PREFACE

From the complex molecular control of endocrine cell differentiation to the amazing physiology of normal growth and puberty, developmental processes represent an integral and recurrent theme within the field of Endocrinology. Our goal in the creation of this book was to incorporate the latest scientific information regarding the development of endocrine systems into a larger context in which molecular genetics is combined with state-of-the-art understanding of endocrine physiology and optimal management of endocrine diseases. Each section is organized according to the chronologic development of the human organism, from the fetal/prenatal period through childhood, adolescence, and in some cases, into adulthood. In parallel with this sequence is a consistent progression of topics, which begins with a focus on molecular genetic aspects of endocrine development and concludes with chapters devoted to the diagnosis and treatment of endocrine disorders. Our hope is that the material contained herein will provide critical information for basic researchers regarding clinical applications of laboratory investigation, and will likewise benefit practitioners by elucidating the underlying pathophysiology of the many endocrinopathies encountered in the clinical setting. Ultimately, we aim to promote the collaborative translational efforts that are essential to the dual objectives of advancing knowledge of human biology and improving our ability to care for our patients. We wish to thank our authors for their invaluable contributions to this project. Lastly, this book is dedicated with utmost love and gratitude to our husbands and to our children, Aliza, Alex, Ari, Ariana, Naomi, Sophia, and Lydia: May you always follow your dreams!

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II Growth

2 Molecular Mutations in the Human Growth Hormone Axis

Zvi Laron, MD

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INTRODUCTION

Human growth hormone (hGH) is secreted from somatomammotrophic cells in the anterior pituitary in a pulsatile pattern that results from a diurnal rhythmically changing disequilibrium between two hypothalamic hormones: GHRH (GH-releasing hormone) and SMS (somatostatin = GH secretion inhibiting hormone) *(1)*. GHRH induces hGH synthesis and secretion whenever the somatostatinergic tone is low *(2)*. It is thus evident that SMS plays a central role in the regulation of GH secretion. The actions of SMS are not restricted to GH alone, but also affect other hormones, as seen in Fig. 1, which illustrates the GH cascade. Not illustrated is the inhibitory effect of somatostatin on TSH,

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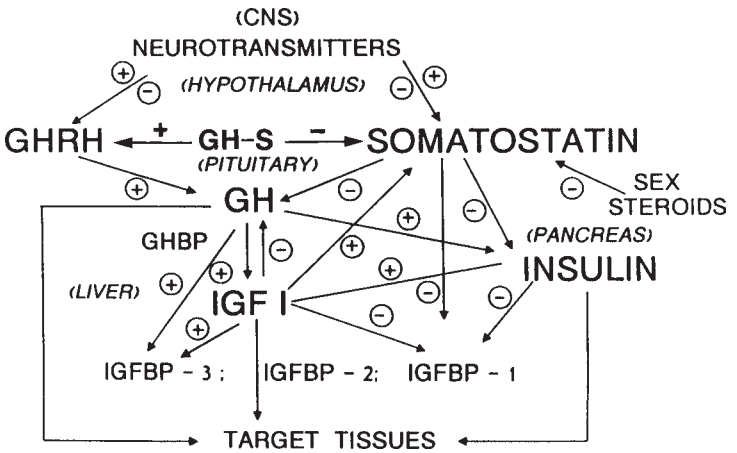

Fig. 1. The growth hormone axis. GH, growth hormone; GH-S, GH secretagog; GHRH, GH-releasing hormone; IGF-1, insulin-like growth factor-1; GHBP, GH binding protein; IGFBP, insulin-like growth factor; binding proteins; +, stimulates; –, inhibits.

and glucagon secretion *(3)*. The regulation of somatostatin secretion is not yet completely elucidated, but there is evidence that insulin-like growth factor-1 (IGF-1) stimulates SMS *(4)*, and that GH-S (GH secretagogs) inhibit SMS secretion *(5)*. Growth hormone secretagogs are small peptides, or nonpeptide substances synthesized in recent years, that act in synergism with GHRH to stimulate GH secretion *(6)*. Several analogs of these substances have been found active in vitro and in vivo; however, whether they are natural products or man-invented pharmacological substances related to natural products remains to be elucidated. The finding of a GH-S receptor *(7)* indicated that such a hormone exists in reality.

Indeed recently Kojima et al. *(8)* described a 28 amino acid peptide extracted from the stomach that specifically binds to this receptor. It is called GHRELIN and releases GH both in vitro and in vivo. Its human gene has been encoded *(8)* and is located on chromosome 3p26-25 *(9)*. It has 4 exons spanning 4.1 Kb of genomic DNA. The 117 amino acids have a 82% homology with the rat gene. It is also expressed in the arcuate nucleus of the hypothalamus *(8)*.

Recent studies have shown a close relationship between Ghrelin and Motilin, another hormone synthesized in the stomach *(10)*. Thus, the amino acid sequence of human prepro-motilin-related peptide (Prepro-MTLRP) is identical with human prepro-ghrelin, except Serine 26, which is not octanoylated in Prepro-MTLRP *(11)*. Also the gastrointestinal motilin receptor (MTL-R) and the GHS-R are both G-protein-coupled receptors that show a high degree of homology *(12)*. Motilin has also been found in the central nervous system (CNS) *(13)*. Interactivity between these two hormones is not yet clear, but Ghrelin in addition to stimulating GH release in humans *(14)* releases appetite-stimulatory signals from the stomach *(15)*, and induces adiposity in rodents *(16)*. The orexigenic effect of Ghrelin does not seem to be GH-dependent, but acts by increasing hypothalamic neuropeptide y (NPY) *(17)*. Standard meal intake after an overnight fast in 10 healthy young adults resulted in a significant decrease in plasma Ghrelin (120 min after the meal) correlating with the gastric emptying time *(18)*. Thus Ghrelin seems to regulate between nutrient intake, gastric motility, and the CNS.

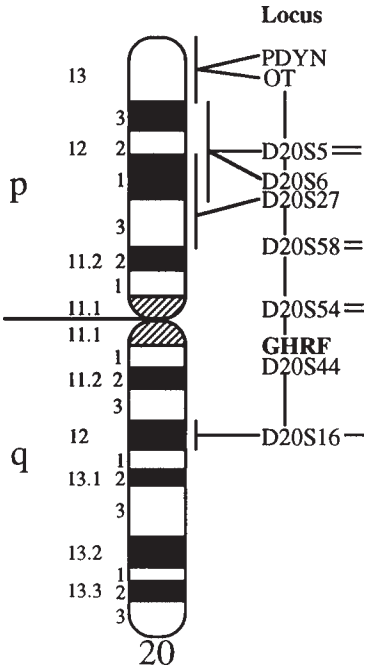

Fig. 2. Representation of chromosome 20 and location of the GHRH gene. Adapted with permission from ref. (*26*).

Ghrelin has also been identified in the placenta *(19)*. Whether it plays a role in the secretion of placental lactogen remains to be established, as is the possibility that mutations in Ghrelin or its receptor may be involved in overeating and obesity.

The cloning of the genes of the hormones of the GH axis and their receptors in recent years and the advancement in molecular biology techniques have enabled the elucidation of the etiology of many conditions of abnormal growth. This chapter is a review of what is known at present on molecular defects in man related to the GHRH, GH, and IGF-1 molecules and their receptors, as well as a summary of the resulting clinical sequelae.

GROWTH HORMONE RELEASING HORMONE (GHRH)

Historical Perspective

In 1961, Reichlin demonstrated that lesions of the ventromedial nucleus of the rat hypothalamus resulted in cessation of growth as a result of GH deficiency *(20)*. The isolation and characterization of human GHRH was made possible by the extraction of pancreatic tumors causing acromegaly *(21,22)*.

The GHRH Gene

The GHRH gene is a member of a large family of hormones and factors, which includes glucagon, secretin, vasoactive intestinal polypeptide (VIP), and others *(23,24)*. Humans have a single copy of the GHRH gene *(25)*. It is localized on chromosome 20q12 and p11.23 *(26)* (Fig. 2) and has 5 exons spanning over 10 kilobase pairs (Fig. 3). GHRH is localized in the arcuate and ventromedial nuclei of the hypothalamus, but also in the

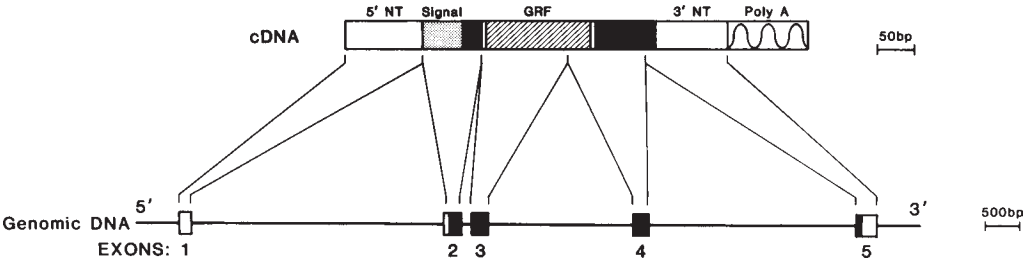

Fig. 3. Structure of the human GHRH cDNA and gene. GRF, GHRH. Adapted with permission from ref. (*25*).

gastrointestinal tract including pancreas *(27)*, the testis and placenta *(28)*, and other tissues as well as tumors *(29,30)*.

Chemical Structure

GHRH is secreted in three molecular forms GHRH 1-44NH2, GHRH 1-40-OH, and GHRH 1-37-OH *(31)*. All three forms are biologically active, even a 1-29 fragment *(32)*.

GHRH Gene Defects

Although isolated GH deficiency (IGHD) owing to complete or partial absence of GHRH has been diagnosed by indirect methods *(33–35)*, no patients with a GHRH gene deletion or mutation in the GHRH gene have been described so far.

Clinical Aspects

The patients suspected or proved to have GHRH deficiency present the clinical and biochemical changes typical of IGHD (*see* later). The diagnosis is made by finding a GH response to GHRH and a negative one to insulin hypoglycemia and/or clonidine, or arginine.

THE GHRH-RECEPTOR (GHRH-R)

Historical Perspective

GHRH stimulates the transcription of the GH gene *(36)* and induces proliferation of the somatotroph cell *(37)* acting as a hypophyseotropic hormone. Successful cloning of the GHRH-R was achieved in 1992 by Mayo *(38)*. This enabled a better insight into the mechanism of action of GHRH on the GH synthesis and secretion *(39)*. The first abnormalities in the GHRH-R gene were detected in the little (lit) mouse *(40)*, which paved the way to findings in man.

The Human GHRH Receptor Gene

The GHRH-R gene is located in the anterior hypophysis. GHRH stimulates adenylate cyclase resulting in increased cyclic adenosine monophosphate (cAMP) production indicating the intermediary action of a G-protein *(41)*. The GHRH-R is homologous to a subfamily of G-protein-coupled receptors, which include VIP, GLP-1, secretin, glucagon, GIP, PACAP, calcitonin, PTH, and CRH *(42)*. The human GHRH-R gene is located on chromosome 7p 13-p21 *(43)* (Fig. 4) and probably at p15 *(44)*. It contains a frame of 1269

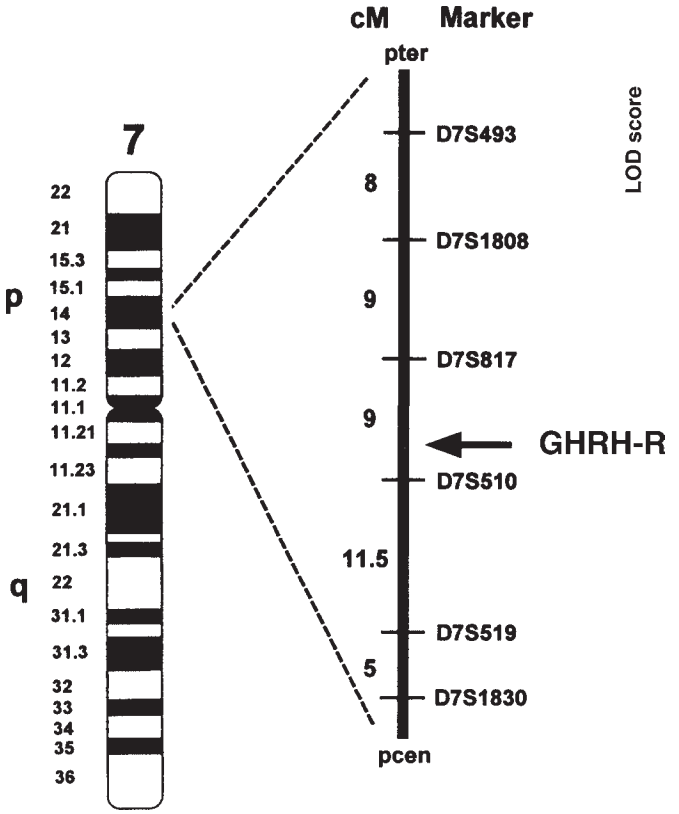

Fig. 4. Representation of chromosome 7 with location of the GHRH receptor gene. Adapted with permission from ref. (*46*).

bp coding for 432 amino-acids and 7 transmembrane-spanning helices *(38)* (Fig. 5). The mature GHRH-R is a 401 amino acid residue peptide with a large extracellular domain of 108 amino acids.

GHRH-Receptor Gene Mutations in Man

The finding of an inactivating mutation in the GHRH-R in the little (lit) mouse *(40)* suggested that similar defects may occur in man. So far four kindreds have been described, three originating from the Indian peninsula and one from Northeast Brazil *(45–48)*. The first described patients by Wajnrajch et al. *(45)* are Indian Moslems and originate from Bombay. They belong to a very consanguineous kindred of which two cousins, a boy (age 16 yr) and a girl (3.5 yr) were investigated. Both were very short (–4.2 and –7.4 height SDS), and had frontal bossing and truncal obesity, the typical phenotype of severe isolated GH deficiency (IGHD) *(49)* or GH resistance (Laron syndrome; LS) *(50)*. They had IGHD as demonstrated by no rise in serum GH upon oral clonidine, insulin hypoglycemia, and intravenous GHRH after sex-hormone priming. All other pituitary hormones were normal. DNA analysis revealed a nonsense mutation in the extracellular domain of the GHRH receptor, namely a G→T transversion at position 265 resulting in a Glu 72 stop (calculated with the signal protein). Treatment by hGH resulted in a growth spurt of 13 and 17 cm, respectively, in the first year of treatment.

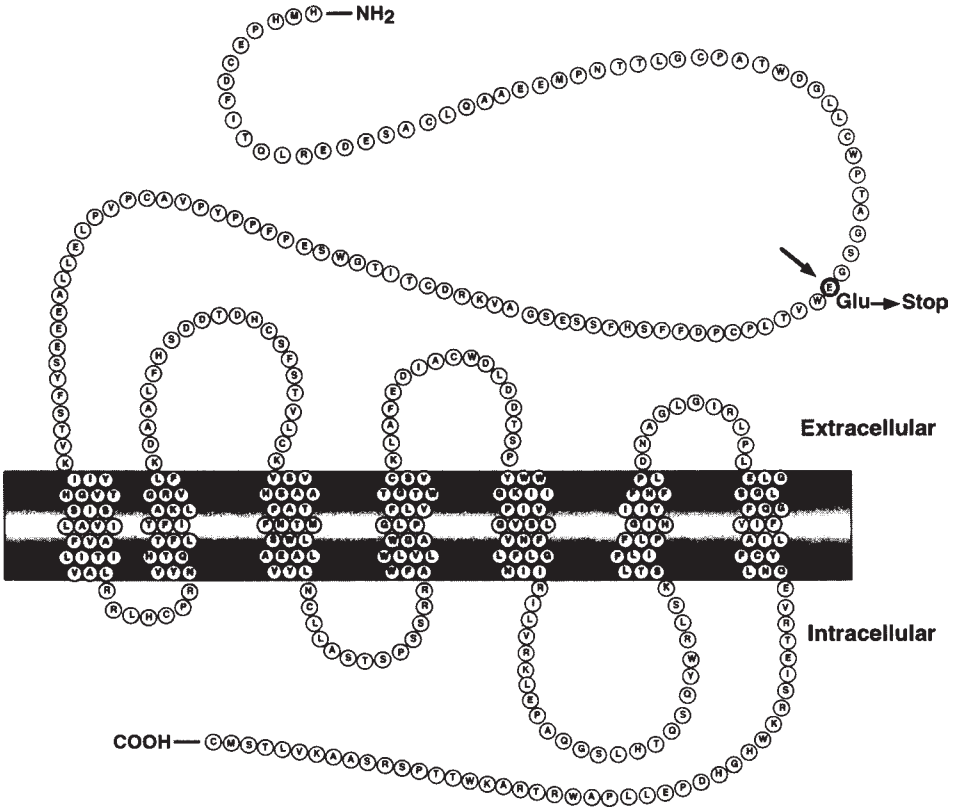

Fig. 5. The GHRH receptor gene and the GHRH-R mutation in the Brazilian kindred *(48)*. Adapted with permission from ref. (*46*).

The second consanguineous kindred originated in Sindh/Pakistan. Mahashwari et al. *(46)* examined 18 affected subjects, all very short (–7.2 to –8.3 height SDS), with a small head circumference (–4.3 SDS), possible facial hypoplasia, and some increase in adiposity. Puberty was delayed and the patients had high-pitched voices. Four patients had endocrine evaluations and no response of serum hGH was found to various stimuli, including GHRH. As expected, serum IGF-1 and IGFBP-3 were very low: 5.2 ± 2 ng/mL and 420 ± 130 ng/mL, respectively. Serum GHRH was found within the normal range and not elevated *(46)*. DNA analysis revealed the same mutation as in the patients reported by Wajnrajch et al. *(45)*.

Two additional brothers reported by Netchine et al. *(47)* were of Tamilian origin from Delf, an island between India and Srilanka. They were very short (–4 and –5 height SDS) and not responsive to GHRH stimulation. Despite having the same GHRH-R defect causing a truncated nonactive receptor as the patients previously reported, they had no frontal bossing, nor a small penis. MRI of the skull revealed a hypoplastic anterior pituitary. They too responded well to hGH therapy.

A fourth report coming from Itabaininha in Northeastern Brazil, a region with a population with a high degree of consanguinity, described 22 very short patients (–4.5 to –6 height SDS) belonging to a kindred of at least 105 affected families *(48)*. Adult statures ranged from 105–135 cm; they were obese, had delayed puberty but normal

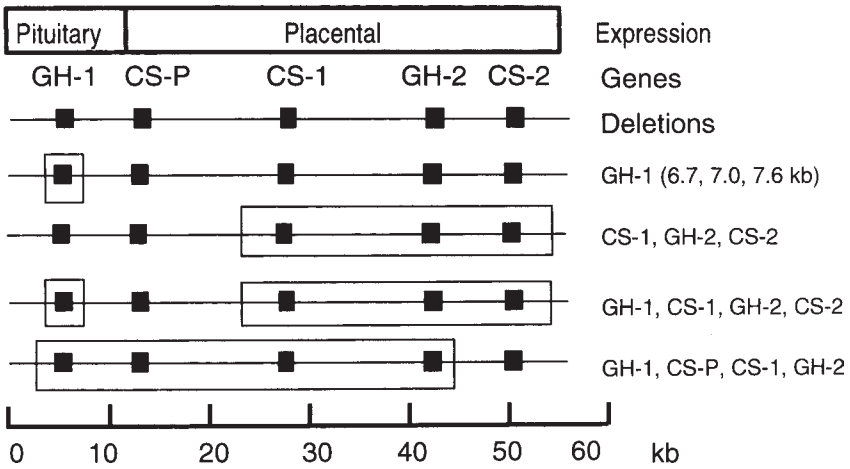

Fig. 6. The growth hormone and chorionic somatotropin gene cluster. Adapted with permission from ref. (*84*).

reproduction, and high-pitched voices. All 22 patients investigated had no response of hGH to stimuli including GHRH, and IGF-1 and IGFBP-3 were very low. DNA analysis revealed a novel mutation affecting the junction of exon 1 with intron 1 IVS1+1 G→A) (Fig. 5). Thirty of the affected subjects were homozygous for this mutation. The heterozygote subjects had a normal phenotype.

CONCLUSIONS

The patients with GHRH-R defects identified so far stem from inbred populations and all have been described to have various degrees of the typical phenotype of IGHD *(49)* or GH insensitivity (LS) *(50)*. Of interest is the finding of a hypoplastic anterior pituitary in one report *(47)*.

Diagnostic Hint

Patients with severe IGHD that show no rise of serum GH upon intravenous administration of GHRH should be screened for a defect in the GHRH-R.

HUMAN PITUITARY GROWTH HORMONE (hGH)

Historical Perspective

Human GH was isolated in 1956 *(51)* and its gene cloned in 1979 *(52)*. The diagnosis of IGHD was made possible only after the introduction of specific radioimmunoassays *(53)* and immunocytochemistry *(54)*.

The hGH Gene Family

Human GH consists of a cluster of five similar genes in the following order: 5 hGH-1, (or – N), CSHP (chorionic somatomammotropin pseudo gene, CSH-1 (chorionic somatomammotropin); hGH-2 (or V) or placental GH, which differs from the primary sequence of hGH-N by 13 amino acids *(55)* and replaces pituitary GH in the maternal circulation during the second half of pregnancy (Fig. 6). The hGH genes are located on a 78kb section of the long arm of chromosome 17q22-24 *(56)*.

CSH-1 and CSH-2 encode chorionic somatomammotropin, and CSH-P gives rise to low levels of alternatively spliced mRNAs and does not encode a known hormone *(57)*. Only hGH-1 has anabolic growth promoting actions. The genes for GH and chorionic somatomammotropins have 5 exons separated by 4 introns. The human CSH genes have no anabolic or growth activity *(58)*.

hGH Chemical Structure

Human GH is produced as a single chain, 191 amino acid 22-Kd protein *(59)*. It contains two disulfide bonds and shares homology with GH-2. Under normal conditions 75% of pituitary hGH is of the mature 22Kd form. Alternate splicing of the second codon resulting in deletion of amino acids 31–46 yields a 20 Kd form (about 5–10% of pituitary hGH) *(60)*. A small amount of 17 Kd hGH is formed as well *(61)*. The spectrum of biological activity of the 20 Kd hGH form is very similar to that of the 22 Kd hGH *(62)* although a lesser insulinotropic effect has been occasionally found.

The relationship between the integrity of the GH molecule and its biological activities has been a topic of great interest since the isolation of hGH. In contradistinction to ACTH and GHRH in which shortened molecules are fully active; with respect to hGH this seems to be true only for the 20 and 22 Kd variants. Nevertheless, it is of interest that hGH fragments 1-43 and 44-191 have been found to have potent in vivo effects on glucose homeostasis in rodents, and the 44-191 fragment has low-affinity binding to recombinant hGHBP *(63)*.

MOLECULAR DEFECTS IN THE HUMAN GH GENE AND HORMONE

Abnormalities in the structure of the hGH molecule or GH gene deletion have been suspected to occur in humans for some time, but could not be proven until adequate laboratory methods were developed and the right patients found.

A seemingly innocuous defect is the omission of exon 3, which causes the production of 17 Kd hGH *(64)*. hGH-N gene deletions are being diagnosed more and more frequently in patients with hereditary IGHD from consanguineous families. A classification attempt has been made *(65)* (Table 1). Three or possibly four forms of IGHD due to defects in the hGH-1 gene are now recognized. In some forms of familial IGHD the exact molecular defect has not yet been found.

IGHD Type IA

Type IA was first described by Illig et al. *(66)* in a Swiss inbred family. Phillips et al. *(67)* found that the etiology was the lack of the hGH-1 gene. There followed descriptions from other countries *(68–81)*. The sizes of the deletions are heterogenous. DNA analysis revealed that most (70–80%) patients with IGHD Type I have a 6.7 kb deletion in the GH gene, the remainder (20–30%) have a 7.6 or 7.0 kb deletion *(81)*.

The frequency of GH-1 deletions as a cause of IGHD varies among populations. Analyzing patients with severe IGHD (height SDS below 4) the prevalences cited by Mullis et al. *(82)* are 9.4% (Northern Europe), 13.6% (Mediterranean), 16.6% (Turkey), 38% (Oriental Jews), and 12% Chinese. Parks et al. *(83)* suggest that GH gene deletion is the most common cause of severe GHD among Oriental Jewish children. This seems to be true also for the Israeli Arab including Bedouin population (Laron, unpublished observation).

Table 1
Isolated Growth Hormone Deficiencies (IGHD)

Category	*Inheritance*	*GH-RIA*	*Candidate Gene*	*Status*
IGHD IA	Autosomal recessive	Absent	hGH-1	Deletions Mutations (signal peptide)
IGHD IB	Autosomal recessive	Absent/low	hGH-1	Frameshifts Stop codon Splice site mutations
			GHRH	Unlikely
			GHRH-receptor	Mutations
			Trans-*acting* factors	Mutations/deletions
			Cis-*acting* elements	Mutations/deletions
IGHD II	Autosomal dominant	Low	hGH-1	Splice site mutations
IGHD III	X-linked	Low	Unknown	

Adapted with permission from ref. (*65*).

Dependent on the size of the deletion also the CSH cluster or hGH-2 genes can also be deleted *(79)*, although the clinical implications of such deletions is unknown. Institution of hGH replacement therapy induces in most patients the formation of high titers of hGH antibodies leading to growth arrest *(69)*. It is not yet understood why some patients do not develop antibodies *(70,78)*. It seems that patients with a 7.6 kb gene deletion respond well to hGH treatment without antibody formation in contradistinction to patients with a 6.7 kb gene deletion. Gene deletion could result from incorrect alignment of chromosomes during meiosis.

Missense and nonsense mutations as well as small deletions of the GH-1 gene also cause familial IGHD *(84)*. Thus a homozygous nonsense mutation in codon 20 of the signal peptide was reported in two patients of a Turkish family *(85)*. Igarashi et al. *(86)* reported a Japanese compound heterozygote patient with a 6.7kb deletion and a 2bp deletion in exon 3 of the GH-1 gene, which produced a frameshift and generated a stop codon at amino acid residue 131 in exon 4. Nishi et al. *(87)* reported an affected child with a compound heterozygous deletion of 6.7 kb inherited from the mother and point mutations (at positions 123 and 250) inherited from the father. Phenotypically the patients are very short (> –4 SDS), with protruding forehead, acromicria, and obesity.

Treatment

The patients with hGH-1 gene deletions who do not develop antibodies against hGH or only low titers, can be treated by hGH *(70,88)*. The patients who develop blocking antibodies to hGH need to be treated by IGF-1 *(89)*.

Isolated GH Deficiency Type IB

IGHD Type IB is a not very clearly defined entity *(65,90)*. It also has an autosomal recessive mode of inheritance and is characterized by low but detectable levels of serum hGH after stimulation (partial GHD). This is in contradistinction to Type IA IGHD where no circulating hGH is detectable. Cogan et al. *(85)* reported two patients from a Saudi Arabian family in which a first-base transition of the intron 4 (+1G→C) causes an activation of

a cryptic splice in exon 4, thereby deleting aminoacids 103 to 126 (in exon 4) and the frameshift in exon 5.

Recently, Abdul-Latif et al. *(91)* described several patients with IGHD belonging to a large consanguineous Bedouin kindred in Israel. They were short (height SDS between –3.6 to –5.2) and revealed no or very low-serum GH response to pharmacological stimuli. This family presented a novel mutation: a G→C transversion at the fifth base of intron 4, but it resulted in the same cryptic splice site as the patients from Saudi Arabia *(85,90)*. The excess of patients with IGHD among Arab families may reflect the high incidence of consanguinity rather than spontaneous mutations *(92)*.

Isolated GH Deficiency Type II

In contrast to IGHD Type I, IGHD Type II has an autosomal dominant mode of inheritance *(65,84)*. The diagnostic criteria resemble IGHD Type IB. The patients are short but less than type IA and respond to hGH treatment. In a Turkish family a T→C transition of base 6 of the donor splice site of intron 3 caused the splicing out or skipping of exon 3 and the loss of amino acids 32–71 of the hGH molecule *(81)*, so that the truncated molecule corresponds to the 17.5 Kd isoform of hGH. Saitoh et al. *(93)* reported a 1-yr-old Japanese boy and his father with IGHD. Both were found to have a G→C transition of the first base of the donor splice site of intron 3 of the hGH-1 gene.

Subsequently, a G→A transition at the first base of intron 3 has been identified in several families of different ethnic backgrounds *(94–96)*. Recently Hayashi et al. *(97)* described a de novo mutation in a Japanese boy. He had a G→C transversion at the fifth nucleotide of intron 3, causing the skipping of exon 3.

Isolated GH Deficiency Type III

This type of IGHD has an X-linked recessive mode of inheritance. Some patients have hypo- or agammaglobulinemia (deficiency of IgG, IgA, IgM, and IgE) *(98,99)*. As the hGH-1 gene is normal, this disease is considered to affect steps proximal to the hGH-1 gene *(100)* or a combination between X-linked agammaglobulinemia and hGH gene deletions *(101)*. Some patients with IGHD have been found to have interstitial deletion at chromosome X p22.3 *(102)* or duplication of X q13.3- q21.2 *(103)*. Recently four patients with 22q 11.2 deletion, short stature and GH deficiency were reported *(104)*. Two of them had a hypoplastic anterior pituitary gland and one of them also had an abnormal insertion of the infundibular stalk.

CONCLUSION

IGHD can be caused by various defects of the hGH-1 gene, from deletions to single mutations *(105)*. Whereas IGHD Type IA and Type II seem clearly defined, the etiologies and definitions of Type IB and Type III remain to be improved.

Diagnostic Hint

Patients with severe IGHD, who show no rise of serum GH upon intravenous administration of GHRH should also be screened for a defect in the hGH-1 gene; patients with a family history of short stature and partial GHD on repeated tests, should also be investigated, as well as short children with immunoglobulin deficiencies.

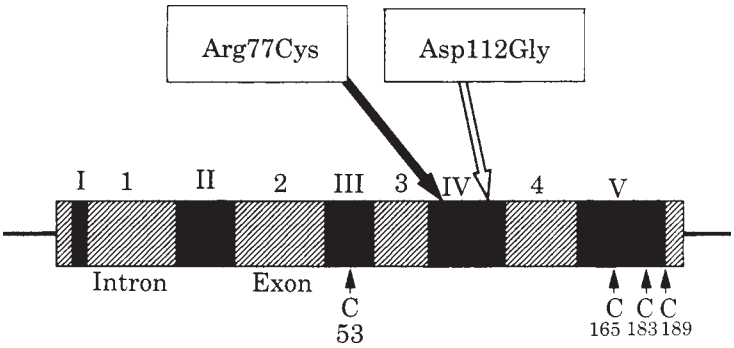

Fig. 7. The localizations of the mutations of the hGH-1 gene leading to bio-inactive growth hormone. Adapted with permission from ref. (*108*).

Growth Hormone Deficiency Owing to Mutant Human Growth Hormone

Although the existence of short stature due to biologically inactive growth hormone had been postulated, the case was only proven recently. Takahashi et al. *(106,107)* reported the first documented patients. Both are products of nonrelated parents. The first patient *(106)* had a birth length of 39 cm and measured 81.7 cm at age 4.9 yr (–6.1 height SDS). He had a prominent forehead, serum hGH levels ranged from 7–14 μg/mL, and rose upon pharmacological stimulation to 35 μg/mL. Serum GHBP was low 70 pmol/L (normal: 107–337 pmol/L). Linear growth responded only temporarily to hGH. The molecular analysis of the hGH gene revealed a heterozygous missense mutation, which converted codon 77 in exon 4 from Arg→Cys (Fig. 7) *(108)*. The second patient *(107)*, a girl, was born with a normal length but slowed her growth so that at the age 3 she measured 79.4 cm (–3.6 height SDS). Her mother was also short (147 cm). She had a prom-inent forehead. Serum hGH rose from 11 to 26 μg/mL upon hypoglycemia stimulation and up to 51 μg/mL after intravenous GHRH. The low IGF-1 rose from 0.28 U/mL to 1.21 U/mL after 3 daily hGH injections and further after successful treatment (11cm/yr) of 1 yr hGH treatment. DNA analysis revealed a heterozygous missense mutation which converted codon 112 in exon 4 from Asp→Gly. The presence of mutant hGH was further confirmed in both patients by isoelectric focusing. In addition, the functional properties of the mutant hGHs were determined by the investigation. The 112 G mutant tended to form a 1:1 GH-GHBP complex instead of a 1:2 complex as produced by the wild-type hGH, a crucial step for GH signal transmission. Thus the mutant was less potent in the phosphorylation of JAK 2 and activation of STAT 5 in IM-9 cells (*see* later). In the case of the other patient, the affinity of the mutant hGH to GHBP was six times higher than the wild-type hGH, and acting as an antagonist failed to stimulate tyrosine phosphorylation and inhibited the activity of wild-type hGH upon simultaneous addition in vitro.

Diagnostic Hint

Whenever there is severe short stature (–3.5 height SDS or more) and the phenotype resembles IGHD, the serum hGH is measurable and responsive to stimuli, but serum IGF-1 is low and only partially responsive to exogenous hGH, the presence of a mutant, biologically inactive hGH molecule should be considered.

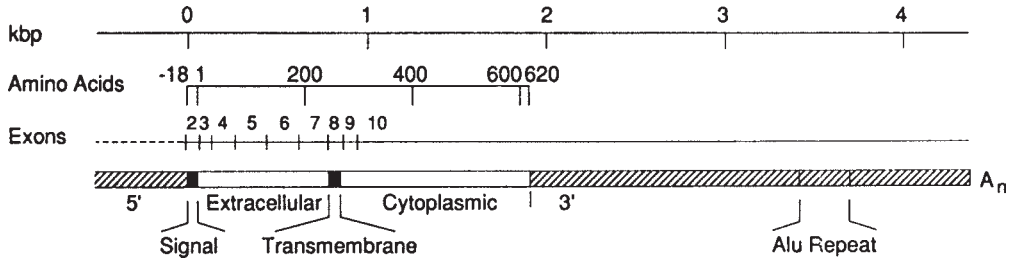

Fig. 8. The hGH receptor gene. Adapted with permission from ref. (*111*).

THE GROWTH HORMONE RECEPTOR

The growth hormone receptor (GH-R) belongs to the family of cytokine receptors which includes receptors for prolactin, erythropoietin, and interleukins *(109)*. The human GH-R gene was cloned in 1987 by Leung et al. *(110)*. It is a protein of 620 aminoacids and consists of 10 exons and spans 87 Kb *(111)*. Exons 2 through 7 encode the extracellular domain (246 residues), exon 8 the single membrane-spanning domain (23 residues), and exons 9 and 10 the intracellular (cytoplasmatic) domain (351 residues) (Fig. 8) *(111)*. The extracellular domain is identical in structure to the GH binding protein (GHBP) *(110)*. The human GH-R gene is located on the short arm of chromosome 5p 13.1 *(112)*.

GH-R form homodimers in the course of binding a single GH molecule *(113,114)*. First the hGH molecule binds at binding site A and then at site B on the second receptor molecule. Sites A and B of binding on hGH are distinct but those on the GHBP overlap *(115)*. The species specificity in the recognition of hGH by the human GH-R is claimed to reside in the interaction between an aspartic acid residue at position 171 of hGH with an arginine residue 43 of the GH-R *(116)*. The binding sites of hGH to the GH-R are located in the cysteine-rich domain of the extracellular domain *(115)*. Receptor occupancy leads to auto-phosphorylation of the Janus 2 (JAK 2) kinase *(117)* and subsequent phosphorylation of the receptor itself. The intracellular signalling cascade includes activation of mitogen-activated protein kinase (MAPK) and of transcription factors known as STATS (signal transducers and activation of transcription) *(118)*.

GROWTH HORMONE BINDING PROTEIN (GHBP)

Herington et al. *(119)* and Baumann et al. *(120)* independently described a serum protein capable of binding GH with high affinity. This GH binding protein (GHBP) was shown to be identical in structure with the extracellular hormone-binding domain of the GH-R *(110)*. Its quantitative measurements revealed that its serum concentrations change with age, being low in neonates and reaching maximal values in young adulthood *(121)*. Whether GHBP can be synthesized de novo, in addition to being formed by the splicing of the extracellular domain of the GH-R *(122)* with which it shares structural identity *(110)* is not known. The presence of mutated GHBP in the circulation has not yet been described. Between 30–50% of the circulating GH is bound to this protein.

Determination of serum GHBP can be used as a simple quantitative estimation of the extracellular domain of the GH-R; its absence indicating a defect in this domain of the receptor and resulting in classical Laron syndrome *(50,123,124)*. A low-serum GHBP concentration in relatives of patients with LS helps identify heterozygous carriers *(125)* of mutations in the extracellular domain of the receptor.

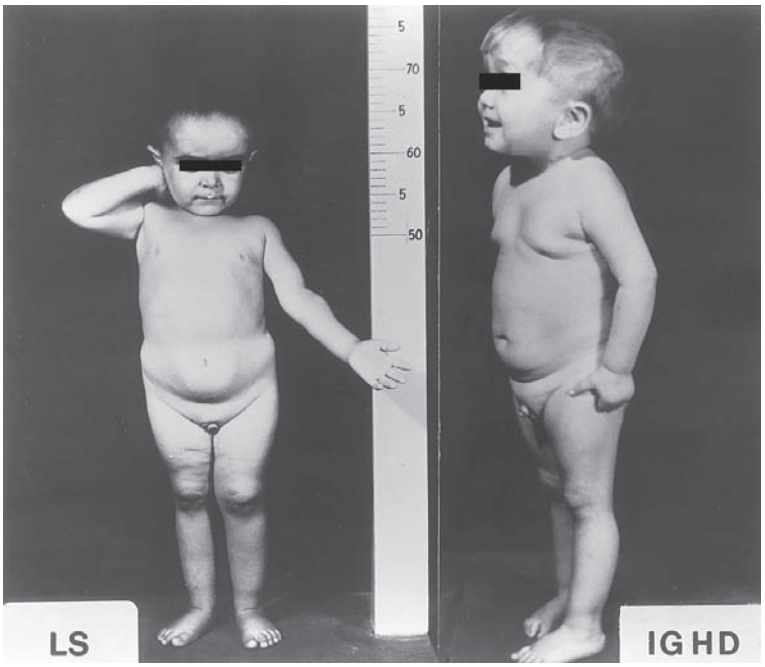

Fig. 9. Similarity between a boy with Laron syndrome (LS) and one with isolated GH deficiency (IGHD) due to GH-1 gene deletion.

Normal or elevated serum GHBP in typical LS patients denotes a defect in the transmembrane, intracellular or downstream of the GH-R.

MOLECULAR DEFECTS OF THE HUMAN GH RECEPTOR (LARON SYNDROME)

Historical Perspective

The first description of patients with this syndrome was made by Laron et al. in 1966 *(126)* who reported 22 patients in 1968 *(127)*. The patients resembled phenotypically those with IGHD (Fig. 9) but had excessively high circulating GH levels, and very low serum IGF-1 (sulfation factor) generation *(128)*, which did not respond to administration of exogenous GH *(129)*. The first assumption that the GH molecule is abnormal was excluded by findings between 1973 and 1985 that their high circulating hGH was normal both by immunologic *(130,131)* and radioreceptor testing *(132,133)*. The proof that the GH resistance, the characteristic of these patients, is the result of a defect in the GH-R was provided by Eshet et al. in 1984 *(134)* by demonstrating that liver membranes of two patients prepared from open biopsies do not bind human GH. The cloning of the GH-receptor in 1986 *(111)* enabled the study of molecular defects.

Geographical Distribution

Following the early descriptions, patient reports from many continents followed, a majority originating from the Mediterranean, Mid-Eastern, or South Asian regions, known to have a high incidence of consanguineous marriages.

Today several hundreds of patients are known; the majority, though, are probably still undiagnosed. The largest cohorts known so far are in Ecuador: 79 patients *(135)*, consisting of subjects originating in Spain, possibly of Jewish origin, and the Israeli cohort consisting of 51 Jews originating from Yemen, Iran, Afghanistan, Middle East, North Africa, and Israeli Arabs *(136)*, with smaller cohorts in Turkey *(137)*, Iran *(138)*, India *(123)*, and Bahamas *(140)*. Patients in families or isolated patients have been reported from Italy, France, Spain, Denmark, Germany, Slovakia, Slovenia, Russia, Poland, North Africa, Japan, Vietnam, Cambodia, Mexico, and South and North America. They are listed in review papers *(141–143)*. Recently an additional 14-yr-old girl of Slavic origin from Russia was reported *(144)*.

Analysis of the Israeli cohort led to the conclusion that LS is caused by an autosomal fully penetrant recessive mechanism *(145)* with one exception of a father and two of his children in whom a dominant transmission is assumed *(146)*.

DEFECTS OF THE GH-RECEPTOR (GH-R)

In 1989 Godowski et al. *(111)* characterized the genomic organization of the GH-R gene and reported two patients from the Israeli cohort who were homozygous for the deletion of exons 3, 5 and 6. In the same year Amselem et al. *(147)* using the newly developed polymerase chain reaction (PCR) methodology described several point mutations in patients with Laron syndrome. Since then a series of patients have been investigated and the findings are listed in Table 2 *(148–163)*. As seen, the molecular defects range from deletions, nonsense-frameshift, splice to missense mutations. The majority of defects reported today are located in the extracellular domain of the human GH-R gene. In almost all instances the patients were found to be homozygous for the same mutant allele, as expected in recessive hereditary transmission. However, occasionally there were patients who were compound heterozygotes for mutations *(160,161)*.

As the GHBP is identical in structure to the extracellular domain *(110)*, mutations in this part of the receptor usually result in undetectable or very low serum GHBP. This measurement represents a simple and fast screening for the ascertainment of a molecular defect in the extracellular domain of the GH-R, and identification of heterozygotes for defects in this domain *(125)*.

So far only two mutations in the transmembrane region (exon 8) *(156,157)* and three instances of mutations in the intracellular domain (exons 9 or 10) *(159–161)* have been reported. In all these patients the serum levels of GHBP are normal or high. The patients described by Ayling et al. *(160)* had a dominant transmitted single heterozygous mutation: from mother to daughter, a G→C transversion at 876-1 affecting the 3' splice receptor site preceding exon 9, causing the deletion. The patients of Iida et al. *(161)* also had a G→A transversion at 876, and also revealed a dominant negative transmission from mother to two children.

Post GH-R Defects

Until now only two reports on downstream defects in Laron syndrome have been described. Laron et al. *(163)* described three siblings of Palestinian Arab origin, with high serum hGH, normal GHBP, and a normal GH-R structure. Exogenous administration of hGH for 7 d did not raise the undetectable or very low-serum IGF-1, but caused a rise in serum IGFBP-3, indicating a functioning GH-R. The exact defect is under study. Freeth

et al. *(164)* described four girls with LS of two unrelated Asian families with normal GHBP in whom no mutations of the GH-R were detected. Further studies of the GH signaling pathway performed in skin fibroblasts of these patients *(165)* revealed that GH failed to activate the STAT pathway in fibroblasts of one family, being normal in the second family denoting different signalling defects in the two families.

Clinical Features

The clinical and biochemical characteristics of patients with primary IGF-1 deficiency (GH insensitivity = Laron syndrome) in childhood and adulthood are summarized in Table 3. Despite a wide spectrum of variability *(141,143,146,166)*, the characteristic clinical features resemble IGHD (Fig. 9), i.e., severe growth failure (–4 to –10 height SDS), small cranium, underdevelopment of the facial bones resulting in protruding forehead *(141)*, sparse hair *(167)*, crowded and defective teeth *(127)*, acromicria, and small genitalia and gonads *(168)*. Most patients have a high-pitched voice *(127,146)*. Body proportions show a high upper/lower ratio; skeletal maturation is markedly retarded *(169)*, with osteopenia and osteoporosis developing in young adulthood *(170)*. There is delayed motor development *(50,127)* and intellectual impairments of variable degrees *(171)*. Puberty is delayed *(172)* but reproductive potential is preserved *(50)*, the heterozygote children having a normal phenotype. Obesity is evident in young age and progresses markedly in adulthood *(173)*, the patients also developing hyperlipidemia and insulin resistance despite a tendency for hypoglycemia *(174)*. Final height ranges from 108–136 cm in females and 119–142 cm in males *(50)*. Some of the patients with positive serum GHBP, i.e., those with a molecular defect in the transmembane, intracellular, or postreceptor pathways, seem to be slightly less short *(166,175)*. The few patients with a postreceptor defect seem to be less obese *(163,164)*, possibly due to a preserved direct GH effect.

Nomenclature

The nomenclature used for this syndrome is confusing. A consensus nomenclature has been published, proposing that primary GH resistance or insensitivity (GHIS) be synonymous with Laron syndrome (LS), differentiating it from secondary GH resistance *(176)*. Some authors use only GHIS, without differentiation; others use GH receptor deficiency (GHRD) *(135,177)*.

Diagnostic Hint

The findings of abnormally high serum GH levels in patients with the clinical characteristics of IGHD should serve as an alert to the diagnosis of LS. The confirmation is low-serum IGF-1, which does not rise upon the daily administration of exogenous hGH for 4–7 d *(129,146)*. Location of a defect in the extracellular domain of the GH-R is evidenced by a low or undetectable serum GHBP *(119,120)*. The finding of a normal or high serum GHBP denotes a defect in the transmembrane or intracellular domain.

Treatment

The only possible therapy is administration of IGF-1, which has been practiced by us since 1988 *(178)* and subsequently by three other groups in the US, Ecuador, and Europe *(179–181)*. IGF-1 stimulates linear growth *(179–183)*, but is less efficient than hGH in the treatment of IGHD *(184)*. IGF-1 treatment improves also biochemical abnormalities

Table 2
Growth Hormone Receptor Mutations Reported in Patients with Laron Syndrome[a]

Mutations	*Molecular defect*	*Nucleotide change*	*Exon involved*	*Domain[b]*	*GHBP[c]*	*Authors*	*Reference*
Deletion	Exons 3-5-6		Exons 3-5-6	EC	–	Godowski et al. (1989)	(*111*)
Nonsense	C38X	C→A at 168	4	EC	–	Amselem et al. (1991)	(*148*)
	R43X	C→T at 181	4	EC	–	Amselem et al. (1991)	(*148*)
	Q65X	C→T at 197	4	EC	–	Sobrier et al. (1997)	(*150*)
	W80X	C→A at 293	5	EC	–	Sobrier et al. (1997)	(*150*)
	W157X	C→A at 525	6	EC	?	Sobrier et al. (1997)	(*150*)
	E183X	C→T at 601	6	EC	?	Berg et al. (1994)	(*151*)
	R217X	C→T at 703	7	EC	–	Amselem et al. (1993)	(*152*)
	Z224X	G→T at 724	7	EC	–	Kaji et al. (1997)	(*242*)
Frameshift	21delTT	delTT at 118	4	EC	–	Counts and Cutler (1995)	(*153*)
	36delC	delC at 162	4	EC	–	Sobrier et al. (1997)	(*150*)
	46delTT	delTTat192-193	4	EC	–	Berg et al. (1993)	(*154*)
	230delT	delT at 744	7	EC	–	Sobrier et al. (1997)	(*150*)
	230delAT	delATat 743-744	7	EC	–	Berg et al. (1993)	(*154*)
	309delC	delC at 981	10	IC	–	Kaji et al. (1997)	(*242*)
Splice	Intron 2	G→A at 70+1		EC	?	Sobrier et al. (1997)	(*150*)
	Intron 4	G→A at 266+1		EC	–	Amselem et al. (1993)	(*152*)
	Intron 5	G→A at 71+1		EC		Berg et al. (1993)	(*154*)
	Intron 5	G→C at130-1		EC		Berg et al. (1994)	(*151*)
	Intron 6	G→T at 189-1		EC		Berg et al. (1993)	(*154*)
	Intron 5	G→C at 440-1		EC	–	Amselem et al. (1993)	(*152*)
	Intron 6	G→T at 619-1		EC	–	Berg et al. (1993)	(*154*)
	E180splice	A→G at 594	6	EC	+	Berg et al. (1992)	(*155*)
	Gly236GLY	C→T at 766		EC	–	Baumbach et al. (1997)	(*140*)
	G223G	C→T at 723	7	EC	–	Sobrier et al. (1997)	(*150*)
	Intron 7	G→C at 785-1	7/8	EC/TM	+++	Silbergeld et al. (1997)	(*156*)

	R274T	G→C at 874	8	TM	++	Woods et al. (1996)	(*157*)
	GHR(1-277)[d]	G→A at 876+1	9	TM/IC	++	Iida et al. (1998)	(*161*)
	GHR(1-277)[e]	G→C at 876-1	9	TM/IC	+	Ayling et al. (1997)	(*160*)
Missense	C38S	T→A at 166	4	EC	?	Sobrier et al. (1997)	(*150*)
	S40L	C→T at 173	4	EC	?	Sobrier et al. (1997)	(*150*)
	W50R	T→C at 202	4	EC	–	Sobrier et al. (1997)	(*150*)
	R71K	G→A at 266	4	EC	–	Amselem et al. (1993)	(*152*)
	F96S	T→C at 341	5	EC	–	Amselem et al. (1989)	(*147*)
	V125A	T→C at 428	5	EC	–	Amselem et al. (1993)	(*152*)
	P131Q	C→A at 446	6	EC	?	Walker et al. (1998)	(*162*)
	V144D	T→A at 485	6	EC	–	Amselem et al. (1993)	(*152*)
	D152H	G→C at508	6	EC	+	Duquesnoy et al. (1994)	(*158*)
	R161C	C→T at 535	6	EC	–	Amselem et al. (1993)	(*152*)
	R211G	C→G at 685	7	EC	–	Amselem et al. (1993)	(*152*)
	C422F[f]	C→T at 1362	10	IC	–	Kou et al. (1993)	(*159*)
	P561T[f]	C→T at 1778	10	IC	–	Kou et al. (1993)	(*159*)

[a]Primary growth hormone insensitivity = resistance.
[b]EC, extracellular; TM, transmembrane; IC, intracellular.
[c]?, not available; +, detectable; ++, high levels; +++, very high levels.
[d]at the +1 position of the 5'-donor splice site of intron 9.
[e]at the 3'-splice acceptor site preceding exon 9.
[f]These two mutations were identified on the same GHR allele.

Table 3
Early and Late Consequences of Primary IGF-1 Deficiency[a]

Perinatal and during childhood
Subnormal birth length (−10–30%)
Disproportional growth
Acromicria including facial bones
Defective and crowded teeth
Sparse hair growth
Small gonads and genitalia
Obesity
Retarded skeletal maturation
Retarded brain growth (head circumference)
Delayed motor development
Narrow larynx (high-pitched voice)
Delayed puberty
Hypoglycemia
High-serum GH
Adulthood
Very short stature (final height: 108–142 cm, i.e., −4 to −10 height SDS)
Marked progressive obesity
Osteoporosis
Muscle underdevelopment and weakness
Cardiomicria
Varying intellectual deficits (from retardation to normal)
Hyperinsulinemia
Hypercholesterolemia
Glucose intolerance and diabetes

[a]GH insensitivity = Laron Syndrome.

such as hyperlipidemia, insulin resistance, glucose utilization, and renal function in children as well as adults *(170,173,174)*.

It is regrettable that IGF-1 is available to only a very few of the many patients in need of replacement therapy *(185)*.

PARTIAL GROWTH HORMONE INSENSITIVITY (GHI)

In recent years the possible existence of partial GH insensitivity as one of the causes of so-called idiopathic short stature (ISS) has been raised *(186)* as children with ISS do not respond to exogenous hGH as well as children with GHD. Goddard et al. *(187)* found in 14 out of a series of children with ISS, selected because of low GHBP in the presence of normal GH levels, 5 GH receptor mutations. in four patients. One patient was a double heterozygote with a missense mutation in exon 4 (GLU44→Lys) and a missense mutation in exon 6 (Arg161→Cys). The exon 4 mutation was inherited from the father and the exon 6 mutation from the mother. It is of interest that this patient did not have severe growth failure. Three other patients were heterozygotes for a nonsense mutation in exon 5 introducing a premature stop codon (Cys 122 stop) and two other patients were heterozygotes for missense mutations in exon 7 (Arg211→His or GLU 224→ASP), without defects in the other allele.

There is no strong evidence that heterozygous mutations of only one allele cause GH resistance as most children studied by Goddard et al. *(187)* showed a response to GH therapy. In our cohort of patients with classical LS *(50)*, 1/15 heterozygote males and 10/16 heterozygote females were below the 3rd centile of height (Tanner charts). However, because most belonged to a generation of new immigrants from underprivileged countries, it is possible that the growth failure resulted from environmental circumstances. Some of the short and normal-sized heterozygous of classical LS patients had below normal GHBP values *(125)*.

In conclusion, the clinical and biochemical features of partial GHI have not yet been clearly elucidated *(186)* and this entity appears to be very rare. Some double heterozygotes for a GH-R mutation have severe GH resistance and the complete LS phenotype *(161)*, although some do not *(187)*. Most heterozygous family members described so far were of normal height.

The Pygmies

The African Pygmies resemble patients with LS (primary GH insensitivity) in several aspects *(188)*. They are short, both at birth and at final height (males: 145–150 cm; females: 130–145 cm) *(189)*. They have full sexual development and normal reproduction. Their serum GH levels are normal and upon stimulation by hypoglycemia or arginine reach levels up to 30 ng/mL and they are hypoglycemia-unresponsive *(190)*. Serum IGF-1 is low *(191,192)* and does not rise upon short-term hGH administration *(192,193)*, denoting GH resistance. The molecular cause of the GH receptor abnormality in pygmies is still unknown, however, like patients with LS, it was found that they have reduced GHBP *(194)*. Furthermore, it has been shown that both GH and IGF-1 fail to augment colony formation of T-lymphocytes from Efe pygmies *(195)*, denoting hormone resistance in vitro.

The absence of high levels of serum GH in the pygmies may disprove classical GH resistance, as do the low IGF-1 levels preclude IGF-1 resistance. Studies are needed to determine the molecular etiology of these short people.

INSULIN-LIKE GROWTH FACTOR-1 (IGF-1)

Historical Perspective

The IGFs (1 and 2) were identified in 1957 by Salmon and Daughaday *(196)* and designated sulfation factor by their ability to stimulate ^{35}sulfate incorporation into rat cartilage. Froesch et al. *(197)* described the nonsuppressible insulin-like activity (NSILA) of two soluble serum components (NSILA I and II). In 1972 the labels "sulfation factor" and "NSILA" were replaced by the term "somatomedin," denoting a substance under control and mediating the effects of GH *(198)*. In 1976 Rinderknecht and Humbel *(199)* isolated two active substances from human serum and due to this structural resemblance to proinsulin were renamed "insulin-like growth factor I and II" (IGF-1 and 2). IGF-1 is the mediator of the anabolic and mitogenic activity of GH *(200)*.

Chemical Structure

The IGFs are members of a family of insulin-related peptides, which include relaxin and several peptides isolated from lower invertebrates *(201)*. IGF-1 is a small peptide consisting of 70 amino acids with a molecular weight of 7649 Da *(202)*. Like insulin, IGF-1 has

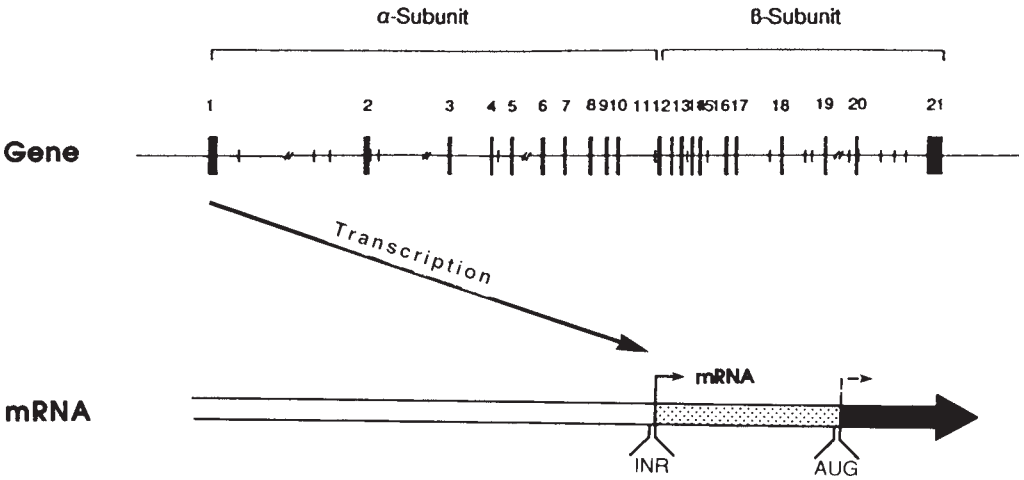

Fig. 10. The Type 1 IGF receptor gene and mRNA. Adapted with permission from ref. (*206*).

an A and B chain connected by disulfide bonds. The C-peptide region has 12 amino acids. The structural similarity to insulin explains the ability of IGF-1 to bind (with low affinity) to the insulin receptor.

The IGF-1 Gene

The IGF-1 gene is encoded on the long arm of chromosome 12q23-23 *(203,204)*. The human IGF-1 gene consists of 6 exons including two leader exons and has two promoters *(205)* (Fig. 10).

INSULIN-LIKE GROWTH FACTOR BINDING PROTEINS (IGFBPs)

The IGFs circulate in plasma 99% complexed to a family of binding proteins that modulate the availability of free IGF-1 to various tissues. There are 6 binding proteins *(207)*, and possibly more *(208)*. In humans almost 80% of circulating IGF-1 is carried by IGFBP-3 a ternary complex consisting of one molecule of IGF-1, one molecule of IGFBP-3, plus a molecule of an 88 Kd protein named acid-labile subunit (ALS) *(209)*. IGFBP-1 is regulated by insulin and IGF-1 *(210)*. IGFBP-3 is controlled mainly by GH but also to some degree by IGF-1 *(211)* In states of GHD, serum IGFBP-3 is low *(212)* but IGFBP-1 is elevated *(210)* due to a negative insulin and IGF-1 feedback mechanism.

The IGF-1 Receptor

The human IGF-1 receptor (Type 1 receptor) is the product of a single-copy gene spanning over 100 Kb of genomic DNA at the end of the long arm of chromosome 15q 25-26 *(213)*. The gene contains 21 exons (Fig. 10) and its organization resembles that of the structurally related insulin receptor *(214)*. The Type-1 IGF-receptor gene is expressed in virtually every tissue and cell type even during embryogenesis *(215)*.

It is of interest that the liver, the organ with the highest levels of IGF-1 ligand expression, exhibits almost undetectable levels of IGF-1 receptor mRNA, possibly due to the downregulation of the receptor by the local production of IGF-1. Like the insulin recep-

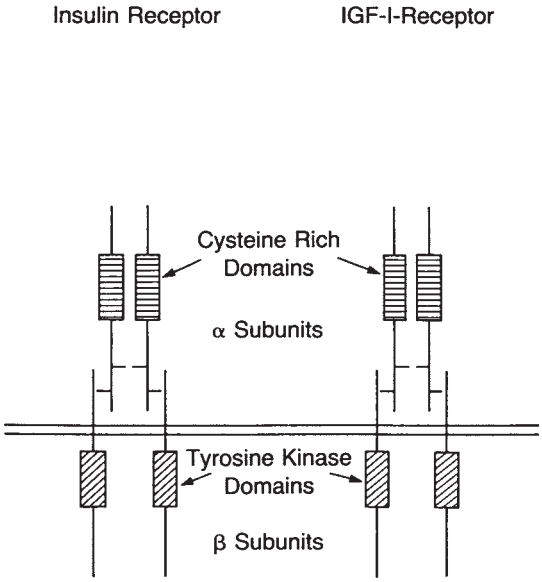

Fig. 11. Resemblance between the IGF-1 and insulin receptors.

tor, the Type-1 IGF receptor is a heterotetramer composed of two extracellular-spanning α subunits and transmembrane β subunits. The α subunits have the binding sites for IGF-1 and are linked by disulfide bonds (Fig. 11). The β subunit has a short extracellular domain, a transmembrane, and an intracellular domain. The intracellular part contains a tyrosine kinase domain, which constitutes the signal-transduction mechanism. Similar to the insulin receptor, the IGF-1 receptor undergoes ligand-induced autophosphorylation, mainly on tyrosines 1131, 1135, and 1136 *(216)*. The activated IGF-1 receptor is capable of phosphorylating other tyrosine-containing substrates, such as IRS-1 (insulin receptor substrate 1) and continue a cascade of enzyme activations via PI3-kinase (phosphatidylinositol-3 kinase), Grb2 (growth factor receptor-bound protein 2), Syp (a phosphotyrosine phosphatase), and Nck (an oncogenic protein) *(217–219)*. Another pathway of the activated IGF-1 receptor is phosphorylation of Shc (src homology domain-protein), which associates with Grb2, and activates Raf leading to a cascade of protein kinases including Raf, MAP kinase, 5 G kinase, and others *(220)*.

Physiological Aspects

IGF-1 is secreted by many tissues and the secretory site seems to determine its actions. The majority of IGF-1 is secreted by the liver and by its transport to other tissues, it acts as an endocrine hormone *(221)*. IGF-1 secreted by other tissues *(222)*, such as cartilagenous cells, acts locally in a paracrine fashion *(223)*. It is also assumed that IGF-1 can act in an autocrine manner as an oncogene *(224,225)*.

The role of IGF-1 in the metabolism of many tissues has recently been reviewed *(211, 226)*. Its effect on pre- and postnatal growth of the skeleton, organs, and tissues including the nervous system have been clearly established in man *(227)* and experimentally in animals, including knockout of the IGF-1 gene *(228)*.

DEFECTS OF THE IGF-1 GENE AND RECEPTOR

Only one patient with a defective IGF-1 gene has been described so far. In 1996 Woods et al. *(229)* described a very short 15.8-yr-old boy (height 119 cm = –6.9 height SDS). He had a small head circumference, small jaw, hypogonadism, and mental retardation, and severe bilateral sensorineural deafness. He had high-serum hGH (stimulated peaks up to 175 µg/mL; normal IGFBP-3 levels, but undetectable serum IGF-1). DNA analysis revealed deletion of exons 4 and 5 of the IGF-1 gene. One year of treatment with hGH resulted in poor growth, indicating that he was GH-resistant.

IGF-1 Resistance

Very few reports of short children fit this category, and so far no convincing evidence of a true homozygous IGF-1 receptor defect has been reported. Two heterozygous deletions of the distal arms of chromosome 15, the site of the IGF-1 receptor gene in man, have been reported.

Bierich et al. *(230)* described a very short girl with typical features of LS. Her birth length was 48 cm, she had hypoglycemic episodes, and both her basal GH and IGF-1 were high. In addition there was a 50% reduction of the specific binding of IGF-1 by the patient's fibroblasts. Momoi et al. *(231)* reported a 14-yr-old dwarfed girl born after 40 wk gestation with a birth length of 43 cm. There is no mention of her appearance but on several occasions her serum GH and IGF-1 were high, the latter reaching values of 4860 U/L. Not consistent with resistance to IGF-1 was the finding that the patient's cultured fibroblast-bound IGF-1 similarly to control cells. A possible etiology of IGF-1 resistance may be the deletion of one copy of the gene encoding the IGF-1 receptor on the long arm of chromosome 15 *(232,233)*.

Diagnostic Hints

Children born very short (≥-4 SDS height) with decreased postnatal growth who may not present with all the signs of congenital IGF-1 deficiency but who have elevated serum GH levels should be investigated for a possible abnormality in the IGF-1 gene (low to undetectable serum IGF-1) or IGF-1 receptor gene (high serum IGF-1 levels), once a defect in the GH-R has been excluded.

Comment

Experimental animal models such as the IGF-1 gene knockout *(228)* are helpful in the study of the basic physiological role of IGF-1. A recent report on the selective knockout of the hepatic IGF-1 gene challenges the concept that circulating IGF-1 (originating from the liver) can replace GH for normal postnatal growth *(234)*. However, IGF-1 plays an essential role in GH-induced postnatal growth *(235)*. IGF-1 receptor knockout mice do not survive after birth *(228)*.

Treatment

Patients with IGF-1 gene deletion or gene mutations should be treated by exogenous IGF-1 administration. For potential patients with IGF-1 receptor defects, there are no available treatments.

Table 4
Similarities and Differences Between Patients with Molecular Defects in the hGH or IGF-1 Genes or Their Receptors (R)

Characteristics	*GHRH-R gene mutation*	*hGH-I gene deletion*	*hGH-I deletion or mutation*		*Post-hGH-R mutation GHBP+*	*IGF-1 gene deletion*	*IGF-1-R mutation*
			GHBP–	*GHBP+*			
Dwarfism	+	+	+	+	+	+	+
Short at birth	+	+	+	+	+	+	+
Small cranium	+	+	+	+	+	+	+
Acromicria	+	+	+	+	+	+	?
Obesity	±	+	+	+	–	–	+
Small genitalia and testes	+	+	+	+	+	+	?
Serum hGH	↓	↓	↑	↑	↑	↑	↑
Serum IGF-1	↓	v↓	v↓	v↓	v↓	v↓	↑
Serum insulin	↓	↓	↑	↑	N	?	↓

v, very.

GENOTYPE-PHENOTYPE RELATIONSHIP

Patients with genetic abnormalities along the GH axis present a wide spectrum of phenotypic expression *(236,237)* (Table 4); however, they have in common severe short stature from −3.5 to −10 height SDS below the mean normal (Tanner growth charts). Typical features of the classical LS *(50,183)* have been described in patients ranging from receptor defects *(45,48)* to IGF-1 resistance *(230)*. These patients have a small head circumference, a protruding forehead, acromicria, hypogenitalism, and hypogonadism.

Insufficient data is available to explain the variations of expression in the nervous tissue, including psychological maturation *(171,238–240)*, glucose and adipose tissue metabolism, and so forth *(113,114)*. Some differences in the latter may be explained by the absence or presence of GH signal transmission in instances of mutations downstream of the GH-R, thus permitting some non-IGF-1-dependent actions. It was observed that there are slight differences between the height of GHBP- positive and GHBP-negative patients with LS, the former being slightly less short *(175,241,242)*. As more molecular data becomes available both from patients and their family members, a better understanding of variations in the phenotypic expression of molecular defects along the GH axis will become available.

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