions of phenotype and cannot predict responses to GH or IGF-I therapy. Endocrine abnormalities have closer correlations with phenotype and may thus be a better guide to therapeutic responsiveness.

Introduction

The child with short stature presents a diagnostic puzzle in which the clinical phenotype, endocrine characteristics and genetic factors may all contribute to the categorisation of the patient into a specific diagnostic group. The development of molecular genetics has changed the face of diagnostic endocrinology and there may be a temptation to short-circuit the traditional process of clinical evaluation through careful history taking, detailed clinical assessment and appropriate investigations. The analysis of the patient’s genotype without taking into account these fundamental steps should not be encouraged, because the interpretation of the genetic findings can only be performed in the light of the knowledge of the extent to which an endocrine mechanism is disturbed and hence attributable to the genetic defect.

The term idiopathic short stature (ISS) is descriptive of a wide range of short children without specific aetiologies (1). In the ISS patient, specific causes such as growth hormone (GH) deficiency, Turner syndrome, short stature due to birth weight, small for gestational age, other dysmorphic syndromes and chronic paediatric illness have been excluded. The exclusion of these causes leaves a large heterogeneous selection of children with short stature, which will include patients with genetic or familial short stature, constitutional growth delay and those who are abnormally short for their parental target height, who might have an unrecognised endocrine defect (1, 2).

It is this latter group that is important from the therapeutic point of view. In broad terms, if patients in this group have unrecognised GH deficiency, they will respond well to GH therapy, whereas if they have GH resistance, they may be candidates for treatment with recombinant human insulin-like growth factor-I.
Endocrine features of ISS

By definition, children with ISS have normal GH secretion, which is almost always investigated by a pharmacological GH provocation test. Assessment of spontaneous GH secretion is very rarely included in the clinical evaluation of short stature. The entity of GH neurosecretory dysfunction (3) remains controversial; however, most clinicians have seen patients conforming to the description of a short child with a normal peak GH value after pharmacological stimulation, who is growing slowly and responds well to GH therapy. Our group studied spontaneous GH secretion in a series of ISS patients and found that overall mean GH secretion was slightly decreased (4). GH secretion, expressed in SDS, compared with 66 normal stature controls was: basal GH $-0.48$ ($-0.84–0.93$), height of GH peaks compared with zero $-0.36$ ($-1.26–1.51$; both $P<0.05$), total GH secretion $-0.76$ ($-1.22–0.42$) and total GH secretion above baseline $-0.67$ ($-1.21–0.94$; both $P<0.01$).

Children with ISS have relatively normal levels of GH binding protein (GHBP). However, some patients who had been selected for treatment with GH were found to have low concentrations of GHBP suggesting reduced GH receptor (GHR) function (5). These patients tend to have lower IGF-I levels yet higher endogenous GH secretion, suggestive of partial GH insensitivity (6). Baseline IGF-I levels are usually low to low normal in children with ISS (4). However, the degree of IGF-I deficiency in ISS is less marked than that in severe GH deficiency or in classical or atypical GHI patients.

Some studies of the IGF-I generation test in children with ISS have demonstrated that IGF-I and IGF binding protein (IGFBP-3) production is reduced, consistent with some degree of GH resistance, but remains much greater than in patients with homozygous GHR defects (7). Our group demonstrated satisfactory IGF-I and IGFBP-3 generation during standard and low-dose IGF-I generation tests, indicating that most children with ISS can respond to short-term stimulation with GH (4). Abnormalities of the GH–IGF-I axis in ISS patients are well recognised (8).

Genetic studies in ISS

An overlap exists between ISS patients and those with partial or atypical GH insensitivity (GHI). This was appreciated from the study of the European cohort of GHI patients (9), some of whom did not have the typical appearance of Laron syndrome. In fact, some had milder short stature and normal facial appearance with less biochemical abnormalities (10).

It should be emphasised here that no relationship was demonstrated between homozygous mutations of the GHR and clinical phenotypes in the European GHI series (11). This contrasted with the close positive relationship which was reported between the biological defect, expressed as IGFBP-3 SDS values, and height SDS scores (11).

In 1997, Ayling et al. provided new insights into the genetics of abnormal growth from the study of a family with short stature without Laron syndrome features (12). The child and her mother were reported to have the first heterozygous mutation with a dominant negative effect. The mutation (IVS8as-1 G→C) was situated in the acceptor splice site of intron 8 resulting in the skipping of exon 9 and the production of a truncated GHR. The mutant GHR formed heterodimers with the wild-type GHR and exerted a dominant negative effect on the normal protein. A second mutation (IVS9ds+1 G→A) leading to the same consequence was described by Iida (13). Both patients had positive GHBP and normal facial appearance.

We described a similar phenotype in four siblings with a mutation causing the insertion of a pseudoexon between exons 6 and 7 (14). The 108 bp insertion caused the addition, in frame, of 36 amino acids between codons 206 and 207 (Fig. 1). We predicted that this would affect dimerisation of the receptor; however, crystal structure modelling of the mutant GHR showed no alteration of the dimerisation domain and cell studies resulted in a defect in trafficking. A more recent report described our further experience of several more patients with this mutation; however, the lack of genotype–phenotype correlation remains (15).

Further heterozygous GHR mutations in ISS

Patients with ISS and normal GH secretion have been evaluated for GHR abnormalities. Although more than

![Figure 1](https://www.eje-online.org)

**Figure 1** Aberrant splicing in the GH receptor gene. The nucleotide base change (A→G) activates the pseudoexon (6ψ) and causes splicing in of 36 amino acids, in frame, between codons 206 and 207 of the mature protein.
60 molecular defects in the GHR have been described (16), the majority of ISS patients have been found to have normal coding regions of the GHR.

In 1995, Goddard et al. studied a group of ISS patients with low serum GHBP suggestive of partial GHIS (17). Four patients had heterozygous GHR mutations. In a compound heterozygote, the two deleterious mutations (E44K and R161C) would explain the patient’s short stature. In the other three cases, there may have been a second unidentified mutation in the intracellular domain giving rise to the ISS because the trans-membrane and intracellular domains of these patients were not sequenced. Further to this, Goddard’s group studied 100 patients across the spectrum of ISS, resulting in the discovery of three more carriers of heterozygous extracellular mutations and one patient with a heterozygous mutation (A478T) in exon 10 (18). Similarly a study of 17 ISS subjects found a novel heterozygous mutation (V144I) in exon 6 of one patient and no mutation on the other allele (19). Another study of 26 ISS patients resulted in one patient with a heterozygous GHR mutation described previously (R161C; 20). A more recent study of 37 patients with ISS revealed two novel GHR mutations (21; C94C, V144A) not found in 100 controls. These studies relied primarily on the examination of exons by single-strand conformational analysis rather than complete sequencing of the GHR gene. In summary, it can be estimated that not more than 5% of patients with ISS have heterozygous GHR mutations, of which the role on causing growth disturbance remains uncertain (Fig. 2).

**Single-nucleotide polymorphisms and short stature**

Polymorphisms in the GHR have also been identified in patients with ISS. Two mutations (C422F and P561T) were associated with ISS, but proof is lacking that either of these is functional. No difference in signalling between the wild-type and mutant C422F GHR was demonstrated (22). The P561T change was found in 15% of the normal population and showed no correlation with height (23).

**New genetic defects of GH action relevant to short stature**

**GHR intracellular signalling (STAT5b) defects**

Two studies have shown the absence of GH-induced tyrosine phosphorylation of the STAT protein in patients with ISS, but the authors could not identify any mutations in these patients (24, 25). Only recently did the first reports appear of a defect in the GH-signalling cascade. Kofod et al. reported a homozygous mutation in exon 15 of the STAT5b gene and demonstrated that the mutant protein could not be activated by GH, therefore failing to activate gene transcription (26). This child had features of severe GHI together with immunodeficiency consistent with a non-functional STAT5b.

On careful scrutiny of the different cases reported, now numbering seven, and recently reviewed by Rosenfeld et al. (27), it is clear that this genetic mutation is associated with a growth phenotype, which is subtly less severe than that seen in Laron syndrome caused by a homozygous GHR mutation. Our own experience of two cases agrees with this. Nevertheless, the biochemical features demonstrate severe and unequivocal GHI.

**Acid-labile subunit (ALS) defect**

IGF-I, the key GH-dependent effector protein regulating human growth, circulates as a ternary complex consisting of IGF-I, IGFBP-3 and ALS (28). An ALS knock out animal model provided new insights into the role of ALS in the IGF-I system, with growth deficits seen 3 weeks after birth (29). GH levels were normal, however, IGF-I and IGFBP-3 were significantly decreased. In 2004, Domene et al. (30) reported the first case of an inactivating ALS mutation. The defect was a guanine deletion at position 1338, resulting in a frameshift and the appearance of a premature stop codon (1338delG, E35fsX120). The patient had minimal post-natal growth impairment but basal GH levels were increased, associated with reduction in IGF-I and IGFBP-3, and undetectable ALS, unresponsive to stimulation by GH. Several additional cases of ALS mutation have since been reported. The relatively subtle growth defect could be explained by the preservation of local IGF-I production in the growth plate stimulated by an up-regulated GHR (Fig. 3).
GH or IGF-I therapy for ISS?

As discussed above, ISS comprises a wide selection of patients with differing causes of short stature. Some may have a degree of GH deficiency and respond well to GH replacement, whereas others may have GH resistance and benefit more from IGF-I therapy. Experience of IGF-I therapy in ISS patients has not yet been reported.

On the other hand, there are now many reports of GH therapy in ISS (31–34). The FDA approved GH for therapy in ISS in 2003 and this review will not discuss the benefits of GH therapy in non-GH-deficient short stature patients. As might be expected in any heterogeneous group of patients, there will be good responders and those who do not respond well. This is clearly, to some extent, a function of GH responsiveness or sensitivity. Circulating IGF-I levels during treatment correlate with the degree of response (35).

Conclusions

Genetic analysis has brought an additional dimension to the investigation of short stature. However, the nature of a particular mutation does not provide a sensitive prediction of the response to a specific growth-promoting therapy. Genotype–phenotype correlations are poor in the field of GH-resistant disorders. A better prediction of growth can be achieved by the study of basal and stimulated IGF-I levels. The identification of a specific single-gene mutation is, however, of great importance in clarifying the aetiology of a growth defect, as demonstrated by STAT5b and ALS mutations. Identification of gene defects, as opposed to polymorphisms, can help to elucidate physiological mechanisms, but currently fall short of sensitive predictions of optimal therapeutic choices or responsiveness.

Disclosure

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