Growth Hormone Is Effective in Treatment of Short Stature Associated with Short Stature Homeobox-Containing Gene Deficiency: Two-Year Results of a Randomized, Controlled, Multicenter Trial

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Background: The short stature homeobox-containing gene, SHOX, located on the distal ends of the X and Y chromosomes, encodes a homeodomain transcription factor responsible for a significant proportion of long-bone growth. Patients with mutations or deletions of SHOX, including those with Turner syndrome (TS) who are haploinsufficient for SHOX, have variable degrees of growth impairment, with or without a spectrum of skeletal anomalies consistent with dyschondrosteosis.

Objective: Our objective was to determine the efficacy of GH in treating short stature associated with short stature homeobox-containing gene deficiency (SHOX-D).

Design and Methods: Fifty-two prepubertal subjects (24 male, 28 female; age, 3.0–12.3 yr) with a molecularly proven SHOX gene defect and height below the third percentile for age and gender (or height below the 10th percentile and height velocity below the 25th percentile) were randomized to either a GH-treatment group (n = 27) or an untreated control group (n = 25) for 2 yr. To compare the GH treatment effect between subjects with SHOX-D and those with TS, a third study group, 26 patients with TS aged 4.5–11.8 yr, also received GH. Between-group comparisons of first-year and second-year height velocity, height SD score, and height gain (cm) were performed using analysis of covariance accounting for diagnosis, sex, and baseline age.

Results: The GH-treated SHOX-D group had a significantly greater first-year height velocity than the untreated control group (mean ± SE, 8.7 ± 0.5 cm/yr vs. 5.2 ± 0.2 cm/yr; P < 0.001) and similar first-year height velocity to GH-treated subjects with TS (8.9 ± 0.4 cm/yr; P = 0.592). GH-treated subjects also had significantly greater second-year height velocity (7.3 ± 0.2 cm/yr vs. 5.4 ± 0.2 cm/yr; P < 0.001), second-year height SD score (−2.1 ± 0.2 vs. −3.0 ± 0.2; P < 0.001) and second-year height gain (16.4 ± 0.4 vs. 10.5 ± 0.4 cm; P < 0.001) than untreated subjects.

Conclusions: This large-scale, randomized, multicenter clinical trial in subjects with SHOX-D demonstrates marked, highly significant, GH-stimulated increases in height velocity and height SDS during the 2-yr study period. The efficacy of GH treatment in subjects with SHOX-D was equivalent to that seen in subjects with TS. We conclude that GH is effective in improving the linear growth of patients with various forms of SHOX-D. (J Clin Endocrinol Metab 92: 219–228, 2007)
sequent studies, SHOX mutations and deletions are also found in patients with an unremarkable short stature phenotype, often referred to as idiopathic short stature (ISS) (15–17). Although initially diagnosed with ISS for lack of etiological explanation, some of these SHOX-D patients have subtle signs of skeletal disproportion and should be excluded from the nonspecific diagnosis of ISS (18).

Mutations or deletions of the SHOX gene are associated with a broad spectrum of phenotypic effects, ranging from short stature without dysmorphic signs to profound somelic skeletal dysplasia, a form of short stature characterized by disproportionate shortening of the middle (mesial) segments of the upper and lower limbs (i.e. the forearms and lower legs) (8, 17). This skeletal anomaly is typically observed in patients with LWS (11, 19) and to a lesser degree in patients with TS. The features include bowing of the forearms and lower legs, cubitus valgus, Madelung deformity (dinner fork-like wrist) or partial dislocation of the ulna at the wrist and elbow, short fourth metacarpals, and high-arched palate. These clinical findings are usually accompanied by a number of characteristic radiological signs (7, 14, 20). The rare homozygous (or compound heterozygous) form of SHOX-D, referred to as Langer mesomelic dysplasia, is characterized by extreme dwarfism, profound mesomelia, and severe limb deformity (21–24). On the basis of a number of screening studies, SHOX-D appears to be a relatively frequent cause of short stature. Deletions or mutations of the SHOX gene have been reported in approximately 70% of patients with LWS and approximately 2–15% of children with the clinical phenotype of ISS (15–17). Overall, SHOX-D appears to have a greater prevalence than TS, which occurs in 1 in 2000 live female births (25), equivalent to approximately one in 4000 total births.

GH treatment of short stature associated with TS is well established on the basis of over 20 yr of clinical trial data (26–28) including a randomized, controlled study to adult height (29). However, experience with GH treatment in patients with SHOX-D is limited to case reports and small, uncontrolled studies (14, 20, 30, 31). Therefore, the third study arm enrolled 26 subjects with TS to GH treatment only. Treated subjects in both the SHOX-D and TS groups received a daily sc injection of 50 μg/kg GH [Humatrope (somatropin, rDNA origin); Eli Lilly & Co., Indianapolis, IN].

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committees of the participating institutions. Written informed consent was obtained from the subjects’ parent(s) or legal guardian(s) before conducting any study-related procedure.

**Molecular/genetic analyses for SHOX gene defects**

DNA samples from eligible children (n = 1608) were screened for a SHOX gene defect by one of two methods: 1333 samples were screened by PCR analysis for the presence of three microsatellites in the vicinity of the SHOX locus (CA-SHOX, CAII, and DXYS233), and 279 samples were screened by analysis of a number of exonic and intronic single-nucleotide polymorphisms. Samples that showed homozygosity for all screened markers (microsatellites or single-nucleotide polymorphisms) were analyzed by fluorescence in situ hybridization using a SHOX gene-containing cosmid probe. Presence of only a single SHOX signal confirmed deletion of one SHOX allele. The DNA of all 1608 individuals was also screened for single-nucleotide mutations by denaturing HPLC using a WAVE DNA-Fragment Analysis System (Transgenomic Inc., Cheshire, UK). Evidence of a DNA sequence alteration on denaturing HPLC was confirmed by DNA sequencing using a MegaBACE sequencer with the DYEnamic ET terminator Cycle Sequencing Kit (Amersham Biosciences, Piscataway, NJ). The diagnosis of TS was confirmed by Karyotyping at individual study sites. Female subjects with a partial deletion of the short arm of the X chromosome were classified as having SHOX-D rather than TS if the deletion was located distal to the gene for ocular albinism (OA1) at the junction between Xp22.2 and Xp22.3.

**Clinical and biochemical assessments**

Enrolled subjects were evaluated at baseline for standing height and preexisting conditions. Subsequent evaluations were performed at 3 and 6 months and then at 6-monthly intervals for the remainder of the 2-yr study. Left hand and wrist x-rays for bone age were obtained at baseline and 1 yr, and the films were assessed centrally according to the standards of Greulich and Pyle (32). Routine blood chemistry, hematology, fasting blood glucose, TSH, and free T4 were obtained at baseline and first year. Blood was drawn for measurement of IGF-1 and IGF-binding protein 3 (IGFBP-3) concentrations at baseline, at 3 and 6 months, and at 6-monthly intervals thereafter. The analyses were performed at a central laboratory, using previously reported methods (33).

In addition to standard reporting of serious adverse events, data were collected by the use of specific directed questions on the case report forms for the following potentially GH-related conditions (in alphabetical order): arthralgia, benign intracranial hypertension, edema, gynecomastia (males), hyperglycemia, hypoglycemia, hypothyroidism, increase in size of cutaneous nevi, neoplasia, recurrent otitis media, scoliosis, and slipped capital femoral epiphysis.

**Statistical analysis**

To account for differences in sex and age of the subjects, a number of variables were analyzed after conversion to SD scores (SDS). Because the

Subjects and Methods

Subjects

Subjects were invited to participate in genetic screening for this study if they fulfilled the following entry criteria: chronological age at least 3 yr and prepubertal (males, genital stage Tanner 1 and testes ≤ 2 ml; females, breast stage Tanner 1), height less than third percentile of the local reference range or height less than 10th percentile with height velocity less than 25th percentile, bone age less than 10 yr for boys and less than 8 yr for girls or less than 9 yr for TS, no GH deficiency or GH resistance, no chronic disease, and no known growth-influencing medications.
The majority of subjects originated from central European countries, height SDS was calculated using a central European reference (34). Bone age SDS was calculated as (bone age – chronological age)/sd of bone age corresponding to chronological age using the Greulich and Pyle (32) standards. Height velocity SDS was calculated based on the standards of Preece (35). Body mass index was calculated as weight (kilograms)/height (meters) squared and was converted to SDS by the method of Cole (36). Sex- and age-adjusted IGF-I SDS and IGFBP-3 SDS values were calculated using the reference values established in the central laboratory (37).

The primary aim of this study was to test the hypothesis that first-year height velocity of GH-treated subjects with SHOX-D would be greater than that of untreated subjects. The primary analysis, prespecified in the protocol, was an analysis of covariance for GH-treated vs. untreated subjects with first-year height velocity as the response variable and treatment group, diagnosis (LWS vs. ISS), sex, and baseline age as explanatory variables. One subject who discontinued with no post-baseline height data was excluded from efficacy analyses; all subjects were included in safety analyses.

Baseline variables were compared between groups using ANOVA for continuous variables and Fisher exact tests for categorical variables. Additional analyses were performed using ANOVA for between-group differences in height velocity SDS, height gain in centimeters, height SDS, bone age, and bone age SDS at various time points among all subjects, subjects with the ISS phenotype, and subjects with the LWS phenotype. We also investigated whether or not the impact of treatment on first-year height velocity depended on the values of the following variables: sex, baseline age, diagnosis (LWS vs. ISS), baseline height SDS, target height SDS, and baseline IGF-I. This was evaluated by examining the interaction term in a model with terms for treatment, variable, and interaction. Laboratory variables were analyzed using ANOVA models for between-group comparisons. Except where otherwise stated, results from statistical models are presented as least-squares mean ± se with two-sided statistical significance level set at 0.05.

**Results**

**Molecular defects in the SHOX gene**

During the screening phase of the study, SHOX gene deletions or mutations were detected in 68 subjects (34 with ISS phenotype, 32 with LWS phenotype, and two with unspecified phenotype); of these, 52 subjects were subsequently enrolled in this GH intervention study. Of these 52 subjects, 34 (65.4%; 16 untreated control, 18 GH-treated) had a complete deletion of the SHOX gene, four (7.7%; two in each group) had partial gene deletions, and 14 (26.9%; seven in each group) had point mutations. Of the 14 subjects with point mutations, three had a nonsense mutation (one with E61X, two with R195X), 10 had a missense mutation (Q112P, K116E, L132V, Y141D, R168W, R168L, A170P, R173H, and two with X226bR), and one subject had an insertion (insH229-L232). Missense mutations were judged to be clinically relevant if they fulfilled any of the following criteria: *in vitro* testing confirmed loss of function (L132V, R168W, A170P, and R173H) (38), a severe phenotype (LWS) was present (L132V, R168L, R173H, and X226bR), the short stature phenotype segregated with the genotype in pedigree analysis (Q112P, L132V, Y141D, A170P, R168W, and insH229-L232), or the mutation had previously been described in the literature as clinically relevant (L132V, R168W, A170P, and R173H) (14, 23, 39). Amino acids L132, R168, and R173 are conserved in human, chicken, and fish (http://www4.ncbi.nlm.nih.gov/).

**Baseline data**

There were no significant differences among the three study groups for most of the demographic and auxological parameters (age, bone age, height, etc.) at baseline (Table 1). However, target height SDS was lower in subjects with SHOX-D than in those with TS, probably reflecting the pseudoautosomal dominant inheritance of SHOX-D in many of these subjects. There were no significant differences between the groups with SHOX-D (GH-treated vs. untreated control) for the proportion of male vs. female subjects or for the proportion of subjects in each group with the LWS vs. ISS phenotype.

**Response to GH treatment**

Fifty-one of 52 randomized subjects with SHOX-D, and all 26 enrolled subjects with TS, completed the 2-yr GH treatment period. One untreated control subject with SHOX-D discontinued the trial within the first 3 months, based on the subject’s decision. Height velocity and height SDS improved markedly in response to GH in the treated SHOX-D and TS groups but changed minimally in the untreated control SHOX-D group (Fig. 1, A and B). As shown in detail in Table 2, the GH-treated SHOX-D group had significantly greater first-year height velocity than the untreated control group and similar first-year height velocity to GH-treated subjects with TS. GH-treated subjects with SHOX-D also had significantly greater second-year height velocity, second-year height SDS, and second-year height gain than untreated subjects with SHOX-D and similar values for these parameters.

**TABLE 1. Baseline characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Untreated SHOX-D (n = 25)</th>
<th>GH-treated SHOX-D (n = 27)</th>
<th>GH-treated TS (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male (%)</td>
<td>52/48</td>
<td>56/44</td>
<td>100/0</td>
<td>0.689</td>
</tr>
<tr>
<td>LWS/ISS (%)</td>
<td>56/40</td>
<td>44/56</td>
<td>1.4 0.058</td>
<td></td>
</tr>
<tr>
<td>Chronological age (yr)</td>
<td>6.6 ± 2.8</td>
<td>6.5 ± 2.0</td>
<td>7.5 ± 1.9</td>
<td>0.914</td>
</tr>
<tr>
<td>Bone age (yr)</td>
<td>3.7 ± 2.1</td>
<td>6.7 ± 1.6</td>
<td>0.928</td>
<td></td>
</tr>
<tr>
<td>Bone age – chronological age</td>
<td>1.0 ± 0.9</td>
<td>0.8 ± 1.0</td>
<td>0.809</td>
<td></td>
</tr>
<tr>
<td>Bone age SDS</td>
<td>1.2 ± 1.1</td>
<td>1.0 ± 1.0</td>
<td>0.641</td>
<td></td>
</tr>
<tr>
<td>Height SDS</td>
<td>–3.3 ± 0.8</td>
<td>–3.7 ± 0.9</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>Target height SDS</td>
<td>–1.3 ± 0.9</td>
<td>–1.5 ± 0.9</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Body mass index SDS</td>
<td>0.2 ± 0.9</td>
<td>0.6 ± 0.9</td>
<td>0.147</td>
<td></td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>–0.8 ± 1.0</td>
<td>–0.9 ± 1.0</td>
<td>0.521</td>
<td></td>
</tr>
<tr>
<td>IGFBP-3 SDS</td>
<td>0.6 ± 1.3</td>
<td>0.1 ± 1.1</td>
<td>0.058</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD. Efficacy variables presented represent pretreatment values.
TABLE 2. Growth parameters at baseline and 1 and 2 yr on study

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>SHOX-D UnTx</th>
<th>SHOX-D GH</th>
<th>TS GH</th>
<th>P value (SHOX-D): GH vs. UnTx</th>
<th>P value: SHOX-D GH vs. TS GH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HV (cm/yr)</td>
<td>14</td>
<td>5.0 ± 0.5</td>
<td>18</td>
<td>4.8 ± 0.3</td>
<td>19</td>
</tr>
<tr>
<td>Baseline HV SDS</td>
<td>10</td>
<td>-1.0 ± 0.6</td>
<td>12</td>
<td>-1.2 ± 0.3</td>
<td>7</td>
</tr>
<tr>
<td>Baseline Ht SDS</td>
<td>24</td>
<td>-3.2 ± 0.2</td>
<td>27</td>
<td>-3.3 ± 0.2</td>
<td>26</td>
</tr>
<tr>
<td>First-year HV (cm/yr)</td>
<td>24</td>
<td>5.2 ± 0.2</td>
<td>27</td>
<td>8.7 ± 0.3</td>
<td>26</td>
</tr>
<tr>
<td>First-year HV SDS</td>
<td>22</td>
<td>-0.7 ± 0.2</td>
<td>25</td>
<td>3.0 ± 0.3</td>
<td>26</td>
</tr>
<tr>
<td>First-year Ht SDS</td>
<td>24</td>
<td>-3.1 ± 0.2</td>
<td>27</td>
<td>-2.6 ± 0.2</td>
<td>26</td>
</tr>
<tr>
<td>Second-year HV (cm/yr)</td>
<td>24</td>
<td>5.4 ± 0.2</td>
<td>27</td>
<td>7.3 ± 0.2</td>
<td>26</td>
</tr>
<tr>
<td>Second-year HV SDS</td>
<td>22</td>
<td>-0.4 ± 0.1</td>
<td>27</td>
<td>3.3 ± 0.3</td>
<td>26</td>
</tr>
<tr>
<td>Second-year Ht SDS</td>
<td>24</td>
<td>-3.0 ± 0.2</td>
<td>27</td>
<td>-2.1 ± 0.2</td>
<td>26</td>
</tr>
<tr>
<td>2-yr Ht gain (cm)</td>
<td>24</td>
<td>10.5 ± 0.4</td>
<td>27</td>
<td>16.4 ± 0.4</td>
<td>26</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± se. Ht, Height; HV, height velocity; UnTx, untreated subjects.
about 1 yr in all groups, and although there was a trend toward greater catch-up of bone age in the GH-treated SHOX-D group than the untreated control group (respective means, 1.34 ± 0.07 and 1.16 ± 0.09 yr; P = 0.161), the groups overlapped significantly in terms of individual subject response. This is demonstrated in Fig. 3, which depicts the ratios of change in bone age vs. change in chronological age in individual subjects. Similarly, there was no evidence of an

Fig. 2. Group means (± se) and individual data for height velocity (cm/yr) (A), height velocity SDS (B), and height SDS (C) by treatment groups in patients with SHOX deficiency or TS.
effect of GH treatment on progression into puberty in subjects with SHOX-D. All subjects were prepubertal at baseline; at 2 yr, six GH-treated subjects with SHOX-D and four untreated control subjects with SHOX-D had entered puberty (P = 0.731). Two subjects with TS also spontaneously entered puberty during the 2-yr study period.

Safety

There were no discontinuations due to adverse events in this study. No serious adverse events were reported for subjects with SHOX-D. The three serious adverse events reported in this study occurred in three subjects with TS (scoliosis in two subjects and a fall resulting in a clavicle fracture in a third subject).

At least one treatment-emergent adverse event was reported for 68% of the untreated SHOX-D group, 85% of the treated SHOX-D group, and 96% of the TS group. However, the majority of these events represented common childhood illnesses that would be expected in a pediatric population (such as viral illness, upper respiratory infection, etc.). Because clinical trial reports of treatment-emergent adverse events typically garner a high frequency of events apparently unrelated to treatment, this study specifically collected data in a prospective fashion on a number of events that have been previously reported in subjects receiving GH, although not necessarily in a causal manner, as listed in Table 3.

These events were reported in small numbers of GH-treated and untreated control subjects with SHOX-D (GH-treated vs. untreated control: arthralgia, three of 27 vs. two of 25; gynecomastia (males), one of 12 vs. zero of 12; increased number of cutaneous nevi, two of 27 vs. zero of 25; recurrent otitis media, one of 27 vs. one of 25; scoliosis, one of 27 vs. zero of 25). No subject in this study developed diabetes.

Laboratory data

IGF-I SDS values at baseline were on average in the low-normal range in each of the study groups, increasing to the upper-normal range during GH treatment but remaining in the low-normal range in the untreated control group (Fig. 4A). IGF-I concentrations exceeded +2 SDS at least once during GH treatment in 10 (37%) subjects with SHOX-D and in nine (35%) subjects with TS; no untreated subject had an IGF-I that exceeded +2 SDS at any visit. IGFBP-3 SDS at baseline were closer to the normal mean than the corresponding IGF-I SDS in all study groups and increased to the upper-normal range in the treated groups (Fig. 4B). As demonstrated in Fig. 4C, there was a strong relationship between IGF-I SDS and IGFBP-3 SDS values during GH treatment, such that no subject had an IGF-I SDS in the upper tertile accompanied by an IGFBP-3 SDS in the lower tertile (the hypothetical risk relationship). No significant changes were noted in thyroid function.

Discussion

This study, the first large-scale, randomized, controlled, multicenter clinical trial of GH treatment in subjects with SHOX-D, demonstrates the efficacy of GH in increasing linear growth in this patient population over a 2-yr study period. Compared with those who received no treatment, the GH-treated group demonstrated a rapid, highly significant increase in height velocity that was evident by 3 months on study. After 1 yr of treatment, the GH group was growing on average 3.5 cm faster than the untreated group. Although the height velocity declined as expected over the second year of treatment, as reported in other conditions (40–43), the GH group nevertheless still had a significantly greater height velocity than the untreated control group at the second-year time point. The increase in height velocity during the 2-yr study period was comparable to the height velocity increase reported in patients with ISS who received similar GH doses (43, 44). The significant increase in height velocity translated into progressive gains in height SDS for the GH-treated group, whose average height SDS almost attained the lower end of the normal range (−2.0 SDS) by the end of the second year. Within the SHOX-D group, treatment response was similar for males and females, for subjects with the ISS phenotype and those with the LWS phenotype. In terms of individual subject responses, 41% of GH-treated subjects with SHOX-D had height within the normal range (above −2.0 SDS) by the end of the second year, whereas only one untreated subject (the tallest subject at study entry) had a normal height at 2 yr. Little information has been published to date regarding GH treatment of patients with SHOX-D, and the data that are available derive from individual case reports or small, nonrandomized series (14, 20, 31). Responses to GH in these reports have varied from negligible to pronounced.
providing no clear picture of GH treatment effect. The randomized, controlled study reported here clearly demonstrates a significant GH treatment effect in this patient population.

Because of the similar etiology of the growth disorder in patients with TS and those with SHOX-D, and the well-established efficacy of GH treatment in girls with TS, this study also included a nonrandomized group of subjects with TS to evaluate the comparability of the GH treatment effect across the two different forms of SHOX deficiency. The TS group was somewhat shorter at baseline than the group with SHOX-D, possibly due to additional factors such as aneuploidy or chromosomal imbalance (8, 9); however, the response to GH was very similar between the groups, reflected by the increases in height velocity and height SDS.

![Graphs showing individual data for IGF-I SDS (A), IGFBP-3 SDS (B), and the relationship between IGF-I SDS and IGFBP-3 SDS (C) at baseline (□) and 2-yr endpoint (■) in patients with SHOX-D or TS.](https://academic.oup.com/jcem/article-abstract/92/1/219/2598520)
The effect of GH on skeletal maturation in this study was similar among subjects with SHOX-D and those with TS. Bone age was mildly delayed at baseline and caught up somewhat in all treatment groups by the end of the second year. There was a trend toward greater catch-up in both GH-treated groups (SHOX-D and TS) compared with the untreated SHOX-D group, although the difference did not reach statistical significance. The tendency for GH treatment to induce catch-up of skeletal maturation has been observed in other patient populations but has not compromised adult height gain (40, 41, 45, 46). No GH effect was observed with respect to pubertal development, although the subject numbers were small and most of the subjects were still too young at the end of the study for puberty to have begun. The absence of GH effect on the onset or tempo of puberty in long-term studies of subjects with ISS (47) further supports the projection that adult height gains in subjects with SHOX-D will be significant.

There was no evidence of any new or unexpected GH-related adverse events in the SHOX-D patient population. As would be expected because of their higher rates of certain health problems at baseline, the TS group had the highest rate of adverse events. However, the majority of these events represented common childhood illnesses typically seen in pediatric studies or were conditions known to occur with greater frequency in girls with TS, such as edema and otitis media (48). Overall, GH treatment in subjects with SHOX-D appears to have a safety profile comparable to that reported in other pediatric indications for which GH has been previously approved (49, 50).

The mechanism by which SHOX, a homeodomain transcription factor, regulates linear growth and why deficiency of this factor results in short stature is not completely understood. The protein is expressed during pre- and postnatal skeletal development and regulates aspects of chondrocyte differentiation in the growth plate (3–5). Given the relatively low baseline IGF-I concentrations in our subjects, it is tempting to speculate that SHOX may at least in part be involved in regulation of IGF-I gene expression or metabolism. However, IGF-I concentrations responded briskly to GH treatment, the below-average mean baseline value increasing to about 1 sd above the normal mean. This indicates that even if there is an association between SHOX-D and reduced IGF-I, there is no evidence of GH resistance or insensitivity.

Although over one third of treated study subjects had at least one IGF-I measurement that fell more than 2 sd above the mean for age and sex, a similar increase occurred in IGFBP-3 concentrations, such that no subject had an elevated IGF-I value in the presence of a low IGFBP-3 concentration, a hypothetical risk profile with respect to neoplasia suggested by a number of epidemiological studies (51–55).

In conclusion, this study confirms that defects in the SHOX gene are a fairly frequent cause of short stature and that GH treatment is effective in improving the linear growth of patients with various forms of SHOX-D.

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