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EXTENSIVE PERSONAL EXPERIENCE

Phenotype: Genotype Relationships in Growth Hormone Insensitivity Syndrome*

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ABSTRACT

GH insensitivity syndrome (GHIS) is associated with many different mutations of the GH receptor (GHR) gene. We examined the phenotypic and biochemical features in 82 GHIS patients from 23 countries, each fulfilling diagnostic criteria of GHIS. There were 45 males and 37 females [mean age, 8.25 yr; mean height, −6.09 SD score, and mean insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3), −7.99 SD score]. Sixty-three were GH-binding protein (GHBP) negative; 19 were GHBP positive (>10% binding). The mean height in GHBP-negative subjects was −6.5 SD score, and that in GHBP-positive patients was −4.9 SD score (P = <0.001). Clinical and biochemical heterogeneity was demonstrated by the wide range of height (−2.2 to −10.4 SD score) and IGFBP-3 (−1.4 to −14.7 SD score) values, which were positively correlated (r^2 = 0.45; P = <0.001). This contrasted with the lack of correlation between mean parental height SD score and height SD score (r^2 = 0.01).

Fifteen different GH receptor gene mutations were identified in 27 patients. All had homozygous defects, except 1 who had a compound heterozygous defect. The mutations were 5 nonsense, 2 frame shift, 4 splice, 4 missense, and 1 compound heterozygote. There was no relationship between mutation type or exon of the GHR gene involved and height or IGFBP-3 SD score.

In conclusion, GHIS is associated with wide variation in the severity of clinical and biochemical phenotypes. This variation cannot clearly be accounted for by defects in the GHR gene. Other genetic and/or environmental factors must, therefore, contribute to phenotype in GHIS. (*J Clin Endocrinol Metab* **82:** 3529–3535, 1997)

LARON *et al.* (1) described the first patients with a phenotype of GH deficiency and normal circulating GH concentrations. This autosomal recessive disorder, subsequently known as GH insensitivity syndrome (GHIS), is characterized by resistance to the physiological actions of GH (2). Two large cohorts of patients with GHIS have previously been reported: 43 mainly Oriental Jewish patients from Israel (3) and 63 patients from 2 neighboring provinces in Ecuador (4, 5).

The clinical characteristics of the affected patients are very similar to those seen in GH deficiency secondary to mutations of the GH gene, namely hypoglycemic episodes, severe growth failure, and a typical craniofacial appearance (1–4, 6–9). Intellectual retardation was reported in the Israeli cohort (3), but in the Ecuadorian patients school performance was exceptionally good (5). Biochemically, GH levels are elevated combined with extremely low levels of insulin-like growth factor I (IGF-I), IGF-binding protein-3 (IGFBP-3), and IGF-II (3, 4, 10). GHIS is confirmed by the failure of exogenously administered GH to elevate levels of IGF-I or IGFBP-3 significantly (4, 11). GH-binding protein (GHBP; measured as serum GH-binding activity) was initially found to be absent (12, 13), but more recent reports have suggested that some patients with GHIS may also have normal levels of GHBP (4, 14, 15).

The molecular defect in GHIS originates in the GH receptor (GHR) gene, with over 30 different mutations now reported (16–24). Although one of the first mutations identified was a complex gene deletion (16), almost all the defects have been point mutations located in exons 2–7 of the GHR gene that encode the extracellular domain of the GHR. These mutations are thought to impair receptor action by affecting GH binding, hence the finding of GHBP (a circulating form of the extracellular domain) lacking binding activity in many patients. More recently, mutations have been reported in patients with normal or even elevated serum GHBP levels

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that are thought to affect other functions of the GHR, such as dimerization or intracellular signaling (25, 26).

We recently reported clinical and biochemical details in 27 patients with GHIS from a genetically heterogeneous background, selected using a scoring system and assembled for treatment with recombinant IGF-I (27). Eighty-two patients from 22 countries have now been recruited into this study, and molecular studies of the GHR gene have been performed in 31 of these patients. We now report phenotype-genotype relationships.

Subjects and Methods

Subjects

Clinical details and serum samples from patients with suspected GHIS were sent to Pharmacia & Upjohn (Stockholm, Sweden) for central evaluation. Heights were measured using a stadiometer and were converted into SD scores using Tanner standards (28). Fasting serum GH, IGF-I, IGF-II, IGFBP-1, IGFBP-3, and GHBP were measured in each patient, followed by an IGF-I generation test (Genotropin, 0.1 U/kg BW, sc, daily for 4 days) and the measurement of fasting IGF-I and IGFBP-3 on day 5. A scoring system (Table 1) (27, 29) identified 82 patients with GHIS (score $\geq$5/7).

Laboratory investigations

Fasting serum GH, IGF-I, IGF-II, IGFBP-3, and IGFBP-1 in each patient were measured in central laboratories as previously described (27). Measurement of GHBP was performed in INSERM U-344 (Paris, France) (30). GH binding is expressed as the radioactivity in the individual peak divided by the total radioactivity in peaks I, II, and III (30). To evaluate nonspecific binding to peak-II-BP, 5 μg hGH were added to the plasma incubation. For plasma samples containing high levels of GH (>6 ng/mL), a correction was made for the estimation of peak II-BP.

Statistical analysis

The data are expressed as the mean ± SD (or medians and ranges when log-normally distributed), and means were compared using Student's *t* test. Correlations were determined using regression analysis.

Molecular analysis

We report data on 31 patients, 26 studied at the Molecular Genetics Laboratory (Créteil, France) and 5 studied at the Molecular Endocrinology Laboratory, St. Bartholomew's Hospital (London, UK). To determine whether the disease was linked to the GHR, haplotype analysis was performed using the intron 9 GHR-negative gene polymorphism previously characterized (17). In 1 family in which this analysis suggested the disease may not be linked to the GHR, 2 polymorphic dinucleotide repeat markers (D5 S419 and D5 S477) located close to the GHR gene locus were used.

Exons 2–9 of the GHR gene were amplified using intronic primers. Exon 10 was amplified in three partially overlapping fragments (10A, 10B, and 10C) (18). DNA fragments were then sequenced directly after separation using streptavidin-coated magnetic beads (Dynal, Oslo, Norway) and single stranded sequencing techniques, as reported previously (26). Screening for single nucleotide changes in the GHR gene was performed by analyzing PCR-amplified fragments by means of denaturing gradient gel electrophoresis. The sequence of DNA samples showing a shift in mobility on denaturing gradient gel electrophoresis was determined after asymmetric amplification.

TABLE 1. Scoring system for the diagnosis of GHIS

Test	Parameter	Criterion	Score
Auxology	Height	<−3 SD score	1
Basal GH	GH	>2.5 ng/mL	1
Basal IGFs	IGF-I	≤50 μg/L	1
	IGFBP-3	<−2 SD	1
IGF-I generation	IGF-I increase	<15 μg/L	1
	IGFBP-3 increase	<0.4 mg/L	1
GH binding	% GH bound	<10%	1

The maximum total score was 7 points. Patients with a score of 5 points or more were included in the study.

Results

Clinical features

Eighty-two patients (from 69 families) were studied. The patients resided in 23 different countries; Belgium, United Kingdom, Ireland, France, Italy, Spain, Germany, Denmark, Sweden, Norway, Greece, Turkey, Slovenia, Romania, Argentina, Brazil, Mexico, Malaysia, Iran, Saudi Arabia, Japan, Australia, and South Africa. The clinical details of the patients are given in Table 2.

Auxology. The mean height SD score was −6.09 ± 1.7 SD (males, −6.06 ± 1.8 SD; females, −6.2 ± 1.7 SD; P = NS). Height SD scores varied from −2.2 to −10. A correlation between age and height SD score was observed, with increasing age associated with decreasing height SD score (r^2 = 0.08). Mean birth length was −1.01 SD, and birth weight was −0.36 SD.

Hypoglycemia, mental retardation, and microphallus. A history of hypoglycemia was present in 75.3% (61 of 81) of the patients, and according to a crude assessment, mental retardation was present in 13.5% (11 of 81) of the patients. There was no association between hypoglycemic episodes and severity of height deficit. Mental retardation occurred no more frequently in those patients with hypoglycemia (7 of 61 patients; 11%) than in those with no reported hypoglycemia (4 of 20; 20%). Microphallus was present in 12 of 29 (41%) males.

Endocrine investigations

Biochemical details of the patients are summarized in Table 3. Mean basal GH was elevated at 17.62 ng/mL (normal range, <10 ng/mL), although it was extremely variable, ranging from 0.3–319 ng/mL. Basal IGF-I was very low, being for the most part below the limit of sensitivity of the assay (median, <20 μg/L; range, <20 to 135). After administration of human GH in the IGF-I generation test, the average increment in IGF-I was 0 μg/L, although a range of responses was seen (−77 to 52 μg/L). IGFBP-3 was also extremely low, but had a wide range (median, 435 μg/L; range, 95–1762 μg/L; median IGFBP-3 SD score, −8.5; range, −1.4–14.9). IGF-II levels were low (median, 96 μg/L; range, 26–315 μg/L) and correlated strongly with IGFBP-3 levels (r^2 = 0.67). Mean IGFBP-1 levels were elevated (27) at 165 ng/mL (range, 28–521).

Relationship of height SD score to IGFBP-3 SD score

The height SD score correlated positively with IGFBP-3 SD score (r^2 = 0.37; P = 0.005; Fig. 1). As the height SD score deficit increases with age in the absence of effective treatment, we used multiple regression analysis, with age being a covariate to examine the correlation of IGFBP-3 with

TABLE 2. Clinical details of patients with GHIS

	n	Sex (M/F)	Age (y)	Ht SD score	Birth wt SD score	Birth length SD score
All patients	62	45/37	8.3 (0.3–21.9)	−6.09 (−2.2 to −10.4)	−0.36 (−4.16 to +2.17)	−1.01 (−5.17 to +2.55)
GHBP negative	63	37/26	7.3 (0.3–21.9)	−6.45 (−3.0 to −10.4)	−0.37 (−3.75 to +2.17)	−1.03 (−5.17 to +2.01)
GHBP positive	19	8/11	8.1 (1.9–18.2)	−4.89 (−2.2 to −8.94)	−0.34 (−4.16 to +1.26)	−0.98 (−4.37 to +2.55)

Values are the mean and range (in *parentheses*). SD scores are derived from the data of Tanner (28).

TABLE 3. Biochemical details of patients with GHIS

	Basal GH (ng/mL)	Basal IGF-I (μg/L)	IGF-I post-hGH (μg/L)	IGFBP-3 (μg/L)	IGFBP-3 SD score	GHBP (%)	IGF-II (μg/L)	IGFBP-1 (μg/L)
All patients	17.6 (0.3–319)	<20 (<20 to 135)	<20 (<20 to 82)	435 (95–1762)	−8.50 (−1.4 to −14.9)	0 (0–78.2)	96 (26–315)	165 (28–521)
GHBP negative	19.1 (0.8–95.5)	<20 (<20 to 42)	<20 (<20 to 58)	371 (95–1762)	−9.04 (−1.4 to −14.9)	0 (0–10)	81 (26–315)	180 (43–521)
GHBP positive	9.0 (0.3–319)	23 (<20 to 135)	27 (<20 to 82)	651 (180–1670)	−6.04 (−1.7 to −10.6)	28.15 (13.6–78.2)	154.5 (39–283)	141 (28–367)

Values are the median and range (in *parentheses*). Levels of IGF-I, IGFBP-3, IGF-II, and IGFBP-1 are age dependent (35). The normal range for GHBP is 14.2–45.9% (30). The detection threshold for GHBP was 2%.

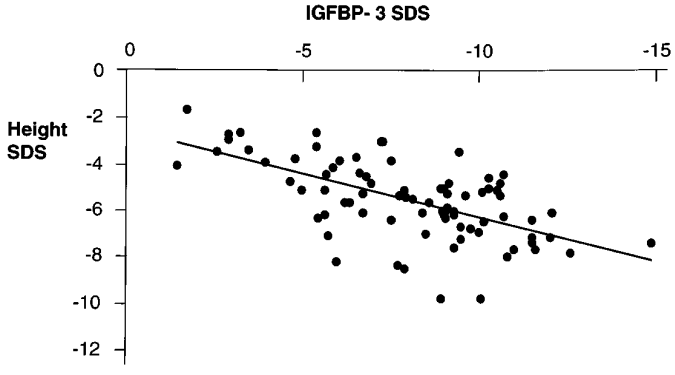

FIG. 1. Correlation of height SD score and IGFBP-3 SD scores in GHIS patients (n = 82; $r^2 = 0.45$; $P = <0.001$).

height SD score with age as an independent variable. As expected, this strengthened the relationship between height and IGFBP-3 SD score ($r^2 = 0.45$; $P = <0.001$). No analysis to correlate IGF-I with height was performed as most IGF-I values were below the limit of deletion of the assay (<20 μg/L).

Comparison of GHBP-negative and -positive patients

The patients were divided into GHBP-negative (GHBP, ≤10%) and positive (GHBP, >10%) groups. Twenty-three percent (19 of 82) were GHBP positive (Fig. 2). Although there was wide variation between individuals, the GHBP-positive group was, in general, less severely affected, with mean height SD score in GHBP-negative *vs.* GHBP-positive patients (−6.45 ± 1.54 *vs.* −4.9 ± 1.7; $P = < 0.001$; Fig. 3). Both mean IGFBP-3 SD score ($P = 0.003$) and IGF-I ($P = < 0.001$) were also significantly higher in the GHBP-positive group, and IGF-II was significantly higher ($P = < 0.001$). When the relationship between height SD score and IGFBP-3 SD score was examined in the GHBP-positive group, it remained highly significant ($r^2 = 0.45$; $P = < 0.001$).

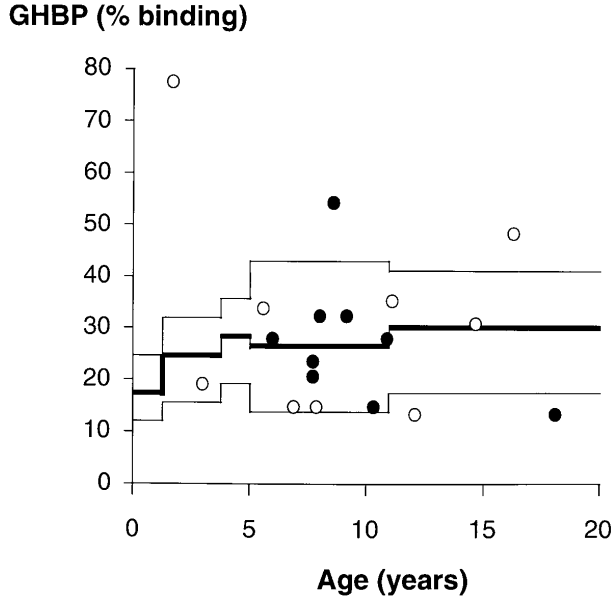

FIG. 2. Individual values of GHBP in GHBP-positive GHIS patients (n = 19) plotted against the mean ± SE values for age. ●, Male; ○, female. The patient with GHBP of 78% had a homozygous splice site mutation in exon 8 resulting in a mutant GH receptor virtually identical to GHBP (26).

Parental heights

Data on parental heights were available for 77 fathers and 76 mothers. Height SD scores in both parents were significantly reduced compared to Tanner standards [paternal, −1.14 ± 1.2 ($P = <0.001$); maternal, −1.22 ± 1.18 ($P = <0.001$)]. In 7 of 67 (10.5%) fathers and 25 of 68 (36%) mothers, height SD score was less than −2. There was no significant correlation between mean parental SD score and patient height SD score ($r^2 = 0.08$; Fig. 4). There was no difference between the parental height SD score in the GHBP-positive group (paternal, −1.12 ± 1.10; maternal, 0.82 ± 1.25) and the GHBP-negative group (paternal, −1.14 ± 1.10; maternal, −0.82 ± 1.25).

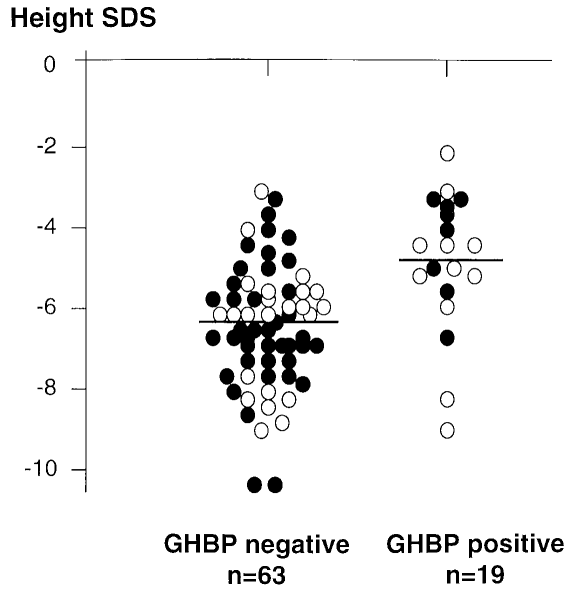

FIG. 3. Height SD scores of GHBP-negative and -positive GHIS patients. ●, Male; ○, female.

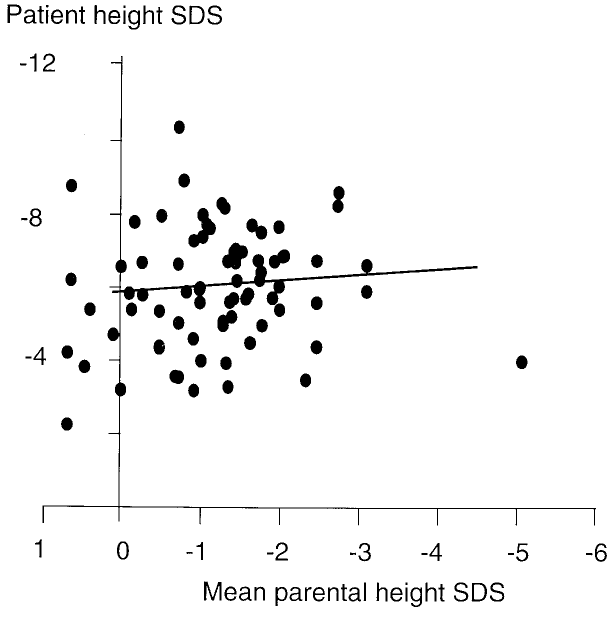

FIG. 4. Relationship between patient height SD scores and mean parental height SD scores.

Phenotype-genotype analysis

GHR mutations were identified in 27 patients (22 GHBP negative and 5 GHBP positive). Twenty-six patients had homozygous mutations: 8 missense, 8 nonsense, 3 frame shift, 7 splice site, and 1 compound heterozygote (nonsense and missense; Table 4). In 4 GHBP-positive patients from 1 highly consanguineous pedigree (Table 4, family 21), segregation analysis using the intron 9 GHR-negative gene polymorphism and the polymorphic dinucleotide repeat markers D5 S419 and D5 S477 suggested that the disease was not linked to the GHR (Table 4 and Fig. 5).

No clear relationship was observed between either type or site (exon) of mutation and either patient height SD score (Fig. 6, a and b) or IGFBP-3 SD score. Furthermore, the same mutation could be associated with wide variations in biological severity; for example, the missense mutation in exon 6 (D152H) was associated with height SD scores of −4.39, −4.34, and −5.35 in one family and −8.94 in another family.

Discussion

This cohort of GHIS patients is unique in terms of both its size and its diverse origins, contrasting in particular with the more genetically homogeneous cohort in Ecuador (4, 5). The patients studied provide an interesting insight into clinical, biochemical, and phenotype-genotype relationships in GHIS.

In many respects, the clinical data presented confirm the findings of the other two major studies of GHIS in the Israeli and Ecuadorian populations and our previous data on a smaller group of these patients (3–5, 27). The frequency of hypoglycemia (75%) is higher than that observed previously (45% in both Israel and Ecuador). One of the areas that remains in question is that of intellectual development in GHIS. Although our patients were not formally tested, 13.5% were reported to be mentally retarded, which is well above the prevalence in other populations [0.5–1.7% in Atlanta (31) and 2.3% in Bangladesh (32)]. It should be remembered that the high rate of consanguinity would favor an increased incidence of mental retardation. One possibility is that the mental impairment may be secondary to hypoglycemia, but this was not supported by our data.

In terms of auxological parameters, there is a much wider variation of height SD score in our patients (−2.2 to −10.4 SD) than found in either the Israeli (−4 to −8 SD) or Ecuadorian (−6.8 to −9.6 SD) populations, with a particular increase in patients at the mild end of the spectrum. The correlation between height and IGFBP-3 SD score we previously observed remained strong (27), indicating that levels of IGFBP-3 are good indicators of the biological severity of GH insensitivity. In contrast, we found no correlation between parental and patient height SD scores, suggesting that the biological defect is so severe that the influence of parental growth genes is abolished.

The range of mutations identified in the 31 patients in whom the GHR was analyzed confirms the genetic heterogeneity of our sample. We could not identify any association between the site and/or type of mutation and clinical severity of the patient. Furthermore, the same mutation was associated with wide variation in phenotype, as observed in the Ecuadorian cohort (4, 5, 19).

One of the major findings of our previous study was the high prevalence of GHIS patients with normal levels of GHBP (27). The frequency of the GHBP-positive phenotype remains essentially unchanged in this larger cohort, emphasizing that suspected GHIS should not be excluded on the basis of normal GHBP. Comparison of GHBP-positive and GHBP-negative patients revealed that GHBP-positive patients had a significantly milder phenotype. The molecular basis of GHBP-positive GHIS is of interest, as the molecular defect in such patients would be expected to disrupt functions of the GHR other than GH binding or may even po-

TABLE 4. Molecular analysis of GHIS patients: biochemical and molecular details

Type of mutation	Family	Molecular defect	Exon	Age (yr)	Ht SD score	IGFBP-3 SD score	GHBP (%)	Maternal ht SD score	Paternal ht SD score	Ref. to first report
Nonsense	1	Q65X	4	12.2	−4.97	−6.6	0		−1.76	24
	2	R43X	4	17.8	−5.4	−6.94	0	−2.2	−1.76	22
	3	C38X	4	8.0	−6.72	−6.69	0	−2.37	−1.46	22
	4	C38X	4	14.2	−6.58	−8.97	0	−0.41	0.47	22
	5	R217X	7	3.9	−7.04	−10.16	0	−2.22	−0.63	18
				6.8	−6.69	−8.39	0			
	6	R217X	7	6.8	−6.22	−6.19	0	−2.35	−1.31	18
	7	W157X	6	5.6	−6.43	−9.1	0	−1.28	−2.2	24
Frame shift	8	36delC	4	8.5	−4.71	−5.87	0	0.97	−0.71	24
	9	230delTA	7	5.9	−8.0	−11.5	0	−1.6	−0.41	20
				11.9	−7.4	−9.77	0			
Splice	10	G>A 70+1	Intron 2	11.5	−5.69	−5.6	0	−0.08	−1.92	24
				12.7	−6.98	−11.5				
	11	G>A 70+1	Intron 2	9.4	−5.59	−9.0	0	−1.48	−0.47	24
				11.7	−5.99	−7.91	0			
	12	G>C 440−1	Intron 5	3.6	−6.85	−10.70	0	−3.03	−1.01	18
	13	G>C 874−1	Intron 8	1.9	−5.4	−10.6	78.2	−0.37	1.23	26
	14	223C>T	7	13.3	−6.74	−5.6	0	−2.45		24
Missense	15	S40L	4	8.5	−5.62	−10.3	0	−1.7	−1.01	24
	16	V125A	5	2.8	−5.82	−6.68	0	−3.23	0.05	18
	17	R161C	6	6.3	−6.19	−6.34	0	−0.37	−2.51	18
				7.8	−6.89	−9.07	0			
	18	D152H	6	14.8	−8.94	−7.7	29.8	−0.37	−1.16	25
	19	D152H	6	2.8	−4.39	−7.5	18.9	0.13	−2.51	25
				15.8	−5.35	−4.6	37.4			
				16.8	−4.34	−4.76	45.9			
Compound heterozygote	20	R43X/V144D	4/6	11.0	−6.43	−9.1	0	−1.28	−2.21	
Nonlinked to GHR	21	None found		4.2	−4.4	−6.0		−3.0	−1.9	
				8.1	−5.6	−8.9	31.9	−3.0	−1.9	
				5.8	−4.0	−3.4	28.1	−1.3	−1.0	
				8.6	−3.3	−2.9	51.7	−1.3	−1.0	

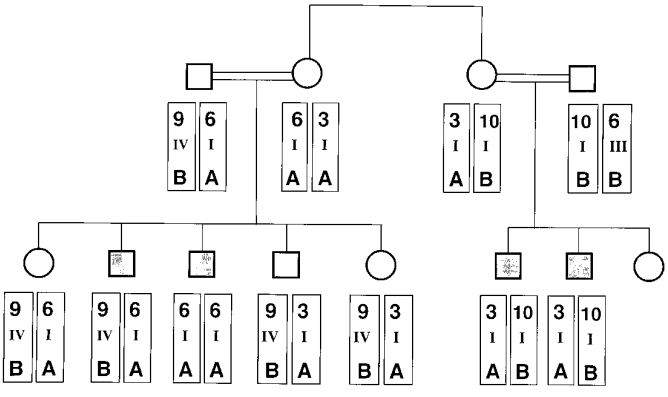

FIG. 5. Family pedigree and haplotype analysis of family with GHIS not linked to the GHR. The family contains four affected individuals (all male), consisting of two pairs of brothers who are first cousins. Affected individuals are indicated by *filled symbols*; unaffected subjects are indicated by *unfilled symbols*. Haplotypes: Arabic numbers (3, 6, 9, and 10) correspond to the D5 S419 genotype; Roman numerals (I, III, and IV) correspond to the GHR intron 9 polymorphism genotype, and letters (A or B) correspond to the D5 S477 genotype.

tentially involve genes other than the GHR. Among the 11 GHBP-positive patients who were studied, 5 mutations were identified in 7 patients, of which 1 (D152H) has been shown to affect GHR dimerization (25) and another (R274T) to severely truncate the receptor, leaving only the extracellular domain intact (26). In 4 patients from 1 inbred pedigree, there was no linkage to the GHR, suggesting that the defect in these patients may affect other genes, potentially involved in downstream signaling from the GHR to the nucleus.

Heterozygous GHR defects were reported in patients with short stature and low GHBP, raising the possibility that they may impair the functioning of the GHR (33). The mean heights of both mothers and fathers were reduced in our cohort compared to British standards from 1958. These are not ideal for comparison in view of the diverse ethnic origin of the patients, but the finding that 36% of significant parental short stature does suggest the possibility of a heterozygote effect. Among the 19 families in whom we found homozygous GHR defects in the affected children, the height deficit between the two parents was generally not uniform, perhaps suggesting that other genes may be influencing the magnitude of heterozygote effect in each individual. Certain mutations producing the GHBP-positive phenotype, in which GH binding is normal, may also be more likely to act in a semidominant manner (34). This is because GH binding is a prerequisite for GHR dimerization and activation; therefore, such mutant receptors that bind GH normally could dimerize with wild-type receptors, reducing the number of active wild-type homodimers. Testing this hypothesis among our cohort, we would expect that the mean parental height SD scores in our GHBP-positive group would be lower than those in the GHBP-negative group. In fact, we found no such differences.

In summary, we have studied phenotype-genotype relationships in a large, ethnically diverse group of children

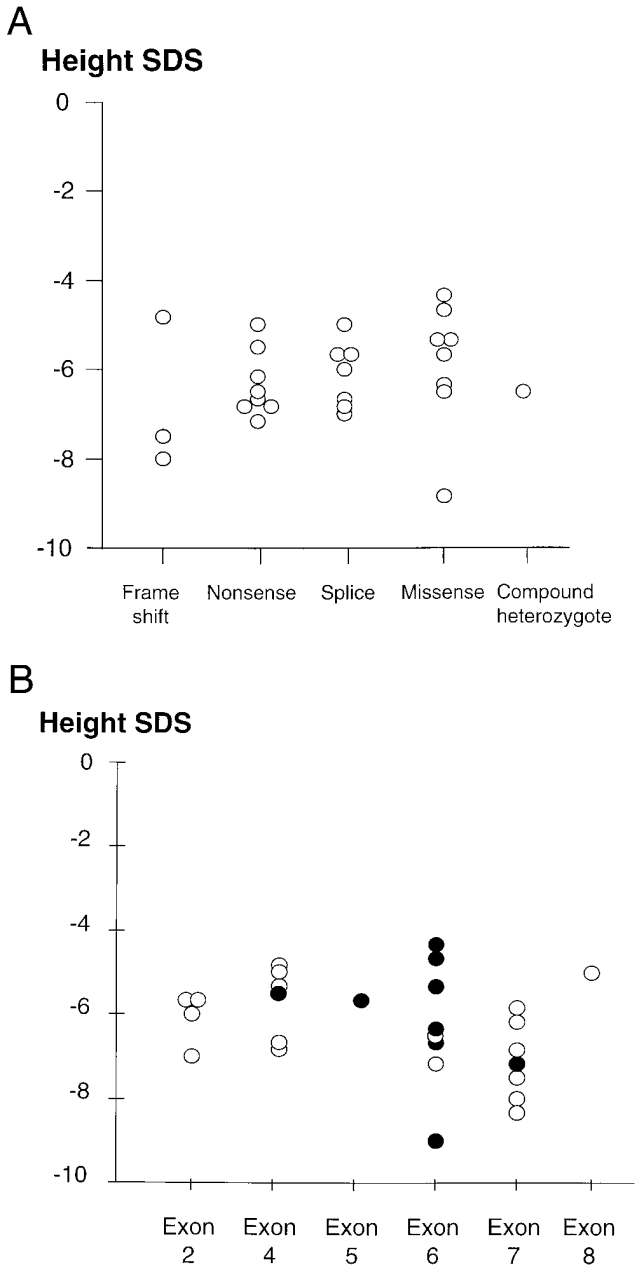

FIG. 6. a, Relationship between type of GHR mutation and height SD score in patients with GHIS (n = 27). b, Relationship between site (exon involved) and type of GHR mutation and height SD score in patients with GHIS (n = 27). ●, Missense mutation; ○, frameshift, nonsense, or splice site mutation.

with GHIS. Despite finding wide heterogeneity of phenotype, there was no clear association between site or type of GHR mutation and severity of disease. There was some evidence for a heterozygote effect in the parents of the affected children. We suggest that GHIS is a highly variable condition, existing possibly as a continuum from the severely affected patient with classical GH insensitivity to the larger group of patients with idiopathic short stature. Furthermore, genes other than the GHR may contribute to the phenotype of GHIS either in a causative role or by modulating GHR activity in the context of GHR dysfunction.

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