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

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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

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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.