Deficiency of the Insulin-Like Growth Factor-Binding Protein Acid-Labile Subunit (ALS) of the Circulating Ternary Complex in Children with Short Stature

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Abstract

The acid-labile subunit (ALS) protein is a key component of the circulating 150-kDa IGF ternary complex. The main role of ALS is the extension of IGF-I half life by protecting it from degradation and preventing the passage of IGF-I to the extravascular compartment. In humans, complete ALS deficiency is characterized by severe reduction of IGF-I and IGFBP-3 that remain low after GH treatment, associated with mild growth retardation, much less pronounced than the IGF-I deficit. Pubertal delay in boys and insulin insensitivity are common findings. At least 21 patients with ALS deficiency have been described presenting 16 different homozygous or compound heterozygous inactivating mutations of the IGFALS gene. Although the effect of ALS deficiency on prenatal growth is still uncertain, postnatal growth is clearly affected, with the majority of the patients presenting a height between -2 to -3 SDS before and during puberty. In the assessment of a child with short stature ALS deficiency should be considered in those patients presenting: 1) a normal response to GH stimulation test, 2) low IGF-I levels associated with more profoundly reduced IGFBP-3 levels, 3) a mild growth retardation, apparently out of proportion to the degree of IGF-I and IGFBP-3 deficits, 4) lack of response to an IGF generation test and 5) insulin insensitivity.

The relatively mild growth retardation in relation to the severe IGF-I deficit might be related to the preserved autocrine/paracrine action of locally produced IGF-I. The observation that in families of ALS deficient patients, heterozygous carriers for IGFALS gene mutations, are shorter than their wild type relatives and the relatively high frequency of heterozygosity for this gene in children with idiopathic short stature suggests a requirement of normal levels of ALS for the attainment of maximal growth potential.

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***Key words**: Acid-Labile Subunit; Insulin-Like Growth Factor-I; Insulin-Like Growth Factor Binding Protein; Growth Hormone Insensitivity; IGFALS Gene Mutations*

Background

The insulin-like growth factors (IGF-) I and II play a critical role in pre and post natal mammalian growth (1). The growth promoting actions of these two growth factors are exerted through binding to the type I receptor (IGF1R), a transmembrane receptor belonging to the tyrosine kinase family of receptors (2). The mannose-6-phosphate, or IGF type II receptor, with higher affinity for IGF-II than IGF-I, acts predominantly as a scavenger receptor, allowing the rapid depuration of IGF-II. In the fetus, these two growth factors are ubiquitously expressed, mainly acting close to the place of synthesis by paracrine/autocrine mechanisms. However, low concentrations of IGFs are found in the circulation mostly as 50 kDa binary complexes with IGFBP-2. After birth IGFs, specially IGF-I, are stimulated by growth hormone (GH) and although IGF-I expression remains in almost all tissues, liver IGF-I shows the higher level of expression and constitutes

the source of the majority of circulating IGF-I. Although in the circulation IGFs can form binary complexes with six high affinity IGF binding-proteins (IGFBP-1 to -6), they are found mostly in a 150-kDa ternary complex consisting of a molecule of IGFBP-3 or -5, a molecule of IGF-I or -IGF-II and a unique acid-labile subunit (ALS) (3). This 84-86 kDa glycoprotein, first suggested by the observation that acidification results in the dissociation of the ternary complex (4), belongs to the superfamily of leucine-rich repeat (LRR) proteins, characterized by their ability to participate in protein-protein interactions (5). ALS has a relatively high affinity for the IGFs/IGFBP-3 or -5 binary complexes forming ternary complexes with no discernible affinity for isolated IGF-I or IGFBP-3. In the circulation up to 85% of the IGFs circulate in these ternary complexes, 10-15% in binary complexes with IGFBPs and less than 1% as unbound or free IGF-I (6). While the half life of free IGF-I is approximately 10 min, it is extended to 30-90 min when in binary complexes, and to more than 12 hours when in the ternary complexes (7).

ALS protein has received much less attention compared with other IGFBPs, probably due to its completely different structure and its relatively lower affinity for complexed IGFs compared to other IGFBPs (8). However, the development of an animal model for ALS deficiency (the ALS-KO mouse) (9) and the description of a patient with an inactivating mutation of the *IGFALS* gene (10), have demonstrated the important physiological role of this protein in the circulating IGF system and the impact of its absence on postnatal growth as well as on carbohydrate and probably on bone metabolisms. In this review we will discuss the recent findings of auxological and metabolic consequences of human ALS deficiency and will elaborate on the clinical significance of the characterization of the *IGFALS* gene in children with short stature.

ALS Deficiency

Complete ALS deficiency, the result of homozygous inactivation of the *IGFALS* gene, was first described in a 14.6 year old boy with mild growth retardation, marked reduction of IGF-I and IGFBP-3 levels that remained low after GH stimulation, associated with pubertal delay and insulin resistance (10).

Since the original report, 20 additional patients have been diagnosed with this condition (11-19), suggesting that complete ALS deficiency could be more prevalent than previously suspected. Sixteen different mutations of the *IGFALS* gene have been identified, and while twelve patients harbor homozygous, nine present compound heterozygous mutations (**Table 1**). Consanguinity was reported in only 3 of the 16 families studied, suggesting that heterozygous carriers for *IGFALS* mutations may be present in the general population. All reported mutation are encoded by exon 2 of the *IGFALS* gene including 9 missense, 1 nonsense, 4 frameshift and 2 in-frame duplications (**Table 1** and **Figure 1**). ALS levels were completely absent or barely measurable in these patients indicating that, regardless the type of mutation, all result in mutated proteins that are unable to be normally secreted or that they are unstable and rapidly cleared from the circulation.

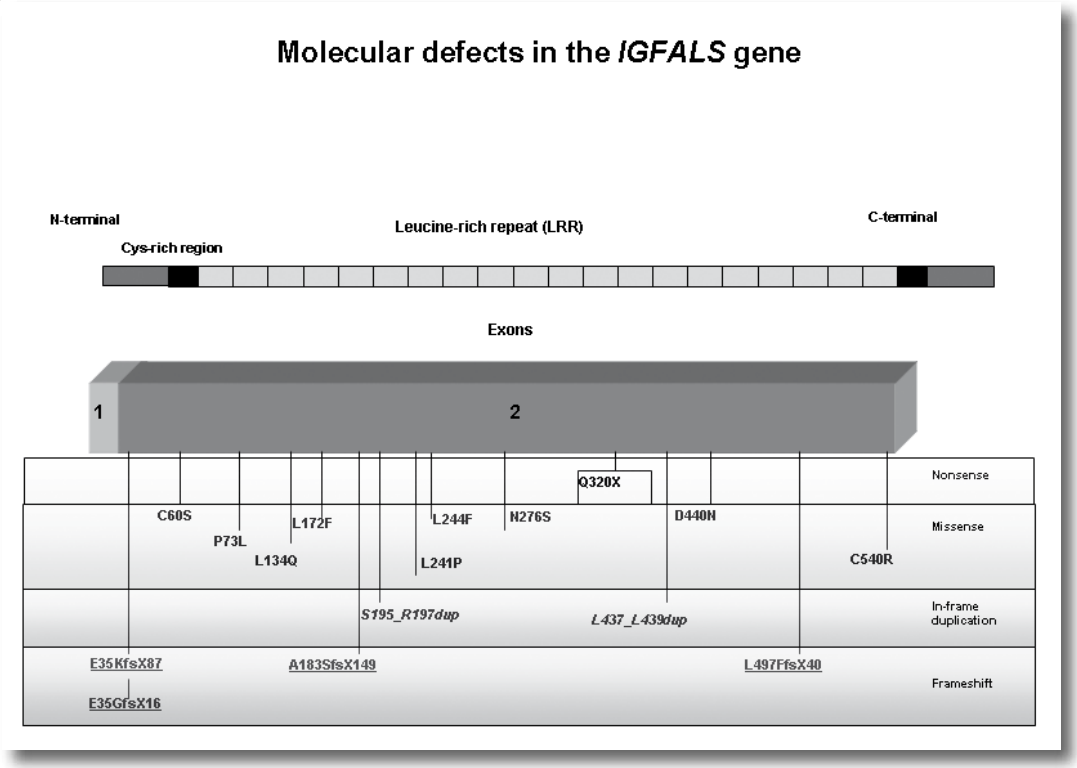

***Figure 1**. Schematic representation of the ALS protein and the IGFALS gene indicating the position of 16 described homozygous and compound heterozygous mutations*

Mutation N	Protein	Type of Mutation	Homozygous / Heterozygous	Ethnic Origin	Reference Number
1.	p.E35KfsX87	Frameshift, premature stop codon	Homozygous	Argentinean	10
2.	p.D440N	Missense	Homozygous	Turkish	11
3.	p.C540R	Missense	Compound	Norwegian/German	12
4.	p.S195_R197dup	In-frame duplication of 3 amino acids, SLR	heterozygous		
5.	p.N276S	Missense	Homozygous	Spanish	13
6.	p.Q320X	Nonsense	Homozygous	Spanish	
7.	p.L497FfsX40	Frameshift, premature stop codon	Homozygous	Kurdish	14
8.	p.L437_L439dup	In-frame duplication of 3 amino acids, LEL.	Homozygous	Mayan	15
9.	p.C60S	Missense	Compound	Jewish/Eastern European	
10.	p.L244F	Missense	heterozygous	(Polish, Russian, Austrian-Hungarian)/Icelandic/ European (French, English)	
11.	p.L134Q	Missense	Homozygous	Indian/Pakistani	
12.	p.P73L	Missense	Compound	Ashkenazi Jewish	
13.	p.L241P	Missense	heterozygous		
11.	p.L134Q	Missense	Compound heterozygous	British Asian	17
14.	p.A183SfsX149	Frameshift, premature stop codon			
12.	p.P73L	Missense	Homozygous	British Asian	
15.	p.L172F	Missense	Homozygous	Swedish	18
15.	p.L172F	Missense	Compound heterozygous	Swedish	
4.	p.S195_R197dup	In-frame insertion of 3 amino acids, SLR	Compound heterozygous		
5.	p.N276S	Missense	Compound heterozygous	Spanish	19
16.	p.E35GfsX17	Frameshift, premature stop codon			

The amino acid numbering system was based on the precursor protein, with the initial methionine numbered as +1

***Table 1**. Reported mutations in the IGFALS gene in patients with complete ALS deficiency*

ALS deficiency has been classified as a particular type of GH insensitivity because patients with this condition present short stature associated with normal GH response to pharmacological tests, and subnormal levels of IGF-I and IGFBP-3 (20) (**Table 2**). In addition, a lack of response of IGF-I and IGFBP-3 to short term GH administration has also been observed together with lack of change of these factors and insufficient response in growth acceleration to GH therapy. However, in contrast to other IGF-I deficient/GH insensitivity syndromes, ALS deficiency presents different phenotypic characteristics: 1) a predominant reduction of IGFBP-3 levels compared with those of IGF-I; and 2) an out of proportion reduction in IGF-I and IGFBP-3 deficit compared to the mild effect on post natal growth. Indeed, while IGF-I levels were -5.81±2.68 SDS and IGFBP-3 levels -9.84±6.12 SDS in 15 ALS deficient patients, their height deficit was only of -2.63±0.92 SDS (**Figure 2**). Different explanations have been suggested to explain this lack of proportion between the severity of IGF deficiency and its relative modest impact on post natal growth (the "mismatch syndrome" as it has been referred to by Dr. M.O. Savage). Although normal free-IGF-I levels could possibly maintain growth near normal limits (21), when they were measured, free- and also bio-IGF-I

levels showed to be below normal limits (22). It was also proposed that since ternary complex formation, responsible for maintaining IGF-I in the vascular compartment, is not formed without ALS, an increased efflux of IGF-I could impact on peripheral tissues without accumulation in the circulation. However, this hypothesis sounds also unlikely because it is difficult to envisage how liver IGF-I, the main source of circulating IGF-I, could reach its distant target (the growth plates in long bones) before being rapidly cleared from the circulation. The most likely explanation for the relative preservation of growth in ALS-deficient patients is in agreement with observations derived from mouse models showing that: 1) conditional KO of liver IGF-I, resulting in marked circulating IGF-I deficiency, has little or no effect on post natal growth (23) and 2) that ALS-KO mouse with similar reduction of IGF-I and IGFBP-3 and lack of ALS had only a 13% reduction in size compared to control mouse (24). These findings suggest that, in ALS-deficient children, locally produced IGF-I under the stimulation of normal, or even increased GH levels, is able to sustain post natal growth close to normal limits by acting through an autocrine/paracrine mechanism.

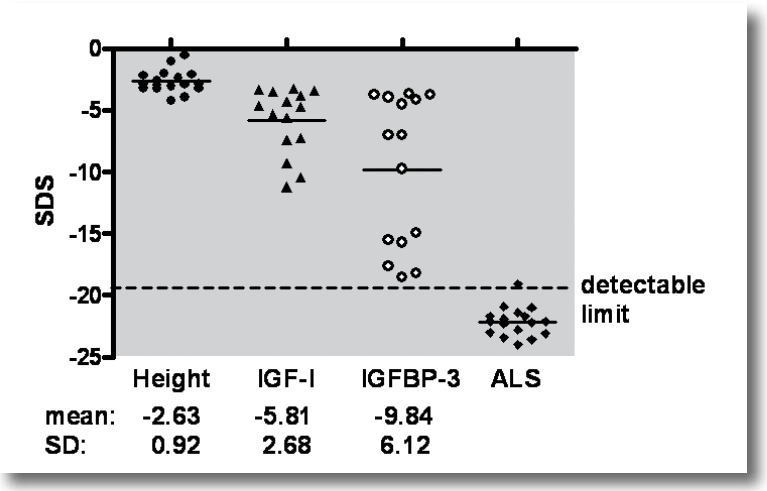

***Figure 2**. Height and IGF-I, IGFBP-3 and ALS levels are expressed in SDS in 15 children and adolescents with ALS deficiency*

1) Congenital defects
GH receptor (*GHR*) gene defects
- Extracellular domain mutations
- Transmembrane domain mutations
- Intracellular domain mutations

GH signal transduction defects
- *STAT5b* gene mutations
- *IKBKG* gene mutations

IGF transport defects
- *IGFALS* gene defects

IGF-I synthesis or action defects
- IGF1 gene mutations (including bioinactive IGF-I)
- IGF1R gene mutations

2) Acquired defects
- Malnutrition
- Parenchymal liver diseases
- Type 1 diabetes
- Catabolic states
- Chronic inflammatory diseases
- GH neutralizing antibodies

***Table 2**. Growth hormone insensitivity syndromes*

Impact on the IGF System

In ALS deficiency, levels of IGF-I and -II are reduced (13,14,22), while IGFBP-3 levels are more diminished. In addition, levels of IGFBP-1 and IGFBP-2 are frequently reduced, although to a lesser degree. Thus, ALS deficiency results in a generalized deficiency of the circulating IGF system affecting the two ligands (IGF-I and IGF-II) as well as the most abundant circulating IGFBPs: IGFBP-1, -2, and -3. As the result of IGF-I deficiency feedback inhibition of GH secretion is impaired and spontaneous or stimulated GH secretion is usually increased. However, despite IGF-I levels being reduced to a similar degree to that in GH insensitivity resulting from either GHR or STAT5b gene mutations, the increase in GH secretion is only moderate. This suggests that the feed back control of GH secretion by IGF-I is not only mediated by circulating IGF-I, but that local hypothalamic IGF-I production may also contribute to control of GH synthesis and secretion (**Figure 3**). Supporting this interpretation, a possible physiological inhibitory effect of hypothalamic expressed IGF-I on GH secretion has been shown, acting by decreasing GHRH expression and enhancing somatostatin expression (25,26).

Insulin Insensitivity is a Common Finding in ALS Deficiency

In those patients in whom carbohydrate metabolism has been explored, insulin insensitivity was revealed by: 1) high basal or glucose-stimulated insulin levels, 2) elevated HOMA index (homeostasis model assessment index) with normal glucose levels, and 3) low IGFBP-1 levels (16). The pathophysiological mechanism involved is not completely understood, but increased GH levels may contribute to impaired insulin action

by multiple mechanisms (increased levels of free fatty acids by the lipolytic effect of GH excess, impairment of insulin signaling by cross talk between GH receptor and insulin receptor signaling pathways, among others) (27,28). However, it seems unlikely that the mild elevation of GH levels observed in ALS-deficient patients can be the only cause of insulin insensitivity. Since IGF-I is able to improve glucose uptake, particularly by skeletal muscle, it is likely that the marked decrease in IGF-I levels may also contribute to the insulin insensitivity observed in these patients (29).

Bone Metabolism

In agreement with the observed reduction in total bone mineral density (BMD) in ALS knockout mice (30), the first described ALS-deficient patient presented a marked reduction in BMD at lumbar spine (z-score -4.7 SDS at 16 year of age), with a partial recovery after puberty (-2.1 SDS at the age of 19) (31). Severely reduction in BMD was also reported in two of the ALS-deficient patients from Kurdistan, who have had fracture after minor trauma. However, as reduction of BMD was also present in heterozygous carriers and wild type relatives, a different factor not related to ALS could be involved in this highly consanguineous family (14). Furthermore, in other ALS-deficient patients BMD was reported to be normal (13).

Growth in ALS-Deficient Patients

Mutations in the *IGFALS* gene have been reported in children and adults of short stature presenting with low levels of IGF-I and IGFBP-3. However, the association of ALS deficiency with growth retardation may represent some degree of ascertainment bias, as measurements of IGF-I and IGFBP-3 levels are not usually determined in individuals of normal stature.

The effect of ALS deficiency on prenatal growth is still uncertain because length and weight at birth have been reported in only a few patients. However, the observed mean birth weight of -1.0 SDS suggests that this condition may produce some mild deleterious effect (16). Postnatal growth was clearly affected, with the majority of the patients presenting a height between -2 and -3 SDS before and during puberty. Because pubertal delay has been observed in at least half of the male patients, it is not surprising that adult height SDS was found to be greater

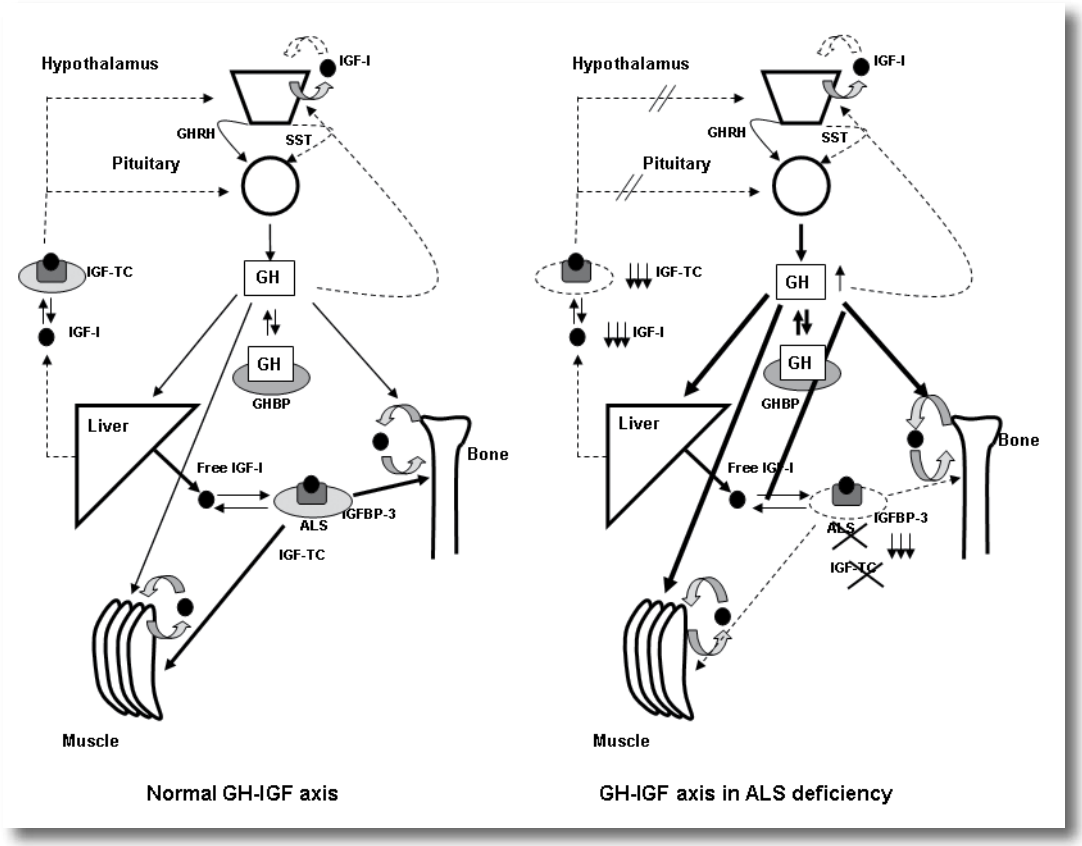

***Figure 3**. The IGF system in ALS deficiency*
In normal situations GH promotes IGF-I synthesis on both liver and extrahepatic tissues (bone and muscle among others). Circulating IGF-I, mostly derived from liver, associates to IGFBP-3 and ALS in a 150-kDa ternary complex (IGF-TC) that extend half life of both IGF-I and IGFBP-3. In ALS-deficient patients, harboring inactivating mutations of two IGFALS gene alleles, ALS is not present in the circulation, levels of IGF-I and IGFBP-3 are both markedly reduced and feed back inhibition on hypothalamus of GHRH is decreased with the consequent increase in GH secretion. Despite the marked reduction in circulating IGF-I, locally expressed IGF-I may act normally by paracrine/ autocrine mechanisms, maintaining linear growth near to normal limits.
Solid lines indicate stimulation effects (with thicker lines indicating greater effects), while dashed lines denote inhibitory effects. GHRH: growth hormone- releasing hormone; SST: somatostatin; GHBP: growth hormone-binding protein; IGF-TC: insulin-like growth factor ternary complex.

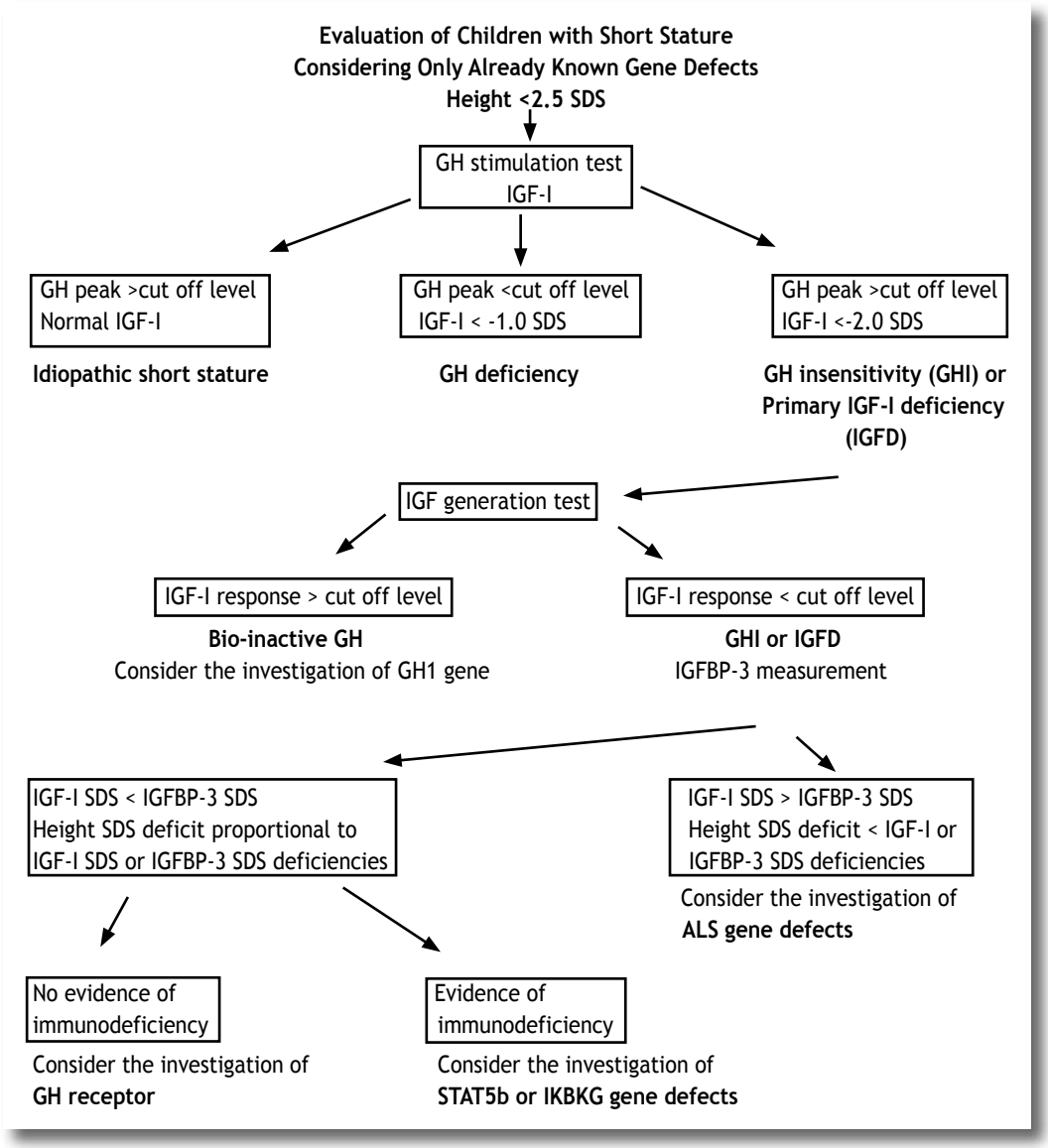

***Table 3**. Flow chart for the diagnosis of known gene defects resulting in GH insensitivity (GHI) or primary IGF-I deficiency (IGFD)*

than prepubertal height, but still around 1.0 SDS lower than midparental target height SDS (16). When growth spurt was documented, it was normal (12,13,22), resulting in an improvement in post pubertal height SDS. However, in some cases, a subnormal growth spurt rendered these patients into more profoundly reduced adult height (14).

A limited response to GH treatment (periods from 6 months to 2 years) in ALS- deficient patients has been observed (10,12,13,15). IGF-I therapy was initiated in a patient after a poor response to GH treatment, but its response has not yet been reported (15).

When Should We Suspect ALS Deficiency in a Patient with Short Stature?

The prevalence of ALS deficiency is unknown at present in non GH-deficient children with short stature. Although it is clear that some patients with complete ALS deficiency may present with normal height, ALS deficiency resulting from *IGFALS* gene mutations, should be considered in children with short stature presenting most of the following characteristics: 1) a normal response to GH stimulation test, 2) low levels of IGF-I associated with more profoundly reduced IGFBP-3 levels, 3) mild growth retardation, apparently out of proportion to the degree of IGF-I and IGFBP-3 deficits, 4) lack of response of IGF-I and IGFBP-3 to an IGF generation test, 5) insulin insensitivity characterized by normal glucose levels in the face of elevated insulin levels, and 6) pubertal delay, especially in male patients. **Table 3** illustrates a flow-chart for the study of children with short stature, with special attention to the characterization of already known gene defects associated with GH insensitivity syndromes, particularly ALS deficiency.

Is There an Effect of Heterozygosity for IGFALS Gene Mutations in Post Natal Growth?

The observation that mean parental height obtained from heterozygous carriers for *IGFALS* gene mutations is approximately 1.3 SDS below population's mean, suggests that carrying a mutated *IGFALS* allele may lead to a mildly affected growth phenotype (14,16,32). Two independent preliminary reports have shown a relatively high frequency of heterozygosity for *IGFALS* gene mutations in children with idiopathic short stature (33,34). It has been observed that: 1) heterozygous carriers usually exhibit decreased levels of IGF-I, IGFBP-3 and ALS, and 2) in families of ISS children, short stature and low levels of members of the IGF system segregate with heterozygous status. These findings indicate that both gene alleles are required to maintain optimal ALS levels and to fulfill growth potential, suggesting a possible involvement of haploinsufficiency of *IGFALS* gene in the etiology of short stature in a subset of short children presenting reduced levels of IGF-I and IGFBP-3. *In vitro* characterization of the binding properties of mutated ALS proteins and the impact on ternary complex formation is required to confirm the involvement of haploinsuficiency of *IGFALS* gene on post natal growth. These studies (33,34) have expanded the spectrum of *IGFALS* gene defects in children with abnormal growth and have confirmed the crucial role of ALS in maintaining the integrity of the circulating IGF system.

Final Remarks

ALS deficiency has been described in South and North America and in Europe in patients from diverse ethnical background, suggesting that it may be more prevalent than originally expected. In contrast to other autosomal recessive diseases, most of ALS deficient patients belong to non-consanguineous families. An hypothetical explanation for this finding is that in contrast to what is observed in patients carrying mutations in other genes of the GH-IGF axis (such as GHR or STAT5b), homozygous or compound heterozygous for IGFALS gene mutations might not be under a strong negative selection pressure, and because fertility is expected to be preserved, this may result in a relatively greater prevalence of heterozygous carriers in the population.

It is remarkable that not a single patient with a complete inactivation of the IGFBP-1 to -6 has yet been described, suggesting that due to the overlapping and relatively redundant actions of these proteins, the effect of lacking a single IGFBP may well be compensated by the remaining IGFBPs, while the requirement for ALS in ternary complex formation, and the resulting effect in the extension of IGF-I and IGFBP-3 half life, could not be compensated for by other members of the IGFBP family.

Another important physiological consequence of complete ALS deficiency is that this condition supports the concept that normal circulating IGF-I levels are not a requirement to sustain almost normal post natal growth. In ALS deficiency, the unaffected synthesis and autocrine/paracrine action of IGF-I might sustain growth near or even within normal limits. However, growth promoting actions of circulating IGF-I are evident and a normal circulating IGF system is necessary to fulfill full growth potential.

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References

1. Stewart CE, Rotwein P. Growth, differentiation, and survival: multiple physiological functions for insulin-like growth factors. Physiol Rev 1996;76:1005-1026
2. Ullrich A, Gray A, Tam AW, Yang-Feng T, Tsubokawa M, Collins C, Henzel W, Le Bon T, Kathuria S, Chen E, Jacobs S, Francke U, Ramachandran J, Fujita-Yamaguchi Y. Insulin-like growth factor I receptor primary structure: comparison with insulin receptor suggests structural determinants that define functional specificity. EMBO J 1986;5:2503-2512
3. Baxter RC, Dai J. Purification and characterization of the acid-labile subunit of rat serum insulin-like growth factor binding protein complex. Endocrinology 1994;134:848-852
4. Furlanetto RM. The somatomedin C binding protein: evidence for an heterologous subunit structure. J Clin Endocrinol Metab 1980;51:12-19
5. Janosi JB, Ramsland PA, Mott MR, Firth SM, Baxter RC, Delhanty PJ. The acid-labile subunit of the serum insulin-like growth factor-binding protein complexes. Structural determination by molecular modeling and electron microscopy. J Biol Chem 1999;274:23328-23332
6. Baxter RC. Circulating levels and molecular distribution of the acid-labile a-subunit of the high molecular weight insulin-like growth factor-binding protein complex. J Clin Endocrinol Metab 1990;70:1347-1353
7. Guler H-P, Zapf J, Schmid C, Froesch ER. Insulin-like growth factors I and II in healthy man. Estimations of half-lives and production rates. Acta Endocrinol 1989;121:753-758
8. Boisclair YR, Rhoads RP, Ueki I, Wang J, Ooi GT. The acid-labile subunit (ALS) of the 150kDa IGF-binding protein complex: an important but forgotten component of the circulating IGF system. J Endocrinol 2001;170:63-70
9. Ueki I, Ooi GT, Tremblay ML, Hurst KR, Bach LA, Boisclair YR. Inactivation of the acid labile subunit gene in mice results in mild retardation of postnatal growth despite profound disruptions in the circulating insulin-like growth factor system. Proc Nat Acad Sci 2000; 97:6868-6873
10. Domené HM, Bengolea SV, Martinez AS, Ropelato MG, Pennisi P, Scaglia P, Heinrich JJ, Jasper HG. Deficiency of the circulating insulin-like growth factor system associated with inactivation of the acid-labile subunit gene. New Engl J 2004:350:570-577
11. Hwa V, Haeusler G, Pratt K, Little B, Frisch H, Koller D, Rosenfeld R. Total absence of functional acid labile subunit, resulting in severe insulin-like Growth factor deficiency and moderate growth failure. J Clin Endocrinol Metab 2006;91:1826-1831

12. Domené HM, Scaglia PA, Lteif A, Mahmud FH, Kirmani S, Frystyk J, Bedecarrás P, Gutiérrez M, Jasper HG. Phenotypic effects of null and haploinsufficiency of acid-labile subunit in a family with two novel IGFALS gene mutations. J Clin Endocrinol Metab 2007;92:4444-4450
13. Heath KE, Argente J, Barrios V, Pozo J, Díaz-González F, Martos-Moreno GA, Caimari M, Gracia R, Campos-Barros A. Primary acid-labile subunit deficiency due to recessive IGFALS mutations results in postnatal growth deficit associated with low circulating insulin growth factor (IGF)-I, IGF binding protein-3 levels, and hyperinsulinemia. J Clin Endocrinol Metab 2008;93:1616-1624
14. Van Duyvenvoorde HA, Kempers MJ, Twickler TB, van Doorn J, Gerver WJ, Noordam C, Losekoot M, Karperien M, Wit JM, Hermus AR. Homozygous and heterozygous expression of a novel mutation of the acid-labile subunit. Eur J Endocrinol 2008;159:113-120
15. Fofanova-Gambetti OV, Hwa V, Kirsch S, Pihoker C, Chiu HK, Högler W, Cohen LE, Jacobsen C, Derr MA, Rosenfeld RG. Three novel IGFALS gene mutations resulting in total ALS and severe circulating IGF-I/IGFBP-3 deficiency in children of different ethnic origins. Horm Res 2009;71:100-110
16. Domené HM, Hwa V, Argente J, Wit JM, Camacho-Hübner C, Jasper HG, Pozo J, van Duyvenvoorde HA, Yakar S, Fofanova-Gambetti OV, Rosenfeld RG; International ALS Collaborative Group. Human acid-labile subunit deficiency: clinical, endocrine and metabolic consequences. Horm Res 2009;72:129-141
17. David A, Rose S, Miraki-Moud F, Metherell L, Klark A, Savage M, Camacho-Hubner C. Acid-labile subunit gene mutations: clinical, biochemical and molecular study in two unrelated families. Horm Res 2008;70 (Suppl 1):31. Abstract, 71st Annual Meeting of the European Society for Pediatric Endocrinology, Istanbul, Turkey, September 30-23, 2008
18. Bang P, Fureman A-L, Nilsson A-L, Boström J, Kriström B, Ekström K, Hwa V, Rosenfeld R, Carlsson-Skwirut C. A novel missense mutation of the ALSIGF gene causing a L172F substitution in LRR6 is associated with short stature in two Swedish children homozygous or compound heterozygous for the mutation. Horm Res 2009;72 (Suppl 3):86. Abstract, 8th Joint LWPES/ESPE Meeting, New York, September 9-12, 2009
19. Gallego-Gomez E, Sanchez del Pozo J, Rojo JC, Zurita-Munoz O, Gracia-Bouthelier R, Health KE, Campos-Barros A. Novel compound IGFALS mutation associated with impaired postnatal growth and low circulating IGF-I and IGFBP-3 levels. Horm Res 2009;72 (Suppl 3):90. Abstract, 8th Joint LWPES/ESPE Meeting, New York, September 9-12, 2009
20. Savage MO, Attie KM, David A, Metherell LA, Clark AJL, Camacho-Húbner C. Endocrine assessment, molecular characterization and treatment of growth hormone insensitivity disorders. Nat Clin Pract Endocrinol Metab 2006;2:395-407
21. Daughaday WH, Domené HM, Martínez A, Jasper HG. N Engl J Med 2004;350:1906 (Correspondence)
22. Domené HM, Martinez AS, Frystyk J, Bengolea SV, Ropelato MG, Scaglia PA, Chen J-W, Heuck C, Wolthers OD, Heinrich JJ, Jasper HG. Normal growth spurt and final height despite low levels of all forms of circulating Insulin-like growth factor-I in a patient with acid-labile subunit deficiency. Horm Res 2007;67:243-249
23. Yakar S, Liu JL, Fernandez AM, Wu Y, Schally AV, Frystyk J, Chernausek SD, Mejia W, Le Roith D. Liver-specific igf-1 gene deletion leads to muscle insulin insensitivity. Diabetes 2001;50:1110-1118
24. Ueki I, Ooi GT, Tremblay ML, Hurst KR, Bach LA, Boisclair YR. Inactivation of the acid labile subunit gene in mice results in mild retardation of postnatal growth despite profound disruptions in the circulating insulin-like growth factor system. Proc Natl Acad Sci USA 2000;97:6868-6873
25. Sato M, Frohman LA. Differential effect of central and peripheral administration of growth hormone (GH) and insulin-like growth factor on hypothalamus GH-releasing hormone and somatostatin gene expression in GH-deficient dwarf rats. Endocrinology 1993;133:793-799
26. Ohlsson C, Mohan S, Sjögren K, Tivesten Å, Isgaard J, Isackson O, Jansson J-O, Svensson J. The role of liver-derived insulin-like growth factor-I. Endocr Rev 2009;30:494-535
27. Segerlantz M, Bramnert M, Manhem P, Laurila E, Groop LC. Inhibition of the rise in FFA by Acipimox partially prevents GH-induced insulin resistance in GH-deficient adults. J Clin Endocrinol Metab 2001;86:5813-5818
28. Dominici FP, Argentino DP, Muñoz MC, Miquet JG, Sotelo AI, Turyn D. Influence of the crosstalk between growth hormone and insulin signalling on the modulation of insulin sensitivity. Growth Hormone and IGF Research 2005;15:324-336
29. Clemmons DR. The relative roles of growth hormone and IGF-1 in controlling insulin sensitivity. J Clin Invest 2004;113:25–27
30. Yakar S, Rosen CJ, Beamer, Ackert-Bicknell CL, Wu Y, Liu JL, Ooi GT, Setser J, Frystyk J, Boisclair YR, LeRoith D. Circulating levels of IGF-I directly regulate bone growth and density. J Clin Invest 2002;110:771-781
31. Domené HM, Bengolea SV, Jasper HG, Boisclair YR. Acid-labile subunit deficiency: Phenotypic similarities and differences between human and mouse. J Endocrinol Invest 2005;28:43-46
32. Fofanova-Gambetti OV, Hwa V, Wit JM, Domené HM, Argente J, Bang P, Hogler W, Kirsch S, Pihoker C, Chiu HK, Cohen L, Jacobsen C, Jasper HG, Rosenfeld RG. Auxological implications of heterozygous IGFALS mutations. Horm Res 2009;72(Suppl 3):89. Abstract, 8th Joint LWPES/ESPE Meeting, New York, September 9-12, 2009
33. David A, Rose S, Miraki-Moud F, Metherell L, Jones J, Edwards R, Camacho-Hubner C, Johnston L, Savage M, Klark A. Heterozygous defect of the acide-labile subunit gene in idiopathic short stature. Horm Res 2008;70(Suppl 1):31. Abstract, 71st Annual Meeting of the European Society for Pediatric Endocrinology, Istanbul, Turkey, September 30-23, 2008
34. Scaglia PA, Domene HM, Martinez AS, Keselman AC, Pipman VR, BengoleaSV, Karabatas LM, Lescano EM, Ropelato MG, Ballerini MG, Heinrich JJ, Jasper HG. Heterozygous IGFALS gene mutations are present in both idiopathic short stature (ISS) and in normal children: impact on height and acid-labile subunit (ALS) levels. Horm Res 2009; 72(Suppl 3):246. Abstract, 8th Joint LWPES/ESPE Meeting, New York, September 9-12, 2009
35. Wu S, Walenkamp MJ, Lankester A, Bidlinmaier M, Wit JM, De Luca F. Growth hormone and insulin-like growth factor I insensitivity of fibroblasts isolated from a patient with an IκBa mutation. J Clin Endocrinol Metab 2010