J Clin Res Ped Endo 2009;(Suppl 1):8–14
DOI: 10.4008/jcrpe.v1i1.30

ISSN: 1308-5727
Online ISSN: 1308-5735

JCRPE
www.jcrpe.org

Genetics of Growth Hormone Deficiency

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Keywords:
growth hormone, pituitary gland, hereditary, genetics

Received: 14 October, 2008
Accepted: 22 October, 2008

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ABSTRACT

From the initiation of the primordium to the expression of mature growth hormone (GH)1 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.

Conflict 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)
- Transcriptonal factors(3, 4)
- The epigenetic control of the nuclear formation and organisation of the chromatin.(5)

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:

SUPPLEMENT

- 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, infindibulum 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 microopthalmia/anopthalmia, 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. Mutations of PITX1 and 2 result in normally developed 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 hormone-MSH secreting cells of the anterior pituitary) are defective. In humans heterozygotic 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/homeobox (LHX) gene family encoding for LIM homeodomain class of TF. LHX3 is expressed from the early stage on to the maturity period. 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 restricted body movement associated with developmental disorder of the spinal motorneurons in specific cases.(12, 13)

LHX4

The LHX4 LIM-homeodomain transcription factor is expressed at early stages of embryological development and is required for adenohypophyseal cell proliferation and nervous system development. Heterozygous mutations in the LHX4 are associated with combined deficiencies in all anterior pituitary hormones. Aberrant sella turcica morphology has also been described. So far only one case of mutation with autosomal dominant inheritance has been observed.(14)

GLI3

The GLI-Kruppel family member, also known as GLI3, is a human gene associated with Greig cephalopolysyndactyly syndrome. This gene encodes a protein belonging to the C2H2-type zinc finger proteins, subclass of the GLI family, characterized as DNA-binding TFs mediating development of the sonic hedgehog (SHH) signalling system derived from the diencephalon and the oral ectoderm and required for the normal development of the hypophysis. To date only four cases of mutations have been identified, associated with multiple hypophyseal hormone deficiency.

PROP1

PROP1 (homeobox protein prophet of PIT-1) is a paired-like homeodomain TF expressed solely in the embryonic anterior hypophysis. Its expression leads to ontogenesis 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 hormone 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 deficiencies. 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 genotype-phenotype correlation is not good in the mutants.(16, 17, 18, 19, 20)

Sustained Notch signaling in progenitor cells is required for the sequential emergence of distinct cell lineages during organogenesis. 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.(21) 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.(23) 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 the thyrotrophs 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.(24) 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(25) 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 expresion of the GHRH receptor (GHRHR) is absent, and this results in the absence of GHRH-stimulated GH synthesis and release.

Isolated Familial GH Deficiency(26)

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

- **Type1A**(27) is characterised by complete absence of GH, association with different mutations in the GH1 gene and autosomal recessive transmission.
- **Type1B**(28) is milder than Type1A and characterised by measurable GH levels, associatied with mutations in the GH1 or the GHRHR and autosomal recessive transmission.
- **Type2**(29) is the most frequently observed type, associated with heterozygous mutations in the GH1 gene and shows autosomal dominant transmission.
- **Type3**(30) transmission is X-chromosome- linked; its gene is unkown 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 primodial 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.

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