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# Long-Term Growth Hormone Therapy in Adulthood Results in Significant Linear Growth in Siblings with a PROP-1 Gene Mutation

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**PROP-1 gene mutations result in impaired production of GH, gonadotropins, TSH, and prolactin. We describe three adult siblings, aged 18–25 yr, with short stature, hypothyroidism, and lack of pubertal maturation, who were homozygous for 301–302delAG PROP-1 mutation. We had the unique opportunity to treat them in adulthood with GH for 4–5 yr and thyroid replacement before sex steroid replacement. Sibling 1, a female, had a chronological age (CA) of 25 yr 8 months, a bone age (BA) of 12.5 yr, and height of 128.7 cm [–5.29 SD score (SDS)]; sibling 2, a younger sister had a CA of 22 yr 5 months, a BA of 13 yr, and height of 137.5 cm (–3.94 SDS); and sibling 3, a male, had a CA of 18 yr 4 months, a BA of 11.5 yr, and height of 127.5 cm (–6.38 SDS). Despite delay in treatment and fairly advanced BA, all responded to GH and thyroid hormone therapy with a dramatic increase in linear growth: 22.3 cm for sibling 1, 22 cm for sibling 2, and 34.5 cm for sibling 3. After sex hormone replacement, siblings 1, 2, and 3 grew another 2.6, 3, and 9.5 cm to final heights of 153.6, 162.5, and 171.5 cm, respectively. In conclusion, the substantial linear growth in adult siblings with a PROP-1 mutation illustrates that despite an advanced BA, linear growth potential remains in adulthood in the setting of sex steroid deficiency. (*J Clin Endocrinol Metab* 89: 4850–4856, 2004)**

MUTATIONS OF TRANSCRIPTION factor genes controlling anterior pituitary growth and differentiation have been identified in recent years. Pit-1/POU1F1 mutations were the first identified as a cause of combined pituitary hormone deficiency in mice and humans (1–4). Mutations of Pit-1/POU1F1 (human homolog of mouse Pit-1) result in deficiencies of GH, TSH, and prolactin (PRL) (3, 4). More recently, the PROP-1 (Prophet of Pit-1) gene, another pituitary-specific transcription factor, was first isolated in the Ames dwarf mouse (5). The PROP-1 gene encodes a paired-like homeodomain transcription factor that is important in gonadotroph differentiation in addition to its role as precursor of Pit-1 gene expression (6). Consequently, in addition to GH, TSH, and PRL deficiencies, patients with a PROP-1 gene mutation have impaired production of FSH and LH. PROP-1 mutations account for significantly more cases of combined pituitary hormone deficiency than Pit-1/POU1F1 gene defects (7).

To date, there are numerous reports describing familial and sporadic cases of the PROP-1 gene mutation. However, almost all patients began GH therapy during childhood with the exception of two unrelated patients who received 1–2 yr of GH treatment for the first time in adulthood (8, 9).

This paper describes three siblings with a PROP-1 mutation who were treated in adulthood with GH, for 4–5 yr, and thyroid replacement therapy before initiation of sex hormone replacement therapy.

Abbreviations: BA, Bone age; CA, chronological age; PRL, prolactin; SDS, SD score.

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## Subjects and Methods

### *Subjects*

Three affected siblings from a family of five siblings in the Dominican Republic (Fig. 1) were evaluated and treated in adulthood. Informed written consent was obtained from the affected siblings and their parents for genetic studies.

All three affected siblings were products of normal vaginal deliveries with normal early developmental milestones and no major childhood illnesses. Although growth failure was first noted at age 8 in sibling 1, age 6 in sibling 2, and at age 3 in sibling 3, no further evaluation or therapy was initiated at that time because of a lack of resources. The patients were referred to us in adulthood.

Sibling 1, a female, is the oldest child. Before GH therapy at chronological age (CA) 25 yr 8 months, her height was 128.7 cm [–5.29 SD score (SDS)] and weight was 32.9 kg. Menarche had not occurred. On physical examination, she had severe short stature with absence of breast development, pubic hair, and axillary hair. She was enrolled in college at the time of diagnosis.

Sibling 2, a female, is the third child of the family. Before GH therapy at CA 22 yr 5 months, her height was 137.5 cm (–3.94 SDS) and weight was 25.4 kg. Examination revealed a proportionally short female without evidence of secondary sexual development; menarche had not occurred. At the time of diagnosis, she had completed high school.

Sibling 3 is the youngest child and only affected male. Before GH therapy at CA 18 yr 4 months, his height was 127.5 cm (–6.38 SDS) and weight was 28.4 kg. On examination, he had child-like facies, no facial hair, Tanner I genitalia and pubic hair distribution, and testicular volume less than 2 $cm^3$ bilaterally. He was finishing high school at the time of diagnosis.

There is no history of parental consanguinity. The parents and two other siblings had normal growth and secondary sexual development. The father whose grandparents emigrated from Spain is 176 cm (–0.02 SDS); the mother, a Dominican, is 151 cm (–1.87 SDS) in height. The

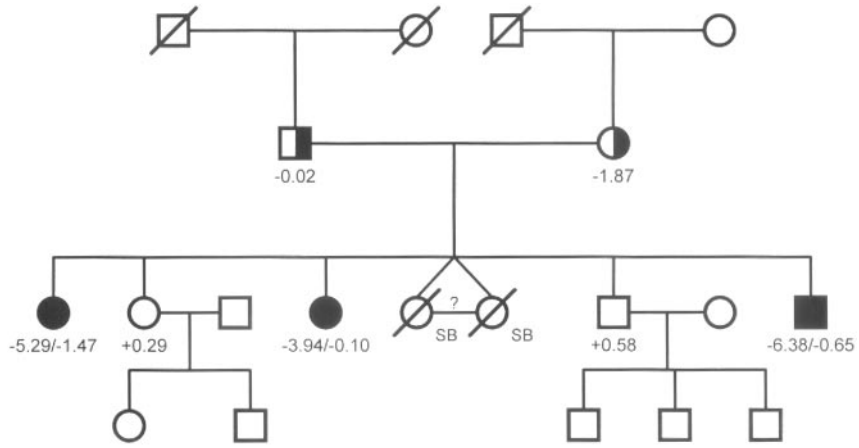


FIG. 1. Pedigree of the siblings with a PROP-1 gene mutation. *Circles* and *squares* denote females and males, respectively. *Solid symbols* represent affected homozygotes, and *semisolid symbols* represent carriers. *Symbols* with a *slashed line* denote deceased individuals. SB, Stillbirth. *Below the symbols* are the height SDSs of the unaffected family members and pre- and posttreatment for affected siblings.

**TABLE 1.** GH and IGF-I values before and after stimulation

| Sibling | Age (yr/months) | GH post-i ($\mu$U/liter), b→p | GH post-e ($\mu$U/liter), b→p | GH post-GHRH ($\mu$U/liter), b→p | IGF-I post-GHRH (U/ml), b→p |
|---|---|---|---|---|---|
| 1 | 17/09 | 0.5→0.8 | 0.5→1.0 | 0.9→0.9 | 0.14→0.13 |
| 2 | 14/06 | 0.5→0.3 | | 0.9→0.9 | 0.13→ |
| 3 | 10/05 | 0.5→0.5 | 0.5→0.5 | 0.9→0.9 | 0.10→0.11 |

Stimulated GH <5 $\mu$U/liter indicates GH deficiency. Normal IGF-I levels are 0.45–2.2 U/ml (women) and 0.34–1.9 U/ml (men). b→p, baseline→peak; post-i, after insulin; post-e, after exercise.

**TABLE 2.** Baseline hormone levels

| | Sibling 1 | Sibling 2 | Sibling 3 | Reference range (C) |
|---|---|---|---|---|
| PRL (ng/ml) | 0.70 (0.70) | 0 (0) | | 4.6–37 |
| FSH (mIU/ml) | 0.20 (0.20) | 1.40 (1.40) | | 1.4–9.6 |
| LH (mIU/ml) | <0.10 (<0.10) | 0.62 (0.62) | | 0.8–26 |
| TSH ($\mu$U/ml) | 0.02 (0.02) | 1.76 (1.76) | | 0.4–4.6 |
| Free $T_4$ (ng/dl) | 0.40 (5.15) | 0.40 (5.15) | | 0.8–2.0 |
| $T_4$ ($\mu$g/dl) | <1.00 (<12.87) | <1.00 (<12.87) | | 5.0–12.0 |
| $T_3$ (ng/dl) | <40 (<0.61) | <40 (<0.61) | | 40–180 |
| T (ng/ml) | 0.03 (0.13) | 0.05 (0.22) | | F 0.2–0.6 |
| | | | 0.03 (0.13) | M 3–10 |
| DHT (ng/ml) | N/D | 0.02 (0.07) | | F 0.05–0.25 |
| | | | 0.03 (0.10) | M 0.3–0.8 |
| Δ4 (ng/ml) | 0.12 (0.42) | 0.32 (1.12) | | F 0.5–2 |
| | | | 0.47 (1.64) | M 0.5–1.5 |
| DHEAS (ng/ml) | 20 (0.05) | 200 (0.54) | | F 1500–4500 |
| | | | 600 (1.63) | M 1500–4500 |
| 17 OHP ($\mu$g/liter) | 0.22 (0.67) | 0.58 (1.76) | | F 0.5–1.5 |
| | | | 1.09 (3.30) | M 1–2.5 |

Baseline morning cortisol levels were normal in all three siblings. SI units are indicated in *parentheses*. Conversion factors to obtain SI units are as follows: PRL (1 for $\mu$g/liter), FSH (1 for IU/liter), LH (1 for IU/liter), TSH (1 for mU/liter), free $T_4$ (12.87 for pmol/liter), $T_4$ (12.87 for nmol/liter), $T_3$ (0.01536 for nmol/liter), testosterone (T) (3.467 for nmol/liter), 5$\alpha$-dihydrotestosterone (DHT) (3.448 for nmol/liter), androstenedione (Δ4) (3.492 for nmol/liter), dehydroepiandrosterone sulfate (DHEAS) (0.002714 for $\mu$mol/liter), and 17$\alpha$-hydroxyprogesterone (17-OHP) (3.026 for nmol/liter). C, Conventional units; F, female; M, male; N/D, not detectable.

unaffected male sibling (age 20) is 180.3 cm (+0.58 SDS) tall, and the unaffected female sibling (age 24) is 165 cm (+0.29 SDS) tall. Twins were born prematurely between the third and fourth child; one was stillborn, and one died shortly after birth.

## *Methods*

*Hormone measurements.* The plasma GH responses to pituitary stimulation were studied with insulin tolerance and exercise testing. Two of the siblings had both tests performed (Table 1). In addition, GHRH was administered with GH levels drawn at –15, 0, 15, 30, 60, and 120 min. IGF-I levels were drawn at 0 min in all three patients and 120 min in two patients after administration of GHRH (Table 1). Samples were sent to the National Institutes of Health for measurement of serum GH and IGF-I levels. FSH, LH, TSH, free $T_4$, $T_4$, $T_3$, and PRL were measured by RIA. In addition, plasma cortisol and androgen levels including testosterone (T), 5$\alpha$-dihydrotestosterone, androstenedione, dehydroepiandrosterone sulfate, and 17$\alpha$-hydroxyprogesterone were measured by RIA at baseline by methods previously described (10) (Table 2).

*Radiological imaging.* Before initiation of GH, radiographs of hands and wrists were performed to determine bone age (BA) and were read by an experienced radiologist using the standards of Greulich and Pyle (11). Imaging studies of the pituitary were not performed because of the lack of imaging equipment availability in the Dominican Republic at the time of diagnosis.

*GH treatment and height measurements.* Recombinant human GH was given im to all siblings three times/wk in divided doses according to calculated doses of 0.3–0.4 mg/kg·wk (10–13.8 mg/wk). Intramuscular

GH administration was the standard of therapy at the time of treatment. GH was administered to sibling 1 from age 25 yr 8 months to 29 yr 11 months (4 yr, 3 months); to sibling 2 from age 22 yr 5 months to 27 yr 7 months (5 yr, 2 months); and to sibling 3 from age 18 yr 4 months to 22 yr 11 months (4 yr, 7 months). All the siblings received oral L-$T_4$ (100 $\mu$g/d) and hydrocortisone replacement (20 mg/d) just before initiation of GH therapy, and subsequently the doses were adjusted as needed. They have remained on replacement doses of L-$T_4$ and hydrocortisone.

During GH therapy, height measurements were obtained approximately every 3 months by the same physician in the Dominican Republic. Sex hormone replacement was initiated after GH treatment in all siblings. The final heights were obtained after 10 yr of sex steroid replacement therapy.

Target height range, also known as midparental height, was calculated for the affected siblings with the 10th to 90th percentile being determined using the following formulas: male target height = [father's height + (mother's height + 13)]/2 ± 7.5 cm; female target height = [(father's height –13) + mother's height]/2 ± 6 cm (12). Predicted height was determined by the Bayley-Pinneau method (13).

*Detection of PROP-1 gene mutation.* Genomic DNA was isolated from peripheral blood leukocytes, and the concentration was determined by UV absorbance at 260 nm as previously described (14). The coding region of the PROP-1 gene was amplified by PCR using the following specific pairs of primers: 5′-cgaacattcagagacagagtcccaga-3′ and 5′-gaattcaccatgatctccca-3′ for exon 1, 5′-agactcgagtgctc caccct-3′ and 5′-acctggattcgggcctcact-3′ for exon 2, and 5′-tcttgccagagtccactgcttg-3′ and 5′-tggtggtgctgcgtaagaatag-3′ for exon 3. The PCR contained 1 $\mu$mol/liter of each oligonucleotide primer, 200 $\mu$mol/liter of each of four deoxyribonucleotide triphosphates, 10 mmol/liter Tris-HCl (pH 8.3), 50 mmol/liter KCl, 1 mmol/liter $MgCl_2$, 240 ng genomic DNA, and 2.5 U *Taq* DNA polymerase (Promega, Madison, WI). The samples were heated at 94 C for 2 min and then underwent 35 cycles of 94 C for 15 sec, 60 C for 30 sec, and 72 C for 30 sec, and a final cycle consisted of 72 C for 10 min. For hot PCR, 10 $\mu$Ci of [$\alpha$-$P^{32}$]dATP was added in the reaction to label the PCR product.

The radiolabeled PCR fragments were screened by the single-strand DNA conformational polymorphism analysis as previously described (14, 15). Once a difference in DNA mobility was detected between the normal control and the patients, the mutation was then identified by DNA sequencing using the *fmol* DNA sequencing system (Promega) from both directions (15).

## Results

### *PROP-1 gene mutation*

Figure 1 shows the family pedigree. The PROP-1 gene was analyzed in all affected siblings and their parents by single-strand DNA conformational polymorphism screening (Fig. 2A) and DNA sequencing (Fig. 2B). All three affected siblings are homozygous for a 2-bp deletion (301–302delAG) in exon 2 of the PROP-1 gene, leading to a frame-shift in the coding sequence starting at codon 101, with premature termination at codon 109. The altered protein lacks DNA-binding and transcriptional activation functions when expressed *in vivo* (6). The mother and the father are heterozygous for the mutation. The two unaffected siblings were not studied.

### *Hormone and BA data*

Hormonal measurements are summarized in Tables 1 and 2. GH deficiency in all three siblings was confirmed by the negligible rise in serum GH and IGF-I levels after pituitary stimulation tests (Table 1). The GHRH stimulation test was done a few years after initiating thyroid hormone therapy. The GH measurements after stimulation tests with exercise and insulin and IGF-I were done before initiation of thyroid hormone replacement. Recent baseline hormone measurements of GH and IGF-I on sibling 1 at age 42 and sibling 2 at age 37, both on thyroid, hydrocortisone, and sex hormone replacement, revealed values significantly below the lower range of normal. Sibling 1 had a GH of less than 0.2 ng/ml and IGF-I of 20 ng/ml; sibling 2 had a GH of less than 0.1 ng/ml and IGF-I of 31 ng/ml (normal range for GH = <10 ng/ml; IGF-I = 90–360 ng/ml). Siblings 1 and 2 had low to normal TSH levels and undetectable $T_4$ and $T_3$ levels as well as deficiencies of gonadotropins and PRL at baseline; antithyroglobulin and anti-thyroid peroxidase antibodies were negative. Baseline plasma adrenal androgens were low in all three siblings (Table 2). Baseline BA radiographs of the three siblings before GH therapy are shown in Fig. 3.

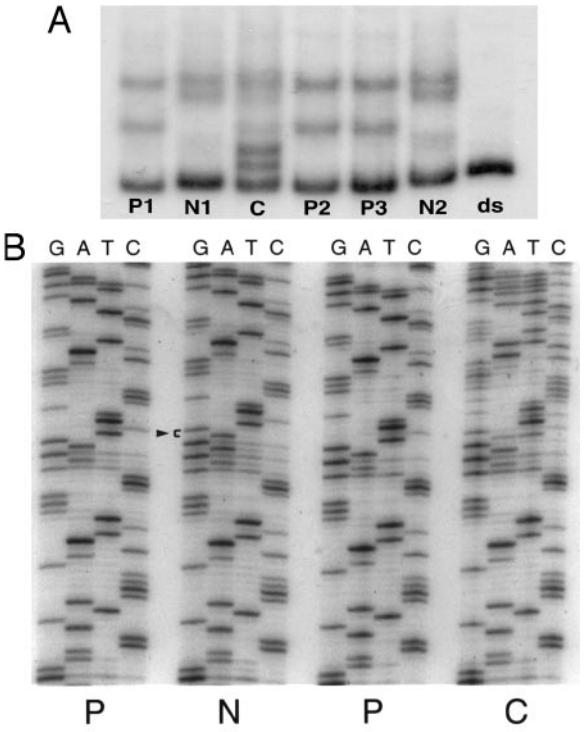


FIG. 2. A, A representative single-strand DNA conformational polymorphism analysis shows a differential migration pattern of single-stranded DNAs among the normal controls (N1 and N2), the affected (homozygous) patients (P1, P2, and P3), and the carrier (C). B, A representative DNA sequencing showing the mutation of the PROP-1 gene in an affected (homozygous) subject (P) compared with a normal subject (N) and a carrier (heterozygous) subject (C). ➤⊂ points to the two bases (AG) in the normal sequence that is deleted in the mutation.

### *Treatment results*

The heights of the three siblings during treatment were plotted on U.S. standard growth charts as shown in Fig. 4 with cross-sectional data provided by the National Center for Health Statistics (16). All siblings were placed on thyroid hormone replacement therapy a few weeks before initiation of GH therapy.

*Sibling 1.* GH therapy was administered for 4 yr and 3 months. It was initiated at CA of 25 yr 8 months, BA of 12.5 yr, and height of 128.7 cm (–5.29 SDS). The growth velocity during the first, second, third, and fourth years of therapy was 8.8, 4.3, 6.7, and 2.5 cm/yr, respectively. GH dosage was increased from 3.3 to 4.0 mg three times/wk during the

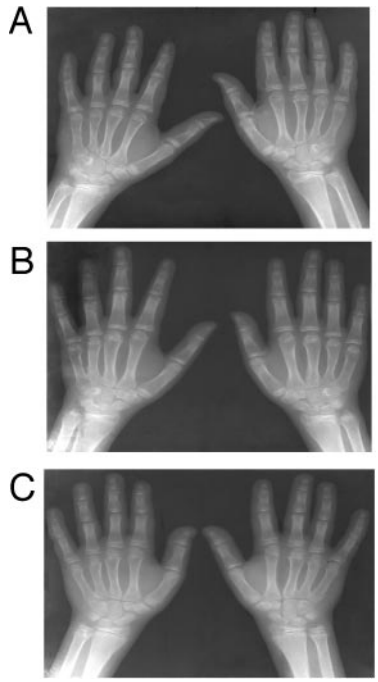


FIG. 3. Baseline hand and wrist radiographs of sibling 1 (A; BA 12.5 yr), sibling 2 (B; BA 13 yr), and sibling 3 (C; BA 11.5 yr) before GH therapy.

fourth year when the growth velocity began to diminish and further increased to 4.6 mg three times/wk until end of the treatment period. At the end of GH treatment, her height was the same as her mother at 151 cm (–1.87 SDS), an increase of 22.3 cm. Estrogen and progesterone replacement therapy was added; she underwent maturation of secondary sexual characteristics and began menstruating at age 30, shortly after being given sex steroids. Her final height was 153.6 cm (–1.47 SDS), which is 18.6 cm taller than her baseline predicted height of 135 cm. The final height is within the genetic target height range of 157 cm ± 6 cm.

*Sibling 2.* At the start of GH therapy (CA 22 yr 5 months; BA 13 yr), her height was 137.5 cm (–3.94 SDS). The growth velocity during the first, second, third, fourth, and fifth years of therapy was 5, 5.6, 7.9, 2.5, and 1 cm/yr, respectively. GH dosage was increased from 3.3 to 4.0 mg three times/wk at the beginning of the second year and further increased to 4.6 mg three times/wk during the last year of therapy. At the end of GH therapy, the patient's height was 159.5 cm (–0.56 SDS), an increase of 22 cm. After 5 yr and 2 months of therapy, GH was discontinued. With estrogen and progesterone replacement therapy, sibling 2 reached a final height of 162.5 cm (–0.10 SDS), which is 20.5 cm taller than the predicted height (142 cm). Her final height is also within the target height range of 157 cm ± 6 cm. Menses began at age 29. Despite adequate sex steroid replacement for over 9 yr, breast development has not proceeded beyond Tanner II–III.

*Sibling 3.* When GH therapy was initiated (CA 18 yr 4 months; BA 11.5 yr), his height was 127.5 cm (–6.38 SDS). The growth velocity during the first, second, third, fourth, and fifth years of therapy was 9.7, 9.7, 6.1, 6, and 3 cm/yr, respectively. GH dosage was increased from 3.3 to 4.0 mg three times/wk at the beginning of fourth year and further increased to 4.6 mg three times/wk during the last year of therapy. After 4 yr and 7 months of GH therapy, the patient's height was 162 cm (–1.94 SDS), an increase of 34.5 cm. Testosterone replacement was started soon after discontinuation of GH, and he underwent secondary sexual development. With testosterone therapy, he gained another 9.5 cm and reached a final height of 171.5 cm (–0.65 SDS), which is 17.5 cm taller than the predicted height (154 cm); his final height is within the genetic target height range of 170 cm ± 7.5 cm.

Pictures of the siblings before and after GH therapy are shown in Fig. 5. Siblings 1 and 2 have completed college and are employed; sibling 3 is currently completing college while working part-time.

## Discussion

The human PROP-1 gene, cloned and mapped in 1998, is located on chromosome 5q and has three exons (17). It encodes a 226-amino-acid transcription factor that plays an essential role in anterior pituitary cell differentiation and development (17). Over 150 reported cases of combined pituitary hormone deficiencies are attributable to PROP-1 gene mutations, and 12 distinct mutations have been identified (6–9, 17–30).

The three siblings described in this report are homozygous for the 301–302delAG mutation. By far, the most common mutations are 2-bp deletions in exon 2 at positions 296–302 (GAGAGAG) accounting for approximately 50% of all mutations (7), which leads to a frame-shift-causing truncation of the protein at codon 109. Over half of the 2-bp deletions are localized to position 301–302, the mutation present in the siblings described in this report (6, 9, 18, 22, 23, 26, 28). Tandem repeats (*e.g.* GAGAGAG located in position 296–302) are highly prone to DNA misalignment during replication, thus providing an explanation for the frequent occurrence of this mutation.

Phenotypic variability exists among patients with PROP-1 mutations. Interestingly, a varied clinical phenotype is also seen among patients with the same mutation (25, 29). Although patients with PROP-1 mutations are deficient in GH, TSH, PRL, and gonadotropins, the time periods for the development of the deficiencies as well as the severity of deficiency vary considerably. The most consistent phenotype appears to be severe growth failure at an early age.

To date, all patients with a 301–302delAG mutation (also referred to as 296delGA), similar to our patients, fail to undergo spontaneous puberty (8, 9, 17, 18, 22–24, 28, 30). Molecular studies demonstrate that this mutation results in complete loss of DNA-binding capacity and transcriptional activation. The 301–302delAG mutation is more disruptive and appears to cause a more severe clinical phenotype than other mutations in the PROP-1 gene.

ACTH deficiency can occur with age (18). The presence of ACTH deficiency was not observed in the original reports of this mutation; however, current evidence indicates that a majority of ACTH-deficient subjects have the more disruptive 301–302delAG mutation, as present in the three siblings described in this report (8, 18, 20, 23, 28, 30). The initial presence of normal cortisol levels in patients with this con-

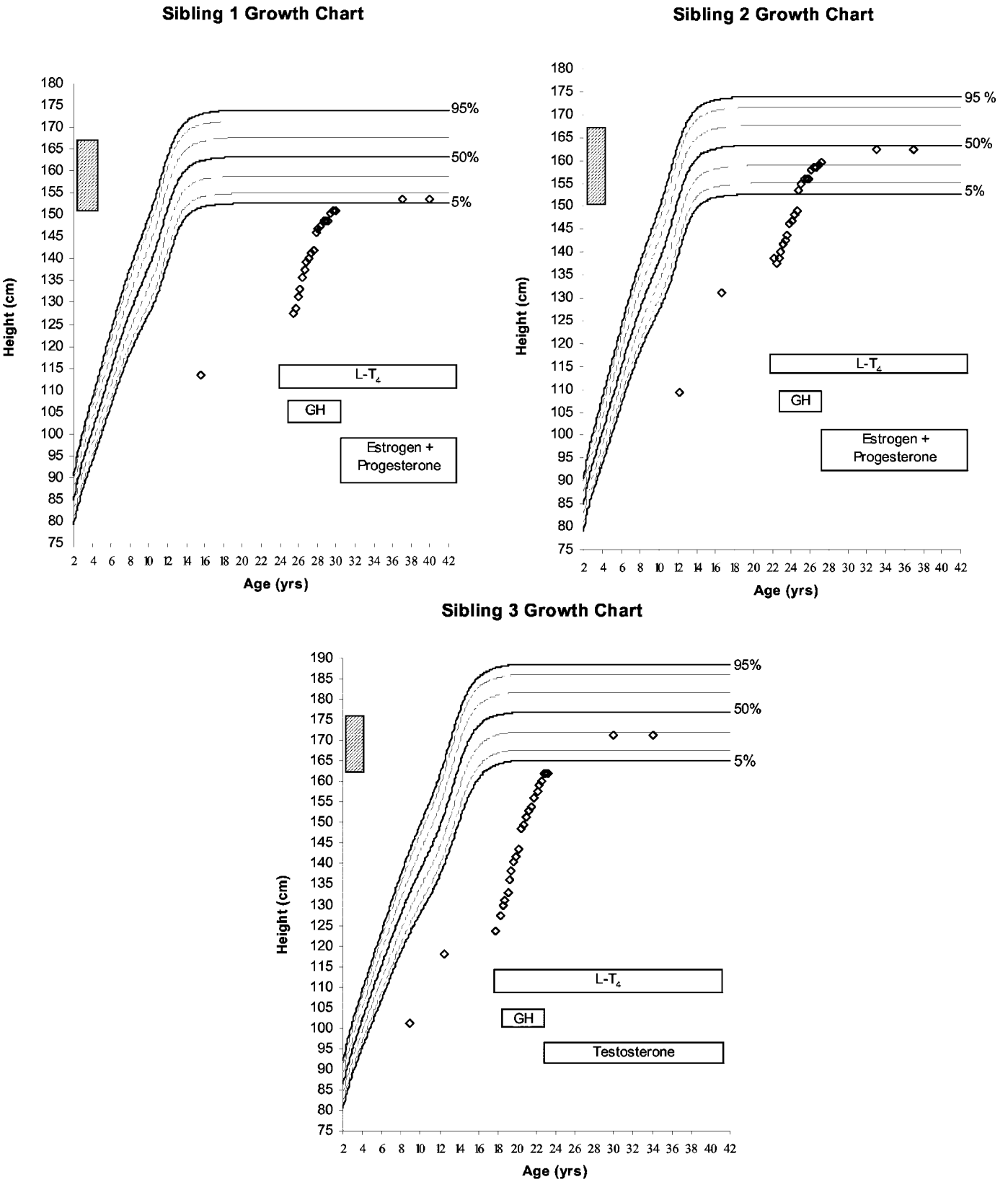


FIG. 4. Growth charts of the siblings. The *shaded block* represents mean parental height. Female height = 157 cm ± 6 cm (siblings 1 and 2); male height = 170 cm ± 7.5 cm (sibling 3).

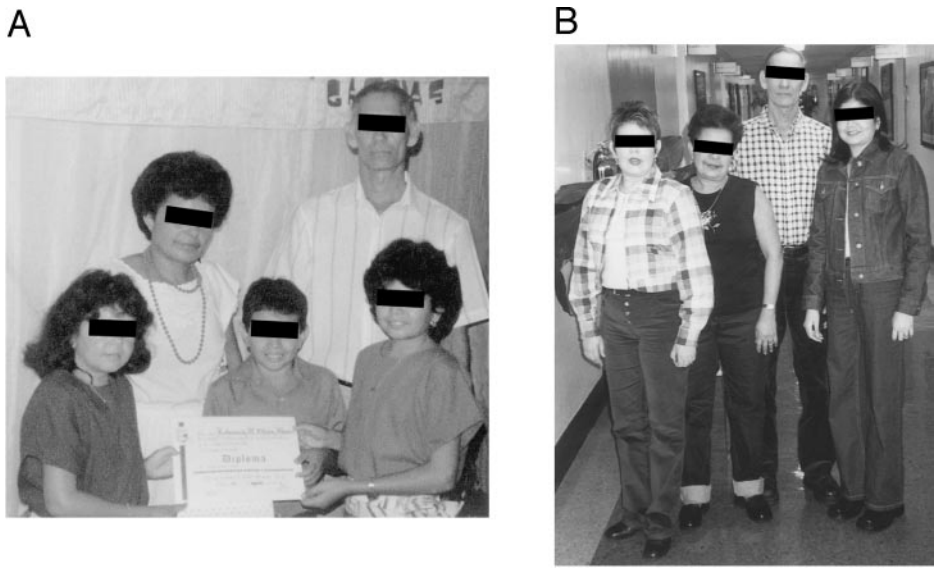


FIG. 5. Photographs of the affected siblings with their parents before (A) and after (B) GH therapy. The ages of the siblings are indicated in the *parentheses*. From left to right: A, sibling 1 (25 yr), mother, sibling 3 (18 yr), father, and sibling 2 (22 yr); B, sibling 1 (40 yr), mother, father, and sibling 2 (37 yr).

dition suggests that PROP-1 is not necessary for corticotroph differentiation, but may play an important role in maintaining corticotroph cells. Thus, it has been speculated that the ACTH deficiency that occurs with age in PROP-1 patients is the result of gradual apoptosis of the corticotroph cells because of lack of vital signals from other pituitary cell lines (18, 20). Although baseline cortisol levels were normal in our patients with a 301–302delAG mutation, hydrocortisone replacement was started prophylactically in the absence of formal testing and in the setting of uniformly low baseline adrenal androgens.

Our three siblings were treated with GH in adulthood, which is the unique aspect of this study. It is not surprising that there are limited data regarding the use of GH in adult patients with growth failure due to GH deficiency, because patients are commonly diagnosed and treated before adulthood (age 18 and older) (8, 9, 18, 20, 23, 25, 27, 30, 31). Patients have also been reported to be treated in childhood and retreated again in adulthood (9). Only two reports describe patient treatment with GH that was initiated in adulthood. Crone *et al.* (9) reported one patient who initially began GH at age 19 and was treated intermittently for 1 yr and then treated later on with thyroid hormone and sex hormone replacement therapy with a total height gain of 33 cm at age 41. Vallette-Kasic *et al.* (8) described another patient who began GH in adulthood and was treated consistently for 2 yr. Their female patient was treated simultaneously with GH, estrogen replacement, and L-$T_4$ at a CA of 41 yr and a BA of 12 yr. Her height during the 2 yr of combined hormone therapy increased 9 cm (from 125 to 134 cm).

In this report, three siblings were given GH in adulthood, for a longer period of time than previously reported. They were treated from 4–5 yr before sex hormone replacement, and a remarkable growth response occurred to GH therapy. This was followed by further growth after sex hormone replacement therapy. Before GH therapy, the Bayley and Pinneau (13, 32) predicted heights based on the BAs of siblings 1, 2, and 3 are 135, 142, and 154 cm, respectively. The final gains in height after sex hormone replacement therapy were 24.9 cm for sibling 1, 25 cm for sibling 2, and 44 cm for sibling 3, and the final heights were 17–20 cm higher than had been predicted: 153.6 cm (sibling 1), 162.5 cm (sibling 2), and 171.5 cm (sibling 3). The varied growth response among the siblings can be explained by the height (Fig. 4) and BAs at the start of therapy as well as gender differences. Siblings 1 and 2, both females, had the more advanced BA, 12.5 and 13 yr, respectively, and grew approximately the same amount (~22 cm). Sibling 3, a male, had less advanced BA, 11.5 yr, and CA and had a greater response to GH therapy (~34.5 cm). He also had a greater growth spurt with testosterone replacement therapy than his sisters with their appropriate hormone replacement therapy. Thus, the final total gains in height for the female siblings were the same, whereas the final gain was greater for the male sibling.

Limited gains in height with GH therapy were expected because of the fairly advanced skeletal ages, particularly in the female siblings. However, it should be kept in mind that the published standards of Greulich and Pyle (11) for BA determination were developed in normally growing children. Additionally, the methods used to predict adult heights, including the one used here, are all based on normative data from children (13, 32). Consequently, the accuracy of using such methods to predict final heights in subjects with profound growth failure who lack GH as well as gonadotropins and other trophic hormone abnormalities may not be applicable in this instance.

The patients were treated in the Dominican Republic in their usual nutritional environment during the entire GH treatment period. GH dosages were determined using pediatric dosing recommendations to promote linear growth. The initiation of L-$T_4$ replacement shortly before GH therapy in these siblings and the delay in replacing sex steroids no doubt contributed to the remarkable linear growth observed (9). The short interval between the start of L-$T_4$ and the initiation of GH does not allow assessment of the effect of L-$T_4$ alone on growth velocity in these patients. Regardless of the factors involved, the fact that all three adult siblings were able to reach their genetic target height range illustrates the

significant growth potential that remains in adults with this condition.

In conclusion, our unique experience allows us to demonstrate the potential for significant linear growth during adulthood, despite fairly advanced BA, in adult subjects with a PROP-1 mutation. The dramatic linear growth observed, despite the advanced BA, further suggests that BA is not a reliable predictor of growth potential in adult patients with PROP-1 mutations.

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