Genetics of Growth Hormone Deficiency

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ABSTRACT

From the initiation of the primordium to the expression of mature growth hormone (GH) gene, a variety of genes, transcription factors, signalling pathways, and epigenetic control factors take part in the embryological development of the anterior hypophyseal somatotrophic cells. A defect in this process may result in multiple pituitary deficiency or isolated growth hormone deficiency depending on the temporal or spatial position of the individual factor. This article reviews these factors in a chronological order. This review presents some of these genetic mutations that result in obesity.

Conflicts of interest: None declared

INTRODUCTION

The adenohypophysis consists of embryologically different cell types. The progenitor cells destined to become the adenohypophysis undergo a chain of morphological changes and form the Rathke’s Pouch in response to the inductive signals from the ventral diencephalon. (1) The adenohypophysis develops as a result of the processing put to effect by different combinations of transcriptional factors (TF) formed at different times in response to extrinsic and intrinsic signals. The control of the signalling events and of the expression of the TF are absolutely necessary for the healthy development of the organ.

The determinants of the embryological development of an organ involve:
- Signal pathways (2, 3)
- Transcriptional factors (3, 4)
- The epigenetic control of the nuclear formation and organisation of the chromatin (5)

SUPPLEMENT

Signal pathways

Intercellular signalling by proteins are known to take place during embryological development. There are at least 7 known signal pathways. Those engaged in the embryonic development of the adenohypophysis have been identified as (2, 3, 4, 5): 
- FGF (fibroblast growth factor) signalling
- SHH (Sonic Hedgehog) signalling
- Notch signalling

Transcription factors

Most genes are normally inactive. The “on-off” states of a gene depend on the number, the levels and combinations of the type of (activator/repressor) transcriptional factors acting on the regulator regions of that gene. The temporal and spatial expression of these TFs are essential for the embryonic development of the organs. A review of some of the essential terminology used in reference to the TFs is useful for the understanding of the functional significance of these proteins:
• Transcription: Transferral of the information coded in the DNA to mRNA by the mediation of RNA polymerases.
• TFs bind the DNA by means of the ‘DNA binding domain’ on its structure.
• TFs bind via their DNA binding domain the regulator (e.g., promoter, enhancer) region causing the activation (upregulation) or the repression (downregulation) of the transcription of the gene.
• TFs usually play a role in embryonic development.
• Homeobox is the approximately 180-base pair long DNA sequence found within genes, called the homeobox genes, involved in the regulation of morphogenesis in living organisms.
• Homeodomain is a protein domain, which can bind DNA, encoded by the homeobox.

**Nuclear structure and the epigenetic control of chromatin organisation**

Some genes are tightly bound by chromatin consisting mainly of histone proteins which must be structurally modified to enable the access of the TFs to these genes.\(^{5}\)

The genes involved in a chronological order in the development of the hypophysis are reviewed below within the framework of the brief background given above.

**HESX1**

HESX1 is a paired-like homeodomain transcription factor with two repressor domains known to be the earliest to operate in the development of the hypophysis. It functions as a repressor of PROP1-mediated gene stimulation. Inheritance of mutations in HESX1 are autosomal recessive or autosomal dominant. The development of Septo-Optic Dysplasia (SOD) which is mostly sporadic\(^ {6}\) is manifested by the following defects, two of which are required for the correct diagnosis of the condition:
1. Hypoplasia of the optic nerve,
2. Midline brain defects (agenesis of corpus callosum, and of septum pellicidum) and ectopic posterior hypophysis,
3. Hypopituitarism, anterior hypophyseal hypoplasia.

The associated hormonal deficiencies include those of growth hormone (GH) + thyroid stimulating hormone (TSH) ± prolactin (PRL) ± follicle stimulating hormone (FSH) ± lutenizing hormone (LH).\(^ {7}\) In only 1% of the SOD cases HESX1 mutation has been demonstrated, suggesting that other environmental, toxic and viral factors could bring about the observed anomalies. To date some 13 different mutations of the HESX1 have been described.\(^ {6, 7}\)

**SOX3**

This transcription factor gene is located in the SRY (sex determining region Y)-related box 3 gene of the HMG box family of TFs and it is expressed during the early phase of embryonic development in the brain, hypothalamus, infundibulum and the ventral diencephalon, but not in Rathke’s pouch. In patients with Xq27 cytogenetic duplication, anterior hypophyseal hypoplasia and GH ± other hormone deficiencies appear. Mental retardation and growth retardation are observed. Infundibular and anterior hypophyseal hypoplasia and neurohypophyseal ectopy have been described.\(^ {8, 9}\)

**SOX2**

This TF, also known as the SRY-box2 , is of the same family as SOX3. Mutations in this gene result in growth retardation and infertility in the rat. In humans mutations have been associated with microphthalmia/anophthalmia, hypogonadotropic hypogonadism, oesophageal atresia, loss of hearing, and adenohypophyseal hypoplasia.\(^ {10}\) Unlike the rat model, shortness of stature is not seen in man.

**PITX1/PITX2**

Paired-like homeodomain TFs 1 and 2 are both expressed early in the oral ectoderm and its derivative, Rathke’s pouch, which develops into the pituitary gland.
tations of PITX1 and 2 result in normally de-
veloped Rathke’s pouch; however, the cells
cannot proliferate and apoptosis is increased.(11) PITX2 mutation is more important
in that in the animal model all cells but the
corticotrophs (the adrenocorticotrop hormone-
ACTH and melanocyte stimulating horm-
one-MSH secreting cells of the anterior pi-
tuitary) are defective. In humans heterozy-
gotic mutation causes Rieger’s syndrome
-presenting with eye, navel, heart and tooth
anomalies and rarely with short stature.(11)

LHX3
This TF is a member of the LIM/homeo-
box (LHX) gene family encoding for LIM ho-
meodomain class of TF. LHX3 is expressed
from the early stage on to the maturity peri-
od. So far 12 cases have been identified with
LHX3 mutations presenting with deficiency of
all anterior pituitary hormones except
ACTH, and loss of neck rotation and restric-
ted body movement associated with de-
velopmental disorder of the spinal motorneu-
rions in specific cases.(12, 13)

LHX4
The LHX4 LIM-homeodomain transcripti-
on factor is expressed at early stages of emb-
ryological development and is required for
adenohypophysyal cell proliferation and
nervous system development. Heterozygous
mutations in the LHX4 are associated with
combined deficiencies in all anterior pitui-
tary hormones. Aberrant sella turcica morp-
hology has also been described. So far only
one case of mutation with autosomal domi-
nant inheritance has been observed.(14)

GLI3
The GLI-Kruppel family member, also
known as GLI3, is a human gene associated
with Greig cephalopolysyndactyly syn-
drome. This gene encodes a protein belonging
to the C2H2-type zinc finger proteins, sub-
class of the GLI family, characterized as DNA-
binding TFs mediating development of the
sonic hedgehog (SHH) signalling system de-
rived from the diencephalon and the oral ec-
toderm and required for the normal deve-
lopment of the hypophysis. To date only fo-
ur cases of mutations have been identified,
associated with multiple hypophysyal hor-
mone deficiency.

PROP1
PROP1 (homeobox protein prophet of
PIT-1) is a paired-like homeodomain TF ex-
pressed solely in the embryonic anterior
hypophysis. Its expression leads to ontoge-
nesis of pituitary gonadotropes, as well as
somatotropes, lactotropes, and caudomedial
thyrotropes. As seen in the AMES mouse, a
natural animal model,(15) all cell types are
affected by PROP1 except the corticotrophs.
Inactivating mutations in the PROP1 result
in deficiencies of GH, PRL, LH, FSH and
TSH, as seen in combined pituitary hormo-
ne deficiency (CPHD). To date 22 different
types of mutations have been identified in
170 cases. About 50% of all familial CPHD
cases are explained by autosomal recessive
transmission of the PROP1 mutations.(16)
Differences are seen in the order and the
age of presentation of the hormone defici-
encies. In some cases even ACTH deficiency
enters the picture. Despite the possibility of
total absence of puberty in some cases, late
menarche and completion of puberty is also
possible in some. In magnetic resonance
imaging (MRI) visualisation of the anterior
hypophysis is small. In PROP1 mutation,
PIT1 expression is also absent. The genoty-
pe-phenotype correlation is not good in the
mutants.(16, 17, 18, 19, 20)
Sustained Notch signaling in progenitor
cells is required for the sequential emer-
gence of distinct cell lineages during organ-
genesis. Notch signalling, which is a
pathway protected throughout evolution in
the embryological development system, is
required for the expression of PROP1
which in turn is required for generation of
the PIT1 lineage.

The ligands and receptors involved in
Notch signalling are cell surface proteins.
When the Notch protein binds the specific receptor, the Notch intracellular domain (NICD) is released. NICD enters the nucleus to form a complex with the DNA-binding protein Rbp-J to initiate transcription by the activation of histone deacetylase and other factors. Knock out of the Rbp-J gene, which encodes the major mediator of the Notch pathway, leads to premature differentiation of the progenitor cells and the conversion of the late PIT1 lineage into the early corticotrope lineage. In the late phase of hypophyseal development the Notch signals disappear which enables the cells to achieve their final functional phenotypes.

POU1F1
Previously referred to as PIT1, the POU1F1 is a member of the homeodomain TF which is expressed late and is essential for the development of somato-, lacto- and thyrotrophic cells. Snell mouse has been used as the animal model for research presenting generally with autosomal recessive and on occasions with autosomal dominant mutations of the POU1F1. In humans, 22 autosomal recessive and 5 autosomal dominant transmissions have been demonstrated. The anterior hypophysis is hypoplastic in MRI visualisation. TSH deficiency may appear late but GH and PRL deficiency is present at birth. During the development of the hypophysis, the development of the somato-, lacto- and thyrotrhophs also requires WNT/β-catenin signalling pathway which is characteristically temporally and spatially active. Beta-catenin is a key component of the WNT signalling pathway and interacts with TFs activating the transcription of the WNT target genes. Hence, it forms a complex with PROP1 and brings about PIT1 expression through the PIT1 early enhancer and also inhibits the repressor HESX1. In the β-catenin knock-out model, the hypophysis remains hypoplastic with failure of the somato-, lacto- and thyrotrophs to develop. Human hypophyseal dysfunction as a result of the malfunction of the WNT/β catenin pathway has not yet been described. The process of regulating the transcriptional programs via the organisation of the enzymes that modify the chromatin is referred to as epigenetic control. LSD1 is a histone demethylase and in the LSD1 knock-out model the cells developing through the PIT1 path cannot attain the final, hormone secreting stage of their development since genes targeted by PIT1, like the GH1 gene, have to be activated at their promoter region by the reaction of PIT1 and LSD1.

Math3
The Math3 gene involved in neuronal development, has been studied using the mouse Math3 (Math3) gene. Math3 expression in the hypophysis is regulated by POU1F1. In the Math3 knock-out model the expression of the GHRH receptor (GHRHR) is absent, and this results in the absence of GHRH-stimulated GH synthesis and release.

Isolated Familial GH Deficiency
Four types have been described of this disorder which is transmitted according to the Mendelian rules.

- **Type1A** is characterised by complete absence of GH, association with different mutations in the GH1 gene and autosomal recessive transmission.
- **Type1B** is milder than Type1A and characterised by measurable GH levels, associated with mutations in the GH1 or the GHRHR and autosomal recessive transmission.
- **Type2** is the most frequently observed type, associated with heterozygous mutations in the GH1 gene and shows autosomal dominant transmission.
- **Type3** transmission is X-chromosome-linked; its gene is unknown and may present in combination with agammaglobulinaemia.

GHRH
A mutation that causes morbidity in humans has not yet been described.
**GHRHR**

It is one of the genes on which mutations are encountered most frequently. The E72X is the most frequently occurring mutation worldwide. The Little mouse is the natural animal model of this gene defect which shows autosomal dominant transmission.

**GHRELIN (GHS)**

Ghrelin is primarily released in the stomach. It has an orexigenic activity. It has potent GH stimulatory effect compared to GHRH. Obestatin is derived from the same pre-pro-hormone but has an anorexigenic effect. Any GH deficiency associated with GHS has not been described in man.

**GHSR1a**

Ghrelin induced secretion of stored GH is mediated by the growth hormone secretagogue receptor (GHSR1A). GHRH on the other hand acts as a primer to stimulate de novo GH biosynthesis. Deficiency of GH associated with a mutation in the GHSR has not been reported. (31)

**GH1**

GH is an 191-amino acid polypeptide. Occurrence of numerous small and large deletions, splice sites, missense and nonsense mutations have been described on the GH1 gene encoding for GH. The transmissions are autosomal recessive or dominant type.

In conclusion, starting with the primordial form, many genes, TFs, signal pathways and epigenetic control mechanisms play specific roles in the sequential processes resulting in the cellular expression of the mature GH1. Defects in this process result in CDPH or isolated GH deficiency depending on the time and site of their occurrence.

**REFERENCES**


