Growth Hormone & IGF Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Genetic disorders of GH action pathway

Horacio M. Domené[a,*], Gustavo Fierro-Carrión[b]

[a] Centro de Investigaciones Endocrinológicas (CEDIE-CONICET), "Dr. César Bergadá", División de Endocrinología, Hospital de Niños R. Gutiérrez, Buenos Aires, Argentina
[b] Escuela de Medicina, Colegio de Ciencias de la Salud, Universidad San Francisco de Quito, Quito, Ecuador

ARTICLE INFO

Keywords:
GH insensitivity
IGF-I insensitivity
Molecular defects of GH action
IGF1
GH receptor
IGF1 receptor
STAT5B
STAT3
IGFALS
PAPPA2

ABSTRACT

While insensitivity to GH (GHI) is characterized by low IGF-I levels, normal or elevated GH levels, and lack of IGF-I response to GH treatment, IGF-I resistance is characterized by elevated IGF-I levels with normal/high GH levels. Several genetic defects are responsible for impairment of GH and IGF-I actions resulting in short stature that could affect intrauterine growth or be present in the postnatal period. The genetic defects affecting GH and/or IGF-I action can be divided into five different groups: GH insensitivity by defects affecting the GH receptor (*GHR*), the intracellular GH signaling pathway (*STAT5B*, *STAT3*, *IKBKB*, *IL2RG*, *PIK3R1*), the synthesis of insulin-like growth factors (*IGF1*, *IGF2*), the transport/bioavailability of IGFs (*IGFALS*, *PAPPA2*), and defects affecting IGF-I sensitivity (*IGF1R*).

Complete GH insensitivity (GHI) was first reported by Zvi Laron and his colleagues in patients with classical appearance of GH deficiency, but presenting elevated levels of GH. The association of GH insensitivity with several clinical sings of immune-dysfunction and autoimmune dysregulation are characteristic of molecular defects in the intracellular GH signaling pathway (*STAT5B*, *STAT3*, *IKBKB*, *IL2RG*, *PIK3R1*). Gene mutations in the *IGF1* and *IGF2* genes have been described in patients presenting intrauterine growth retardation and postnatal short stature. Molecular defects have also been reported in the *IGFALS* gene, that encodes the acid-labile subunit (ALS), responsible to stabilize circulating IGF-I in ternary complexes, and more recently in the *PAPPA2* gen that encodes the pregnancy-associated plasma protein-A2, a protease that specifically cleaves IGFBP-3 and IGFBP-5 regulating the accessibility of IGFs to their target tissues.

Mutations in the *IGF1R* gene resulted in IGF-I insensitivity in patients with impaired intrauterine and postnatal growth.

These studies have revealed novel molecular mechanisms of GH insensitivity/primary IGF-I deficiency beyond the GH receptor gene. In addition, they have also underlined the importance of several players of the GH-IGF axis in the complex system that promotes human growth.

1. Background

The GH/IGF axis plays an important role in pre- and postnatal growth [1]. In the prenatal period growth factors IGF-I and IGF-II are essential for longitudinal growth [2]. In the fetus, placental lactogen (PL) and nutritional factors play an important role in the control of IGF-I expression [3].

2. Introduction

Insensitivity to GH (GHI) is characterized by low IGF-I levels associated with normal or elevated GH levels and lack of IGF-I response to GH treatment. On the other hand, IGF-I resistance is characterized by elevated IGF-I levels with normal/high GH levels. Several genetic defects are responsible for impairment of GH and IGF-I actions resulting in short stature that could affect intrauterine growth or be present in the postnatal period [4–6]. The genetic defects affecting GH and/or IGF-I action can be divided into five different groups (Table 1).

3. Defects affecting GHR (MIM # 262500, Laron syndrome, GH insensitivity syndrome, GH receptor deficiency)

The first description of GH insensitivity (GHI) was reported in 1966 by Laron et al. [7] in two siblings with the classical clinical appearance of GH deficiency, but presenting elevated levels of GH. It was not until 1989 that the molecular defect was characterized in patients with this

* Corresponding author at: Laboratorio de Biología Molecular, Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE), CONICET, FEI, División de Endocrinología, Hospital de Niños "Ricardo Gutiérrez", Gallo 1330, C1425EFD Buenos Aires, Argentina.
E-mail address: hdomene@cedie.org.ar (H.M. Domené).
URL: http://www.cedie.org.ar (H.M. Domené).

https://doi.org/10.1016/j.ghir.2017.12.004
Received 24 October 2017; Received in revised form 5 December 2017; Accepted 9 December 2017

Table 1
Molecular defects affecting GH and/or IGF-I action.

- ➢ GH insensitivity by defects affecting the GH receptor (*GHR*).
- ➢ GH insensitivity by defects affecting the intracellular GH signaling pathway (*STAT5B*, *STAT3*, *IKBKB*, *IL2RG*, *PIK3R1*).
- ➢ GH insensitivity by defects affecting the synthesis of insulin-like growth factors (*IGF1*, *IGF2*).
- ➢ GH insensitivity by defects affecting the transport/bioavailability of insulin-like growth factors (*IGFALS*, *PAPPA2*).
- ➢ IGF-I insensitivity (*IGF1R*).

condition presenting a partial deletion of *GHR* gene [8]. Laron and his colleagues described a total of 30 patients with 18 adults presenting a final height ranged from 108 to 136 cm [9]. A few years later, 20 patients with GHR deficiency were described among members of an inbred white population from the province of Loja in southern Ecuador [10,11]. Presently, about 70 different mutations affecting the *GHR* gene have been reported in more than 300 patients [12]. Most of the cases were homozygous for *GHR* gene mutations, usually in consanguineous families [12]. Frequently, mutations affect the extracellular domain of the receptor, resulting in abnormal GH binding and low to undetectable GHBP levels. Other *GHR* gene mutations may result in defects in receptor dimerization, cell membrane anchorage, or transduction of the signal [12]. Although in most of the cases the condition is inherited as an autosomic recessive condition, there are few cases where heterozygous *GHR* mutations exert a dominant negative effect [13–15]. These last cases, as well as those caused by an intronic mutation and the activation of a pseudoexon [16], present a less pronounced growth retardation and a milder clinical phenotype. While in complete GH insensitivity rhIGF-I is the only therapeutical option to improve linear growth, it is of note that patients with less severe GH insensitivity, such as those presenting activation of the pseudoexon or heterozygous *GHR* mutations, may benefit from rhGH or from a combination of rhGH and rhIGF-I [15].

4. Defects affecting the intracellular GH signaling pathway

4.1. GH insensitivity with immunodeficiency (MIM # 245590)

The STATs (signal transducers and activators of transcription) family includes seven members that are activated by multiple growth factors and cytokines. Although GH activates four members of this family, STAT5b is the key mediator of GH promoting actions. In 2003, a homozygous mutation in *STAT5B* gene was described in a 16-year-old girl with severe post-natal growth retardation and IGF-I deficiency [17]. The patient had a history of recurrent pulmonary infections and lymphocytic interstitial pneumonia, presenting immunodeficiency characterized by a defect in T cell immunity. Since STAT5b is also required in the signaling of several cytokines such as interleukine-2 and γ-interpheron, it seems likely that the growth failure and the immune defect are both due to its inactivation. At least ten patients with STAT5b deficiency have been reported and they all present severe growth failure, complete GH insensitivity and moderate to severe immunodeficiency. While all described patients present severe GH insensitivity that result in a marked growth retardation, the severity of immune deficiency and the pulmonary disease are more variable [17–23]. Heterozygous *STAT5B* mutations appear to affect growth, since heterozygous carriers are shorter than their wild-type relatives [24].

4.2. Autoimmune disease, multisystem, infantile-onset 1 (MIM # 615952)

Heterozygous gain-of-function mutations in the *STAT3* gene have been recently described associated with a variable degree of immune dysregulation and the early appearance of different autoimmune diseases (type-1 diabetes, autoimmune enteropathy, thyroid dysfunction, pulmonary disease, hemolytic anemia, thrombocytopenia, neutropenia, juvenile-onset arthritis, eczema [25–27]. Most of the described patients present growth failure associated with marked IGF-I deficiency. It has been shown that the constitutive activation of STAT3 could induce increased expression of SOCS3 [25]. Suppressor of cytokines signaling (SOCS) family members are STAT targets that block STAT activation by turning off the initial signal [28]. Epstein-Barr virus-transformed cell lines derived from patients carrying activating *STAT3* mutations display reduced STAT5b phosphorylation in response to Interleukine-2, a plausible explanation for the observed GH insensitivity [27]. In contrast to STAT5b deficiency, patients carrying activating STAT3 mutations preserve some degree of responsiveness to rhGH treatment [27,29]. Similarly to what was reported in STAT5b deficiency, the severity of the immune disorder and autoimmunity caused by germline *STAT3* gain-of-function mutations results in a severe life-threatening condition. Recent therapeutic approaches include bone marrow transplantation and anti-IL6R monoclonal antibody. Finally, small-molecule inhibitors of STAT3 are under clinical investigation [27].

4.3. Immunodeficiency 15 (MIM # 615592)

Members of the nuclear factor κB family of transcription factors form homo or heterodimers and modulate gene expression by their binding to specific DNA regulatory elements. In the unstimulated state NF-κB homo or heterodimers are sequestered in the cytoplasm and bound to IκB, preventing the translocation to the nucleus [30], thereby maintaining NF-Kb in an inactive state. Heterozygous mutations in *IKBKB* gene, that encodes for the inhibitory IκBα protein, have been described in two patients with immune disorder, growth retardation and partial GH and IGF-I insensitivity [31].

4.4. Severe combined immunodeficiency, X-linked, T cell-negative, B-cell-positive, NK cell-negative (SCID, MIM # 300400)

This condition is caused by mutations in the gene encoding the gamma subunit of the interleukin-2 receptor (*IL2RG*) [32]. It has been shown that some patients with mutations in the *IL2RG* gene, present a diminished or absent response to rhGH treatment both in terms of IGF-I increase as well as growth acceleration [33]. In addition, the stimulation of mutated B cells shows no phosphorylation of STAT5b and lack of nuclear translocation, suggesting that growth failure in X-linked SCID is primarily related to the genetic alteration of *IL2RG* [34].

4.5. SHORT syndrome (MIM # 269880)

This syndrome has historically been defined by its acronym: short stature (S), hyperextensibility of joints and/or inguinal hernia (H), ocular depression (O), Rieger abnormality (R) and teething delay (T) [35]. An autosomal dominant inheritance has been confirmed by the identification of heterozygous mutations in *PIK3R1* as the cause of SHORT syndrome [36]. More recently several research groups have identified *PIK3R1* mutations in several patients affected with SHORT syndrome [37,38]. *PIK3R1* codes for the regulatory subunits of the phosphatidyl inositol-3 kinase of classes IA (PI3K) and is involved in activation of the AKT/mTOR pathway to ensure proper growth and cell proliferation [39]. Persistently low levels of IGF-I with insufficient response to rhGH has been shown in some patients, indicating some degree of GH insensitivity [40].

5. GH insensitivity by defects affecting the synthesis of growth factors

5.1. IGF-I deficiency (MIM # 608747)

In 1996 the first molecular defect in the *IGF1* gene was described in a patient homozygous for a deletion of exons 4 and 5 in the *IGF1* gene.

The 15-year-old boy presented severe intrauterine growth retardation, postnatal growth failure, sensorineural deafness, mental retardation, microcephaly, and delayed puberty. Marked insulin-resistance was also present, likely related to the abnormally high GH levels and a functional GH receptor [41]. Several additional patients with *IGF1* gene mutations have been reported, all showing pre- and post-natal growth failure, mental retardation, and hearing loss [42,43]. Interestingly, a homozygous missense mutation (Val44Met) was detected in a 55-year-old patient presenting severe intrauterine and postnatal growth retardation, microcephaly, and sensorineural deafness. Functional analysis demonstrated a 90-fold reduced affinity of the mutant-Val44Met-IGF-I for the IGF-I receptor [43]. The classical phenotype with prenatal growth retardation was observed in those cases presenting both alleles affected. However, a different clinical presentation with no intrauterine growth retardation, microcephaly or deafness has been described in several members of a family, carriers for a frameshift mutation that, if expressed, would result in a truncated and presumably inactive protein [44]. A patient with non-dysmorphic phenotype presenting a less severe affected pre- and post-natal growth retardation was homozygous for a missense mutation that reduces the affinity of the mutant IGF-I for the IGF-1 receptor two- to three-fold. [45]. Molecular defects at the *IGF1* gene are rare, and only about 9 patients have been described [46].

5.2. IGF-II deficiency (severe growth restriction with distinct facies, MIM #616489)

In 2015 Begemann et al. reported an *IGF2* variant with evidence of pathogenicity in a multigenerational family with four members presenting growth restriction [47]. Confirming the monoallelic expression of the maternally imprinted *IGF2* gene, in those tissues involved in growth, only the transmission of the paternally affected allele resulted in growth impairment. The affected patients have severe intrauterine and postnatal growth restriction and a Silver-Russell syndrome-like phenotype. More recently, two independent reports described two patients with frameshift and missense *de novo* mutations in the *IGF2* gene, presenting a characteristic Silver-Russell syndrome (SRS)-phenotype [48,49], indicating that this alteration could arise as a *de novo* mutation in non-familial patients affected with SRS.

6. GH insensitivity by defects affecting the transport/ bioavailability of growth factors

6.1. Acid-labile subunit deficiency (ACLSD, MIM # 615961)

In a 17-year-old boy with delayed onset of puberty, slow pubertal progress, and marked IGF-I and IGFBP-3 levels that remained unchanged after GH stimulation, complete absence of ALS was reported [50]. He presented an inactivating mutation in the *IGFALS* gene encoding the acid-labile subunit (ALS), a key factor for stabilizing IGF-I in the circulation. Although ALS has no discernible affinity for IGF-I and IGF-II, it is capable to bind binary complexes formed by IGF-I or IGF-II with IGFBP-3 or IGFBP-5, forming ternary complexes [51]. The main role of ALS is to maintain up to 80–90% of the circulating IGFs in this ternary complex, extending the half-life of free IGF-I from 10 min to more than 12 h. So far, at least 62 patients have been described with ALS deficiency [52]. Thirty-two of them have been described early this year [53,54], suggesting that once the clinical characteristics and biochemical phenotype of acid-labile subunit deficiency become recognized, this alteration was more often diagnosed. In these patients, whereas circulating levels of IGF-I are dramatically decreased, local production appears to be preserved. Circulating IGF-II, IGFBP-1, -2, and -3 levels are also reduced, with the greatest reduction observed for IGFBP-3. Insulin resistance, characterized by normal glucose levels, hyperinsulinemia, and low levels of IGFBP-1, were common findings [55]. Commonly, height SDS before puberty was between − 2 and − 3. Adult height SDS was higher than prepubertal height, but still 1.0 SD lower than the midparental height SDS. Interestingly, despite a profound circulating IGF-I deficiency, there is only a mild impact on postnatal growth. Local expression of IGF-I, under the control of normal and/or increased GH levels, could be responsible for the preservation of linear growth near normal limits [56]. It is noteworthy that heterozygous *IGFALS* gene mutations are present in a subgroup of idiopathic short stature children presenting partial acid-labile subunit deficiency [57,58]. The characterization of children presenting partial ALS deficiency may result clinically relevant, because these patients have shown responsiveness to rhGH treatment increasing IGF-I levels and accelerating their growth velocity [59,60]. Whether this initial response results in an improvement in their adult height remains to be determined.

6.2. Pregnancy-associated plasma protein A2 deficiency (PAPP-A2)

A completely new syndrome has been recently described, involving the first genetic defect in a specific IGFBP-protease. Pregnancy-associated plasma protein-A2 (PAPP-A2) is a serum and tissue protease responsible for the proteolysis of IGFBP-3 and IGFBP-5, regulating the accessibility of IGF-I and IGF-II to their target tissues. Five affected subjects from two families presenting a moderate growth retardation and elevated circulating levels of IGF-I, IGF-II, IGFBP-3, IGFBP-5, and ALS have been described [61]. Most of the IGFs remain in the ternary complexes and there is a reduction in bioactive IGF-I. Interestingly, a 1-year treatment with hrIGF-I resulted in a clear increase in growth velocity and height in two siblings. Bioactive IGF-I was increased, and spontaneous GH secretion was diminished after acute administration of rhIGF-1, whereas serum total IGF-1 and IGFBP-3 levels remained elevated [62].

7. IGF-I insensitivity

7.1. IGF-I resistance (MIM # 270450)

Intrauterine human growth requires the normal expression of IGF-I/IGF-II and the type 1-IGF receptor. Haploinsufficiency of the *IGF1R* gene (encoding the IGF1 receptor) is associated with impaired intrauterine and postnatal growth. The complete absence of *IGF1R* expression in humans may be lethal. This could explain why, except for two compounds heterozygous [63,64] cases, and two homozygous patients [65,66], only heterozygous cases have been reported. The few patients presenting mutations in both *IGF1R* alleles appear to retain some degree of IGF1R activity. The first mutations in this gene were detected in patients with intrauterine growth retardation or short stature and elevated IGF-I levels [63]. One was a girl compound heterozygous for two different missense mutations in the *IGF1R* gene and the other a boy heterozygous carrier for a non-sense mutation. Functional *in vitro* studies of naturally occurring *IGF1R* mutations suggest that different mechanisms could explain the impairment of IGFs action: receptor haploinsufficiency, decreased biosynthesis, reduction of binding affinity, interference of transmembrane signaling, and disruption of the tyrosine kinase activity [67]. The impact of *IGF1R* mutations on intrauterine growth is variable, but is frequently more severe when maternally inherited, indicating that maternal IGF-I resistance during pregnancy is one factor contributing to the severity of the growth retardation, possibly by decreasing placental growth [68]. As much as 20 patients have been described with *IGF1R* mutations [63–75]. These patients have shown a poor to moderate clinical response to rhGH treatment [67].

8. Conclusion

From the description of the first patients with complete GH insensitivity by Laron and his collaborators 50 years ago, advances in genetic tools have resulted in the molecular characterization of a dozen

of different molecular defects affecting either GH or IGF-I actions resulting in monogenic causes of short stature. Before 2010 the main strategy was the gene candidate approach, by using clinical data and biochemical profiles to select the more likely candidate gene(s) to be studied. The characterization of molecular defects in *STAT5B* [17] and *IGFALS* [50] genes represent illustrative examples of the success of this approach. Since the development of next generation sequencing (NGS) methods, capable of determining the complete exome sequence (WES) or even the complete genome (WGS) within weeks, associated with copy number variation (CNV) techniques, useful to detect deletions and duplications, new genetic clinical conditions have been elucidated in patients where clinical and biochemical data did not suggest an obvious candidate gene. Examples of this novel strategy are the recently described molecular defects in *STAT3* [25], *PAPPA2* [61], and *IGF2* [47] genes. In addition, it has been shown that in a small percentage of cases more than one gene could be affected with a single base substitution or copy-number variant, resulting in a more complex clinical presentation, usually presenting overlapping phenotypic features [76]. In the case of GH insensitivity, novel heterozygous *STAT5B* mutations associated with novel heterozygous *IGFALS* variants have been described [77].

It has been proposed that a genetic evaluation of short stature is indicated in those cases that present severe GH deficiency, multiple pituitary hormone deficiency, unequivocal GH insensitivity, small for gestational age without catch-up growth, additional congenital anomalies or dysmorphic features, evidence of skeletal dysplasia, associated intellectual disability, microcephaly, and severe growth retardation [78]. Even by a carefully selection of patients with apparent GH or IGF-I insensitivity, only in 30 to 42% of the cases a genetic diagnosis is obtained [79]. It is remarkable, that aside from the well-recognized monogenic causes of GH insensitivity, such as genetic defects in *GHR* and *IGFALS* genes, likely pathogenic variants in genes associated to 3M syndrome (*OBSL1* and *CUL7*) or Noonan syndrome (*PTPN11*) are identified by WES [79].

With more accessibility to WES and CNV methods, a significant number of likely pathogenic variants associated to GH and IGF-I resistance have been described. These variants appear both in genes previously associated with these conditions as well as in completely novel genes. A greater effort in the development of well-designed *in vitro* functional assays is required to determine the real contribution of these findings.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

Supported by PICT 2010 No. 1916 (ANPCYT) and SANDOZ International GmbH, Business Unit Biopharmaceuticals.

References

[1] A. Spagnoli, R.G. Rosenfeld, The mechanisms by which growth hormone brings about growth. The relative contributions of growth hormone and insulin-like growth factors, Endocrinol. Metab. Clin. North Am. 25 (1996) 615–631.
[2] R. Randhawa, P. Cohen, The role of the insulin-like growth factor system in prenatal growth, Mol. Genet. Metab. 86 (2005) 84–90.
[3] J. D'Ercole, The insulin-like growth factors and fetal growth, in: E.M. Spencer (Ed.), Modern Concepts in Insulin-like Growth Factors, Elsevier, New York, 1991, pp. 9–24.
[4] A. David, V. Hwa, L.A. Metherell, et al., Evidence for a continuum of genetic, phenotypic, and biochemical abnormalities in children with growth hormone insensitivity, Endocr. Rev. 32 (2011) 472–497, http://dx.doi.org/10.1210/er.2010-0023.
[5] M.O. Savage, Phenotypes, investigation and treatment of primary IGF-1 deficiency, Endocr. Dev. 24 (2013) 138–149, http://dx.doi.org/10.1159/000342578.
[6] J.M. Wit, W. Oostdijk, M. Losekoot, H.A. van Duyvenvoorde, C.A. Ruivenkamp, S.G. Kant, Mechanisms in endocrinology: novel genetic causes of short stature, Eur. J. Endocrinol. 174 (2016) R145–R173, http://dx.doi.org/10.1530/EJE-15-0937.
[7] Z. Laron, A. Pertzelan, S. Mannheimer, Genetic pituitary dwarfism with high serum concentration of growth hormone — a new inborn error of metabolism? Israel J. Med. Sc. 2 (1966) 152–155.
[8] P.J. Godowski, D.W. Leung, L.R. Meacham, et al., Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism, Proc. Natl. Acad. Sci. 86 (1989) 8083–8087, http://dx.doi.org/10.1073/pnas.86.20.8083.
[9] Z. Laron, R. Sarel, A. Pertzelan, Puberty in Laron type dwarfism, Eur. J. Pediatr. 134 (1980) 79–83.
[10] A.L. Rosenbloom, J. Guevara Aguirre, R.G. Rosenfeld, P.J. Fielder, The little women of Loja — growth hormone-receptor deficiency in an inbred population of southern Ecuador, N. Engl. J. Med. 323 (1990) 1367–1374.
[11] A.L. Rosenbloom, A half-century of studies of growth hormone insensitivity/Laron syndrome: a historical perspective, Growth Horm. IGF Res. 28 (2016) 46–50, http://dx.doi.org/10.1016/j.ghir.2015.08.001.
[12] M.O. Savage, V. Hwa, A. David, R.G. Rosenfeld, L.A. Metherell, Genetic defects in the growth hormone-IGF-I axis causing growth hormone insensitivity and impaired linear growth, Front. Endocrinol. (Lausanne) 2 (2011) 95, , http://dx.doi.org/10.3389/fendo.2011.00095.
[13] R.M. Ayling, R. Ross, P. Towner, et al., A dominant-negative mutation of the growth hormone receptor causes familial short stature (letter), Nature Genetics 16 (1997) 13–14, http://dx.doi.org/10.1038/ng0597-13.
[14] K. Iida, Y. Takahashi, H. Kaji, et al., Growth hormone (GH) insensitivity syndrome with high serum GH-binding protein levels caused by a heterozygous splice site mutation of the GH receptor gene producing a lack of intracellular domain, J. Clin. Endocrinol. Metab. 83 (1998) 531–537.
[15] K. Vairamani, L. Merjaneh, P. Casano-Sancho, et al., Novel dominant-negative GH receptor mutations expands the spectrum of GHI and IGF-I deficiency, J. Endocr. Soc. 1 (2017) 345–358, http://dx.doi.org/10.1210/js.2016-1119.
[16] L.A. Metherell, S.A. Akker, P.B. Munroe, et al., Exon activation as a novel mechanism for disease resulting in atypical growth-hormone insensitivity, Am. J. Hum. Genet. 69 (2001) 641–646, http://dx.doi.org/10.1086/323266.
[17] E.M. Kofoed, V. Hwa, B. Little, et al., Growth hormone insensitivity associated with a STAT5b mutation, N. Engl. J. Med. 349 (2003) 1139–1147.
[18] S. Vidarsdottir, M.J. Walenkamp, A.M. Pereira, et al., Clinical and biochemical characteristics of a male patient with a novel homozygous STAT5b mutation, J. Clin. Endocrinol. Metab. 91 (2006) 3482–3485.
[19] A. Bernasconi, R. Marino, A. Ribas, et al., Characterization of immunodeficiency in a patient with growth hormone insensitivity secondary to a novel STAT5b gene mutation, Pediatrics 118 (2006) e1584–1592.
[20] A. Boyanovsky, A. Lozano, G. Testa, et al., Growth hormone insensitivity and immunodeficiency: mutation in the STAT5B gene, 8th Joint Meeting of the Lawson Wilkins Pediatric Endocrine Society/European Society for Paediatric Endocrinology, 2009 P01-067.
[21] V. Hwa, K. Nadeau, J.M. Wit, R.G. Rosenfeld, STAT5b deficiency: lessons from STAT5B gene mutations, Best Pract. Res. Clin. Endocrinol. Metab. 25 (2011) 61–75, http://dx.doi.org/10.1016/j.beem.2010.09.003.
[22] P.A. Scaglia, A.S. Martínez, E. Feigerlová, et al., A novel missense mutation in the SH2 domain of the STAT5B gene results in a transcriptionally inactive STAT5b associated with severe IGF-I deficiency, immune dysfunction, and lack of pulmonary disease, J. Clin. Endocrinol. Metab. 97 (2012) E830–E839, http://dx.doi.org/10.1210/jc.2011-2554.
[23] V. Hwa, STAT5B deficiency: impacts on human growth and immunity, Growth Horm. IGF Res. 28 (2016) 16–20, http://dx.doi.org/10.1016/j.ghir.2015.12.006.
[24] R.C. Scalco, V. Hwa, H.M. Domené, et al., STAT5B mutations in heterozygous state have negative impact on height: another clue in human stature heritability, Eur. J. Endocrinol. 173 (2015) 291–296, http://dx.doi.org/10.1530/EJE-15-0398.
[25] S.E. Flanagan, E. Haapaniemi, M.A. Russell, et al., Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease, Nat. Genet. 46 (2014) 812–814, http://dx.doi.org/10.1038/ng.3040.
[26] E.M. Haapaniemi, M. Kaustio, H.L. Rajala, et al., Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3, Blood. 125 (2015) 639–648, http://dx.doi.org/10.1182/blood-2014-04-570101.
[27] J.D. Milner, T.P. Vogel, L. Forbes, et al., Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations, Blood 125 (2015) 591–599, http://dx.doi.org/10.1182/blood-2014-09-602763.
[28] D. LeRoith, P. Nissley, Knock your SOCS off!, J. Clin. Invest. 115 (2005) 233–236.
[29] P. Scaglia, A. Keselman, M. Gutiérrez, et al., Severe IGF-I deficiency and multiorgan autoimmune disease associated with novel STAT3 mutations, Horm. Res. Paediatr. 84 (suppl 1) (2015) 107 (Abstract).
[30] P.A. Baeuerle, D. Baltimore, NF-kappa B: ten years after, Cell 87 (1996) 13–20.
[31] S. Wu, M.J. Walenkamp, A. Lankester, M. Bidlingmaier, J.M. Wit, F. De Luca, Growth hormone and insulin-like growth factor I insensitivity of fibroblasts isolated from a patient with an I{kappa}B{alpha} mutation, J. Clin. Endocrinol. Metab. 95 (2010) 1220–1228, http://dx.doi.org/10.1210/jc.2009-1662.
[32] F.S. Rosen, S.P. Gotoff, J.M. Craig, J. Ritchie, C.A. Janeway, Further observations on the Swiss type of agammaglobulinemia (alymphocytosis): the effect of syngeneic bone-marrow cells, N. Engl. J. Med. 274 (1966) 18–21.
[33] M.V. Ursini, L. Gaetaniello, R. Ambrosio, et al., Atypical X-linked SCID phenotype associated with growth hormone hyporesponsiveness, Clin. Exp. Immunol. 129 (2002) 502–509.
[34] M. Adriani, C. Garbi, G. Amodio, et al., Functional interaction of common gamma-chain and growth hormone receptor signaling apparatus, J. Immunol. 177 (2006) 6889–6895.
[35] R.J. Gorlin, A selected miscellany, Birth Defects Orig. Art. Ser. XI2 (1975) 46–48.
[36] D. Aarskog, L. Ose, H. Pande, N. Eide, Autosomal dominant partial lipodystrophy

associated with Rieger anomaly, short stature, and insulinopenic diabetes, Am. J. Med. Genet. 15 (1983) 29–38.
[37] M.E. Conley, A.K. Dobbs, A.M. Quintana, et al., Agammaglobulinemia and absent B lineage cells in a patient lacking the p85-alpha subunit of PI3K, J. Exp. Med. 209 (2012) 463–470, http://dx.doi.org/10.1084/jem.20112533.
[38] C. Thauvin-Robinet, M. Auclair, L. Duplomb, et al., PIK3R1 mutations cause syndromic insulin resistance with lipoatrophy, Am. J. Hum. Genet. 93 (2013) 141–149, http://dx.doi.org/10.1016/j.ajhg.2013.05.019.
[39] M. Avila, D.A. Dyment, J.V. Sagen, et al., Clinical reappraisal of SHORT syndrome with PIK3R1 mutations: towards recommendation for molecular testing and management, Clin. Genet. 89 (2016) 501–506, http://dx.doi.org/10.1111/cge.12688.
[40] G. Alonso, D. Liberatore, A. Bernasconi, et al., Growth hormone insensitivity in a girl with hyper IgM-like syndrome due to mutation in PIK3R1, Horm. Res. Paediatr. 86 (suppl 2) (2016) Abstract. DOI: https://doi.org/10.1159/000451040.
[41] K.A. Woods, C. Camacho-Hubner, M.O. Savage, A.J. Clark, Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene, N. Engl. J. Med. 335 (1996) 1363–1367.
[42] I. Netchine, S. Azzi, Y. Le Bouc, M.O. Savage, IGF1 molecular anomalies demonstrate its critical role in fetal, postnatal growth and brain development, Best Pract. Res. Clin. Endocrinol. Metab. 25 (2011) 181–190, http://dx.doi.org/10.1016/j.beem.2010.08.005.
[43] M.J.E. Walenkamp, M. Karperien, A.M. Pereira, et al., Homozygous and heterozygous expression of a novel insulin-like growth factor-I mutation, J. Clin. Endocr. Metab. 90 (2005) 2855–2864.
[44] J.S. Fuqua, M. Derr, R.G. Rosenfeld, V. Hwa, Identification of a novel heterozygous IGF1 splicing mutation in large kindred with familial short stature, Horm. Res. Paediatr. 78 (2012) 59–66, http://dx.doi.org/10.1159/000337249.
[45] I. Netchine, S. Azzi, M. Houang, Partial primary deficiency of insulin-like growth factor (IGF)-I activity associated with IGF1 mutation demonstrates its critical role in growth and brain development, J. Clin. Endocrinol. Metab. 94 (2009) 3913–3921, http://dx.doi.org/10.1210/jc.2009-0452.
[46] M.J. Walenkamp, M. Losekoot, J.M. Wit, Molecular IGF-1 and IGF-1 receptor defects: from genetics to clinical management, Endocr. Dev. 24 (2013) 128–137, http://dx.doi.org/10.1159/000342841.
[47] M. Begemann, B. Zirn, G. Santen, et al., Paternally inherited IGF2 mutation and growth restriction, N. Engl. J. Med. 373 (2015) 349–356, http://dx.doi.org/10.1056/NEJMoa1415227.
[48] K. Yamoto, H. Saitsu, N. Nakagawa, et al., De novo IGF2 mutation on the paternal allele in a patient with Silver-Russell syndrome and ectrodactyly, Hum. Mutat. 38 (2017) 953–958, http://dx.doi.org/10.1002/humu.23253.
[49] D. Liu, Y. Wang, X.A. Yang, D. Liu, De novo mutation of paternal IGF2 gene causing Silver-Russell syndrome in a sporadic patient, Front. Genet. 8 (2017) 105, http://dx.doi.org/10.3389/fgene.2017.00105.eCollection 2017.
[50] H.M. Domené, S.V. Bengolea, A.S. Martínez, et al., Deficiency of the circulating insulin-like growth factor system associated with inactivation of the acid-labile subunit gene, N. Engl. J. Med. 350 (2004) 570–577.
[51] Y.R. Boisclair, R.P. Rhoads, I. Ueki, J. Wang, G.T. Ooi, The acid-labile subunit (ALS) of the 150 kDa IGF-binding protein complex: an important but forgotten component of the circulating IGF system, J. Endocrinol. 170 (2001) 63–70.
[52] H.M. Domené, V. Hwa, J. Argente, et al., Human acid-labile subunit deficiency: clinical, endocrine, and metabolic consequences, Horm. Res. 72 (2009) 129–141, http://dx.doi.org/10.1159/000232486.
[53] E. Işık, B. Haliloglu, J. van Doorn, et al., Clinical and biochemical characteristics and bone mineral density of homozygous, compound heterozygous and heterozygous carriers of three novel IGFALS mutations, Eur. J. Endocrinol. 176 (2017) 657–667, http://dx.doi.org/10.1530/EJE-16-0999.
[54] P.A. Scaglia, A.C. Keselman, D. Braslavsky, a.l. et, Characterization of four Latin American families confirms previous findings and reveals novel features of acid-labile subunit deficiency, Clin. Endocrinol. (Oxf) 87 (2017) 300–311, http://dx.doi.org/10.1111/cen.13361.
[55] H.M. Domené, P.A. Scaglia, H.G. Jasper, Deficiency of the insulin-like growth factor-binding protein acid-labile subunit (ALS) of the circulating ternary complex in children with short stature, Pediatr. Endocrinol. Rev. 7 (2010) 339–346.
[56] H.M. Domené, V. Hwa, H.G. Jasper, R.G. Rosenfeld, Best Pract. Res. Clin. Endocrinol. Metab. 25 (2011) 101–113, http://dx.doi.org/10.1016/j.beem.2010.08.010.
[57] H.M. Domené, P.A. Scaglia, A.S. Martínez, et al., Heterozygous IGFALS gene variants in idiopathic short stature and normal children: impact on height and the IGF system, Horm. Res. Paediatr. 80 (2013) 413–423, http://dx.doi.org/10.1159/000355412.
[58] L.C. Martucci, M.L. Gutiérrez, L.M. Karabatas, et al., Assessment of pathogenicity of natural IGFALS gene variants by in silico bioinformatics tools and in vitro functional studies, Mol. Cell. Endocrinol. 429 (2016) 19–28, http://dx.doi.org/10.1016/j.mce.2016.03.031.
[59] A. Grandone, E. Miraglia del Giudice, et al., Clinical features of a new acid-labile subunit (IGFALS) heterozygous mutation: anthropometric and biochemical characterization and response to growth hormone administration, Horm. Res. Paediatr. 81 (2014) 67–72, http://dx.doi.org/10.1159/000355017.
[60] H.M. Domené, El déficit de ALS en la talla baja idiopática, Rev. Esp. Endocrinol. Pediatr. 8 (Suppl) (2017) 8–13.
[61] A. Dauber A, M.T. Muñoz-Calvo, V. Barrios, et al., Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability, EMBO Mol. Med. 8 (2016) 363-374. doi: http://dx.doi.org/10.15252/emmm.201506106.
[62] M.T. Muñoz-Calvo, V. Barrios, J. Pozo, et al., Treatment with recombinant human insulin-like growth factor-1 improves growth in patients with PAPP-A2 deficiency, J. Clin. Endocrinol. Metab. 101 (2016) 3879–3883.
[63] M.J. Abuzzahab, A. Schneider, A. Goddard, et al., IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation, N. Engl. J. Med. 349 (2003) 2211–2222.
[64] P. P Fang, Y.H. Cho, M.A. Derr, R.G. Rosenfeld, V. Hwa, C.T. Cowell, Severe short stature caused by novel compound heterozygous mutations of the insulin-like growth factor 1 receptor (IGF1R), J Clin Endocrinol Metab 97 (2012) E243–E247, http://dx.doi.org/10.1210/jc.2011-2142.
[65] M.H. Gannagé-Yared, J. Klammt, E. Chouery, et al., Homozygous mutation of the IGF1 receptor gene in a patient with severe pre- and postnatal growth failure and congenital malformations, Eur J Endocrinol 168 (2012) K1–K7, http://dx.doi.org/10.1530/EJE-12-0701.
[66] P. Prontera, L. Micale, A. Verrotti, V. Napolioni, G. Stangioni, G. Merla, A new homozygous IGFr variant defines a clinically recognizable incomplete dominant form of SHORT syndrome, Hum. Mutat. 36 (2015) 1043–1047, http://dx.doi.org/10.1002/humu.22853.
[67] J. Klammt, W. Kiess, R. Pfäffle, IGF1R mutations as cause of SGA, Best Pract. Res. Clin. Endocrinol. Metab. 25 (2011) 191–206, http://dx.doi.org/10.1016/j.beem.2010.09.012.
[68] H.A. van Duyvenvoorde, P.A. van Setten, M.J. Walenkamp, Short stature associated with a novel heterozygous mutation in the insulin-like growth factor 1 gene, J. Clin. Endocrinol. Metab. 95 (2010) E363–E367, http://dx.doi.org/10.1210/jc.2010-0511.
[69] P. Ocaranza, M.C. Golekoh, S.F. Andrew, et al., Expanding genetic and functional diagnoses of IGF1R haploinsufficiencies, Horm. Res. Paediatr. 87 (2017) 412–422, http://dx.doi.org/10.1159/000464143.
[70] T. Wallborn, S. Wüller, J. Klammt, A heterozygous mutation of the insulin-like growth factor-I receptor causes retention of the nascent protein in the endoplasmic reticulum and results in intrauterine and postnatal growth retardation, J. Clin. Endocrinol. Metab. 95 (2010) 2316–2324, http://dx.doi.org/10.1210/jc.2009-2404.
[71] L. Soellner, S. Spengler, M. Begemann, H.A. Wollmann, G. Binder, T. Eggermann, IGF1R mutation analysis in short children with Silver-Russell syndrome features, J. Pediatr. Genet. 2 (2013) 113–117, http://dx.doi.org/10.3233/PGE-13059.
[72] A.C. Leal, L.R. Montenegro, R.F. Saito, et al., Analysis of the insulin-like growth factor 1 receptor gene in children born small for gestational age: in vitro characterization of a novel mutation (p.Arg511Trp), Clin. Endocrinol. 78 (2013) 558–563, http://dx.doi.org/10.1111/cen.12048.
[73] M. Juanes, G. Guercio, R. Marino, et al., Three novel IGF1R mutations in microcephalic patients with prenatal and postnatal growth impairment, Clin. Endocrinol. (Oxf) 82 (2015) 704–711, http://dx.doi.org/10.1111/cen.12555.
[74] S. Burkhardt, J. Gesing, T.M. Kapellen, et al., Novel heterozygous IGF1R mutation in two brothers with developing impaired glucose tolerance, J. Pediatr. Endocrinol. Metab. 28 (2015) 217–225, http://dx.doi.org/10.1515/jpem-2014-0132.
[75] R. Solomon-Zemler, L. Basel-Vanagaite, D. Steier, et al., A novel heterozygous IGF-1 receptor mutation associated with hypoglycemia, Endocr. Connect. 6 (2017) 395–403, http://dx.doi.org/10.1530/EC-17-0038.
[76] J.E. Posey, H. Tamar, P. Liu, et al., Resolution of disease phenotypes resulting from multifocus genomic variation, N. Engl. J. Med. 376 (2017) 21–31, http://dx.doi.org/10.1056/NEJMoa1516767.
[77] J.M. Wit, H.A. van Duyvenvoorde, S.A. Scheltinga, et al., Genetic analysis of short children with apparent growth hormone insensitivity, Horm. Res. Paediatr. 77 (2012) 320–333, http://dx.doi.org/10.1159/000338462.
[78] A. Dauber, R.G. Rosenfeld, J.N. Hirschhorn, Genetic evaluation of short stature, J. Clin. Endocrinol. Metab. 99 (2014) 3080–3092, http://dx.doi.org/10.1210/jc.2014-1506.
[79] L. Shapiro, S. Chatterjee, D. Ramadan, et al., Whole exome sequencing gives additional benefits compared to candidate gene sequencing in the molecular diagnosis of children with growth hormone or IGF-1 insensitivity, Eur. J. Endocrinol. 177 (2017) EJE-17-0453, , http://dx.doi.org/10.1530/EJE-17-0453 (485–501).