Pituitary

Mohamad Maghnie^a, Andrea Secco^a and Sandro Loche^b

^aDepartment of Pediatrics, Istituto di Ricovero e Cura a Carattere Scientifico, Giannina Gaslini, University of Genova, Italy

^bOspedale Regionale per le Microcitemie, Cagliari, Italy

Mechanism of the year

A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis

Niedernhofer LJ, Garinis GA, Raams A, Lalai AS, Robinson AR, Appeldoorn E, Odijk H, Oostendorp R, Ahmad A, van Leeuwen W, Theil AF, Vermeulen W, van der Horst GT, Meinecke P, Kleijer WJ, Vijg J, Jaspers NG, Hoeijmakers JH. Center for Biomedical Genetics, Medical Genetic Center, Department of Cell Biology and Genetics, Erasmus Medical Center, Rotterdam, The Netherlands

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Background: Experimental evidence reconciling the apparently disparate mechanisms of progeroid syndrome and natural ageing is lacking. Patients with xeroderma pigmentosum (XPF) carrying a mutation and severe progeroid symptoms, along with mice-generated models, may serve to understand mechanisms related to ageing.

Methods: Cell lines were established from skin biopsies of patients or from mouse embryos. Nucleotide excision repair was measured by a clonogenic survival assay after exposure of cells to UV irradiation. Transcription-coupled nucleotide excision repair and XPF-ERCC1, an endonuclease required for repair of helix-distorting DNA lesions, were measured. XPF cDNA were sequenced and *Ercc1*^{-/-} mice were generated. IGF-1 and insulin concentrations were determined.

Results: *Ercc1*^{-/-} mice showed mild retardation and growth arrest in the second week followed by death at 4 weeks. There was a striking similarity between the symptoms of patients and mice as well as between their final outcomes. Expression data from XPF-ERCC1-deficient mice indicated increased cell death and antioxidant defenses, a shift towards anabolism, and reduced GH/IGF-1 signalling.

Conclusion: DNA damage triggers a highly conserved metabolic response, either directly or by interfering with transcription or replication through the GH/IGF-1/insulin pathway, responsible for resources shifting from growth to somatic preservation and life extension.

Several progeroid syndromes are caused by defects in cellular response to DNA damage, including Cockayne syndrome, Werner syndrome, ataxia telangiectasia and trichothiodystrophy, suggesting a close relationship between ageing and genome maintenance. On the other hand, the mitogenic GH/IGF-1 pathway is a determinant of lifespan as shown by the fact that prolonged dampening of the axis genetically or by caloric restriction promotes longevity, whereas persistent upregulation shortens life. Nucleotide excision repair is a multistep 'cut-and-patch' mechanism that removes distorting lesions affecting one strand of DNA, such as those resulting from ultraviolet radiation damage. Two subpathways exist: (1) transcription-coupled nucleotide excision repair – its defect causes Cockayne syndrome and trichothiodystrophy – which removes lesions that block RNA polymerases and rescues transcription and prevents cell death, and (2) global genome nucleotide excision repair – its defect causes XPF – which operates genome-wide preventing mutations. In this study, the authors describe a 15-year-old boy with severe XPF mutation and a combination of progeroid symptoms and sunburn. In addition, the *Ercc1*^{-/-} mice model exhibits a similar phenotype and pattern of senescence of the patient with the XPF defect. In these mice, circulating insulin and IGF-1 levels were reduced without any evidence of hypothalamic-pituitary defect, suggesting a possible suppression of the GH axis as an adaptive response to DNA damage. Diverse metabolic changes and increased apoptotic cells in the *Ercc1*^{-/-} mice were similarly altered in aged mice. This model is in favor of the hypothesis that ageing is genetically regulated but is also the consequence of the accumulation of stochastic damage which in turn is responsible for functional decline.

The human growth hormone gene contains a silencer embedded within an Alu repeat in the 3'-flanking region

Trujillo MA, Sakagashira M, Eberhardt NL

Department of Medicine, Mayo Clinic/Mayo Foundation, Rochester, Minn., USA

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Background: Alu family sequences consist of middle, repetitive short interspersed elements spread throughout vertebrate genomes. Although most Alu repeats are transcriptionally silent, they might have a functional role and may even contribute to genetic diseases. The 3'-flanking region of human growth hormone (hGH)-1 and hGH-2 genes contains an Sx Alu repeat, whose close proximity to the hGH coding region makes it an ideal candidate for studying the potential transcription role of these sequences.

Methods: Plasmid construction, deletion of the sequences 3' containing the 3' Alu element, and functional analysis of the hGH-1 3'-flanking region sequences were carried out.

Results: hGH expression in transfected rat anterior pituitary tumor cell (GC) cells was increased in the reporter constructs in which the Sx Alu sequences were deleted. This result is consistent with the hypothesis of the presence of a repressor element within this region, mapping between nts 2158 and 2572 (the region comprising the Sx Alu repeat). Functional analysis and gene sequences lead to the identification of four discrete entities that are essential for silencer function: a core repressor domain, an anti-silencer domain (comprising mediators of the orientation-independent silencer activity), and two domains flanking the core repressor domain/anti-silencer domain that regulate silencer activity in a core repressor domain-dependent manner. The hGH-1 silencer was found to be active in human placental syncytiotrophoblast, supporting the hypothesis that the hGH 3'-flanking region silencer is a tissue-specific element and promoter-dependent. The silencer was able to inhibit transcription by a mechanism involving histone deacetylation, resulting in a significant decrease of RNA polymerase II recruitment to the promoter.

Conclusion: This study provides a comprehensive functional analysis of the hGH 3'-flanking region sequences and found that a silencer/anti-silencer cassette resides in the proximal 3'-flanking region of the hGH gene.

As they are the most effectively transposed primate-specific short interspersed elements, Alu elements are present in more than 1 million copies in the human genome and include most recently transposed subsets of AluY elements that are polymorphic in humans. Although Alu elements are commonly thought to play an essential role in the shaping and functioning of primate genomes, the understanding of the impact of recent Alu insertions on human gene expression is far from being comprehensive. Mobilization of Alu elements is thought to occur through an RNA polymerase III-derived transcript by means of a retroposition process. The effect does not depend on sequences of Alu elements and their orientation, but is likely to be cell type specific [1]. Although Alu sequences accumulate preferentially in gene-rich regions, the probability that the insertion event occurs within or in a coding region is extremely low; consequently, Alu insertions would contribute to only 0.1% of genetic diseases, and their consequences at the molecular level have only been studied in a few cases. Alu-containing exons may also be skipped through an Alu-mediated rearrangement, as in Hunter disease, or as in Apert syndrome, through disruption of a *FGFR2* splice site. Skipping of an Alu-containing exon has also been described in the *BRCA2* gene for breast cancer, as well as in *HESX1* transcript carrying a deletion of exon 3, leading to pituitary aplasia and coloboma. Although Alu sequences have been associated with silencing activity in many genes, the data presented in this study represent the most detailed dissection of the specific Alu sequences that mediate silencing activity. Further studies will be required to establish whether the domains in the hGH-1 3'Alu element are related to those that mediate repression in other gene systems or whether the hGH-associated 3'Alu members have evolved specialized regulatory features, including those domains that lie outside the Alu repeat which are involved in modulating silencer function.

Identification of novel peptide hormones in the human proteome by hidden Markov model screening

Mirabeau O, Perlas E, Severini C, Audero E, Gascuel O, Possenti R, Birney E, Rosenthal N, Gross C
Mouse Biology Unit, EMBL, Monterotondo, Italy
Genome Res 2007;17:320–327

Background: Several methods have been used to identify new peptide hormones, including biochemical purification coupled with functional assays. The advent of genomic sequence and bioinformatics search strategies has contributed to the development of more powerful systematic bioinformatics methods.

Methods: A bioinformatics search tool based on the hidden Markov model formalism that uses several peptide hormone sequence features to estimate the likelihood that a protein contains a processed and secreted peptide of this class was employed.

Results: This method allows for the identification of two novel peptide hormones named spexin and augurin. Biochemical investigations revealed their presence in secretory granules in a transfected pancreatic cell line. Spexin was expressed in the submucosal layer of the mouse esophagus and stomach. Augurin was found to be expressed in mouse endocrine tissues, such as pituitary and adrenal tissue, as well as in the choroids plexus and atrioventricular node of the heart.

Conclusion: This study proposes the use of a bioinformatics tool to identify novel peptide hormones that might be actively involved in endocrine homeostasis.

The study of peptide hormones has received considerable attention because of their role in modulating a wide range of physiological functions. In fact a large group of peptide hormones serves as both hormones and neurotransmitters as they are secreted into the bloodstream by endocrine cells and released into the synapse by neurons. Peptide hormones are short peptides (<100 amino acids) produced by the proteolytic cleavage of pre-pro-hormone precursors. Following signal peptide removal by the signal peptidase complex, the pro-hormone undergoes cleavage at specific sites by pro-hormone convertases. In many cases, processed peptides undergo post-translational modification, with <50% of peptide hormones becoming amidated at their C-terminus. Mature peptides pass through the secretory pathway and are released into extracellular space, where they can bind to specific cell surface receptors and modulate cellular functions. Several methods have been used to identify new peptide hormones including biochemical purification and functional assays. This study used a sequence-based approach to identify two candidate novel peptide hormones called spexin and augurin, both co-localized with insulin in the secretory pathway; they were processed and secreted following transfection in endocrine cells. This is an additional example that shows that such peptide hormone symbiosis is likely to exist, i.e. obestatin and salusin, produced by the ghrelin and Torsin2A genes, respectively. These findings confirm that peptide hormones in the human proteome can be identified using a bioinformatics approach and that this method could be useful for the systematic screening of proteomes for biologically active peptides.

Important for clinical practice

HESX1 mutations are an uncommon cause of septo-optic dysplasia and hypopituitarism

McNay DE, Turtton JP, Kelberman D, Woods KS, Brauner R, Papadimitriou A, Keller E, Keller A, Haufs N, Krude H, Shalet SM, Dattani MT
Biochemistry, Endocrinology, and Metabolism Unit, Institute of Child Health, London, UK
m.dattani@ich.ucl.ac.uk
J Clin Endocrinol Metab 2007;92:691–697

Background: Mutations in the transcription factor HESX1 were described in patients with septo-optic dysplasia and hypopituitarism.

Methods: Patients with either septo-optic dysplasia or isolated pituitary dysfunction, optic nerve hypoplasia, or midline neurological abnormalities were screened for mutations in the HESX1 gene. Molecular

analysis was performed by heteroduplex detection for mutations in the coding and regulatory regions of the gene.

Results: A novel functionally significant heterozygous mutation (E149K) was found in a patient with isolated GH deficiency and digital abnormalities. The overall incidence of coding region mutations was <1%.

Conclusions: Mutations of HESX1 gene are a rare cause of septo-optic dysplasia and hypopituitarism.

Hormonal, pituitary magnetic resonance, LHX4 and HESX1 evaluation in patients with hypopituitarism and ectopic posterior pituitary lobe

Melo ME, Marui S, Carvalho LR, Arnhold IJ, Leite CC, Mendonca BB, Knoepfelmacher M
Unidade de Endocrinologia do Desenvolvimento, Laboratório de Hormônios e Genética Molecular LIM 42,
Disciplina de Endocrinologia, HCFMUSP, Brazil
medna@usp.br

Clin Endocrinol (Oxf) 2007;66:95–102

Background: LHX4 and HESX1 are transcription factors which play a crucial role in early stages of pituitary development. Mutations in the genes encoding for these proteins cause hypopituitarism which can be associated with ectopic posterior lobe. This study analyzed LHX4 and HESX1 genes and characterized pituitary hormone profiles and their relationships with magnetic resonance imaging (MRI) findings.

Methods: 62 patients with hypopituitarism and ectopic posterior lobe were evaluated. Molecular analysis of LHX4 and HESX1 genes was performed by PCR and automatic sequencing.

Results: In 42 patients, the pituitary stalk was not visualized at MRI whereas in 20 the pituitary stalk was visible. Most patients (95%) with non-visible stalk had combined pituitary hormone deficiency with ACTH deficiency in 85%. In patients with visible pituitary stalk, combined pituitary hormone deficiency was found in 50% of the cohort while ACTH deficiency occurred in 20%. The frequency of ectopic posterior lobe was found to be similar whether the stalk was visible or not. No mutations of the two genes were identified. Three new polymorphisms of the LHX4 gene were found.

Conclusions: Mutations of LHX4 and HESX1 genes are rare causes of hypopituitarism.

Genetic screening of combined pituitary hormone deficiency: experience in 195 patients

Reynaud R, Gueydan M, Saveanu A, Vallette-Kasic S, Enjalbert A, Brue T, Barlier A
Laboratoire de Biochimie et Biologie Moléculaire, Hôpital de la Conception, Marseille, France
J Clin Endocrinol Metab 2006;91:3329–3336

Background: Combined pituitary hormone deficiency can be caused by mutations in transcription factor genes. This study screened a large number of patients with combined pituitary hormone deficiency for mutations known to cause hypopituitarism.

Methods: 195 patients with CPHD from the international GENHYPOPIT network were studied for mutations in POU1F1, PROP1, LHX3, LHX4, and HESX1 genes.

Results: Total prevalence of mutations was 13.3 and 52.4% in 20 patients with familial combined pituitary hormone deficiency. No mutations in HESX1 gene were found in 16 patients with septo-optic dysplasia. A mutation of the LHX4 gene was found in one familial case of combined pituitary hormone deficiency. No mutations in LHX3 gene were found in 109 patients with no extrapituitary abnormalities; 20 had a PROP1 mutation. A mutation in Pit1 gene was found in 1 patient with GH and TSH deficiency.

Conclusions: Mutations in PROP1 gene are the most frequent type in patients with combined pituitary hormone deficiency.

The pathophysiology of combined pituitary hormone deficiency is just beginning to be elucidated, with mutations in genes encoding transcription factors expressed at different stages of pituitary development. Several transcription factors are involved in pituitary development and in the regulation of the transcription of specific pituitary genes. Among them, two closely related genes, LHX3 and LHX4, are believed to share redundant biological properties. LHX3 and LHX4 are members of the LIM homeodomain family of transcription factors and are essential for normal pituitary development. Mutations in the LHX3 gene cause combined pituitary hormone deficiency with rigid cervical spine. More recently, mutations of the LHX3 gene have also been found associated with milder

Table 1. Summary of current gene/MRI correlations in congenital hypopituitarism

Gene	Prevalence	Prevalence among familial cases	Hormone deficiencies	MRI findings					
				Ectopic posterior pituitary	Small anterior pituitary	Skull base abnormalities	Pituitary stalk abnormalities	Optic nerve abnormalities	Extra-pituitary abnormalities
HESX1	<1% of cases labeled as SOD		•	•	•	•	•	•	•
LHX4	2.5% ¹	increased	•	•	•	•	•		•
PROP1	≈20% of cases with PP in place	50%	•		• ²				
POU1F1	1/17 (5.8%)		•		• ³				

Data are collected from: McNay et al., J Clin Endocrinol Metab 2007; Melo et al., Clin Endocrinol (Oxf) 2007; Reynaud et al., J Clin Endocrinol Metab 2006, and from previous publications on the topic cited herein.

¹Based on 1/39 reported by Reynaud et al.: JCEM 2006. The case has been already described by Machinis K et al., Am J Hum Genet 2001;69:961–968 (two families were described).

²PROP1: anterior pituitary gland can be small, normal or large.

³POU1F1: anterior pituitary gland can be normal with evolution to small pituitary.

hypopituitary phenotypes including isolated GH deficiency. Mutations in the HESX1 gene have been described in association with septo-optic dysplasia, with pituitary aplasia as well with isolated defects of the hypothalamic-pituitary axis. Human PROP-1 gene mutations induce combined pituitary hormone deficiency that includes GH, PRL, TSH, gonadotrope and sometimes late ACTH deficiency. Mutations in POU1F1, also known as PIT-1, are associated with GH, TSH, and prolactin deficiency. These three studies show that mutations in LHX3, LHX4 and HESX1 genes are a rare cause of hypopituitarism and septo-optic dysplasia. Mutations of PROP1 gene are the most frequent and therefore remain the first to be looked for. Mutations in PIT-1 gene should be looked for in patients with GH and TSH deficiency. Establishing endocrine and MRI phenotypes is extremely helpful in the selection and management of patients with hypopituitarism, both in terms of possible genetic counselling and for early diagnosis of evolving anterior pituitary hormone deficiencies (table 1).

Adult height in patients with permanent growth hormone deficiency with and without multiple pituitary hormone deficiencies

Maghnie M, Ambrosini L, Cappa M, Pozzobon G, Ghizzoni L, Ubertini MG, di Iorgi N, Tinelli C, Pilia S, Chiumello G, Lorini R, Loche S

Department of Pediatrics, Istituto di Ricovero e Cura a Carattere Scientifico Giannina Gaslini, University of Genoa, Genoa, Italy

mohamadmaghnie@ospedale-gaslini.ge.it

J Clin Endocrinol Metab 2006;91:2900–2905

Background: Adult height in childhood-onset growth hormone deficiency (GHD) has been reported as being greater in patients with multiple pituitary hormone deficiencies than in patients with isolated GHD. These data, however, have not been based on the re-evaluation of GH status after adult height achievement and in addition the outcome of patients with permanent isolated GHD has not been adequately evaluated.

Methods: This was a retrospective multicenter study conducted in university research hospitals and a tertiary referral endocrine unit. 39 patients with IGHD (26 males, 13 females) and 49 with multiple pituitary hormone deficiencies (31 males, 18 females) were re-valuated for GH secretion after adult height achievement. GHD was based on peak GH levels $<3 \mu\text{g/l}$ after an insulin tolerance test or peak GH $<5 \mu\text{g/l}$ after two other tests. Magnetic resonance imaging (MRI) showed congenital hypothalamic-pituitary abnormalities in 73 patients, while no relevant MRI alterations were seen in 15 subjects. Height SD score (SDS) was analyzed at GHD diagnosis, at the onset of puberty (either spontaneous or pharmacological), and at the time of GH withdrawal.

Results: Median height SDS at diagnosis was not significantly different between isolated GHD and multiple pituitary hormone deficiencies patients. Those with isolated GHD entered puberty at a median age of 12.6 years in girls and 13.4 years in boys. In multiple pituitary hormone deficiencies, puberty was induced at a median age of 13.5 years in girls and 14.0 years in boys. Median height SDS at Tanner stage II was similar in both isolated GHD and multiple pituitary hormone-deficient patients. No significant differences in median height SDS were seen at the beginning of puberty between IGHD and MPHD subjects, or in total pubertal height gain and in median adult height (males 168.5 vs. 170.3 cm, females 160.0 vs. 157.3 cm). A positive correlation was found between adult height SDS of the IGHD subjects, height at the time of diagnosis and total pubertal height gain. Differently, adult height SDS of the multiple pituitary hormone-deficient subjects showed a positive correlation with both the duration of GH treatment and height SDS at the time of GHD diagnosis.

Conclusion: No significant differences exist in adult height between patients with permanent isolated GHD with spontaneous puberty and multiple pituitary hormone deficiencies with induced puberty.

In this study, patients with multiple pituitary hormone deficiencies and those with isolated GHD reached similar adult heights, regardless of the timing of puberty, a finding that directly contradicts most earlier studies in the literature. Indeed, the current body of literature suggests that patients with multiple pituitary hormone deficiencies reach a taller adult height than patients with isolated GHD. However, these studies may be biased because no distinction between patients with permanent GHD and transitory GHD within the isolated GHD group was considered. Thus, when GHD is permanent (a diagnosis that should be confirmed in adulthood), GH therapy results in an adult height that is comparable to that of isolated GHD and multiple pituitary hormone-deficient subjects. In fact, this study suggests that the delaying puberty does not increase adult height gain.

Clinical characterization of familial isolated pituitary adenomas

Daly AF, Jaffrain-Rea ML, Ciccarelli A, Valdes-Socin H, Rohmer V, Tamburrano G, Borson-Chazot C, Estour B, Ciccarelli E, Brue T, Ferolla P, Emy P, Colao A, De Menis E, Lecomte P, Penfornis F, Delemer B, Bertherat J, Wemeau JL, De Herder W, Archambeaud F, Stevenaert A, Calender A, Murat A, Cavagnini F, Beckers A
Department of Endocrinology, Centre Hospitalier Universitaire de Liège, Domaine Universitaire du Sart Tilman, Liège, Belgium

J Clin Endocrinol Metab 2006;91:3316–3323

Background: Familial pituitary adenomas usually occur in the context of multiple endocrine neoplasia type 1 (MEN1) or Carney Complex (CNC). This article presents an international, multicenter, retrospective study to identify non-MEN1/CNC families with isolated pituitary adenomas. The characteristics of families with isolated pituitary adenomas and their phenotypic presentation were analyzed and compared with a matched population of patients with sporadic pituitary tumors.

Methods: Families with isolated pituitary adenomas are defined as families containing two or more members with anterior pituitary tumors and no evidence of MEN1 or CNC. Molecular genetic analysis of the MEN1 and PRKAR1A genes was performed to exclude MEN1 or CNC. The study analyzed patients between 1970 and 2004 and was performed in 22 centers in Belgium, France, Italy and The Netherlands. The control group comprised 2,600 patients with sporadic pituitary adenoma. Immunohistochemistry for LH, FSH, TSH, GH, prolactin, ACTH and α -subunit was carried out in the tumor tissue of 74 patients who underwent surgery.

Results: A total of 64 families with isolated pituitary tumors were identified, which included 138 affected individuals (52 males, 86 females). 55 were prolactinomas, 47 somatotropinomas, 28 non-secreting adenomas, and 8 ACTH-secreting tumors. A single tumor phenotype occurred in 30 families, and heterogeneous phenotype in 34. Patients with FIPA were younger at diagnosis than sporadic cases. Macroadenomas

were more frequent in heterogeneous than in homogeneous FIPA families. Prolactinomas from heterogeneous families were larger and had more frequent suprasellar extension than sporadic cases. Isolated familial somatotropinoma cases were younger at diagnosis than sporadic cases. Familial non-secreting adenomas were younger at diagnosis and had more frequent invasive tumors than the sporadic cases.

Conclusions: This study shows that familial isolated pituitary adenomas and sporadic adenomas have differing clinical characteristics and may represent a novel endocrine neoplasia that requires further genetic characterization.

This multicenter international study succeeded in collecting a high number of patients with a condition as rare as familial pituitary adenoma. Careful scrutiny of their clinical history revealed that they differ clinically from patients with sporadic pituitary adenoma. Interestingly, germline mutations in the aryl hydrocarbon receptor-interacting protein gene has been identified in subjects pituitary adenoma (for details, see *New gene* section) indicating that it is possible to identify the causative genetic defects in the low-penetrance conditions even in the absence of a strong family history. Unravelling the genetic basis of this rare condition would be of great help in elucidating the pathogenesis of pituitary adenomas.

Pituitary autoantibodies in autoimmune polyendocrine syndrome type 1

Bensing S, Fetisov SO, Mulder J, Perheentupa J, Gustafsson J, Husebye ES, Oscarson M, Ekwall O, Crock PA, Hokfelt T, Hulting AL, Kampe O

Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

sophie.bensing@ki.se

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Background: Mutations in the autoimmune regulator (AIRE) are responsible for autoimmune polyendocrine syndrome type 1 (APS1), a rare autosomal recessive disease. Diagnosis of APS1 and prediction of disease manifestations are based on a finding of high titer autoantibodies (Aabs) toward intracellular enzymes. The aim of this study was to identify pituitary autoantigens in subjects affected by APS1.

Methods: Screening of a pituitary cDNA expression library with APS1 sera.

Results: A Tudor domain containing protein 6 (TDRD6) cDNA clone was identified. Incubation of in vitro translated TDRD6 fragments with APS1 sera generated positive immunoreactivity in 42 out of 86 patients (49%), but not with sera from patients affected by other autoimmune diseases or from healthy subjects. Sera from 3/6 APS1 patients affected by growth hormone (GH) deficiency showed, by means of immunohistochemistry, a reaction with a small number of guinea pig anterior pituitary cells that was not seen with the sera from healthy controls. Only 40–50% of these cells were GH-positive, while other APS1 Aab-positive cells were probably a novel subpopulation of anterior pituitary cells. Furthermore, 4 of 6 patient's sera stained a fiber plexus in the pituitary intermediate lobe, recognizing monoamine- and GABA-synthesizing enzymes.

Conclusion: This study identified TDRD6 as a major autoantigen recognized by APS1 patients' sera and demonstrates recognition of specific pituitary cell populations or specific nervous tissues by sera from some GH-deficient patients.

The autoimmune polyendocrine syndrome type I (APS1) is a rare autosomal recessive disease with a complex picture drawn by decades of clinical observation and research. Autoantibody screening along with mutational analysis of the disease gene AIRE are important diagnostic tools for this life-threatening syndrome. The initial manifestation appeared within the age range of 0.2–18 years, with an occurrence of mucocutaneous candidiasis in 60% of patients, hypoparathyroidism in 32%, and adrenocortical failure in 5%. 23% of the patients had one to six other manifestations including hepatitis, keratoconjunctivitis, chronic diarrhea and periodic rash with fever [2]. By immunoscreening of a human pituitary cDNA library, the authors of this study have identified TDRD6 (the function of which is still not completely understood) as a major autoantigen in APS1. TDRD6 is known to be mainly expressed in the testis and only at very low levels in other endocrine tissues like the pituitary, adrenal gland, and pancreas. The identification of autoantibodies against guinea pig anterior pituitary cells in sera from half of the GH-deficient APS1 patients may represent an additional marker for autoimmune forms of GH deficiency.

Pegvisomant for the treatment of gsp-mediated growth hormone excess in patients with McCune-Albright syndrome

Akintoye SO, Kelly MH, Brillante B, Cherman N, Turner S, Butman JA, Robey PG, Collins MT
Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, Philadelphia, Pa., USA
akintoye@dental.upenn.edu
J Clin Endocrinol Metab 2006;91:2960–2966

Background: Approximately 20% of the patients affected by McCune-Albright syndrome (MAS) suffer from GH excess. MAS is due to sporadic, post-zygotic, activating mutations of $Gs\alpha$, the cAMP-regulating protein encoded by the *GNAS* gene (gsp oncogene). Approximately one third of the sporadic cases of acromegaly are associated with the same genetic disorder. The aim of this study was to evaluate the effects of pegvisomant, a GH receptor antagonist, on gsp oncogene-related GH hypersecretion and the skeletal disease (fibrous dysplasia of the bone) associated with MAS.

Methods: A randomized, double-blind, placebo-controlled crossover clinical trial was conducted at the National Institutes of Health. Five patients with GH excess-related MAS were treated with Pegvisomant for 12 weeks (20 mg/day s.c. injection). Primary outcome was IGF-1 normalization; secondary outcomes were attainment of lower serum IGF binding protein-3 (IGFBP-3) concentration, reduction of fatigue and sweating, improvement of markers of bone metabolism and bone pain.

Results: Mean reduction of serum IGF-1 was -236.4 ng/ml (53%, $p < 0.005$) at 6 weeks and -329.8 ng/ml (62%, $p < 0.001$) at 12 weeks, while IGFBP-3 levels were lower by 0.8 mg/l (24%, $p < 0.01$) and 2.9 mg/l (37%, $p < 0.005$) respectively. No significant variations were found in signs and symptoms of acromegaly, in markers of bone metabolism, in bone pain, or in pituitary size. Retrospective analysis, performed to evaluate the efficacy of pegvisomant in comparison with other medications (long-acting octreotide $\pm$ dopamine agonist) in the same group, showed no significant differences between the two regimens.

Conclusion: IGF-1 and IGFBP-3 levels benefit from pegvisomant treatment in patients affected by gsp-mediated GH excess without improvement of fibrous dysplasia.

McCune-Albright syndrome and acromegaly: effects of hypothalamopituitary radiotherapy and/or pegvisomant in somatostatin analog-resistant patients

Galland F, Kamenicky P, Affres H, Reznik Y, Pontvert D, Le Bouc Y, Young J, Chanson P
Service d'Endocrinologie et des Maladies de la Reproduction, Hôpital de Bicêtre, Kremlin-Bicêtre, France
J Clin Endocrinol Metab 2006;91:4957–4961

Background: Acromegaly may be associated with McCune-Albright syndrome and often cannot be surgically treated mainly due to technical complications related to dysplasia of the skull base bone. While partial recovery after somatostatin analogs has been reported, a secondary bone sarcomatous transformation makes the use of radiotherapy controversial.

Methods: Retrospective analysis of efficacy and tolerability of various therapeutic options in 6 patients affected by acromegaly secondary to McCune-Albright syndrome was reported. Treatment with fractionated radiotherapy (45–55 Gy) was performed in 5 of the 6 patients (not eligible for surgery and not responsive to somatostatin analogs) who failed to normalize GH/IGF-1 concentrations. Three patients (2 previously irradiated) were also treated with pegvisomant.

Results: A decrease of GH and IGF-1 concentrations (median follow-up 5 years, range 0.5–9) and a parallel improvement of acromegalic symptoms were documented after radiotherapy. Bone sarcomatous transformation occurred in 1 patient at the mandibular site/outside the radiation field. No evidence of normalization of GH/IGF-1 concentrations was observed in the 5 patients receiving radiotherapy alone and/or in combination with somatostatin analogs; a rapid (5–9 months) normalization of IGF-1 levels was observed in the 6 patients treated with pegvisomant (10–20 mg/day).

Conclusion: Radiotherapy may be taken into consideration for the treatment of acromegaly in patients with McCune-Albright syndrome who are not eligible for surgery and not responsive to somatostatin analogs. The risk of bone sarcomatous transformation remains uncertain. This small series of patients affected by severe GH excess confirms the efficacy of pegvisomant in the reduction of IGF-1 levels.

About 20% of adult patients with McCune-Albright syndrome have GH excess and conventional treatments of GH excess include (1) surgery, (2) radiotherapy, which is usually avoided because of potential sarcomatous transformation of bone fibrous dysplasia, and (3) medications such as short- and long-acting analogs of somatostatin, dopamine receptor agonists and more recently the GH receptor antagonist, pegvisomant. Pegvisomant is a pegylated GH analog with eight amino acid substitutions in GH-binding site 1 and the substitution of glycine for alanine at position 120, resulting in both enhanced affinity for the growth hormone receptor and prevention of functional growth hormone-receptor signalling. Pegvisomant blocks the growth hormone-mediated generation of IGF-1 in approximately 90% of patients. During therapy with this agent, growth hormone levels reportedly increase by as much as 76% over baseline levels, an event probably attributable to a loss of negative feedback by lowering IGF-1 levels. Accordingly, IGF-1 measurement is the biomarker for monitoring the success of treatment [3]. Pegvisomant at well-tolerated s.c. doses was considerably more efficacious than octreotide in suppressing the GH axis, resulting in substantial and sustained inhibition of circulating IGF-1, IGF-2, and IGFBP-3 concentrations [4]. The results of these two studies on the short-term treatment of McCune-Albright syndrome and GH excess provide evidence in favor of further testing of the hypothesis that pegvisomant, through blocking the GH receptor-mediated signal transduction pathways, could be effective in treating IGF-1-related diseases. In other words, even in the absence of positive treatment effects on bone in these studies, the reduction of IGF-1 and IGFBP-3 may help avoid direct structural and functional tissue damage, as well as impeding the development of secondary systemic illnesses due to prolonged exposure to elevated endogenous levels of GH/IGF-1. Additional studies in a large cohort with pegvisomant, alone or in combination with somatostatin analogs, may be promising for the treatment of this challenging disorder.

New Mechanisms

Regulation of pituitary cell function by adiponectin

Rodriguez-Pacheco F, Martinez-Fuentes AJ, Tovar S, Pinilla L, Tena-Sempere M, Dieguez C, Castano JP, Malagon MM
Department of Cell Biology, Physiology and Immunology, University of Cordoba, Cordoba, Spain
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Background: Adiponectin is a 30-kDa belonging to the family of adipokines produced by adipose tissue. Adipokines play important roles in the regulation of food intake and energy balance. Adiponectin acts on two specific membrane receptors whose expression has been demonstrated in a wide variety of tissues. Likewise, adiponectin mRNA also shows a widespread distribution. Adipokine is also abundantly expressed in the chicken anterior pituitary. Interestingly, GH has been shown to regulate adiponectin secretion and adiponectin receptor expression in human and mouse adipocytes. This study investigated the effect of adiponectin on pituitary cell function.

Methods: Dispersed isolated cells from rat anterior pituitary were used for in vitro experiments. Pituitary hormones were measured by RIA in culture media. PCR analysis was used to assess the expression of adiponectin and its two receptors, and real-time quantitative PRC was performed to evaluate changes in gene expression in rat pituitary cell cultures exposed to adiponectin.

Results: Adiponectin inhibited GH and LH release as well as both ghrelin-induced GH release and GnRH-stimulated LH secretion in short term (4h) treated cell cultures. Adiponectin increased GHRH-R and GHS-R mRNA content and decreased that of GnRH-R. The pituitary expressed both adiponectin and its receptors.

Conclusions: The findings of this study indicate that adiponectin may play a neuroendocrine role in the control of pituitary function.

Pituitary function is primarily under the regulation of hypothalamic releasing and inhibiting hormones as well as under the regulation of the feedback action of target products. A number of peripheral hormones and metabolic substrates may also influence pituitary function, acting either directly on pituitary cells or via the central nervous system. This study showed that adiponectin, an adipocyte-derived cytokine, modulates pituitary function in vitro. These findings establish another

relationship between peripheral metabolism and pituitary function and suggest that adiponectin may be a link factor in the regulation of metabolism, growth and reproduction.

Cell proliferation and vascularization in mouse models of pituitary hormone deficiency

Ward RD, Stone BM, Raetzman LT, Camper SA

Graduate Program in Cellular and Molecular Biology, University of Michigan, Ann Arbor, Mich., USA

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Background: Mutations in the transcription factors Pit1 and Prop1 are causes of pituitary hormone deficiency and hypopituitarism in mice and humans. The aim of this study was to provide additional information on the vascular system of the pituitary gland in these conditions, associated with pituitary dysfunction and abnormal pituitary morphology.

Methods: Experiments were conducted in Ames and Snell dwarf mice carrying mutations on Pit1 and Prop1 genes. Histological examination of pituitary cells was performed at various stages of fetal and postnatal life. The pituitary vascular system was studied from embryonic day 14.5 and throughout development.

Results: The main recognized feature of Pit1-deficient mice was pituitary hypoplasia after birth, due in the first instance to low cell proliferation rate, although a minor role was shown to be played by apoptosis. No significant alterations in Pit1 pituitary vascularization were found during pituitary development. In contrast, vascularization was significantly reduced in the Prop1-deficient mouse, where apoptosis seems to play a key role. In normal mice, caspase-3 is activated at postnatal day 11 in an apoptosis-independent manner in thyrotropes and somatotropes; this activation does not occur in mutant mice, suggesting that caspase-3 expression needs a normal Prop1 and/or Pit1 function.

Conclusion: These studies provide further insight into the mechanisms for the pituitary growth defect in both the Pit1 and Prop1 mouse models.

The great majority of genetic conditions associated with multiple pituitary hormone deficiency are linked to mutations in the transcription factors expressed at different stages of pituitary development and mainly to mutations in PIT1 (POU1F1) associated with GH, TSH, and prolactin deficiency, as well as in PROP1. Prop1 is one of the transcription factors involved in pituitary development through a progressive reduction of Hesx1 repressor activity. Its expression appears early in embryonic development and is crucial for the differentiation and function of somatotropes, thyrotropes, gonadotropes and lactotropes. While a small anterior pituitary is the most frequently observed pituitary feature in both mice and humans carrying PIT1 mutations, the mouse and human PROP1-deficient pituitary phenotype are different. Indeed, enlarged anterior pituitary with progression from a large and full sella turcica to suprasellar extension of a pituitary mass, followed by areas of cystic change and eventual regression to a large empty sella, has been described in subjects with PROP1 mutations. Several hypotheses have been posited in order to explain the phenomenon of pituitary hyperplasia followed by shrinkage of the pituitary gland including apoplexy. One study provides information about the role of Prop1 in pituitary gland growth, suggesting that pituitary hyperplasia could be due to trapped progenitor cells, while subsequent degeneration could be due to the apoptosis of undifferentiated cells. The same group's research enhances our understanding of the mechanism of PIT1 and PROP1 action by demonstrating that the vascular network of the pituitary gland is affected in Prop1-deficient mice. Inadequate pituitary vascularization in Prop1 may contribute to hypoxia-induced apoptosis whereas an apoptosis-independent caspase-3 activation occurs in normal thyrotropes and somatotropes, suggesting that these transcription factors are necessary for caspase-3 expression.

Pituitary adenoma predisposition caused by germline mutations in the AIP gene

Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, Tuppurainen K, Ebeling TM, Salmela PI, Paschke R, Gundogdu S, De Menis E, Makinen MJ, Launonen V, Karhu A, Aaltonen LA
Department of Clinical Genetics, Oulu University Hospital, Oulu, Finland
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Background: Pituitary adenomas are common benign tumors accounting for approximately 15% of intracranial tumors. Understanding their molecular basis is of great interest. Given the incidence of the disease in Northern Finland, the authors hypothesized the existence of a form of low-penetrance pituitary adenoma predisposition. Low penetrance is defined as hereditary predisposition that relatively rarely leads to disease but which may have more influence on population level compared to high-penetrance disease susceptibility.

Methods: Three clusters of familial pituitary adenoma in Northern Finland were detected. Two clusters appeared to be linked by genealogy while the third appeared separate. A total of 14 patients in the two families were identified. Six had somatotropinoma, 4 had prolactinoma, and 4 had mixed pituitary adenoma. A population-based cohort of patients with somatotropinoma had previously been characterized. To identify the pituitary adenoma predisposition locus, whole-genomic single-nucleotide polymorphism genotyping was performed. Two analyses were performed, one on individuals with somatotropinoma/mixed adenoma (high stringency), and the other on all affected subjects (low stringency).

Results: Linkage analysis using high-stringency criteria provided evidence for linkage in chromosome 11q12–11q13, a region previously implicated in isolated familial somatotropinoma. Expression profiles were obtained in pituitary adenoma predisposed patients and carriers yielding 172 probe sets that mapped in the linked region. The two lowest p values were obtained for the two separate probe sets representing AIP (aryl hydrocarbon receptor interacting protein) gene. Another gene, galectin-12 (LGALS12), was also chosen on the basis of decreased expression. Out of 45 patients from the population-based cohort, a nonsense mutation (Q14X) and a G>A transversion were identified in 16% of patients diagnosed with somatotropinomas and in 40% of a subset of patients who were diagnosed when they were younger than 35 years of age. The possible role of AIP in pituitary adenoma predisposition in other populations was studied in three families with 2 affected individuals. No mutations were found in a German or a Turkish family, whereas a nonsense mutation R304X was detected in an Italian family. Loss of heterozygosity analysis indicated that AIP is likely to act as a tumor suppressor.

Conclusions: These data strongly associate loss of function mutations of AIP to PAP. AIP is an example of a low-penetrance tumor susceptibility gene.

Prevention and early identification of disease are cornerstones of modern medicine. In particular, early diagnosis of tumors is of special importance in order to establish adequate treatment and prevent morbidity. By applying sophisticated genetic analysis, the authors were able to show that mutations in the AIP gene accounted for 16% of all patients with pituitary somatotropinomas and for 40% of the subset who were diagnosed when they were younger than 35 years of age. AIP (aryl hydrocarbon receptor interacting protein) forms a complex with the aryl hydrocarbon receptor, a ligand-activated transcription factor which participates in the cellular signalling pathway. AIP likely acts as a tumor suppressor. Patients with untreated pituitary adenomas typically show slow development of potentially severe symptoms. Patients with pituitary adenomas usually come to our attention due to local compressive effects (visual defects, headache) or for symptoms related to oversecretion of pituitary hormones. Although genetic predisposition to tumors is suggested by epidemiological studies, dissecting the molecular basis of this susceptibility remains a difficult task. This study elegantly presents an example of low-penetrance tumor susceptibility genes, and shows that it is possible to make identification of predisposed individuals. Awareness of pre-existing risk may spare predisposed subjects from late diagnoses and associated morbidity. It is expected that genetic technology will enable us in the future to identify tumor susceptibility in other neoplasms as well.

Sustained Notch signaling in progenitors is required for sequential emergence of distinct cell lineages during organogenesis

Zhu X, Zhang J, Tollkuhn J, Ohsawa R, Bresnick EH, Guillemot F, Kageyama R, Rosenfeld MG
Howard Hughes Medical Institute, Department and School of Medicine, University of California at San Diego,
La Jolla, Calif., USA
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Background: Organogenesis in mammals is the result of the concerted actions of signalling pathways in progenitor cells that induce a hierarchy of transcription factors involved in organ and cell type differentiation. Sustained Notch activity is needed in order to ensure the persistence of the proliferating ability of some progenitor cells, which can give rise to specific late-arising cell types during pituitary organogenesis.

Methods: In situ hybridization was carried out to examine the expression pattern of the known mammalian Notch ligands and receptors, as well as the direct downstream targets of Notch signalling.

Results: Conditional deletion of Rbp-J, which encodes the major mediator of the Notch pathway, leads to premature differentiation of progenitor cells caused by loss of the expression of the basic helix-loop-helix (bHLH) factor Hes1 and conversion of the late (Pit1) lineage into the early (corticotrope) lineage. Notch signal activity is necessary to ensure expression of the tissue-specific paired-like homeodomain transcription factor, Prop1, required for generation of the Pit1 lineage. Terminal differentiation in post-mitotic Pit1⁺ cells requires reduction of Notch signalling, while Math3, the Notch-repressed Pit1 target gene, is essential to differentiation of GH-secreting cells.

Conclusion: Sustained Notch activity in progenitor cells prevents transformation of late-arising cell lineages to early-born cell lineages, ensuring differentiation of various cell types. This mechanism is probably common in mammalian organogenesis.

Recently, there has been the discovery in the adult anterior pituitary of a subset of cells with side population phenotype, enriched for expression of stem/progenitor cell-associated factors like Sca1, and of Notch1 and Hes (hairy and enhancer of split) 1, components of the classical developmental Notch pathway. The present study showed that Notch activity operates in a precise temporal window during pituitary development. The expression patterns reveal that both the ligands and the receptors of the Notch pathway are expressed in early stages of pituitary development, and that subsequent downregulation of expression correlates well with the onset of the pituitary gland maturation. In particular, Notch activation controls the formation of Pit1 precursors while downregulation at a later stage is necessary for terminal differentiation. Whereas in early developmental stages, Notch signalling plays a crucial role in the control of the lineage commitment of Pit1⁺ precursors, in large part by directly regulating the expression of Prop1, its activity is considerably attenuated in Pit1⁺ cells through the expression of other regulator factors. More specifically, one of these factors, Math3, a downstream transcription target of Pit1, is crucial for maturation and expansion of somatotropes through regulation of GHRHR expression. The role of these factors in the cell cycle and in differentiation remains open for further exploration.

Mutations within Sox2/SOX2 are associated with abnormalities in the hypothalamo-pituitary-gonadal axis in mice and humans

Kelberman D, Rizzotti K, Avilion A, Bitner-Glindzicz M, Cianfarani S, Collins J, Chong WK, Kirk JM, Achermann JC, Ross R, Carmignac D, Lovell-Badge R, Robinson IC, Dattani MT
London Centre for Paediatric Endocrinology, Biochemistry, Endocrinology, Institute of Child Health, University College London, London, UK
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Background: SOX2 is a member of the sex-determining region of the Y chromosome-related high mobility group box family of transcription factors. It is expressed in the developing central nervous system and placodes, where it plays critical roles in embryogenesis. Heterozygous Sox2 mice show a reduction in size and male infertility. Heterozygous mutations in SOX2 in humans have been found associated with bilateral anophthalmia/microphthalmia, developmental delay, short stature, and male genital tract abnormalities. This study investigated both the role of Sox2 in murine pituitary development and function and the presence of mutations in humans.

Methods: The pituitaries of embryo and adult mice bearing the Sox2^{Bgeo} mutation were studied by in situ hybridization. Mutation analysis of SOX2 was performed by PCR and direct sequencing. Wild-type and mutant proteins were generated and subcloned into an expression vector for transient transfection and cell localization experiments on CHO cell cultures. Wild-type and mutant SOX proteins were generated using the TNT quick-coupled transcription/translation system (Promega). Following transfection, cells were harvested and assayed for luciferase activity. 235 patients with congenital hypothalamopituitary disorders (142 males and 92 females) were screened for mutations within SOX2. 197 patients had congenital hypopituitarism without any other abnormality, 126 had septo-optic dysplasia, and 12 patients had anophthalmia or microphthalmia.

Results: Mice heterozygous for a targeted disruption of Sox2 did not manifest eye defects, but showed abnormal anterior pituitary development with reduced levels of growth hormone, luteinizing hormone and thyroid-stimulating hormone. Eight patients were identified with heterozygous sequence variations in SOX2. Six were de novo mutations that exhibited partial or complete loss of function. In addition to bilateral eye defects, these mutations were associated with anterior pituitary hypoplasia and hypogonadotropic hypogonadism, variable defects affecting the corpus callosum and mesial temporal structures, hypothalamic amartoma, sensorineural hearing loss, and esophageal atresia.

Conclusions: SOX2 plays a critical role in the normal development and function of the hypothalamic-pituitary and reproductive axes in both mice and humans.

Pituitary development, differentiation and function is under the regulation of a complex network of transcription factors and, ultimately, affects the secretion and function of hypothalamic releasing and inhibiting hormones. A number of transcription factors are expressed at different times in embryogenesis and affect the development of multiple cell lineages. Thus, mutations in these transcription factors not only can cause variable degrees of hypopituitarism, but endocrine dysfunction can be associated with extraendocrine abnormalities. The transcription factor SOX2, expressed from the earliest stages of development, plays an important role in the normal development of the brain and the pituitary, as well as to that of the eyes and inner ear. All patients with SOX2 mutations had marked gonadotropin deficiency and 2 had evidence of GH deficiency. TSH, ACTH, and prolactin secretion were normal. It is conceivable that dysregulation of hypothalamic secretion associated with SOX2 mutations could lead to hypoplasia of the anterior pituitary. A direct effect of Sox2 deficiency in germ cells, where the gene is known to be expressed, could also contribute to hypogonadism. It is also possible that SOX2 participates directly in the regulation of genes such as Hesx1, Prop1, and Aes, all of which show a similar phenotype when mutated. This study shows that mutations in the transcription factor SOX2 cause pituitary hypoplasia associated with a number of extraendocrine abnormalities. Careful clinical characterization of patients with congenital hypopituitarism is thus a crucial step for screening for mutations of candidate genes. Indeed, as in *HESX1* and *LHX4* mutations, both of which are associated with a variable MRI scan including ectopic posterior pituitary (EPP), patients with SOX2 mutations display normal anterior pituitary gland or structural hypothalamic-pituitary abnormalities such as anterior pituitary hypoplasia, EPP and absent infundibulum at MRI examination.

FOXL2 in the pituitary: molecular, genetic, and developmental analysis

Ellsworth BS, Egashira N, Haller JL, Butts DL, Cocquet J, Clay CM, Osamura RY, Camper SA

University of Michigan Medical School, Ann Arbor, Mich., USA

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Background: FOXL2 is a forkhead transcription factor expressed in the eye, ovary, and pituitary gland. Loss-of-function mutations of FOXL2 cause blepharophimosis, ptosis, and epicanthus inversus syndrome, a dominant disorder characterized by eyelid malformations. Since FOXL2 is implicated in the regulation of follicular growth and development, mutations can cause premature ovarian failure in some women, revealed as either primary or secondary amenorrhea. FOXL2 is expressed in the developing pituitary gland at embryonic days 10.5 and 12.5. Patients who are heterozygous for mutations in the FOXL2 gene do not have an obvious pituitary phenotype, whereas FOXL2 knockout mice are smaller than wild-type animals and have reduced IGF-1 levels, suggesting GH insufficiency. Thus, FOXL2 may play a role in pituitary development which is, however, not evidenced in heterozygotes if the pituitary is less sensitive than other affected tissues to reduction in FOXL2 levels. This study reports a comprehensive analysis of the developmental regulation and cell-specific expression of FOXL2 in the pituitary.

Methods: Mouse embryos were obtained from mating wild-type animals or from an intercross of heterozygous mice with mutations in *Prop1*, *PITX2*, *Lhx3*, or *Lhx4*. Immunohistochemistry and in situ hybridization were used to visualize FOXL2 in the pituitary at various embryonic ages. Ovarian tissue was also obtained. Culture cells were transfected to generate a FOXL2-VP16 fusion protein.

Results: FOXL2 protein is present in quiescent cells of the anterior pituitary from embryonic day 11.5 through adulthood, and is co-localized with non-proliferating differentiating cells. FOXL2 regulates α GSU gene (*Cga*) expression in a dose-dependent manner in culture cells. Transgenic mice that overexpress FOXL2 exhibit primarily appropriate expression in the anterior lobe with some ectopic expression in nearby tissue. α GSU is expressed in all areas that express the FOXL2 transgene including ectopic regions. Normal FOXL2 expression requires the transcription factor *Lhx3* and *Lhx4* but not of *Prop1*. Thus, FOXL2 is downstream of *Lhx3* and *Lhx4* in the genetic hierarchy of the control of pituitary development.

Conclusions: This study shows that FOXL2 is involved in the control of pituitary development and suggests a role for it in the regulation of α GSU gene expression.

In recent years, studies of animal models and humans affected by multiple pituitary hormone deficiencies have contributed to elucidating a complex cascade of transcription factors which participate in the control of pituitary development and function. So far, a number of genes have been characterized whose loss of function causes multiple pituitary hormone deficiencies, either associated or not with extraendocrine abnormalities. Among these are the LIM family genes, *HESX1*, *Prop1* and *Pit1*, and the precise developmental expression of these genes has been elucidated. FOXL2 belongs to a class of transcription factors called forkhead factors that are important in a number of developmental processes. Deficiencies in individual forkhead genes have revealed their roles in speech and language disorders, diabetes, immunodeficiency, cleft palate, and eye development. Loss of function mutations of FOXL2 cause blepharophimosis, ptosis, and epicanthus inversus syndrome, a dominant disorder characterized by eyelid malformations. Since FOXL2 is implicated in the regulation of follicular growth and development, mutations can cause premature ovarian failure in some women, revealed as either primary or secondary amenorrhea. This important study shows that FOXL2 is expressed in the pituitary preceding that of most thyrotrope and gonadotrope markers and regulates α GSU gene expression. Most patients with congenital MPHD do not have a recognizable cause of their defect. Elucidating the complex hierarchy of transcription factors which participate in the control of pituitary development as well as their reciprocal interaction will help us to unravel the genetic basis of many undiagnosed cases.

Review

Craniopharyngiomas

Karavitaki N, Cudlip S, Adams CB, Wass JA

Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Headington, Oxford, UK

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Craniopharyngiomas are rare epithelial tumors arising along the path of the craniopharyngeal duct. Two major histological subtypes have been described (adamantinomatous and papillary) with unknown pathogenesis. Despite their benign histological appearance, their frequent tendency to infiltrate into critical parasellar structures and their aggressive behavior may result in significant morbidity and mortality. Their optimal management is controversial and remains a subject of debate. The lack of prospective randomized studies (unlikely to be carried out) makes the therapy of craniopharyngiomas controversial. The goals for the primary or recurrent disease treatment should focus not only on long-term tumor control and survival, but also on the reduction of the disease and treatment-related morbidity and the preservation of quality of life.

A very useful review on a difficult topic. Craniopharyngiomas are the most common tumor affecting the hypothalamic-pituitary region and account for approximately 10% of all childhood intracranial

tumors. Differential diagnosis between craniopharyngioma, Rathke's cleft cyst and other masses can often prove difficult. The information from this review provides a comprehensive and updated contribution to a better understanding and management of this locally devastating tumor. It highlights: (1) epidemiology, (2) pathogenesis, (3) clinical manifestations, (4) imaging features, (5) treatment options, (6) risk factors for recurrence, and (7) long-term outcome.

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