DNA testing in patients with GH deficiency at the time of transition

M.T. Dattani*

Biochemistry, Endocrinology and Metabolism Unit, Institute of Child Health and Great Ormond Street Children's Hospital, London, UK

Abstract

Over the last 10 years, major advances in the understanding of pituitary gland development in the mouse have led to the identification of mutations in a number of genes that then lead to delineation of the phenotype of growth hormone deficiency (GHD), either in isolation (IGHD) or in combination with a number of other hormone deficiencies (e.g., septo-optic dysplasia, SOD). The genetic abnormalities include mutations within: (1) Hesx1 (IGHD, SOD or CPHD); (2) Lhx3 (CPHD with preservation of cortisol secretion and a short stiff neck); (3) Lhx4 (GH, TSH and ACTH deficiency with cerebellar hypoplasia); (4) Prop1 (variable CPHD often associated with pituitary masses); (5) POU1F1 (GH, prolactin and TSH deficiency); (6) GHRHR (IGHD) and (7) GHI (IGHD). There can be variations in inheritance, phenotype and penetrance patterns. Nevertheless, establishing the genetic diagnosis can help in predicting the evolution of the phenotype and in genetic counselling. Therefore, for these reasons it is recommended that all patients with GHD should undergo testing for genetic mutations within the genes associated with IGHD, CPHD and SOD.

© 2003 Elsevier Science Ltd. All rights reserved.

Keywords: Growth hormone deficiency; Mutations; Inheritance; Transcription factors; Homeobox; Septo-optic dysplasia (SOD); Combined pituitary hormone deficiency (CPHD)

1. Introduction

The pituitary gland, which is a midline structure, consists of three lobes: the anterior and posterior lobes and a smaller intervening intermediate lobe. The three lobes are derived from ectodermal tissue; however, the embryological origins of the tissues differ. The posterior lobe arises from neural ectoderm whilst the anterior and intermediate lobes originate from oral ectodermal tissue. The gland is a central regulator of growth and development in children. The mature anterior pituitary gland is populated by five neuroendocrine cell types, each defined by the hormone produced: corticotropes (ACTH), thyrotropes (TSH), gonadotropes (LH, FSH), somatotropes (GH) and lactotropes (PRL). The posterior pituitary secretes oxytocin and antidiuretic hormone (ADH). Recent work provides evidence for an induction model that explains the tissue interaction between the neural and oral ectoderm, a prerequisite for the initial formation of the pituitary gland and subsequent differentiation into its five cell types.

The complex functions of the pituitary are mediated via hormone-signalling pathways that act to regulate the finely balanced homeostatic control in vertebrates. These hormone-signalling pathways coordinate signals from the hypothalamus to the peripheral endocrine organs such as the thyroid, adrenal gland and gonads. Thus, the pituitary gland plays a critical role in regulating many basic processes of life such as metabolism, growth and reproduction. Development of this small gland has been shown to follow a similar pattern in a number of different species, but it has been best studied in rodents such as the mouse and rat. As a result of identification of the various naturally occurring mutations in mice, along with the information generated using murine knock-out models, it has been possible to begin the task of identifying the genes crucial to the development of this gland, and to start placing these genes into some kind of genetic pathway that ultimately determines pituitary development.

Fate-map analyses in frog, chicken and mouse models have shown that the most anterior part of the neural plate, called the anterior neural ridge (ANR), eventually gives rise to non-neural structures such as the anterior pituitary, the nasal cavity ectoderm and the olfactory

---

*Tel.: +44-207-905-2657; fax: +44-207-404-6191. E-mail address: M.Dattani@ich.ucl.ac.uk (M.T. Dattani).
placode. In contrast, the adjacent region of the neural plate gives rise to the most anterior neural structures, including the hypothalamus, posterior pituitary, optic vesicles and ventral forebrain. Hence, before the first visible appearance of Rathke’s pouch – the primordium of the anterior and intermediate lobes of the pituitary – certain cell compartments are already precommitted and possess the competence to develop into an anterior pituitary.

Various intrinsic and extrinsic transcription factors and signalling molecules have been implicated in normal anterior pituitary development. The transcription factors include homeobox genes that encode homeodomain factors. These contain a DNA-binding region called the homeodomain that can then bind to target DNA and regulate its expression, either switching on (activating) or switching off (repressing) the expression of these genes.

As one would expect, the understanding of this process is still in its infancy, and the list of potentially important genes is expanding rapidly. However, with increased knowledge about pituitary development and the genes implicated in this process, it is possible to extrapolate this knowledge to the study of human pituitary disorders. Consequently, molecular defects within the human homologues of genes found to be important during murine pituitary development have been shown to be the cause of some human disorders. In the rodent, 4 distinct stages of anterior pituitary development have been described: (1) pituitary placode formation, (2) development of the rudimentary Rathke’s pouch, (3) formation of the definitive pouch and (4) terminal differentiation of the various cell types in a temporally and spatially regulated manner [1].

Prior to development of any physical appearance of the anterior or posterior pituitary gland, signalling pathways are already being established. Understanding of the molecular basis for the establishment of these pathways has been significantly helped by studies of various mouse mutations. Upon embryonic turning of the head, the ANR is displaced ventrally and forms the stomodeum, the ectoderm that gives rise to the roof of the mouth and its derived structures [2,3]. In mice, the first stage of pituitary organogenesis coincides with a thickening of this initially uniform stomodeal ectoderm on embryonic day (E) 8.5 (pituitary placode stage); this ectoderm then invaginates on E9 to form the rudimentary Rathke’s pouch. The anterior and intermediate lobes of the pituitary evolve from this rudimentary structure. The pouch makes direct cell-to-cell contact with the neuroepithelium of the nascent diencephalon on E8.5–E9 [4]. The apposition of Rathke’s pouch and the diencephalon is maintained throughout the early stages of pituitary organogenesis. This close relationship, together with results of classical embryological experiments in several vertebrate species, suggest that reciprocal inductive interactions between the embryonic diencephalon and the pituitary primordium in this region of contact are essential for the development and proper differentiation of the adenohypophysis, or anterior pituitary.

It has now been established that a signal from the neural ectoderm induces thickening of the underlying oral ectoderm, with subsequent formation of Rathke’s pouch. Molecules such as Fgf8, Bone morphogenetic protein 4 (Bmp4) and Nkx2.1 [5–7], which are expressed in the neural ectoderm and not in Rathke’s pouch, are thought to play a significant role in normal anterior pituitary development, as illustrated by the phenotype of mouse mutants that are either null or hypomorphic for these alleles.

The second stage of pituitary development involves further interaction between the two ectodermal tissues to form the rudimentary Rathke’s pouch. The oral ectodermal epithelial pouch continues to bud upwards, whilst the posterior part of the diencephalon evaginates downwards to form a structure termed the infundibulum. Once again, these two structures maintain close contact throughout the development of the pituitary gland. During this time (E9.5 onwards), mesodermal cells are migrating into this area and proliferating, thus ensuring separation of the brain and oral cavities. The fact that the oral and neural ectodermal tissues maintain contact during this structural rearrangement implies that direct contact and signalling between these two structures is still essential for this stage of pituitary organogenesis.

Between E10.5 and E12, the pouch epithelium continues to proliferate as it closes and separates from the underlying oral ectoderm, forming the definitive Rathke’s pouch (the third stage of development) abutting the neurally derived infundibulum. The pouch is still connected to the oral cavity via an epithelial stalk; however, continued upward growth of the pouch leads to thinning of this stalk, with eventual loss of the connection. The ventral portion of this pouch can then proliferate, leading to terminal differentiation of the cells of the anterior pituitary (the fourth stage of pituitary development).

It has now been established that Rathke’s pouch develops in a two-step process that requires at least two sequential inductive signals from the diencephalon. First, the induction and formation of the pouch rudiment is dependent upon Bmp4 that is present only in the hypothalamus and not in Rathke’s pouch. Secondly, Fgf8, which is also present in the hypothalamus and not in Rathke’s pouch, activates key regulatory genes LIM homeobox 3 (Lhx3) and LIM homeobox 4 (Lhx4), which are essential for subsequent development of the pouch rudiment into a definitive pouch [7].

The final stage of pituitary gland development entails the terminal differentiation of the progenitor cells into
the distinct cell types found within the mature pituitary gland. To facilitate the correct cell specification, a morphogenetic code must be established so that at any point within the pituitary a cell can maintain its identity. This polarisation of the pituitary gland is initiated by extrinsic factors such as Fgf8, Bmp2, Bmp4 and Bmp7 from the emanating surrounding tissues, namely the infundibulum and the juxtapituitary mesenchyme. The effect of the signalling molecules on the anterior pituitary gland is to establish gradients of transcription factors intrinsically, with Lhx3, Six3, Prophet of Pit1 (Prop1) and Nkx3.1 being expressed dorsoventrally, and Islet-1 (Isl1), Lhx4, Six1, Brain-4 (Brn4) and Pituitary-forkhead (P-frk) being expressed ventrodorsally [8–10].

These genetic gradients lead to a wave of cell differentiation along the ventro/dorsal axis, with ventral thyrotrope and corticotrope cells being the first to differentiate, followed by somatotrope, dorsal thyrotrope, gonadotrope and lactotrope cell differentiation in a precise temporal and spatial pattern. The progenitors of the hormone-secreting cell types proliferate ventrally from the pouch between E12.5–E15.5 to populate what will form the anterior lobe, which will contain five different cell types [11]. The remnants of the dorsal portion of the pouch form the intermediate lobe, containing the melanotrope cell type that produces the hormone pro-opiomelanocortin (POMC), the precursor protein to the melanocyte-stimulating hormone (MSH), and endorphins. Each of the five anterior pituitary cell types differentiates in a temporally and spatially regulated manner [12,13], and this process is dependent upon a number of transcription factors. A tissue-specific POU domain factor Pit1 (Pou1f-1) is required for terminal differentiation, growth and survival of somatotropes, lactotropes and thyrotropes [14], whilst the nuclear receptor steroidogenic factor-1 (Sfi) is expressed later in the nascent gonadotrope lineage [15]. The transcription factor Prop1 appears to be required for the determination of the gonadotrope lineage as well as the Pit1-dependent lineage in man.

In comparison to the rodent, very little is known about developmental models in the human. However, certainly the embryological development of the human pituitary appears to mirror that seen in the rodent, and identification of mutations in the rodent associated with human pituitary disease have been invaluable for the management of the human disease. Table 1 provides an overview of relevant murine and human genes, proteins, and phenotypes for comparison.

<table>
<thead>
<tr>
<th>Gene (murine/human)</th>
<th>Protein (murine/human)</th>
<th>Murine loss of function phenotype</th>
<th>Human phenotype</th>
<th>Inheritance murine/human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesx1/HESX1</td>
<td>Hesx1/HESX1</td>
<td>Anophthalmia or microphthalmia,</td>
<td>Variable: SOD, CPHD, IGHD</td>
<td>Dominant or recessive in both</td>
</tr>
<tr>
<td>Lhx3/LHX3</td>
<td>Lhx3/LHX3</td>
<td>Hypoplasia of Rathke's pouch</td>
<td>GH, TSH, gonadotrophin</td>
<td>Recessive in both</td>
</tr>
<tr>
<td>Lhx4/LHX4</td>
<td>Lhx4/LHX4</td>
<td>Mild hypoplasia of anterior pituitary</td>
<td>GH, TSH, cortisol deficiency, persistent craniopharyngeal canal and abnormal cerebellar tonsils</td>
<td>Recessive in both</td>
</tr>
<tr>
<td>Prop1/PROP1</td>
<td>Prop1/PROP1</td>
<td>Hypoplasia of anterior pituitary with reduced somatotrophs, lactotrophs, thyrotrophs and gonadotrophs</td>
<td>GH, TSH, prolactin and gonadotrophin deficiency. Evolving ACTH deficiency. Enlarged pituitary with later involution.</td>
<td>Recessive in both.</td>
</tr>
<tr>
<td>Pou1f1/POU1F1 (also known as Pit1/PIT1)</td>
<td>Pou1f1/POU1F1</td>
<td>Anterior pituitary hypoplasia with reduced somatotrophs, lactotrophs and thyrotrophs</td>
<td>Variable anterior pituitary hypoplasia with GH, TSH and prolactin deficiencies</td>
<td>Recessive in mouse, dominant/recessive in man</td>
</tr>
<tr>
<td>Ghrhr/GHRHR</td>
<td>Ghrhr/GHRHR</td>
<td>Reduced somatotrophs with anterior pituitary hypoplasia</td>
<td>GH deficiency with anterior pituitary hypoplasia</td>
<td>Recessive</td>
</tr>
<tr>
<td>Gh-1/GH-1</td>
<td>Growth hormone (GH)</td>
<td></td>
<td>GH deficiency</td>
<td>Recessive, dominant or X-linked in man</td>
</tr>
</tbody>
</table>
2. Human disorders associated with GHD

Growth hormone deficiency may be isolated (IGHD) or combined with other pituitary hormone deficiencies (combined pituitary hormone deficiency, CPHD). It may also be a component of a number of syndromes such as septo-optic dysplasia (SOD). IGHD is reported to occur with a frequency of 1 in 3,000-4,000, whilst CPHD and syndromic GHD are much less common.

3. Syndromic GHD

The paired-like homeobox gene Hesx1 has now been implicated in the development of some cases of SOD [16]. In the early mouse embryo, the gene is first expressed in the region fated to form the forebrain. Subsequently, the gene is expressed in Rathke’s pouch, following which its expression is down-regulated and extinguished [17,18]. Null mutants for Hesx1, in which the entire coding region is deleted, display a phenotype characterised by anophthalmia or microphthalmia, midline neurological deficits (e.g., absent septum pellucidum) and pituitary hypoplasia, this being highly reminiscent of SOD. Between 1 and 2% of heterozygote mice also manifested a phenotype [16]. The variability of the phenotype has recently been illustrated by more detailed analysis of the murine phenotype. Some of the mice have an absent pituitary whilst others have multiple pituitary glands [19].

SOD is a rare condition in man and classically comprises the triad of optic nerve hypoplasia, midline neuroradiological deficits and pituitary hypoplasia [20–25]. However, the phenotype is highly variable, and only 30% of patients manifest the full phenotype. Pituitary hypoplasia may manifest as endocrine deficits varying from IGHD to CPHD. A decrease in growth rate due to GHD is the most common feature, with hypoglycaemia, polyuria and polydipsia being less common. Either sexual precocity or failure to develop in puberty may occur [26,27], and abnormal hypothalamic neuroanatomy or neurofunction may be a feature, as may diabetes insipidus [28–30]. The endocrinopathy may also be evolutionary, with a progressive loss of endocrine function over time. The most common endocrinopathy is GHD followed by TSH and ACTH deficiency. Gonadotrophin secretion may be retained in the face of other pituitary hormone deficiencies [31].

Several aetiologies have been postulated to account for the sporadic occurrence of SOD, such as viral infections, environmental teratogens, and vascular or degenerative damage [32]. The developmental anomaly appears to occur during a critical period of embryogenesis between 4 and 6 weeks of gestation in humans. Familial cases of SOD are rare, and may be associated with an autosomal recessive inheritance [33,34]. Given the similarities between the murine Hesx1-null mutant phenotype and SOD, the role of the human homologue of this gene, HESX1, was investigated in patients with SOD and milder pituitary phenotypes. Initially, a homozygous missense mutation within the homeobox of this gene was identified in two siblings who had been diagnosed with SOD [16]. These children were born within a highly consanguineous pedigree and presented in the newborn period with hypoglycaemia secondary to cortisol deficiency. Subsequent testing confirmed complete panhypopituitarism. Neuroradiological imaging revealed agenesis of the corpus callosum, optic nerve hypoplasia, a hypoplastic anterior pituitary gland and an ectopic/undescended posterior pituitary gland. The mutation resulted in the substitution of an arginine residue by cysteine at position 160 of the coding region (position 53 of the Hesx1 homeodomain). This arginine residue is highly conserved in the majority of homeodomain proteins and is implicated in the binding of target DNA by the homeodomain. In particular, Arg53 makes contact with the phosphate backbone within the major groove of DNA. Functional analysis of this mutation showed that the mutant protein failed to bind the consensus P3 sequence to which paired-like homeodomain proteins can bind as dimers. Given the rare heterozygous phenotype within the null mutant mice and the in vitro dominant negative effect of the R160C HESX1 mutation [35], a large number of patients with sporadic SOD and its milder variants were screened for heterozygous HESX1 mutations. To date, three novel heterozygous mutations have been published: Q6H, S170L and T181A [36]. All three mutations are associated with a milder phenotype than the homozygous R160C substitution, variously leading to IGHD with or without an ectopic/undescended posterior pituitary and/or optic nerve anomalies. These data suggested that, as with the heterozygous Hesx1-null mutant mice, heterozygous mutations of HESX1 are associated with a milder, variably penetrant phenotype. The presence of heterozygous mutations, associated with a phenotype within a condition in which homozygous mutations have been described and where obligate carriers manifest no phenotype, indicates that the inheritance of this disorder is complex and may involve a number of genes with and without environmental factors.

Lhx3 (P-Lim/Lim-3) is a LIM-containing homeobox gene. Expression of Lhx3 is initially observed throughout the developing brain and spinal cord but is later restricted to the invaginating Rathke’s pouch [37]. In the targeted murine Lhx3 null mutants, initiation of Rathke’s pouch is normal, but further development of the rudimentary pouch is not seen [38,39]. The cells within the anterior pituitary are unable to proliferate and commit to a cellular differentiation pathway so that, with the exception of a small number of corticotropes, no anterior pituitary cells are present. Mutations within the human homologue of
this gene were recently reported in affected individuals within two unrelated consanguineous pedigrees [40]. The affected patients had severe growth retardation and were deficient in all but one of the anterior pituitary hormones (ACTH). Additionally, the patients also presented with a rigid cervical spine leading to limited head rotation. In the first family, a homozygous missense mutation led to the substitution of an invariant tyrosine residue by cysteine (Y116C) within the second LIM domain of this protein, a region involved in forming the zinc-finger binding motif. This motif is implicated in protein-to-protein interactions, and consequently a mutation within this region would be expected to disrupt the function of this protein. In the second family, the mutation was shown to be a homozygous 23 bp deletion that would be expected to result in a severely truncated protein lacking the entire homeodomain. In this instance, both parents were heterozygous for this deletion and manifested no phenotype, suggesting an autosomal recessive phenotype.

Lhx4, a LIM homeobox gene closely related to Lhx3, has a very similar expression pattern within the developing pituitary. Whilst the expression pattern of Lhx3 is relatively broad within the pituitary during development, in comparison, Lhx4 expression is seen in a restricted pattern within the Lhx3 expression domain. Targeted mutagenesis of this gene in mice revealed a much milder phenotype than that observed with the Lhx3+/− mouse gene. Homozygous pups displayed mild hypopituitarism with a reduction in the number of somatotropes and lactotropes and consequent GH, prolactin and LH deficiency [39]. There was no obvious heterozygous phenotype.

A mutation within this second LIM homeobox gene was described within a large human consanguineous family [41]. The probands presented with GH, TSH and ACTH deficiency. Neuroimaging of the affected individuals revealed the presence of a small sella turcica, a persistent craniopharyngeal canal, a hypoplastic anterior pituitary lobe and an ectopic/undescended posterior pituitary. The mutations inherited recessively affect the homeodomain of this gene. The mutations inherited recessively affect the structure of the POUS domain leading to a severely truncated protein lacking 171 amino acids, including half of the POU-S and the whole of the POU-HD regions. Such a protein would be unable to bind to downstream targets such as the GH, PRL and TSH promoters. In addition to recessive mutations, a number of dominant mutations have also been described. Of these, the R271W substitution in the carboxy-terminus of the homeodomain of PIT1 is the most frequently described mutation [43]. In tissue culture studies, this mutation acted as a dominant negative and prevented transcriptional activation by the wild-type protein.

So far, 14 mutations have been described in the PIT1 gene. The mutations inherited recessively affect the structure of the POUS and HD regions, and have phenotypes characterised by severe GH and PRL deficiency with a variable TSH deficiency; whereas, the dominant mutations are generally found outside the DNA-binding domains, with the exception of the R271W mutation.

Prop1 was positionally cloned using a mouse mutant, the Ames dwarf mouse (df) [47]. This spontaneously occurring mouse mutant had a phenotype somewhat similar to those of the Snell (dw) and Jackson (dwj) mice, except that in addition to the lack of thyrotrope, somatotrope and lactotrope cell lineages, consistent with functional studies of this protein showing that expression of the GH, PRL, TSH-β subunit and Ghrhr genes is regulated by Pit1.

Two spontaneously occurring mouse mutants, the Snell (dw) and Jackson (dwj) mice, have been described [46]. Both of these phenotypes, whereby the mice lack somatotrophs, lactotrophs and thyrotrophs, were shown to result from mutations within the Pit1 gene [46]. The first proband described with POU1F1 mutations presented with GH and PRL deficiencies and with severe central hypothyroidism [42]. The mutation in question was a nonsense homozygous mutation within the POUS domain leading to a severely truncated protein lacking 171 amino acids, including half of the POUS and the whole of the POU-HD regions. Such a protein would be unable to bind to downstream targets such as the GH, PRL and TSH promoters. In addition to recessive mutations, a number of dominant mutations have also been described. Of these, the R271W substitution in the carboxy-terminus of the homeodomain of PIT1 is the most frequently described mutation [43]. In tissue culture studies, this mutation acted as a dominant negative and prevented transcriptional activation by the wild-type protein.
and is undetectable by E15.5. Expression of Prop1 is hence observed specifically in those cells that will later express Pit1, although the role of Prop1 in gonadotrope development remains unclear. Patients with a phenotype similar to those shown to have POUIFI mutations were originally screened for mutations within Prop1 without success. It was not until patients with a more severe CPHD phenotype (GH, PRL and TSH deficiency with additional LH and FSH deficiency) were screened that human mutations within this gene were identified [49]. Patients with PROPI mutations were either unable to enter puberty or their puberty was arrested due to gonadotrophin deficiency [50]. Evolving cortisol deficiency has also been described in a small number of patients [50,51]. To date, 14 different recessive mutations have been identified, making PROPI one of the genes most commonly implicated in CPHD. So far, all PROPI mutations are inherited in an autosomal recessive manner. An enlarged sella turcica with appearances suggestive of a pituitary tumour is occasionally observed in association with PROPI mutations [51]. The exact mechanism underlying the pituitary enlargement, with subsequent involution of the mass, remains unclear. This enlargement of the sella turcica is also observed with LHX3 mutations [40]. There is no clear correlation between genotype and phenotype with PROPI mutations.

5. IGHD

Clinically, IGHD may be inherited as an autosomal recessive (Type 1 GHD), autosomal dominant (Type II GHD) or X-linked recessive (Type 3) [52]. IGHD can be due to mutations in either the GHI gene or the GHRH receptor (GHRHR) gene. Rarely, heterozygous mutations within Hesx1 are associated with IGHD, often in association with an undescended or ectopic posterior pituitary.

GHI is the definitive gene involved in the synthesis of pituitary GH. In Type 1A GHD, large homozygous deletions (6.7–45 kB) lead to absence of GH. Type 1B GHD is associated with homozygous splice-site mutations within GHI. Type II GHD is associated with heterozygous mutations affecting splicing, and is therefore, inherited as an autosomal dominant. It is believed that the splice-site mutations lead to the production of an alternatively spliced product with a molecular weight of 17.5–20 kDa. The exact mechanism underlying the dominant effect remains unclear.

To date, relatively few missense mutations have been identified in the GHI gene. These include the R77C mutation, which has been shown to have a greater affinity for the GH receptor than wild-type GH, and which may interfere with the normal dimerisation of the GHR by GH, which is essential for the normal function of GH [53]. An R183H mutation encodes a product that interferes with the secretion of wild-type GH [54]. Additionally, a heterozygous mutation that is translationally silent actually achieves its effects by affecting splicing, once again resulting in the production of an alternatively spliced variant of hGH [55]. The mutation lies within a sequence known as an exon splice enhancer at the beginning of exon 3.

Growth hormone releasing hormone (GHRH) is secreted by the hypothalamus and binds to GHRH receptors (GHRHR) on somatotrophs within the anterior pituitary. The receptor belongs to the G-protein family of receptors that are characterised by the presence of seven transmembrane domains. A recessive mutation within the GHRHR has been documented in the little mouse, and several recessive mutations have now been identified in the human homologue of the gene [56,57]. The mutations are scattered throughout the gene, affecting both the ability of GHRH to bind GHRHR and also its ability to transactivate the receptor.

6. Conclusions

GHD may be isolated or occur in combination with other pituitary hormone deficiencies or syndromes. A number of genetic mutations have been implicated in the aetiology of this condition. These include mutations within PIT1 (POUIFI), PROPI, HESX1, LHX3, LHX4, GHI and the GHRHR genes. The inheritance and penetrance may vary, as may the phenotypes. Identification of mutations within genes implicated in GHD can be extremely useful in predicting potentially evolving phenotypes. For example, PROPI mutations will probably evolve to include gonadotrophin deficiency in the majority of cases, and cortisol deficiency in a smaller proportion of patients. Additionally, patients with a pituitary mass may be found to harbour mutations within PROPI, and in this scenario, identification of mutations may prevent an unnecessary surgical procedure. A further advantage lies in the prospect of genetic counselling. For example, a patient with a dominant R271W mutation within POUIFI may pass on the mutation to their offspring, and hence the physician can be alerted to the possibility of secondary hypothyroidism and GHD in the affected child. Given the controversy surrounding the use of recombinant hGH in adults, identification of mutations within these genes at the time of transition may aid in strengthening the case for the use of hGH in these patients when they reach adulthood.

However, it is important to note that the majority of children do not have identified mutations, suggesting the presence of mutations in non-coding regions of the known genes and the possible role of other, as yet unidentified, genes. Identification of these mutations will
lead to a greater understanding of normal and abnormal pituitary development, and as a consequence, greater understanding of normal and abnormal growth.

References


