Clinic study

Auxological and endocrine phenotype in a population-based cohort of patients with PROP1 gene defects

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Abstract

Objective: Multiple pituitary hormone deficiency (MPHD) may result from defects of transcription factors that govern early pituitary development. We aimed to establish the prevalence of HESX1, PROP1, and POU1F1 gene defects in a population-based cohort of patients with MPHD and to analyse the phenotype of affected individuals.

Design and methods: Genomic analysis was carried out on 74 children and adults with MPHD from the Czech Republic (including four sibling pairs). Phenotypic data were collected from medical records and referring physicians.

Results: One patient carried a heterozygous mutation of POU1F1 (71C > T), and 18 patients (including three sibling pairs) had a PROP1 mutation (genotypes 150delA/301delGA/9/, 301delGA/301-delGA/8/, or 301delGA/349T > A/1/). A detailed longitudinal phenotypic analysis was performed for patients with PROP1 mutations (n = 17). The mean (±S.D.) birth length SDS of these patients (0.12±0.76) was lower than expected based on their mean (±S.D.) birth weight SDS (0.63±1.27; P=0.01). Parental heights were normal. The patients’ mean (±S.D.) height SDS declined to −1.5±0.9, −3.6±1.3 and −4.1±1.2 at 1.5, 3 and 5 years of age, respectively. GH therapy, initiated at 6.8±3.2 years of age (mean dose: 0.022 mg/kg per day), led to substantial growth acceleration in all patients. Mean adult height (n = 7) was normal when adjusted for mid-parental height. ACTH deficiency developed in two out of seven young adult patients.

Conclusions: PROP1 defects are a prevalent cause of MPHD. We suggest that testing for PROP1 mutations in patients with MPHD might become standard practice in order to predict risk of additional pituitary hormone deficiencies.

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Introduction

Pituitary development is governed by activation of a cascade of transcription factors that orchestrate both pituitary morphogenesis and differentiation of all five cell lineages of the anterior pituitary – corticotrophs, gonadotrophs, thyrotrophs, somatotrophs, and lactotrophs. Of those pituitary transcription factors identified so far, defects of HESX1 (1, 2), LHX3 (3), LHX4 (4), PROP1 (5, 6), and POU1F1 (Pit-1) (7, 8) have been found to lead to the phenotype of multiple pituitary hormone deficiency (MPHD) in humans.

The specific phenotype of POU1F1 defects is characterised by a combined deficiency of growth hormone (GH), thyrotropin (TSH), and prolactin (PRL) (9–10). In contrast, endocrine phenotypes of HESX1, LHX3, LHX4, and PROP1 defects (2–4, 11–14) tend to overlap and have been reported to include failure of up to all five cell lineages of the anterior pituitary. To make the understanding of phenotypes even more complex, the influences of these transcription factors on pituitary function seem to be dynamic and to develop throughout the human lifespan (15–17). Therefore, detailed endocrine investigation alone is insufficient for identifying specific genetic defects. Also, additional clinical phenotypic manifestations of defective transcriptional regulation, such as midline defects or abnormal pituitary size (1, 3, 4), may be only somewhat helpful in identifying these defects. Thus, genetic studies of cohorts of patients with MPHD are extremely valuable for establishing the prevalence of gene defects in distinct populations, as well as in increasing understanding of
how the genotype influences the endocrine and clinical phenotype.

We are reporting on a study of genetic causes of MPHD in a population-based cohort of affected patients from the Czech Republic. The structured system of paediatric and paediatric endocrine care within the country provided a unique opportunity to study a substantial proportion of potentially affected individuals and to summarise retrospectively relevant phenotypic data on a longitudinal basis. Patients were analysed with regard to mutations in the HESX1, PROP1, and POU1F1 genes.

**Subjects and methods**

**Recruitment of patients**

The use of GH as a therapeutic agent is restricted to 12 paediatric centres and four centres for adult patients in the Czech Republic. Responsible physicians from all centres countrywide were asked to collaborate in collecting DNA samples and phenotypic data of their patients with idiopathic MPHD.

Patients were included in the study cohort if they were diagnosed as GH-deficient (diagnosis confirmed by peak GH levels below 20 mIU/L in two provocative tests) in combination with at least one additional pituitary hormone deficiency. Patients with a known postnatal cause of acquired hypopituitarism, such as pituitary tumour, cranial irradiation, or trauma, were excluded. Five paediatric centres and one centre for adults reported patients fulfilling these criteria and participated actively in the recruitment of patients. Some patients were recruited through Lilly’s GeNeSIS post-marketing program. DNA samples from all patients were analysed centrally (University Hospital for Children and Adolescents, Leipzig, Germany).

**Collection of data**

In all patients with a confirmed PROP1 gene defect, phenotypic characteristics were evaluated on a longitudinal basis using data recorded by the attending physician on a standardised data collection form. The following data were collected: (a) measured or reported parental heights; (b) perinatal history: week of gestation, type of delivery, birth length/weight, known hypoglycaemic episodes, prolonged neonatal jaundice, maldescent testes; (c) height/weight data as recorded by the general paediatrician at regular visits at the ages of 1, 1.5, 3 and 5 years, up to the start of GH administration; (d) age at start of any hormonal substitution and locally measured hormonal levels before the start of relevant therapy; (e) height and Greulich–Pyle bone age (18) before the start of relevant hormone therapy; (f) GH dose and height velocity at the start of GH treatment and at years 1, 2, and 3 thereafter and (g) adult height, if already available.

**Expression of auxological data**

Data on birth length, birth weight, and postnatal growth are expressed as standard deviation scores (SDS) of population standards derived from the Fifth Nation-Wide Survey of Czech Children and Adolescents in 1991 (19). Parental heights are expressed as SDS of the height of individuals aged 18 to 18.99 years from the same reference data.

**Genetic analyses**

Genomic DNA was extracted from peripheral blood by a simple salting out procedure. Fragments containing exons of HESX1 (three fragments), PROP1 (three fragments), and POU1F1 (six fragments) genes were amplified by PCR on a Mastercycler (Eppendorf) or Mastercycler gradient (Eppendorf, Hamburg, Germany) using specific primers (Table 1). PCR Master Mix (Promega) was used for amplification of fragment 3 of PROP1: 50 μl of reaction solution contained approximately 200 ng of genomic DNA, 12.5 pmol of each primer, and 25 μl of PCR Master Mix (Promega). TaqPCR Core Kit (Qiagen) was used for amplification of all other fragments: 50 μl of reaction solution contained approximately 200 ng of genomic DNA, 12.5 pmol of each primer, 1.25 U of Taq DNA polymerase, 10 nM of each deoxy nucleotide, and 5 μl of PCR buffer. For all primers, the PCR consisted of 5 min at 95°C followed by 33 cycles of 1 minute at 95°C, 1 minute at annealing temperature, and 30 seconds at 72°C.

PCR products were mixed with wild type PCR products and denaturated by heat; then all 888 DNA fragments (12 fragments from each of 74 patients) were screened for the presence of a mutation on the Wave Nucleic Acid Fragment Analysis System (Transgenicomic, Crewe, UK) using a dHPLC mutation detection protocol. The validity of the dHPLC method had been previously evaluated with five different POU1F1 gene mutations and six different PROP1 gene mutations and had been encountered in the laboratory.

After purification of PCR products using the QIAquick PCR Purification Kit (Qiagen), samples that were positive for a mutation upon screening (33 (7% of all) fragments of POU1F1 gene; 87 (39% of all) fragments of PROP1 gene and 13 (6% of all) fragments of HESX1 gene) were sequenced on an ABI PRISM 310 Genetic Analyzer (Applied Biosystem) using the BigDye Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems, Foster city, CA, USA) and according to the cycle-sequencing protocol provided by the manufacturer. The same primers as for PCR were used for sequencing of HESX1 fragments, PROP1 fragment 2, and POU1F1 fragments 1, 2, and 4. The universal primers TGT AAG ACG ACG GCC AGT (sense) and CAG GAA ACA GCT ATG ACC (antisense) were used to amplify the remaining fragments.

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The results of DNA sequencing were evaluated with GeneTool or GeneTool 2.0 (BioTools Incorporated, Edmonton, AB, Canada) software.

**Statistical analyses**

Data are given as mean ± S.D. if not stated otherwise. Paired *t*-tests were used for comparison of paired values, while one-sample *t*-tests were used for comparison of sets of SDS data against the zero-value.

**Ethics**

Patients/parents gave their written informed consent to participate in the study. The Ethics Committee of the 3rd Faculty of Medicine, Charles University, Prague approved study conduct.

**Results**

**Mutation screening**

Of the 74 patients (including four sibling pairs; 44 males and 30 females) with MPHD, 1 male patient had a heterozygous *POU1F1* gene defect, and 18 patients (including three pairs of siblings) had a homozygous or double heterozygous *PROP1* gene defect without any indication of consanguinity. No patient had a *HESX1* gene defect (Table 2). Thus, the overall prevalence of mutation carriers in the three screened genes associated with MPHD was 26% of the study cohort. Of the 140 independent chromosomes investigated, a mutation was detected in 31 chromosomes (22%; 30 independent *PROP1* mutations and one *POU1F1* mutation). All of the identified mutations have been reported previously (6, 20, 21).

**Phenotype in patients with a *PROP1* gene defect**

The identification of a large group of patients with a *PROP1* gene defect (*n* = 18; ten males and eight females) enabled us to perform a detailed analysis of phenotypic characteristics from birth up to adolescence/adulthood in these patients.

Of those patients with a *PROP1* gene defect, a 74-year-old female with an adult height of 120 cm had received no hormonal substitution before her eighth decade of life. At 72 years of age, she was diagnosed to be GH-, TSH-, and PRL-deficient and hypogonadotropic; however, she had normal morning cortisol levels (729 nmol/l; 26.4 µg/dl). Due to the lack of relevant data from her childhood, she was excluded from additional phenotypic analyses.

The remaining 17 patients were aged 6 to 36 years (median age: 17 years). All were diagnosed with MPHD.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Number of affected patients</th>
<th>Prevalence among the study cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>PROP1</em></td>
<td>150delA/301delGA</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>301delGA/301delGA</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>301delGA/349T &gt; A</td>
<td>1</td>
</tr>
<tr>
<td><em>POU1F1</em></td>
<td>71C &gt; T/wild type</td>
<td>1</td>
</tr>
<tr>
<td><em>HESX1</em></td>
<td>Not applicable</td>
<td>--</td>
</tr>
</tbody>
</table>

**Table 2** Genetic findings in patients with MPHD (*n* = 74).
during childhood, and all started hormonal replacement therapy (including GH treatment) before having achieved adult height. Phenotypic data for these 17 patients are presented in the following sections.

**Parental heights**

The mean (±s.d.) heights of both the fathers (−0.35±1.44 SDS) and mothers (−0.18±1.33 SDS) of these patients were not significantly different from normal local standards (19) (Fig. 1).

**Birth and postnatal period**

The median gestational age of these patients was 40 weeks (range: 37 to 42 weeks). Delivery was normal in 12 patients. Two patients showed breech presentation, while 3 patients required Caesarian section. Although there are no corresponding data from the general population for this period, it appears that there was no significant association between PROP1 gene defects and abnormal delivery. The median birth weight of these patients was 3650 g (range: 2150 to 4350 g). When adjusted for sex, the mean (±s.d.) birth weight was 0.63±1.27 SDS (P=0.06 versus 0) (19). The median birth length of these patients was 50 cm (range: 45 to 54 cm). When adjusted for sex, the mean (±s.d.) birth length was 0.12±0.76 SDS (P=0.52 versus 0) (19). However, the mean birth length SDS was lower than expected based on the mean birth weight SDS of these patients (P=0.01), suggesting a modest prenatal restriction of longitudinal growth (Fig. 2). No episodes of neonatal hypoglycaemia were noted in any of the patients. One patient experienced prolonged neonatal jaundice and two of ten males had undescended testes at birth requiring surgery later in childhood.

**Natural history of growth**

Mean±s.d. height SDS of these patients decreased from 0.12±0.76 SDS (birth length) to −1.4±1.2 SDS at 1 year of age, −1.5±0.9 SDS at 1.5 years of age, and −3.6±1.3 SDS at 3 years of age, and −4.1±1.2 SDS at 5 years of age (Figs 3 and 4). These data indicate that the major deficit in statural growth developed between the ages of 1.5 and 3 years.

**Clinical and endocrine characteristics at diagnosis and at start of replacement therapy**

Age, height, bone age and hormonal status at diagnosis of pituitary impairment are summarised in Table 3. The data indicate that hormonal findings at diagnosis are variable. The age at the start of administration of GH, thyroxine, and hydrocortisone in individual patients is shown in Fig. 5. Treatment decisions were based on routine endocrine investigations (growth velocity, GH stimulation tests and IGF-I for GH replacement, T4/fT4 and TSH for thyroxine and low basal morning cortisol for hydrocortisone substitution). Sex steroids were administered to all pubertal and adult patients.

Pituitary imaging was available in 17 patients. Pituitary was enlarged in three, normal-sized in four and hypoplastic in 11 patients.

**Growth rates during GH therapy**

GH was administered at mean (±s.d.) doses of 0.023±0.007 mg/kg per day during the first year, 0.021±0.007 mg/kg per day during the second year, and 0.022±0.007 mg/kg per day during the third year of treatment. The corresponding growth rates are shown in Fig. 6.

**Adult height**

To date, seven of 17 patients have achieved their adult height. The mean (±s.d.) unadjusted adult height of these patients was slightly below normal (−1.0±1.2 SDS; P=0.06) (19), but was normal when adjusted.
for mid-parental height (−0.1 ± 1.3 SDS). Adult heights adjusted for mid-parental height ranged from low-normal (in two older subjects who received sub-optimal GH therapy during childhood) to high-normal (for 1 female with small parents and delayed induction of puberty) (Fig. 7).

Discussion

Within the study population of 74 patients with MPHD, we identified 19 mutation carriers (26% of the study cohort). Mutations included a single-allelic POU1F1 gene mutation and 18 PROP1 gene mutations (homozygous or double heterozygous).

In the case of mutation 71C > T in the POU1F1 gene, leucine replaces proline at position 24 (P24L). This substitution is known to affect the transactivation domain of the protein. The mutant protein exerts normal DNA binding but is expected to act as a dominant inhibitor of Pou1f1 action (20).

Figure 3 Natural history of growth (expressed as height SDS) of patients with PROP1 gene defects, measured from birth to the start of GH therapy. The height SDS values shown at the bottom of the figure are given as mean ± S.D. The horizontal bars represent the means.

![Figure 3](image1.png)

Figure 4 A girl with a PROP1 gene defect (150delA/301delGA) at her (a) first; (b) second; (c) fourth; (d) fifth; (e) sixth and (f) seventh birthdays. She started on GH and thyroxine therapy at 6.7 years of age. Photograph (g) shows her current status at 14 years of age. Typical facial appearance of growth hormone deficiency (frontal bossing, flat nasal bridge) may be noticed during early childhood; however, the typical phenotype disappeared later while under GH therapy. The patient and her parents gave written permission to publish her photographs without masks, as those would hide relevant signs of hypopituitarism.

![Figure 4](image2.png)
Among 18 PROP1 mutation carriers, we identified 3 different mutations – 301delGA, 150delA, and 349T>A. Each mutation results in a distinct alteration of the gene’s protein product. Both the microdeletions 150delA and 301delGA cause a frameshift that leads to premature termination of translation, and to the formation of a truncated, non-functional protein (6, 21). The 349T>A mutation represents a one-amino acid change within the DNA-binding domain of the gene’s protein product that leads to a significant reduction in protein-DNA binding (6).

We found that 301delGA was the most prevalent PROP1 gene mutation within this study population, representing 72% of all identified mutations. This finding is consistent with previous observations (22, 23). As 301delGA and 150delA mutations combined represented 97% of all PROP1 gene derangements, initial screening for these two mutations in candidates for genetic analysis seems reasonable.

The genetic portion of our study shows that PROP1 gene defects are a frequent cause of MPHD among affected individuals in the Czech Republic. Our data, taken from a large, geographically and ethnically defined population of patients with PROP1 gene defects, allowed extension of previous phenotypic analyses and brought novel insight into the impact of PROP1 defects on prenatal and postnatal growth.

The mean heights of these patients’ parents were normal; only a few of them were tested for PROP1 gene mutations and were found to be heterozygotes (data not shown). Assuming that a substantial number of the non-tested parents were also heterozygous for PROP1 gene mutations, the finding of normal height is suggesting that PROP1 haploinsufficiency does not exert any effect on statural growth. These data are in agreement with previous observations (23).

Despite the fact that the patients’ mean birth weights and birth lengths were within the normal range (19), their mean birth length was lower than expected based on their mean birth weight. Discrepancy between birth length and birth weight seems to be obvious in children with deficient antenatal GH secretion and/or action, as shown by Savage (24) in Laron syndrome and by Ranke (25) in a combined cohort of children with Laron syndrome or GH gene deletion (Table 4). Our findings suggest that also PROP1 defects influence the prenatal growth phase, although their impact is minor. Due to the progressive pituitary failure in these patients, GH secretion might have been partly preserved during intrauterine development.

Patients with PROP1 defects did not appear to have an increased prevalence of birth via breech delivery. Neonatal hypoglycaemia was not a prevalent symptom in patients with PROP1 gene defects. Patients with

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (S.D.)</th>
<th>Median (range)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>6.8 (3.2)</td>
<td>6.2 (2.8 to 14.3)</td>
<td>–</td>
</tr>
<tr>
<td>Height SDS</td>
<td>−4.12 (1.40)</td>
<td>−4.43 (−6.05 to −1.95)</td>
<td>−2 to +2</td>
</tr>
<tr>
<td>BA/CA</td>
<td>0.49 (0.18)</td>
<td>0.43 (0.26 to 0.95)</td>
<td>–</td>
</tr>
<tr>
<td>IGF-I (µg/l)</td>
<td>27 (18)</td>
<td>17 (10 to 47)</td>
<td>Age- and sex-dependent*</td>
</tr>
<tr>
<td>TSH (mIU/l)</td>
<td>1.31 (0.69)</td>
<td>1.25 (0.15 to 2.80)</td>
<td>0.25–5.0</td>
</tr>
<tr>
<td>fT4 (pmol/l)</td>
<td>6.6 (4.9)</td>
<td>4.0 (2.1 to 13.3)</td>
<td>10–26</td>
</tr>
<tr>
<td>PRL (µg/l)</td>
<td>5.1 (5.1)</td>
<td>2.6 (0.6 to 12.3)</td>
<td>2.6–23</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>342 (246)</td>
<td>240 (140 to 910)</td>
<td>140–700</td>
</tr>
</tbody>
</table>

* All IGF-I values were considered by the investigators to be clearly below the normal range.

BA/CA, Bone age/chronological age ratio; IGF-I, insulin-like growth factor-I; TSH, thyrotropin; fT4, free thyroxine; PRL, prolactin.

Bone age was estimated according to the method of Greulich & Pyle (18). Cortisol (µg/dl) = (nmol/l) × 0.036; fT4 (ng/dl) = (pmol/l) × 0.078.

The mean heights of these patients’ parents were normal; only a few of them were tested for PROP1 gene mutations and were found to be heterozygotes (data not shown). Assuming that a substantial number of the non-tested parents were also heterozygous for PROP1 gene mutations, the finding of normal height is suggesting that PROP1 haploinsufficiency does not exert any effect on statural growth. These data are in agreement with previous observations (23).

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Patients with PROP1 defects did not appear to have an increased prevalence of birth via breech delivery. Neonatal hypoglycaemia was not a prevalent symptom in patients with PROP1 gene defects. Patients with
neonatal hypoglycaemia of pituitary origin may have a more profound deficit of GH and/or adrenocorticotropic hormone (ACTH) during the neonatal period than that observed in patients with PROP1 mutations. Also, prolonged neonatal jaundice and maldescended testes were quite rare among patients with PROP1 defects, suggesting that severe MPHD is not present at birth or shortly thereafter. We showed that growth retardation started to develop within the first year of life, leading on average to a height deficit of about 1.5 SDS by the first birthday. The most prominent loss of height (an additional −2.1 height SDS) occurred between the ages of 1.5 and 3 years, during the early phase of the childhood component of growth. In those patients not diagnosed and treated in time, growth retardation progressed, leading to a mean height SDS of −4.1 at 5 years of age. The question of when GH deficiency manifests in patients with PROP1 gene defects is a matter of controversy (17, 26, 27). This longitudinal study indicates that growth retardation starts earlier than previously suggested, calling for initiation of GH therapy at young age.

At diagnosis, bone age was severely retarded (mean bone age/chronological age ratio = 0.49), probably due to combined GH and TSH deficiencies in these patients. Data on GH secretion were not summarised, as patients were studied over several decades, using different stimulation tests and GH assays. Nevertheless, available IGF-I levels indicate severe GH deficiency at diagnosis. In most patients, central hypothyroidism was detected at the first endocrine evaluation, and replacement of both GH and thyroxine was commenced at a similar age. Patients’ PRL levels were low or low-normal, while their cortisol levels were within the normal range at initial testing. Only two of seven adult patients required cortisol substitution in early adulthood. Therefore, the prevalence, age of onset and clinical significance of late-onset ACTH deficiency in patients with PROP1 gene defects remains a matter of controversy (17, 23, 26, 27). From our data and published data, it may be concluded that late-onset ACTH deficiency may develop during the third or fourth decade of life in some affected individuals. However, careful and systematic follow-up of adrenal function may lead to an earlier diagnosis.

In conclusion, we have shown a high prevalence of PROP1 gene defects among patients with MPHD in a central-European population of Caucasian origin. Thus, genetic testing may elucidate the aetiology of MPHD in a substantial proportion of affected individuals. With regard to clinical experience and to published data, such a testing may help to predict and to recognise early some of the additional medical problems: (a) TSH deficiency in patients with normal TSH-T4 axis at diagnosis of GH deficiency; (b) gonadotropin deficiency in children expected to enter puberty; (c) a life-long risk of developing ACTH deficiency (23); and (d) abnormal pituitary morphology (28). Therefore we suggest that testing for PROP1 mutations in patients with MPHD should become standard practice.

**Acknowledgements**

We are grateful to the physicians and their staff for their support in collection of data for this study. We would like to thank the patients who took part in this study. The study was supported by Eli Lilly and Company through Lilly’s GeNeSIS postmarketing research program and in part by the research project MSM No. 0021620814.

**Table 4** Data on birth length and birth weight in children with severe prenatal defect of GH secretion or action (Laron syndrome, GH gene deletion) and in patients with PROP1 gene defect (data given as median). In all patients’ cohorts, the birth length in consistently decreased compared to birth weight.

<table>
<thead>
<tr>
<th></th>
<th>Birth length (SDS)</th>
<th>Birth weight (SDS)</th>
<th>Difference (birth length SDS – birth weight SDS)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laron syndrome</td>
<td>–1.59</td>
<td>–0.72</td>
<td>–0.87</td>
<td>(25)</td>
</tr>
<tr>
<td>Laron syndrome or GH gene deletion</td>
<td>–1.38</td>
<td>–0.56</td>
<td>–0.82</td>
<td>(26)</td>
</tr>
<tr>
<td>PROP1 gene defect</td>
<td>+0.10</td>
<td>+0.67</td>
<td>–0.57</td>
<td>(current study)</td>
</tr>
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</table>