Clinical and genetic features of patients with multiple anterior pituitary hormone deficiency caused by mutations in the PROP1 gene; the efficacy of recombinant growth hormone therapy


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Rationale. One of the most common causes of multiple anterior pituitary hormone deficiency (MPHD) is genetic defects in the PROP1 gene. PROP1 deficiency leads to malfunction of somatotrophs, lactotrophs, thyrotrophs, corticotrophs, and gonadotrophs. Now, there is an opportunity to conduct large-scale population studies of patients with genetic MPHD, describe their clinical and genetic heterogeneity, and evaluate the efficacy of long-term therapy of these patients with a recombinant growth hormone (rGH).

Aim. The study aim was to assess the spectrum of PROP1 gene mutations in the Russian population of MPHD patients, rate and expected age of hypopituitarism components, and efficacy of rGH therapy.

Material and methods. We analyzed the data of 27 patients diagnosed with MPHD and genetically confirmed mutations in the PROP1 gene who were treated at the Institute of Pediatric Endocrinology of the Endocrinology Research Center (ERC) in 1978–2016. MPHD was diagnosed based on laboratory data and stimulatory tests characterizing the functional activity of the pituitary gland. The molecular genetic study was performed using high-performance parallel sequencing. We used a custom Am-
MPHD is a rare disease that develops due to impaired pituitary function and is characterized by growth hormone deficiency (GH-deficiency), as well as that of one or more other tropic hormones.

Most of childhood cases are cases of congenital hypopituitarism. The exact causes of disease development remain unclear [1]. Descriptions of familial cases of MPHD served as a basic for searching molecular genetic causes of this condition.

Over the past 20 years, a number of genes have been discovered, whose mutations cause the development of hypopituitarism. These include: ARNT2, GHI, GHRH, GHRHR, GHSR, GLI2, HESX1, LHX3, LHX4, OTX2, PAX6, POU1F1, PROP1, SHH, SOX2, and SOX3. All patients received rGH therapy at a growth-stimulating dose from the time of GH deficiency diagnosis until final height completion. We evaluated the efficacy of therapy by comparing the achieved final height with the genetically expected one.

Results. Non-familial cases prevailed (N=23) in the study cohort of patients with MPHD caused by mutations in the PROP1 gene; only two patients were monochorionic twin sisters; the other two patients were siblings. An analysis of the distribution of PROP1 gene mutations revealed a hot-point mutation c.301_302delAG in 24 patients (89%, 95% CI 71%; 98%). A mutation in the c.150delA locus occurred in 11 patients (41%, 95% CI 22%; 61%). Two patients had other mutations (c.629delC and c.43_49delGGGCGAG). Total GH deficiency was detected in all patients. The rate of secondary hypothyroidism (SHT) in patients of the study sample was 78% (95% CI 58%; 91%) at the time of diagnosis of GH deficiency and 100% (95% CI 81%; 100%) at the time of final height. The rate of secondary hypogonadism (SHG) at the time of final height was 100% (95% CI 81%; 100%), and the rate of secondary hypocorticism (SCH) was 41% (95% CI 22%; 61%). The normal level of prolactin was detected in 83% (95% CI 65%; 94%) of patients. At the time of growth plate closure, patients receiving rGH therapy at the growth-stimulating dose achieved the genetically expected final height.

Conclusion. According to our findings, the most common mutation in the PROP1 gene is a deletion of AG nucleotides in the 101 codon (c.301_302 delAG), which is found in 89% (95% CI 71%; 98) patients. Patients with MPHD caused by mutations in the PROP1 gene have total GH deficiency and are diagnosed with secondary hypothyroidism and secondary hypogonadism in 100% of cases. The possibility of delayed manifestation of hypopituitarism components requires regular screening of tropic hormone levels for the timely start of substitution therapy and prevention of life-threatening conditions. rGH therapy is highly effective for GH deficiency caused by PROP1 gene mutations and allows patients to achieve the genetically expected height in the case of early diagnosis of growth hormone deficiency.

Keywords: multiple anterior pituitary hormone deficiency (MPHD), gene PROP1, GH deficiency, recombinant growth hormone (rGH).
patients were one placental twin sisters, and two others were siblings. The familial variants of MPHD were excluded for 23 patients in the group.

**Eligibility Criteria**

Criteria for inclusion in the study group:
- diagnosis of GH-deficiency confirmed by clonidine and/or insulin probes (maximum stimulated GH level <10 ng/ml);
- mutations in PROP1 gene confirmed by molecular genetic analysis;
- chronological age <16 years and/or «bone age» <15 years for a group of patients who did not reach the final growth and were continuing rhGH therapy;
- chronological age >16 years and/or «bone age» >15 years for a group of patients who reached the final growth;
- the duration of rhGH therapy of at least 2 years at the time of enrollment.

Exclusion criteria:
- The absence of a mutation in PROP1 gene according to molecular genetic analysis;
- Presence of pituitary mass lesions;
- Presence of severe concomitant diseases.

**Conditions of the study**

The data of 27 people living in different cities of the Russian Federation and treated in the Institute of Pediatric Endocrinology of the FGBU ENC in 1978—2016 were analyzed. There was no evaluation of relationship between the patients’ residence areas and the spectrum of mutations in PROP1 gene, the incidence and age of onset of hypopituitarism components, and the effectiveness of rhGH therapy.

**Duration of the study**

The follow-up period ranged from 2 to 38 years.

**Description of medical intervention**

After examination conducted in accordance with the National Consensus on diagnosis and treatment of somatotropic insufficiency [4] and diagnosis of «GH-deficiency», the patients received rhGH replacement therapy at a calculated dose of 0.033 mg/kg/day continuously until the final growth was achieved.

**Primary endpoint**

The final growth of the patients was assessed after reaching the chronological age of >16 years and/or «bone age» of >15 years, as well as at detecting a decrease in the growth rate to less than 2 cm per year while on rhGH therapy.

**Subgroup analysis**

The patients whose chronological age at the time of the analysis was <16 years and/or «bone age» was <15 years were classified as «continuing rhGH therapy» (n=9) and did not participate in the evaluation of the efficacy of rhGH therapy. The patients whose chronological age at the time of the analysis was >16 years and/or whose «bone age» was >15 years were classified as having «attained final growth» (n=18). These patients participated in the evaluation of the effectiveness of rhGH therapy. Both groups were included in assessment of the spectrum of mutations in PROP1 gene, the incidence and age of onset of MPHD components.

**Methods of outcome recording**

A significant growth retardation (more than –2 SD) and low growth rates were the reasons for contacting the FGBU ENC. Measurement of body length was carried out with a mechanical growth meter to within 0.1 cm. To estimate the degree of deviation of a patient’s growth from the population mean, the standard deviation score (SDS) was calculated using Auxology application (Munich Auxology Project, Kromeyer-Hauschild et al, 2001). Genetically predicted growth and its SDS were also calculated using Auxology application (Munich Auxology Project, Kromeyer—Hauschild et al., 2001).

To assess the somatotropic function of the pituitary gland, challenge tests were performed with clonidine and/or insulin. The total GH-deficiency was diagnosed at the maximum stimulated concentration of growth hormone (GH) <7.0 ng/ml, partial one, at a concentration of 7.0 to 10 ng/ml.

The criterion for diagnosis of secondary hypothyroidism (SHT) was lower level of free T4 (fr.T4) in combination with a normal or moderately elevated baseline level of TSH.

Stimulation test with gonadotrobin (LH-RH) was carried out only for two girls and one boy. «Bone age» at the time of the test was 12 and 12.5 years for the girls and 13 years for the boy. Elevation of LH level of <10 U/l was assessed as secondary hypogonadism (SHG).

For the remaining patients (n=15), who achieved chronological age >14 years and had «bone age» characteristic typical for the onset of puberty, the diagnosis of SHG was established based on extremely low baseline LH, FSH, estradiol in girls and testosterone in boys and lack of symptoms sexual maturation. The stage of sexual development was evaluated clinically according to Tanner’s classification.

Diagnostic criteria for secondary hypocorticism (SCH) were low baseline level of cortisol (<175 nmol/l in the morning) and low stimulated level of cortisol in insulin hypoglycemia (<540 nmol/l). The test with synthetic ACTH was not performed because this drug is not registered in the territory of the Russian Federation.

Hypoprolactinemia was diagnosed based on low level of prolactin (<90 mU/l).

The Greulich & Pyle method was used to assess the degree of skeleton differentiation «bone age».

Molecular genetic research was carried out using high-performance parallel sequencing. The Custom Ampliseq HP panel of primers developed in the department
Sequence was performed on a PGM semiconductor sequencer (Ion Torrent, «LifeTechnologies», USA). Bioinformatic processing of the results of the sequencing was carried out using TorrentSuite 4.2.1 software module (Ion Torrent, «LifeTechnologies», USA) and Annovar software package (version 2014Nov12).

To confirm the changes in PROP1 gene, sequencing of the respective sites was carried out using specific primers according to Senger.

Eight patients underwent the genetic study at the GeNeSIS DNA analysis laboratory in Leipzig, Germany (GeNeSIS DNA Laboratory, Leipzig University Children’s Hospital, Leipzig, Germany, head of the laboratory Professor R. Pfaffl e).

Ethical assessment

Ethical assessment was carried out by the local ethical committee of the FGBU «Endocrinology Research Center», Minutes No. 12 of October 22, 2014.

Statistical analysis

Statistical processing of data was carried out using Statistica v.8.0 application software package («StatSoft- Inc.», USA). The median, 1st and 3rd quartiles were used as parameters of distributions of quantitative data. The Mann—Whitney test was used for comparison of independent groups based on the quantitative characteristic, and the Wilcoxon test was used for comparison of dependent groups. The threshold level of statistical significance was 0.05.

The results of checking the statistical hypotheses are given in Tables 1 and 5.

The results presented in Table 1 required no correction for PMS, since none of the null hypotheses was rejected. The results presented in Table 5 were also not corrected for PMS, since 8 out of 10 null hypotheses were not rejected, and the remaining 2 null hypotheses were rejected with a high level of significance, and even the use of Bonferroni’s correction would not have led to their acceptance (at an adjusted significance level of 0.05/10 = 0.005).

95% confidence intervals (CI) for relative frequencies were calculated.

Results

Subjects (participants) of the study

The average age of the patients (n=27) at the time of diagnosis of the GH-deficiency was 6.16 years (5.32, 7.56). At the time of data analysis, 18 patients (44% boys, n = 8) have achieved the final growth, while the remaining children continued their rhGH therapy due to their age «open growth zones». The duration of rhGH therapy in 18 patients who had reached the final growth was 9.64 years (5.00, 11.16).

The growth of patients at the beginning of rhGH therapy was 97.90 cm (90.50, 106.00) (n = 27). In all 27 patients, there was a very pronounced degree of stunting: median SDS of growth at the time of diagnosis of GH-deficiency = –3.77 (–4.46; –3.06). A more pronounced growth retardation was observed in girls (Table 1) and was associated with somewhat later diagnosis of GH deficiency. However, there was no statistically significant differences in SDS of growth at the time of diagnosis of GH deficiency between boys and girls (p = 0.18) (Table 1).

All patients were diagnosed with «total GH-deficiency» based on extremely low stimulated level of GH in a test with clonidine (the maximum stimulated level of the GH was 0.50 ng/ml (0.10, 3.30)) (n=27). Four patients were additionally tested with insulin. This probe also confirmed total GH deficiency (the maximum concentration of GH was 0.6 to 1.96 ng/ml). Median «bone age» at the time of diagnosis of GH-defi-
ciency was 2.0 years (2.0, 4.0). A significantly younger «bone age» compared to the chronological age was not-

detected in all patients (Table 1).

**Main outcomes of the study**

At the time of diagnosis of GH-deficiency, SHT was diagnosed in 21 patients (78%, 95% CI 58—91). Ten 
(48%) patients (95% CI 30—66) were diagnosed with SHT concomitantly with GH deficiency, 7 (52%) pa-
tients (95% CI 34—70) were diagnosed earlier. The me-
dian age at the time of SHT diagnosis was 6.24 years 
(4.40, 9.32). The level of free T4 was 6.40 pmol/l (4.43, 
7.50), baseline TSH, 1.50 mU/l (0.47, 2.26). All patients 
received levothyroxine therapy with regular dose adjust-
ment. SHT was detected in 100% (95% CI 81—100) of 
patients who achieved the final growth (n=18).

It was not possible to evaluate the prevalence of SHG 
at the time of diagnosis of GH deficiency, since all pa-
tients were pre-puberty. However, the analysis of the ar-
chival data of the patients who achieved the final growth 
showed that at the end of the observation, all patients 
were diagnosed with SHG. The age at diagnosis was 
16.56 years (14.56, 17.08), «bone age» was 14.0 years in 
boys (14.0, 14.5) and 13.0 years in girls (13, 0; 14.0). The 
baseline level of LH was 0.70 U/l (0.2, 1.5), of FSH, 0.90 
U/l (0.50, 1.20), testosterone 0.70 nmol/l (0.10, 1.00), 
estradiol, 21.5 nmol/l (20.00, 23.00).

Two girls, whose «bone age at the time of SHG diag-
nosis was 12 and 12.5 years, and one boy, whose «bone 
age» was 13 years, were tested with LH-RGH

(Table 2).

SHC, which at the time of diagnosis of GH-deficien-
cy was not detected in any patient, was identified in 11 
(41%) people (95% CI 25—58) at the time of the analysis 
of the data. The median age at SHC diagnosis was 9.40 
years (9.16, 13.32), baseline level of cortisol was 95.0 
nmol/l (82.0, 98.7).

One of the features of MPHD in patients with muta-
tions in **PROP1** gene is prolactin deficiency. This condi-
tion has no clinical manifestations in children and ado-
lescents and does not require treatment. In our study, the 
absolute majority of 15 (83%) patients (95% CI 65—94) 
had normal baseline prolactin level of 189.50 mU/l 
(95.60, 250.30) at the time of achieving the final growth. 
Only 3 (17%) patients (95% CI 17—35) had low baseline 
level of prolactin.

For the first time, the features of mutations in **PROP1** 
gene were analyzed in a large group of patients in the 
Russian population (Table 3). Among 27 patients, there 
were only 4 familial cases of the disease, whereas most 
similar studies conducted earlier were based on the 
analysis of familial cases.

The most common mutation in **PROP1** gene in our 
study was c.301_302delAG; it was found in homo- 
or heterozygous state in 24 (89%) patients (95% CI 71—98). 
The mutation at c.150delA locus was detected in 3 pa-
tients in homozygous state and in 8 (41%) patients in het-

erzygous one (95% CI 22—61), while one patient had 
other mutations (Table 3).

**Additional outcomes of the study**

Analysis of the final and genetically predicted growth 
of the patients demonstrated high efficacy of rhGH ther-
apy in patients with mutations in **PROP1** gene (Table 4). 
There were no statistically significant differences between 
the final achieved growth and genetically predicted one in 
either boys or girls.

**Adverse events**

The patients were assessed for the following potential 
adverse events, which could lead to dose reduction or dis-
continuation of rhGH therapy and termination of par-
ticipation in the study: edema, arthralgia, benign intra-
cranial hypertension, prepubertal gynecomastia. The 
absence of adverse events was noted in all patients 
throughout the observation period.

**Discussion**

**Summary of the primary endpoint**

The most common mutation in **PROP1** gene is the 
deletion of GA pairs in exon 2 (c.301_302delAG). At the 
time of achieving the final growth 100% patients with 
mutations in this gene were diagnosed with total GH-
deficiency, secondary hypothyroidism and secondary 
hypogonadism. High probability of development of sec-

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**Table 2. Results of LH-RG probe in 3 patients with mutations in **PROP1** gene**

<table>
<thead>
<tr>
<th></th>
<th>1/F</th>
<th>2/F</th>
<th>3/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological age, years</td>
<td>16.32</td>
<td>15.64</td>
<td>17.08</td>
</tr>
<tr>
<td>«Bone age», years</td>
<td>12.5</td>
<td>12.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Baseline level of LH, U/l</td>
<td>0.1</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline level of FSH, U/l</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Maximum stimulated level of LH, U/l</td>
<td>0.1</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Maximum stimulated level of FSH, U/l</td>
<td>0.1</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Baseline level of testosterone, nmol/l</td>
<td>20.00</td>
<td>23.00</td>
<td>0.7</td>
</tr>
<tr>
<td>Baseline level of estradiol, pmol/l</td>
<td></td>
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</tbody>
</table>
Secondary hypocorticism and subsequent severe life-threatening conditions (acute adrenal insufficiency) requires constant monitoring of the baseline cortisol level and, if necessary, immediate initiation of substitution therapy. Hypoprolactinemia occurred in 25% of the patients in the study and did not require medical treatment. All patients with mutations in gene \textit{PROP1} reached their genetically predicted final growth by the time of «closure of growth zones» (\(n=18\)).

\textbf{Discussion of the primary endpoint}

According to international studies, patients with mutations in \textit{PROP1} gene exhibit significant lag in growth, associated with severe intrauterine deficiency of GH and TSH. In our study, at the time of diagnosis of GH deficiency, all patients had extremely pronounced degree of stunting. There were no statistically significant gender differences in growth SDS. These results are consistent with the data of Russian and foreign colleagues, but it should be noted that the age of diagnosis of GH deficiency was lower than in the previous studies.

It has been repeatedly shown that patients with mutations in \textit{PROP1} gene exhibit total GH deficiency. However, in 1995 J. Parks and others [9] first raised the issue of possibility of partial GH deficiency in such patients. The authors described a familial case of MPHD associated with defects in \textit{PROP1} gene, where one of three children with the same mutation had partial GH deficiency. This publication is the only and ambiguous description of partial GH deficiency in a patient with a mutation in \textit{PROP1} gene.

In our work [26], total GH deficiency was detected in all patients. These results are consistent with the latest published data. In a study conducted by F. Pernasetti [11] et al., 10 members of the same family with the \textsuperscript{301}_302delAG mutation in \textit{PROP1} gene had the maximum stimulated level of GH in the range of 0.1 to 2.1 ng/ml. The age of patients at the time of diagnosis of GH deficiency was 8 to 67 years, and growth SDS at the time of sampling was from \(-5.2\) to \(-10\) SD.

\textbf{Table 3. Mutations in \textit{PROP1} gene in 27 patients in the Russian population}

<table>
<thead>
<tr>
<th>Mutation site</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textsuperscript{301}_302delAG p.L102CfsX8/</td>
<td>14</td>
</tr>
<tr>
<td>\textsuperscript{301}_302delAG p.L102CfsX8</td>
<td>8</td>
</tr>
<tr>
<td>\textsuperscript{150}delA p.R43DfsX112/</td>
<td>3</td>
</tr>
<tr>
<td>\textsuperscript{150}delA p.R43DfsX112</td>
<td>1</td>
</tr>
<tr>
<td>\textsuperscript{150}delA p.R43DfsX112/</td>
<td>1</td>
</tr>
</tbody>
</table>

\textbf{Table 4. Characteristics of the group of patients with mutations in \textit{PROP1} gene who have reached the final growth}

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Entire group ((n=18))</th>
<th>Boys ((n=8))</th>
<th>Girls ((n=10))</th>
<th>(P_{\text{boys—girls, Mann—Whitney test}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final growth of the patients, cm</td>
<td>167.3 (161.0; 175.0)</td>
<td>176.0 (172.0; 181.1)</td>
<td>162.6 (158.8; 176.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Genetically predicted growth, cm</td>
<td>168.5 (163.0; 176.5)</td>
<td>177.5 (174.2; 179.2)</td>
<td>163.0 (162.5; 168.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Final growth of the patients (SDS)</td>
<td>0.24 (–0.41; 0.88)</td>
<td>0.24 (–0.41; 0.98)</td>
<td>0.09 (–0.56; 0.88)</td>
<td>0.88</td>
</tr>
<tr>
<td>Genetically predicted growth (SDS)</td>
<td>0.27 (–0.03; 0.72)</td>
<td>0.42 (–0.07; 0.68)</td>
<td>0.16 (0.08; 1.00)</td>
<td>0.978</td>
</tr>
</tbody>
</table>

The frequency, prevalence and age of onset of other components of MPHD in patients with mutations in \textit{PROP1} gene are actively studied. Since the protein encoded by \textit{PROP1} regulates the development of somatotrophs, lactotrophs, thyrotrophs and gonadotrophs, mutations of this gene can lead to deficit of all the hormones produced by these types of cells.

According to the literature, central hypothyroidism is the first manifestation of hypopituitarism in most patients with mutations in \textit{PROP1} gene, and the age of initiation of rhGH therapy often coincides with the age of
administration of thyroxine [13, 19, 20]. In our study, SHT was either the first manifestation of the disease, or it was diagnosed simultaneously with GH deficiency. In patients who did not have SHT at the time of diagnosis, central hypothyroidism developed later, and eventually affected 100% of the patients in the study.

Even though PROP1 factor is important for the differentiation of gonadotrophs during fetal development, the incidence of SHG among patients with mutations in PROP1 gene varies greatly. In addition, the degree of deficiency of gonadotropic hormones can fluctuate from complete absence of puberty to spontaneous development of puberty [6]. The data of our study indicate 100% probability of development of hypogonadism in case of mutations in PROP1 gene. The stage of puberty at the time of reaching pubertal values of «bone age» in both boys and girls corresponded to «Tanner 1». No evidence of spontaneous onset of puberty has been observed in any patient. After the diagnosis of SHG, all patients were prescribed substitution therapy with sex steroids. At the time of follow-up, none of the patients had any children.

The most frequently discussed issue is the prevalence of SHC among patients with mutations in PROP1 gene. In a study by F. Pernasetti et al. [13], insulin hypoglycemia test revealed low cortisol levels in 5 of 6 patients over the age of 40 (43, 48, 51, 58 and 67 years) and in only 1 in 4 patients aged 8 to 20 years. All patients had the homozgyous 301_302delAG mutation in PROP1 gene. In 1999, two family members from the Dominican Republic with the 301_302delAG mutation (age of 17 and 40 years old) were described [21], as well as 5 patients with the c.150delA mutation (patients aged 14—68 years) [19]. Normal levels of baseline cortisol were observed. However, the authors did not report a dynamic observation of these patients.

In 1998 J. Parks and colleagues [22] reported that only one of the three Polish patients with the 301_302delAG mutation in PROP1 gene had ACTH deficiency, but ACTH levels and patient age were not reported. In the study by A. Rosenbloom et al. 5 patients with the R120C mutation at the age of 14—29 years had hypoglycemia test revealed low cortisol levels in 5 of 6 patients over the age of 40 (43, 48, 51, 58 and 67 years) and in only 1 in 4 patients aged 8 to 20 years. All patients had the homozgyous 301_302delAG mutation in PROP1 gene. In 1999, two family members from the Dominican Republic with the 301_302delAG mutation (age of 17 and 40 years old) were described [21], as well as 5 patients with the c.150delA mutation (patients aged 14—68 years) [19]. Normal levels of baseline cortisol were observed. However, the authors did not report a dynamic observation of these patients.

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are found in the sequence of nucleotides in codons 101 and 50 (these changes occur in 97% of the mutations in PROPI gene [19, 24, 26]), the molecular genetic analysis of the causes of hypopituitarism should include the initial screening of the mutations in these codons of PROPI gene.

Limitations of the study
The availability of methods of molecular genetics creates new opportunities for personalized approach to diagnosis, selection of treatment tactics and monitoring of patients with GH deficiency, improving our understanding of etiology and pathogenesis of this condition. Assessment of larger groups of patients with involvement of large medical centers will allow more detailed study of the prevalence of mutations in PROPI gene among patients in the Russian population and more objective assessment of the incidence and age of onset of components of the MPHD. Examination of a larger group of patients, who regularly and continuously receive rhGH therapy before achieving the final growth, will allow more objective evaluation of the effectiveness of this therapy.

Conclusion
According to our study, the most common mutation in PROPI gene, is the deletion of AG bases in codon 101 (p.301-302 delAG (89%, 95% CI 71—98). In patients with MPHD caused by mutations in PROPI gene, total GH deficiency and secondary hypothyroidism and secondary hypogonadism are diagnosed in 100% of cases. Potential delayed manifestation of components of hypopituitarism requires regular screening of tropic hormones level to ensure timely administration of substitution therapy and prevention of development of life-threatening conditions. rhGH therapy is highly effective in case of GH deficiency caused by mutations in PROPI gene, and allows patients to achieve genetically predicted growth in case of early diagnosis of growth hormone deficiency.


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