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Genetics, Gene Expression and Bioinformatics of the Pituitary Gland

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Abstract

Genetic cases of congenital pituitary hormone deficiency are common and many are caused by transcription factor defects. Mouse models with orthologous mutations are invaluable for uncovering the molecular mechanisms that lead to problems in organ development and typical patient characteristics. We are using mutant mice defective in the transcription factors *PROP1* and *POU1F1* for gene expression profiling to identify target genes for these critical transcription factors and candidates for cases of pituitary hormone deficiency of unknown etiology. These studies reveal critical roles for Wnt signalling pathways including the TCF/LEF transcription factors and interacting proteins of the groucho family, bone morphogenetic proteins antagonists, and targets of notch signalling. Current studies are investigating roles of novel homeobox genes and pathways that regulate the transition from proliferation to differentiation, cell adhesion and cell migration.

Pituitary adenomas are a common human health problem, yet most cases are sporadic, necessitating alternative approaches to traditional Mendelian genetic studies. Mouse models of adenoma formation offer the opportunity for gene expression profiling during progressive stages of hyperplasia, adenoma and tumorigenesis. This approach holds promise for identification of relevant pathways and candidate genes as risk factors for adenoma formation, understanding mechanisms of progression, and identifying drug targets and clinically relevant biomarkers.

Keywords

cell proliferation; apoptosis; transcription factors; *Prop1*; *Emx2*

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Introduction

The study of single gene defects that lead to congenital pituitary hormone deficiency in mouse and man has uncovered a cadre of transcription factors that are involved in development of the pituitary gland and transcription of hormone genes (Table 1) [1, 2]. Several of the genes identified in this manner belong to multigene families and some exhibit overlapping functions with related genes within the family, such as *Pitx1* and *Pitx2*, *Lhx3* and *Lhx4*, and *Sox2* and *Sox3* [3–9]. This supports the hypothesis that additional related genes could contribute to a genetic predisposition for pituitary hormone deficiencies. *PROP1* is an intriguing member of this group of critical pituitary transcription factors. It is a member of the paired class of homeobox transcription factors, but phylogenetic analysis places it in an orphan class [9]. Thus, there are no immediately obvious genes that are predicted to exhibit overlapping functions.

Prop1 is a pivotal regulatory gene within the hierarchy of pituitary transcription factors. It is the first known pituitary-specific gene in the pathway, and it is required for repression of the paired homeobox gene *Hesx1* and for activation of *Pou1f1* (a founding member of the POU homeodomain family, formerly known as *Pit1* or *Ghf-1*) [10] (Fig. 1). *Hesx1* is expressed in embryonic stem cells and in Rathke's pouch until approximately e12.5 [11, 12]. *Prop1* expression is detectable in the developing pituitary gland, with onset around e10.5 in mice, peaking at e12.5 and waning to barely detectable levels by e14.5, while *Pou1f1* transcription is detectable at e14.5 and persists through adulthood [7, 13]. The distinctive lag time between peak *Prop1* expression and detection of *Pou1f1* transcripts suggests that there are additional steps in the hierarchy of transcriptional control. Such gene(s) are candidates to investigate causes of panhypopituitarism in patients with features typical of *PROP1* and *POU1F1* mutations, but for which the molecular lesions remain elusive.

Lesions in *Prop1* and *Pou1f1* produce essentially indistinguishable phenotypes in adult mice, namely anterior pituitary hypoplasia, undetectable circulating levels of thyroid-stimulating hormone (TSH), growth hormone (GH) and prolactin (PRL) owing to the failure to produce the cells specialized in synthesis and secretion of these hormones, and dramatically reduced gonadotropin production, which can be corrected by thyroid hormone and GH replacement therapy [14–17]. We selected these genes for the focus of our studies because they are more commonly mutated in patients with panhypopituitarism than any of the other genes discovered to date, and they are the first known genes in the genetic hierarchy that are pituitary specific in their expression [7, 13, 18–20].

Despite the similar phenotypes in adult mutant mice, there are striking differences in the appearance of the pituitary glands of newborn mutants (Fig. 2). At birth the *Prop1* mutants have a highly dysmorphic organ that likely arises from failure of progenitor cells to undergo the transition from proliferation to differentiation. These cells maintain the appearance of flattened, tightly adhered cells instead of adopting a more rounded shape and loosely packed appearance typical of glandular cells, suggesting failure of the epithelial to mesenchymal transition. The changes in migration, cellular conformation and function in the presence of *Prop1* suggests pituitary cells may be regulated by analogous, though opposite, transformations typical of the planar cell polarity pathway [21]. In the absence of *Prop1*, progenitor cells fail to migrate and colonize the anterior lobe, which results in fewer proliferation competent cells in the anterior lobe by birth than is characteristic of normal mice [22, 23]. In addition, the *Prop1* mutant pituitary gland shows signs of poor vascularization and enhanced cell death. In contrast, the *Pou1f1* mutant pituitary glands are indistinguishable from normal glands at birth and exhibit evidence of anterior lobe hypoplasia during the first weeks of life. These striking phenotypic differences in the pituitary glands of *Prop1* and *Pou1f1* mutants suggest that these genes have fundamentally

different roles in organ development. Furthermore, these observations suggest that identification of *Prop1* target genes could reveal promising candidate genes for understanding additional cases of hypopituitarism that remain unexplained.

We have taken several approaches to identifying potential *Prop1* target genes and genes expressed at the critical time of e12.5–e14.5 in mouse pituitary development. Our first forays utilized differential display and subtractive hybridization techniques [24, 25]. Limitations of these approaches are their relatively inefficient nature and the fact that they generate short clones, which are not useful for validation of expression by *in situ* hybridization or for functional studies. Nevertheless, they were fruitful in uncovering some critical signalling pathways. We noticed an enrichment of clones in the canonical and non-canonical Wnt signalling pathways and pursued validation and functional studies with individual knockout mice to determine functional roles for these genes. This work revealed the important roles of *Tcf7l2* (*Tcf4*), *Wnt5a*, and amino-terminal enhancer of split (*Aes*) [26–29]. Although none of these genes are *Prop1* targets, at least one candidate for growth insufficiency in humans arose from these studies, namely *AES*, also known as *groucho-related gene 5* (*GRG5*), which produces a protein that can bind to engrailed repressor domains and act as a co-repressor or de-repressor in a context-dependent manner [30, 31]. The role of the *Tcf7l2* in suppression of pituitary growth suggests that the role of the human orthologue in pituitary adenomas should be explored.

We undertook the generation of full-length cDNAs from developing pituitary gland and deep sequencing to provide a more complete picture of the pituitary transcriptome and to provide cDNA clones suitable for validation and functional studies [32]. In addition, we carried out subtractive hybridization using these full-length clones and methods that were technically advanced compared to our initial efforts (Brinkmeier et al., in press). Preliminary analysis has revealed that this approach was successful in uncovering potential *Prop1* targets and candidate genes for pituitary hypoplasia. We report here the evaluation of the functional role of the *empty spiracles homolog 2* gene (*Emx2*) in pituitary gland development and provide the results of a bioinformatic analysis that suggest candidate genes for involvement in the biological processes of cell proliferation, cell adhesion, cell migration and apoptosis.

Materials and Methods

We prepared RNA and cDNA from pituitary glands dissected from wild-type mice at e12.5 and e14.5 and from *Prop1* mutants at e14.5 using techniques designed to maximize full-length cDNA clones [32]. In addition two sets of subtractive hybridizations were carried out in order to enrich for potential *Prop1* target genes. Details of this research will be published elsewhere (Brinkmeier et al., in press). One subtracted library was optimized for genes transcriptionally activated between e12.5 and e14.5 (e14.5 wild type minus e12.5 wild type) and the other enriched for genes dependent upon *Prop1* for expression at e14.5 (wild type e14.5 minus *Prop1* mutant littermates at e14.5). Single-pass DNA sequencing was carried out from either the 5' or the 3' end on over 50,000 clones representing all five libraries approximately equally. We organized the sequences into a database searchable by gene name, RefSeq and Unigene ID, gene ontology terms (GO), and DNA sequence. Preliminary studies suggest that these gene identifications based on single-pass sequence analysis yield a 1–3% false identification rate. (Footnote: To obtain database access contact Drs. Camper or Lyons at scamper@umich.edu or boblyons@umich.edu.)

Emx2 null mutants were kindly provided by A. Mansouri and P Gruss from the Max-Planck-Institute, Germany, on a part 129/Sv, part C57BL/6J genetic background [33]. They were generated by replacing the second and part of the third helix of the homeobox. For genotyping, a single forward primer, 5' CAC AAG TCC CGA GAG TTT CCT TTT GCA

CAA CG 3' was used for both alleles, and the reverse primers 5' ACC TGA GTT TCC GTA AGA CTG AGA CTG TGA GC 3' was used for the wild type and 5' ACT TCC TGA CTA GGG GAG GAG TAG AAG GTG G 3' was used for the mutant sequence [34] Mice for this paper were maintained at the Wellcome Trust Sanger Institute, Hinxton, UK in compliance with UK Home Office requirements. Wild type, heterozygous, and homozygous null animals were collected from three separate litters at e16.5, fixed and sectioned for immunohistochemical analysis. Four embryos were examined for each genotype, and 10–12 sections were examined for each embryo. Immunohistochemistry with antibodies specific for various pituitary hormones and transcription factors was carried out as described previously [35].

Results and Discussion

cDNA Libraries from Developing Pituitary Provide Transcriptome Information

We have created a searchable database of cDNA libraries representing a partial transcriptome of the developing pituitary that includes cDNA from e12.5 and e14.5 wild-type pituitaries and e14.5 pituitaries deficient for *Prop1* [32]. This database has proven extremely valuable in aiding gene discovery efforts as we detail below.

Transcription Factors are Highly Represented in the Pituitary Transcriptome

Transcription factors comprised the largest class of genes we identified. Over 700 transcription factor genes were detected. Intriguingly, more than 40 of these transcription factors contained homeodomains. At least 12 of these homeobox genes have previously known roles in pituitary development, approximately 6 are known to be expressed in the pituitary gland but their functional roles in intact animals have not been studied directly, and over 20 were completely unexpected. Many of the novel homeobox genes detected in this analysis have only been studied in invertebrates. We present some examples of genes in each of these groups.

Zinc Finger Homeobox Genes

We found expression of two genes in developing pituitary glands, *Zfmx3* and *Zeb2*, which contain numerous zinc fingers in addition to homeodomain(s) (unpublished). *Zfmx3* was originally named *Atbf1* because it was identified as a factor binding to the alpha-fetoprotein enhancer, and it was recently discovered to bind the *Pou1f1* early enhancer [36, 37]. Analysis of a hypomorphic gene trap allele demonstrated that this unusual protein, which contains 4 homeodomains and 23 zinc fingers, is necessary for robust expression of *Pou1f1*, *Gh*, and *Tshb* genes [37]. *Zeb2*, formerly named *Zfmx1b*, is predicted to encode a multifunctional protein with a single homeodomain and eight zinc fingers that interacts with Smads and nucleosome remodelling complexes, acts upstream of Wnt signalling, and effects expression of *Sox2* and E-cadherin [38, 39]. *ZEB2* was also detected in a screen for genes expressed in human pituitary adenomas [40]. Individuals with mutations in *ZEB2* have Mowat–Wilson Syndrome, a dominant disorder characterized by a distinctive facial phenotype in association with mental retardation, microcephaly and short stature [41]. Neural crest-specific disruption in mice causes neurocristopathies that mimic Mowat–Wilson syndrome, but the etiology of the short stature and the role of *Zeb2* in pituitary development have not been defined [42]. Future studies may uncover a role for *ZEB2* in pituitary function and growth regulation.

LIM Homeobox Genes

Several LIM homeodomain genes play important roles in pituitary development, including *Lhx3*, *Lhx4*, and *Isl1* [43–45]. We found a related gene, *Lhx2*, represented by cDNAs in

multiple developing pituitary cDNA libraries (unpublished). This gene was cloned based on its ability to bind an essential promoter element in the *Cga* gene, which encodes the alpha subunit of the glycoprotein hormones TSH, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [46]. The role of this gene in pituitary development has not been explored, although mice homozygous for a disruption of *Lhx2* revealed important requirements for *Lhx2* in multiple organs [47]. It will be intriguing to determine whether its role in the pituitary gland involves cell identity or maintenance of growth and undifferentiated character of progenitors, as has been shown in other organs, and whether there is any link to pituitary adenoma risk, given the role in myeloproliferative disorders [48–50].

ADNP, a POU-Like Homeodomain Protein

Some of the homeobox genes we found in one or more of the five libraries were completely unexpected. An example is the activity-dependent neuroprotective protein gene (*Adnp*), which encodes a POU-like homeodomain protein. *Adnp*-deficient animals die by e8.5–9.5, making it unlikely that *ADNP* loss of function accounts for panhypopituitarism, but it is intriguing that some individuals with Okhiro syndrome are haploinsufficient for *ADNP* [51, 52]. Recent studies have shown that *ADNP* is bound to several members of the SWI/SNF chromatin-remodelling complex and it is necessary for upregulation of *Neurod1*, a gene important for corticotrope development [51, 53, 54]. Thus, future studies may uncover a basic role for *ADNP* in pituitary cell differentiation or maintenance [55].

EMX2, a Potential Tumour Suppressor and Regulator of Progenitor Migration and Differentiation

The presence of *Emx2* cDNAs amongst the pituitary libraries is unexpected and intriguing. *Emx2* encodes a homeodomain protein that is required for viability of mouse embryos and development of multiple organs including the central nervous and urogenital systems [56], yet its expression in the pituitary gland has not been previously described. In humans, *EMX2* is required for normal cortical development and brain function, and it has been implicated as a tumour suppressor due to the presence of *EMX2* loss-of-function mutations in endometrial cancers [57]. In the brain, *EMX2* regulates the transition from early neural progenitors to more mature cells that migrate out of the proliferative zone and differentiate into a variety of neural cell types [58]. This feature is interesting in light of the requirement for pituitary progenitors to migrate away from the lumen of Rathke's pouch and seed the anterior lobe with precursors for several different cell lineages [22, 23]. Another captivating potential parallel is the importance of several signalling pathways in pituitary development, including sonic hedgehog (SHH), beta-catenin, bone morphogenetic protein (BMP) and fibroblast growth factor (FGF), and the involvement of the same signalling pathways in regulation of *Emx2* expression ([27, 59–63]. Taken together these findings suggest the possibility that *Emx2* functions in pituitary ontogeny.

To explore the role of *Emx2* in pituitary development, we compared pituitary morphology and expression of pituitary hormones and lineage-specific transcription factors in normal and *Emx2* mutant mice (Fig. 3). We found no difference in the intensity or pattern of immunohistochemical staining for pro-opiomelanocortin (POMC) in the intermediate or anterior lobes of the pituitary gland, suggesting that differentiation of melanotrope and corticotrope has proceeded normally in the absence of *Emx2*. Somatotrope and thyrotrope appear unaffected also, as immunostaining revealed no differences in expression of *Pou1f1* or its dependent targets, GH and TSH beta in normal and mutant mice. Finally, steroidogenic factor 1 (SF1 or NR5A1) is expressed equivalently in mutant and normal pituitary glands, suggesting that commitment to the gonadotrope lineage has occurred normally. While these results suggest that there is no essential role for *Emx2* in pituitary

ontogeny, its role in postnatal pituitary function or in pituitary adenoma risk still remains to be explored.

Signalling Pathways

Many signalling pathways have been implicated in early pituitary gland ontogeny. Most reviews of early pituitary development posit the hypothesis that opposing dorsal FGF signalling and ventral BMP signalling gradients establish domains of transcription factor expression that produce cell-specific differentiation of unique cell types. However, BMP4 is known to be required for induction of Rathke's pouch [45], and it is produced in the ventral diencephalon, which is located dorsal to the developing pituitary primordium [60, 61]. FGFs are also produced in the ventral diencephalon and are required in a dosage-sensitive manner for stimulation of Rathke's pouch development [60, 61]. In the absence of these FGFs or their receptors, Rathke's pouch undergoes massive cell death resulting in extremely hypoplastic pituitaries [45, 64, 65]. We recently showed that the BMP antagonist, NOGGIN, plays an essential role in attenuating BMP activity in the ventral diencephalon during pouch induction, and that it is necessary to maintain a balance between BMP, Wnt, FGF, and SHH signalling pathways [59]. *Noggin* is also expressed in the adult pituitary where it may regulate the balance of BMP signalling that is known to promote prolactinoma formation, but that is also protective against corticotropinoma formation [59, 66, 67].

We found over 100 genes involved in signalling pathways or in the interaction of signalling pathways in the developing pituitary libraries (Brinkmeier, et al., in press). We find several BMP antagonists in addition to *Noggin* that are expressed in the developing pituitary gland [59]. These antagonists could be important in attenuating BMP activity in a temporally and spatially critical manner, as well as contributing to establishing or maintaining the appropriate balance between signalling pathways. We also detect expression of several members of the Notch pathway (unpublished). This pathway appears to be regulated directly by *Prop1* because *Notch2* is not expressed in *Prop1* mutants [68]. Moreover, some putative downstream targets of this pathway are important for normal pituitary development [69, 70]. Additional studies are necessary to explore the roles of these newly identified signalling genes.

Genes Involved in Proliferation, Apoptosis, Cell Migration and Cell Adhesion

Prop1 is required for migration of precursors away from the lumen of Rathke's pouch, for the production of proliferating cells in the developing anterior lobe, and for invasion of the vasculature [22, 23]. The movement of precursor cells occurs concomitant with changes in cell adhesion and cell shape. The failure of these *Prop1* dependent processes is associated with enhanced cell death. We expected to find cDNAs in the developing pituitary libraries with GO terms relevant to the affected processes in *Prop1*-mutant mice. In fact we found approximately 80 genes with the GO terms proliferation and regulation proliferation, including some known oncogenes and tumour suppressors (unpublished). There were approximately 100 genes with apoptosis as a GO term, 37 with 'cell migration', and 96 with 'cell adhesion'. These are catalogued in Table 2a and b. These cDNAs require DNA sequence verification and confirmation of expression by reverse transcription polymerase chain reaction, *in situ* hybridization, or immunohistochemistry as a basis for future functional studies.

Pituitary Adenomas

Pituitary adenomas are common, comprising 15% of intracranial tumours [71–73]. They tend to be slow growing, benign neoplasms. About one-third of pituitary adenomas are silent, coming to the patient or physician's attention because of compressive effects such as

headaches and visual problems. The remaining two thirds of these adenomas secrete hormones.

A few Mendelian disorders predispose to pituitary adenoma formation: multiple endocrine neoplasia (MEN), Carney complex, and McCune–Albright syndrome [73]. *MENIN* is mutated in MEN1 [74]. It encodes a tumour suppressor; loss of heterozygosity causes parathyroid, endocrine pancreas, and anterior pituitary neoplasias. Carney complex is a genetically heterogeneous, chromosome instability syndrome. Lesions in *protein kinase, cAMP-dependent regulatory, type I, alpha (PRKARIA)* cause adrenal and anterior pituitary neoplasms that are multifocal, commonly involving GH hypersecretion. McCune–Albright syndrome causes precocious puberty and pituitary hyperplasia due to activating mutations in *GNAS1* leading to excess cAMP production. Each of these Mendelian disorders has provided insight into the pathways that regulate pituitary growth. Intriguingly, all three of these genes are represented in the developmental database, implying an early role in pituitary development.

Most pituitary adenomas are sporadic and monoclonal. They often originate as hyperplasia that progresses to adenoma and have evidence of chromosome instability and aneuploidy [71–73]. Mutations that cause these sporadic adenomas are largely unknown. Although approximately 40% of acromegaly cases are caused by *GNAS* mutations that lead to excess GH production, the aetiology of most cases remains elusive. Mutations in the gene for aryl hydrocarbon receptor interacting protein (*AIP*) have been reported to cause GH-producing adenomas in Finnish populations, and many laboratories are working to replicate this result in other ethnic groups and discover the mechanism whereby lesions in this gene could enhance the risk for acromegaly [75]. In addition, the *aryl hydrocarbon receptor gene (Ahr)* and *Aip* are present in our developmental database. *Pituitary tumour transforming gene (PTTG)* expression correlates with tumour size and invasiveness [76, 77]. It was discovered by differential gene expression and led to understanding the role of securin proteins in mitosis, which is relevant to many types of cancers [78, 79]. This suggests that expanded application of the differential expression approach could provide further insight into pituitary adenoma risk factors, biomarkers and treatments. As with *Ahr* and *Aip*, *Pttg* is represented in the developmental database, lending support to the idea that early developmental roles are recapitulated during tumorigenesis.

Gene expression studies have been carried out using human pituitary adenoma tissue, mouse pituitary tumour tissue, and immortalized murine cell lines thought to represent different stages of differentiation [40, 80–83]. An advantage of animal models is that the pituitary tissue is readily accessible at various stages during the progression from hyperplasia to adenoma formation, and following treatment with hormones or drugs that suppress adenoma growth.

We developed two animal models that could be useful in identifying candidate genes involved in progression to adenoma and growth suppression. Constitutive expression of *Prop1* in transgenic mice produced a model with a low penetrance of adenomas. In this model *Prop1* expression was driven by the *Cga* promoter and enhancer sequences, plus an intronic element of the *Prop1* gene that confers expression in the pituitary progenitor cells that line the lumen of Rathke's pouch [84, 85]. One transgenic line exhibits delayed gonadotropin production and delayed puberty, but eventually achieves sexual maturation and fertility [86]. The genetic background and transgene integration site both appear to influence the penetrance of adenoma development in this model. On a mixed background one line developed large nodules that did not express *Prop1*, but fewer adenomas were observed after repeated backcrossing to C57BL6/J mice (unpublished). Recent studies show that female mice with the constitutive *Prop1* transgene can develop GH, PRL, TSH, and/or

gonadotropin-producing adenomas [87]. In contrast the *Cga* (α -*Gsu*) knockout mouse develops thyrotrope adenomas that are multifocal, very highly penetrant, and responsive to thyroid hormone mediated growth suppression [88–90]. We are in the process of using this model to uncover genes that are differentially expressed between normal and mutant mice at a variety of ages (unpublished). We expect that this approach could shed light on growth dysregulation in thyrotrope adenomas, which are rare, but very tenacious, recurrent and difficult to treat.

Conclusion and future directions

The deep sequencing approach we are taking is fruitful for identification of individual genes and pathways that regulate pituitary development. We have proven that several genes discovered with this approach play important roles in pituitary development and function, and at least some of these are candidates for screening patients with panhypopituitarism. This approach can now be done in a less laborious manner using the new technologies that facilitate massively parallel DNA sequencing and bioinformatic analysis of the data using the complete genome sequence and dense annotation of genes. Pyrosequencing using the 454 genome analyzer by Roche can produce 400,000 sequences of up to 250 nucleotides each in a single run [91], and the Illumina (formerly Solexa) Genome Analyzer generates 100 million sequences, each approximately 25–35 base pairs, in a single run [92]. These and other new DNA sequencing technologies promise to provide information with ease and more depth than the traditional approach we report here. These new technologies should also enhance the identification of additional pituitary adenoma risk factors, biomarkers and drug targets.

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References

1. Kelberman D, Dattani MT. Hypothalamic and pituitary development: Novel insights into the aetiology. *Eur J Endocrinol.* 2007; 157 (Suppl 1):S3–14. [PubMed: 17785694]
2. Cushman LJ, Showalter AD, Rhodes SJ. Genetic defects in the development and function of the anterior pituitary gland. *Ann Med.* 2002; 34:179–191. [PubMed: 12173688]
3. Collignon J, Sockanathan S, Hacker A, Cohen-Tannoudji M, Norris D, Rastan S, Stevanovic M, Goodfellow PN, Lovell-Badge R. A comparison of the properties of *sox-3* with *sry* and two related genes, *sox-1* and *sox-2*. *Development.* 1996; 122:509–520. [PubMed: 8625802]
4. Kelberman D, Rizzoti 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. Mutations within *sox2/sox2* are associated with abnormalities in the hypothalamo-pituitary-gonadal axis in mice and humans. *J Clin Invest.* 2006; 116:2442–2455. [PubMed: 16932809]
5. Meijlink F, Beverdam A, Brouwer A, Oosterveen TC, Berge DT. Vertebrate *aristaless*-related genes. *Int J Dev Biol.* 1999; 43:651–663. [PubMed: 10668975]
6. Rizzoti K, Brunelli S, Carmignac D, Thomas PQ, Robinson IC, Lovell-Badge R. *Sox3* is required during the formation of the hypothalamo-pituitary axis. *Nat Genet.* 2004; 36:247–255. [PubMed: 14981518]
7. Sornson MW, Wu W, Dasen JS, Flynn SE, Norman DJ, O'Connell SM, Gukovsky I, Carrière C, Ryan AK, Miller AP, Zuo L, Gleiberman AS, Andersen B, Beamer WG, Rosenfeld MG. Pituitary lineage determination by the *prophet* of *pit-1* homeodomain factor defective in ames dwarfism. *Nature.* 1996; 384:327–333. [PubMed: 8934515]

8. Suh H, Gage PJ, Drouin J, Camper SA. Pitx2 is required at multiple stages of pituitary organogenesis: Pituitary primordium formation and cell specification. *Development*. 2002; 129:329–337. [PubMed: 11807026]
9. Galliot B, de Vargas C, Miller D. Evolution of homeobox genes: Q50 paired-like genes founded the paired class. *Dev Genes Evol*. 1999; 209:186–197. [PubMed: 10079362]
10. Gage PJ, Brinkmeier ML, Scarlett LM, Knapp LT, Camper SA, Mahon KA. The ames dwarf gene, *df*, is required early in pituitary ontogeny for the extinction of *rpx* transcription and initiation of lineage specific cell proliferation. *Mol Endocrinol*. 1996; 10:1570–1581. [PubMed: 8961267]
11. Hermesz E, Mackem S, Mahon KA. *Rpx*: A novel anterior-restricted homeobox gene progressively activated in the prechordal plate, anterior neural plate, and rathke's pouch of the mouse embryo. *Development*. 1996; 122:41–52. [PubMed: 8565852]
12. Thomas PQ, Johnson BV, Rathjen J, Rathjen PD. Sequence, genomic organization, and expression of the novel homeobox gene *hesx1*. *J Biol Chem*. 1995; 270:3869–3875. [PubMed: 7876132]
13. Li S, Crenshaw EB 3rd, Rawson EJ, Simmons DM, Swanson LW, Rosenfeld MG. Dwarf locus mutants lacking three pituitary cell types result from mutations in the pou-domain gene pit-1. *Nature*. 1990; 347:528–533. [PubMed: 1977085]
14. Nasonkin IO, Ward RD, Raetzman LT, Seasholtz AF, Saunders TL, Gillespie PJ, Camper SA. Pituitary hypoplasia and respiratory distress syndrome in prop1 knockout mice. *Hum Mol Genet*. 2004; 13:2727–2735. [PubMed: 15459176]
15. Tang K, Bartke A, Gardiner CS, Wagner TE, Yun JS. Gonadotropin secretion, synthesis, and gene expression in human growth hormone transgenic mice and in ames dwarf mice. *Endocrinology*. 1993; 132:2518–2524. [PubMed: 8504754]
16. O'Hara BF, Bendotti C, Reeves RH, Oster-Granite MI, Coyle JT, Gearhart JD. Genetic mapping and analysis of somatostatin expression in snell dwarf mice. *Mol Brain Res*. 1988; 4:283–292.
17. Buckwalter MS, Katz RW, Camper SA. Localization of the panhypopituitary dwarf mutation (*df*) on mouse chromosome 11 in an intersubspecific backcross. *Genomics*. 1991; 10:515–526. [PubMed: 1889803]
18. Cogan J, Wu W, Phillips JI, Arnhold I, Agapito A, Fofanova O, Osorio M, Bircan I, Moreno A, Mendonca B. The prop1 2-base pair deletion is a common cause of combined pituitary hormone deficiency. *Journal of Clinical Endocrinology & Metabolism*. 1998; 83:3346–3349. [PubMed: 9745452]
19. Cohen LE, Radovick S. Molecular basis of combined pituitary hormone deficiencies. *Endocr Rev*. 2002; 23:431–442. [PubMed: 12202459]
20. Deladoey J, Fluck C, Buyukgebiz A, Kuhlmann BV, Eble A, Hindmarsh PC, Wu W, Mullis PE. "Hot spot" in the prop1 gene responsible for combined pituitary hormone deficiency. *J Clin Endocrinol Metab*. 1999; 84:1645–1650. [PubMed: 10323394]
21. Wang Y, Nathans J. Tissue/planar cell polarity in vertebrates: New insights and new questions. *Development*. 2007; 134:647–658. [PubMed: 17259302]
22. Ward RD, Raetzman LT, Suh H, Stone BM, Nasonkin IO, Camper SA. Role of prop1 in pituitary gland growth. *Mol Endocrinol*. 2005; 19:698–710. [PubMed: 15591534]
23. Ward RD, Stone BM, Raetzman LT, Camper SA. Cell proliferation and vascularization in mouse models of pituitary hormone deficiency. *Mol Endocrinol*. 2006; 20:1378–1390. [PubMed: 16556738]
24. Douglas KR, Camper SA. Partial transcriptome of the developing pituitary gland. *Genomics*. 2000; 70:335–346. [PubMed: 11161784]
25. Douglas KR, Kennell JA, Eswara P, Harrison TA, Patrianakos AI, Sprecher BS, Potok MA, Lyons RH, MacDougald OA, Camper SA. Identification of members of the wnt signaling pathway in the embryonic pituitary gland. *Mammalian Genome*. 2001
26. Brinkmeier ML, Potok MA, Cha KB, Gridley T, Stifani S, Meeldijk J, Clevers H, Camper SA. Tcf and groucho-related genes influence pituitary growth and development. *Mol Endocrinol*. 2003; 17:2152–2161. [PubMed: 12907761]
27. Brinkmeier ML, Potok MA, Davis SW, Camper SA. Tcf4 deficiency expands ventral diencephalon signaling and increases induction of pituitary progenitors. *Dev Biol*. 2007; 311:396–407. [PubMed: 17919533]

28. Cha KB, Douglas KR, Potok MA, Liang H, Jones SN, Camper SA. Wnt5a signaling affects pituitary gland shape. *Mech Dev.* 2004; 121:183–194. [PubMed: 15037319]
29. Potok MA, Cha KB, Hunt A, Brinkmeier ML, Leitges M, Kispert A, Camper SA. Wnt signaling affects gene expression in the ventral diencephalon and pituitary gland growth. *Dev Dyn.* 2008; 237:1006–1020. [PubMed: 18351662]
30. Brantjes H, Roose J, Wetering Mvd, Clevers H. All tcf hmg box transcription factors interact with groucho-related co-repressors. *Nucleic Acids Res.* 2001; 29:1410–1419. [PubMed: 11266540]
31. Zhu C, Dyer M, Uchikawa M, Kondoh H, Lagutin O. Six3-mediated auto repression and eye development requires its interaction with members of the groucho-related family of co-repressors. *Development.* 2002; 129:2835–2849. [PubMed: 12050133]
32. Carninci P, Waki K, Shiraki T, Konno H, Shibata K, Itoh M, Aizawa K, Arakawa T, Ishii Y, Sasaki D, Bono H, Kondo S, Sugahara Y, Saito R, Osato N, Fukuda S, Sato K, Watahiki A, Hirozane-Kishikawa T, Nakamura M, Shibata Y, Yasunishi A, Kikuchi N, Yoshiki A, Kusakabe M, Gustincich S, Beisel K, Pavan W, Aidinis V, Nakagawara A, Held WA, Iwata H, Kono T, Nakauchi H, Lyons P, Wells C, Hume DA, Fagiolini M, Hensch TK, Brinkmeier M, Camper S, Hirota J, Mombaerts P, Muramatsu M, Okazaki Y, Kawai J, Hayashizaki Y. Targeting a complex transcriptome: The construction of the mouse full-length cDNA encyclopedia. *Genome Res.* 2003; 13:1273–1289. [PubMed: 12819125]
33. Pellegrini M, Mansouri A, Simeone A, Boncinelli E, Gruss P. Dentate gyrus formation requires *emx2*. *Development.* 1996; 122:3893–3898. [PubMed: 9012509]
34. Lopez-Bendito G, Chan CH, Mallamaci A, Parnavelas J, Molnar Z. Role of *emx2* in the development of the reciprocal connectivity between cortex and thalamus. *J Comp Neurol.* 2002; 451:153–169. [PubMed: 12209834]
35. Kendall SK, Gordon DF, Birkmeier TS, Petrey D, Sarapura VD, O'Shea KS, Wood WM, Lloyd RV, Ridgway EC, Camper SA. Enhancer-mediated high level expression of mouse pituitary glycoprotein hormone α -subunit transgene in thyrotropes, gonadotropes, and developing pituitary gland. *Mol Endocrinol.* 1994; 8:1420–1433. [PubMed: 7531821]
36. Morinaga T, Yasuda H, Hashimoto T, Higashio K, Tamaoki T. A human alpha-fetoprotein enhancer-binding protein, *atbf1*, contains four homeodomains and seventeen zinc fingers. *Mol Cell Biol.* 1991; 11:6041–6049. [PubMed: 1719379]
37. Qi Y, Ranish JA, Zhu X, Krones A, Zhang J, Aebersold R, Rose DW, Rosenfeld MG, Carriere C. *Atbf1* is required for the *pit1* gene early activation. *Proc Natl Acad Sci U S A.* 2008; 105:2481–2486. [PubMed: 18272476]
38. Miquelajauregui A, Van de Putte T, Polyakov A, Nityanandam A, Boppana S, Seuntjens E, Karabinos A, Higashi Y, Huylebroeck D, Tarabykin V. Smad-interacting protein-1 (*zfhx1b*) acts upstream of wnt signaling in the mouse hippocampus and controls its formation. *Proc Natl Acad Sci U S A.* 2007; 104:12919–12924. [PubMed: 17644613]
39. Verstappen G, van Grunsven LA, Michiels C, Van de Putte T, Souopgui J, Van Damme J, Bellefroid E, Vandekerckhove J, Huylebroeck D. Atypical mowat-wilson patient confirms the importance of the novel association between *zfhx1b/sip1* and *nurd* corepressor complex. *Hum Mol Genet.* 2008; 17:1175–1183. [PubMed: 18182442]
40. Moreno CS, Evans CO, Zhan X, Okor M, Desiderio DM, Oyesiku NM. Novel molecular signaling and classification of human clinically nonfunctional pituitary adenomas identified by gene expression profiling and proteomic analyses. *Cancer Res.* 2005; 65:10214–10222. [PubMed: 16288009]
41. Mowat DR, Croaker GD, Cass DT, Kerr BA, Chaitow J, Ades LC, Chia NL, Wilson MJ. Hirschsprung disease, microcephaly, mental retardation, and characteristic facial features: Delineation of a new syndrome and identification of a locus at chromosome 2q22–q23. *J Med Genet.* 1998; 35:617–623. [PubMed: 9719364]
42. Van de Putte T, Francis A, Nelles L, van Grunsven LA, Huylebroeck D. Neural crest-specific removal of *zfhx1b* in mouse leads to a wide range of neurocristopathies reminiscent of mowat-wilson syndrome. *Hum Mol Genet.* 2007; 16:1423–1436. [PubMed: 17478475]
43. Raetzman LT, Ward R, Camper SA. *Lhx4* and *prop1* are required for cell survival and expansion of the pituitary primordia. *Development.* 2002; 129:4229–4239. [PubMed: 12183375]

44. Sheng HZ, Zhadanov AB, Mosinger BJ, Fujii T, Bertuzzi S, Grinberg A, Lee EJ, Huang SP, Mahon KA, Westphal H. Specification of pituitary cell lineages by the lim homeobox gene *lhx3*. *Science*. 1996; 272:1004–1007. [PubMed: 8638120]
45. Takuma N, Sheng HZ, Furuta Y, Ward JM, Sharma K, Hogan BLM, Pfaff SL, Westphal H, Kimura S, Mahon KA. Formation of Rathke's pouch requires dual induction from the diencephalon. *Development*. 1998; 125:4835–4840. [PubMed: 9806931]
46. Roberson MS, Schoderbek WE, Tremml G, Maurer RA. Activation of the glycoprotein hormone alpha-subunit promoter by a lim-homeodomain transcription factor. *Mol Cell Biol*. 1994; 14:2985–2993. [PubMed: 7513049]
47. Porter FD, Drago J, Xu Y, Cheema SS, Wassif C, Huang SP, Lee E, Grinberg A, Massalas JS, Bodine D, Alt F, Westphal H. *Lhx2*, a lim homeobox gene, is required for eye, forebrain, and definitive erythrocyte development. *Development*. 1997; 124:2935–2944. [PubMed: 9247336]
48. Mangale VS, Hirokawa KE, Satyaki PR, Gokulchandran N, Chikbire S, Subramanian L, Shetty AS, Martynoga B, Paul J, Mai MV, Li Y, Flanagan LA, Tole S, Monuki ES. *Lhx2* selector activity specifies cortical identity and suppresses hippocampal organizer fate. *Science*. 2008; 319:304–309. [PubMed: 18202285]
49. Rhee H, Polak L, Fuchs E. *Lhx2* maintains stem cell character in hair follicles. *Science*. 2006; 312:1946–1949. [PubMed: 16809539]
50. Richter K, Pinto do OP, Hagglund AC, Wahlin A, Carlsson L. *Lhx2* expression in hematopoietic progenitor/stem cells in vivo causes a chronic myeloproliferative disorder and altered globin expression. *Haematologica*. 2003; 88:1336–1347. [PubMed: 14687986]
51. Mandel S, Rechavi G, Gozes I. Activity-dependent neuroprotective protein (adnp) differentially interacts with chromatin to regulate genes essential for embryogenesis. *Dev Biol*. 2007; 303:814–824. [PubMed: 17222401]
52. Borozdin W, Graham JM Jr, Bohm D, Bamshad MJ, Spranger S, Burke L, Leipoldt M, Kohlhase J. Multigene deletions on chromosome 20q13.13-q13.2 including *sall4* result in an expanded phenotype of Okihiro syndrome plus developmental delay. *Hum Mutat*. 2007; 28:830. [PubMed: 17623483]
53. Mandel S, Gozes I. Activity-dependent neuroprotective protein constitutes a novel element in the swi/snf chromatin remodeling complex. *J Biol Chem*. 2007; 282:34448–34456. [PubMed: 17878164]
54. Poulin G, Turgeon B, Drouin J. *Neurod1/β2* contributes to cell-specific transcription of the proopiomelanocortin gene. *Mol Cell Biol*. 1997; 17:6673–6682. [PubMed: 9343431]
55. Mandel S, Spivak-Pohis I, Gozes I. Adnp differential nucleus/cytoplasm localization in neurons suggests multiple roles in neuronal differentiation and maintenance. *J Mol Neurosci*. 2008
56. Miyamoto N, Yoshida M, Kuratani S, Matsuo I, Aizawa S. Defects of urogenital development in mice lacking *emx2*. *Development*. 1997; 124:1653–1664. [PubMed: 9165114]
57. Noonan FC, Mutch DG, Ann Mallon M, Goodfellow PJ. Characterization of the homeodomain gene *emx2*: Sequence conservation, expression analysis, and a search for mutations in endometrial cancers. *Genomics*. 2001; 76:37–44. [PubMed: 11549315]
58. Gangemi RM, Daga A, Muzio L, Marubbi D, Coccozza S, Perera M, Verardo S, Bordo D, Griffero F, Capra MC, Mallamaci A, Corte G. Effects of *emx2* inactivation on the gene expression profile of neural precursors. *Eur J Neurosci*. 2006; 23:325–334. [PubMed: 16420441]
59. Davis S, Camper S. *Noggin* regulates *bmp4* activity during pituitary induction. *Dev Biol*. 2007; 305:145–160. [PubMed: 17359964]
60. Ericson J, Norlin S, Jessell TM, Edlund T. Integrated *fgf* and *bmp* signaling controls the progression of progenitor cell differentiation and the emergence of pattern in the embryonic anterior pituitary. *Development*. 1998; 125:1005–1015. [PubMed: 9463347]
61. Treier M, Gleiberman AS, O'Connell SM, Szeto DP, McMahon JA, McMahon AP, Rosenfeld MG. Multistep signaling requirements for pituitary organogenesis in vivo. *Genes & Development*. 1998; 12:1691–1704. [PubMed: 9620855]
62. Treier M, O'Connell S, Gleiberman A, Price J, Szeto DP, Burgess R, Chuang P-T, McMahon AP, Rosenfeld MG. Hedgehog signaling is required for pituitary gland development. *Development*. 2001; 128:377–386. [PubMed: 11152636]

63. Olson LE, Tollkuhn J, Scafoglio C, Kronen A, Zhang J, Ohgi KA, Wu W, Taketo MM, Kemler R, Grosschedl R, Rose D, Li X, Rosenfeld MG. Homeodomain-mediated beta-catenin-dependent switching events dictate cell-lineage determination. *Cell*. 2006; 125:593–605. [PubMed: 16678101]
64. De Moerloose L, Spencer-Dene B, Revest J, Hajihosseini M, Rosewell I, Dickson C. An important role for the iib isoform of fibroblast growth factor receptor 2 (fgfr2) in mesenchymal-epithelial signalling during mouse organogenesis. *Development*. 2000; 127:483–492. [PubMed: 10631169]
65. Ohuchi H, Hori Y, Yamasaki M, Harada H, Sekine K, Kato S, Itoh N. Fgf10 acts as a major ligand for fgf receptor 2 iib in mouse multi-organ development. *Biochem Biophys Res Commun*. 2000; 277:643–649. [PubMed: 11062007]
66. Paez-Pereda M, Giacomini D, Refojo D, Nagashima AC, Hopfner U, Grubler Y, Chervin A, Goldberg V, Goya R, Hentges ST, Low MJ, Holsboer F, Stalla GK, Arzt E. Involvement of bone morphogenetic protein 4 (bmp-4) in pituitary prolactinoma pathogenesis through a smad/estrogen receptor crosstalk. *Proc Natl Acad Sci U S A*. 2003; 100:1034–1039. [PubMed: 12552124]
67. Giacomini D, Paez-Pereda M, Theodoropoulou M, Labeur M, Refojo D, Gerez J, Chervin A, Berner S, Losa M, Buchfelder M, Renner U, Stalla GK, Arzt E. Bone morphogenetic protein-4 inhibits corticotroph tumor cells: Involvement in the retinoic acid inhibitory action. *Endocrinology*. 2006; 147:247–256. [PubMed: 16195406]
68. Raetzman LT, Ross SA, Cook S, Dunwoodie SL, Camper SA, Thomas PQ. Developmental regulation of notch signaling genes in the embryonic pituitary: Prop1 deficiency affects notch2 expression. *Dev Biol*. 2004; 265:329–340. [PubMed: 14732396]
69. Raetzman LT, Cai JX, Camper SA. Hes1 is required for pituitary growth and melanotrope specification. *Dev Biol*. 2007; 304:455–466. [PubMed: 17367776]
70. Raetzman LT, Wheeler BS, Ross SA, Thomas PQ, Camper SA. Persistent expression of notch2 delays gonadotrope differentiation. *Mol Endocrinol*. 2006; 20:2898–2908. [PubMed: 16840533]
71. Asa SL, Ezzat S. Genetics and proteomics of pituitary tumors. *Endocrine*. 2005; 28:43–47. [PubMed: 16311409]
72. Farrell WE. Pituitary tumours: Findings from whole genome analyses. *Endocr Relat Cancer*. 2006; 13:707–716. [PubMed: 16954426]
73. Heaney AP, Melmed S. Molecular targets in pituitary tumours. *Nat Rev Cancer*. 2004; 4:285–295. [PubMed: 15057288]
74. Chandrasekharappa SC, Guru SC, Manickam P, Olufeni S-E, Collins FS, Emmert-Buck MR, Debelenko LV, Zhuang Z, Lubensky IA, Liotta LA, Crabtree JS, Wang Y, Agarwal SK, Kester MB, Kim YS, Heppner C, Dong Q, Spiegel AM, Burns AL, Marx SJ. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science*. 1997; 276:404–406. [PubMed: 9103196]
75. 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. Pituitary adenoma predisposition caused by germline mutations in the *aip* gene. *Science*. 2006; 312:1228–1230. [PubMed: 16728643]
76. Heaney AP, Horwitz GA, Wang Z, Singson RSM. Early involvement of estrogen-induced pituitary tumor transforming gene and fibroblast growth factor expression in prolactinoma pathogenesis. *Nat Med*. 1999; 5:1317–1321. [PubMed: 10546001]
77. Zhang X, Horwitz GA, Heaney AP, Nakashima M, Bronstein M, Melmed S. Pituitary tumor transforming gene expression in human pituitary adenomas. *J Clin Endocrinol Metab*. 1999; 84:761–767. [PubMed: 10022450]
78. Zou H, McGarry TJ, Bernal T, Kirschner MW. Identification of a vertebrate sister-chromatid separation inhibitor involved in transformation and tumorigenesis. *Science*. 1999; 285:418–422. [PubMed: 10411507]
79. Yu R, Ren SG, Horwitz GA, Wang Z, Melmed S. Pituitary tumor transforming gene (pttg) regulates placental *jeg-3* cell division and survival: Evidence from live cell imaging. *Mol Endocrinol*. 2000; 14:1137–1146. [PubMed: 10935539]
80. Qian X, Scheithauer BW, Kovacs K, Lloyd RV. DNA microarrays: Recent developments and applications to the study of pituitary tissues. *Endocrine*. 2005; 28:49–56. [PubMed: 16311410]

81. Abbud RA, Kelleher R, Melmed S. Cell-specific pituitary gene expression profiles after treatment with leukemia inhibitory factor reveal novel modulators for proopiomelanocortin expression. *Endocrinology*. 2004; 145:867–880. [PubMed: 14576184]
82. Ruebel KH, Leontovich AA, Jin L, Stilling GA, Zhang H, Qian X, Nakamura N, Scheithauer BW, Kovacs K, Lloyd RV. Patterns of gene expression in pituitary carcinomas and adenomas analyzed by high-density oligonucleotide arrays, reverse transcriptase-quantitative pcr, and protein expression. *Endocrine*. 2006; 29:435–444. [PubMed: 16943582]
83. Mould AW, Duncan R, Serewko-Auret M, Loffler KA, Biondi C, Gartside M, Kay GF, Hayward NK. Global expression profiling of murine *men1*-associated tumors reveals a regulatory role for *menin* in transcription, cell cycle and chromatin remodelling. *Int J Cancer*. 2007; 121:776–783. [PubMed: 17455252]
84. Cushman LJ, Watkins-Chow DE, Brinkmeier ML, Raetzman LT, Radak AL, Lloyd RV, Camper SA. Persistent *prop1* expression delays gonadotrope differentiation and enhances pituitary tumor susceptibility. *Hum Mol Genet*. 2001; 10:1141–1153. [PubMed: 11371507]
85. Ward RD, Davis SW, Cho M, Esposito C, Lyons RH, Cheng JF, Rubin EM, Rhodes SJ, Raetzman LT, Smith TP, Camper SA. Comparative genomics reveals functional transcriptional control sequences in the *prop1* gene. *Mamm Genome*. 2007; 18:521–537. [PubMed: 17557180]
86. Vesper AH, Raetzman LT, Camper SA. Role of prophet of pit1 (*prop1*) in gonadotrope differentiation and puberty. *Endocrinology*. 2006; 147:1654–1663. [PubMed: 16384867]
87. Egashira N, Minematsu T, Miyai S, Takekoshi S, Camper S, Osamura R. Pituitary changes in *prop1* transgenic mice: Hormone producing tumors and signet-ring type gonadotropes. *Acta Histochem Cytochem*. 2008
88. Brinkmeier ML, Stahl JH, Gordon D, Ross BD, Sarapura VD, Dowding JM, Kendall SK, Lloyd RV, Ridgway EC, Camper SA. Thyroid hormone responsive pituitary hyperplasia independent of somatostatin receptor 2. *Mol Endocrinol*. 2001 in press.
89. Kendall SK, Samuelson LC, Saunders TL, Wood RI, Camper SA. Targeted disruption of the pituitary glycoprotein hormone alpha-subunit produces hypogonadal and hypothyroid mice. *Genes Dev*. 1995; 9:2007–2019. [PubMed: 7544315]
90. Stahl J, Kendall S, Brinkmeier M, Greco T, Watkins-Chow D, Canpos-Barros A, Lloyd R, Camper S. Thyroid hormone is essential for pituitary somatotropes and lactotropes. *Endocrinol*. 1999; 140:1884–1892.
91. Margulies M, Egholm M, Altman WE, Attiya S, Bader JS, Bemben LA, Berka J, Braverman MS, Chen YJ, Chen Z, Dewell SB, Du L, Fierro JM, Gomes XV, Godwin BC, He W, Helgesen S, Ho CH, Irzyk GP, Jando SC, Alenquer ML, Jarvie TP, Jirage KB, Kim JB, Knight JR, Lanza JR, Leamon JH, Lefkowitz SM, Lei M, Li J, Lohman KL, Lu H, Makhijani VB, McDade KE, McKenna MP, Myers EW, Nickerson E, Nobile JR, Plant R, Puc BP, Ronan MT, Roth GT, Sarkis GJ, Simons JF, Simpson JW, Srinivasan M, Tartaro KR, Tomasz A, Vogt KA, Volkmer GA, Wang SH, Wang Y, Weiner MP, Yu P, Begley RF, Rothberg JM. Genome sequencing in microfabricated high-density picolitre reactors. *Nature*. 2005; 437:376–380. [PubMed: 16056220]
92. Hillier LW, Marth GT, Quinlan AR, Dooling D, Fewell G, Barnett D, Fox P, Glasscock JJ, Hickenbotham M, Huang W, Magrini VJ, Richt RJ, Sander SN, Stewart DA, Stromberg M, Tsung EF, Wylie T, Schedl T, Wilson RK, Mardis ER. Whole-genome sequencing and variant discovery in *c. Elegans* *Nat Methods*. 2008; 5:183–188.

Fig. 1.

Genetic hierarchy of transcription factor regulation of pituitary development. Studies with individual mutants and double mutants have suggested that *Pitx1* and *Pitx2* have overlapping functions required for activation of the LIM homeobox genes *Lhx3* and *Lhx4*. These genes also have overlapping functions and are required for the maintenance of *Hesx1* expression. *Prop1* is critical for timely suppression of *Hesx1* expression, but the genes required for initial activation of *Prop1* transcription are not known. *Prop1* is necessary for activation of *Pou1f1*, but the lag of several days between detection of *Prop1* transcripts and *Pou1f1* transcripts suggests that additional genes are required to activate *Pou1f1*. *Pou1f1* is necessary for expansion of precursor cells that give rise to cells producing *Tshb*, *Gh* and *Prl*. THE Correct figure is shown below. IT SHOULD HAVE A REPRESSOR ARROW BETWEEN HESX1 and PROP1, not an activator.

Fig. 2.

Striking differences in pituitary morphology at birth suggest major differences in *Prop1* and *Pou1f1* function. *Prop1* mutants carrying the spontaneous Ser180Pro mutation, or Ames dwarfs (df), are shown next to normal mice (wt) of the same strain, a non-inbred DF/B stock carrying the pink-eyed dilute mutation *p* [17]. A mouse homozygous for the spontaneous G261T mutation in *Pou1f1* is shown next to a normal mouse on the inbred DW/J stock. Both mutations produce a similar degree of adult pituitary hypoplasia, dwarfism, hypothyroidism and infertility. The lobes of the pituitary are posterior (P), intermediate (I), and anterior (A). Newborn = day of birth, "Mature" = 11 days old. The image of the *Prop1*^{df/df} mouse and wild type littermate is from Buckwalter et al., *Genomics*, 10:515–526, 1991, the *Pou1f1*^{dw/dw} mouse and wild type littermate is from Karolyi et al., *Mammalian Genome*, 18:596–608, 2007, and the pituitary gland sections are all from Ward, et al., *Mol Endocrinol.* 20:1378–90, 2006.

Fig. 3.

Emx2 is not required for normal anterior pituitary morphology or cell specification during development. Sagittal sections from heads of wild type and mutant *Emx2* litter mates were immunostained with antibodies specific for POMC, GH, TSH, POU1F1 and SF1, developed with diaminobenzidine to produce a brown precipitate and counterstained with hematoxylin and eosin. The intensity of staining and the number and distribution of stained cells was similar in mutants and wild types. Typical examples are shown.

Table 1

Transcription factors defects that cause congenital pituitary hormone deficiency

Gene name	Type of protein	Disease *
<i>PITX2</i>	Bicoid-paired homeo	Rieger syndrome (eyes, teeth), GHD
<i>LHX4</i>	LIM homeo	MPHD, cerebellum and skull defects
<i>LHX3</i>	LIM homeo	MPHD, rigid cervical spine
<i>SOX2</i>	HMG box	Brain and eye defects, growth insufficiency
<i>SOX3</i>	HMG box	Mental retardation, hypopituitarism, pituitary dysmorphology
<i>HESX1</i>	Paired homeo	Septo-optic dysplasia, MPHD, GHD
<i>PROP1</i>	Paired homeo	MPHD: lack LH, FSH, GH, TSH, PRL
<i>POU1F1</i>	POU homeo	MPHD: lack GH, TSH, PRL
<i>TBX19</i>	T box	Isolated ACTH deficiency
<i>NR5A1</i>	Nuclear receptor	LH, FSH deficient, hypogonadism, adrenal failure
<i>OTX1</i>	Bicoid-paired	Mice: transient dwarfism and hypogonadism
<i>OTX2</i>	Bicoid-paired	Dysgnathia Complex

Abbreviations: GHD = growth hormone deficiency, MPHD = multiple pituitary hormone deficiency

* Please consult OMIM (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM>) for complete disease annotations

Table 2a

Genes identified with relationships to cell migration and cell adhesion pathways*

GO Terminology and Gene Symbol	Gene Name	GO Terminology and Gene Symbol	Gene Name
Cell migration		Regulation of cell adhesion	
<i>Cdh2</i>	<i>Cadherin 2</i>	<i>Edg1</i>	<i>Endothelial differentiation sphingolipid G-protein-coupled receptor</i>
<i>Cdk5</i>	<i>Cyclin-dependent kinase 5</i>	<i>Pscd2</i>	<i>Pleckstrin homology, Sec7 and coiled-coil domains 2</i>
<i>Gab2</i>	<i>Growth factor receptor bound protein 2-associated protein 2</i>	<i>Stat5b</i>	<i>Signal transducer and activator of transcription 5B</i>
<i>Itga4</i>	<i>Integrin alpha 4</i>	Negative regulation of cell adhesion	
<i>Nck1</i>	<i>Non-catalytic region of tyrosine kinase adaptor protein 1</i>	<i>Cbl1</i>	<i>Casitas B-lineage lymphoma-like 1</i>
<i>Pten</i>	<i>Phosphatase and tensin homolog</i>	<i>Cml1</i>	<i>Camello-like 1</i>
<i>St14</i>	<i>Suppression of tumorigenicity 14</i>	Positive regulation of cell adhesion	
Regulation of cell migration		<i>Pscd3</i>	<i>Pleckstrin homology, Sec7 and coiled-coil domains 3</i>
<i>Amot</i>	<i>Angiomotin-like 1, transcript variant 5</i>	Cell-cell adhesion	
<i>Cdk5</i>	<i>Cyclin-dependent kinase 5</i>	<i>Cdh1</i>	<i>Cadherin 1</i>
<i>Cxcl12</i>	<i>Chemokine (C-X-C motif) ligand 12</i>	<i>Cdh3</i>	<i>Cadherin 3</i>
<i>Ntn1</i>	<i>Netrin 1</i>	<i>Cdh5</i>	<i>Cadherin 5</i>
<i>Pecam1</i>	<i>Platelet/endothelial cell adhesion molecule 1</i>	<i>Cldn5</i>	<i>Claudin 5</i>
<i>Tmsb4x</i>	<i>Thymosin, beta 4, X chromosome</i>	<i>Gats</i>	<i>Opposite strand transcription unit to Stag3</i>

<i>Vcl</i>	<i>Vinculin</i>	<i>Gga2</i>	<i>Golgi associated, gamma adaptin ear containing, ARF binding protein 2</i>
Positive regulation of cell migration		<i>Pkp2</i>	<i>Plakophilin 2</i>
<i>Cbl1</i>	<i>Casitas B-lineage lymphoma-like 1</i>	<i>Pvrl4</i>	<i>Poliovirus receptor-related 4</i>
<i>Col18a1</i>	<i>Procollagen, type XVIII, alpha 1</i>	<i>Vcam1</i>	<i>Vascular cell adhesion molecule 1</i>
<i>Cxcl12</i>	<i>Chemokine (C-X-C motif) ligand 12</i>	Homophilic cell-cell adhesion	
Negative regulation of cell migration		<i>Cdh1</i>	<i>Cadherin 1</i>
<i>Egfl7</i>	<i>EGF-like domain 7</i>	<i>Cdh13</i>	<i>Cadherin 13</i>
<i>Nisch</i>	<i>Nischarin</i>	<i>Cdh17</i>	<i>Cadherin 17</i>
<i>Robo4</i>	<i>Roundabout homolog 4</i>	<i>Cdh2</i>	<i>Cadherin 2</i>
Substrate-bound cell migration, cell extension		<i>Cdh3</i>	<i>Cadherin 3</i>
<i>Myh10</i>	<i>Myosin, heavy polypeptide 10, non-muscle</i>	<i>Cdh5</i>	<i>Cadherin 5</i>
Neural crest cell migration		<i>Clstn3</i>	<i>Calsyntenin 3</i>
<i>Ednrb</i>	<i>Endothelin receptor type B</i>	<i>Gga2</i>	<i>Golgi associated, gamma adaptin ear containing, ARF binding protein 2</i>
<i>Efnb1</i>	<i>Ephrin B1</i>	<i>Pcdh7</i>	<i>Protocadherin 7</i>
Ameboidal cell migration		<i>Pcdhb16</i>	<i>Protocadherin beta 16</i>
<i>Cap1</i>	<i>CAP, adenylate cyclase-associated protein 1</i>	<i>Pcdhb9</i>	<i>Protocadherin beta 9</i>
<i>Wasf2</i>	<i>WAS protein family, member 2</i>	Heterophilic cell adhesion	
Cell migration involved in gastrulation		<i>Cd164</i>	<i>CD164 antigen</i>
<i>Amot</i>	<i>Angiomotin-like 1, transcript variant 5</i>	<i>Mcam</i>	<i>Melanoma cell adhesion molecule</i>
<i>Synpo2</i>	<i>Synaptopodin 2</i>	Calcium-dependent cell-cell adhesion	
Neuron migration		<i>Arvcf</i>	<i>Armadillo repeat gene deleted in velo-cardio-facial syndrome</i>
<i>Itga3</i>	<i>Integrin alpha 3</i>	<i>Cdh17</i>	<i>Cadherin 17</i>
<i>Myh10</i>	<i>Myosin, heavy polypeptide 10, non-muscle</i>	<i>Cdh2</i>	<i>Cadherin 2</i>

<i>Ntn1</i>	<i>Netrin 1</i>	<i>Pcdh18</i>	<i>Protocadherin 18</i>
<i>Pex5</i>	<i>Peroxisome biogenesis factor 5</i>	Cell-matrix adhesion	
<i>Prrxl1</i>	<i>Paired related homeobox protein-like 1</i>	<i>Cdk5</i>	Cyclin-dependent kinase 5
<i>Psen1</i>	<i>Presenilin 1</i>	<i>Epdr2</i>	<i>Ependymin related protein 2</i>
<i>Tyr</i>	<i>Tyrosinase</i>	<i>Grk1</i>	<i>G protein-coupled receptor kinase 1</i>
Axon guidance		<i>Itga3</i>	<i>Integrin alpha 3</i>
<i>Ablim1</i>	<i>Actin-binding LIM protein 1</i>	<i>Itga4</i>	<i>Integrin alpha 4</i>
<i>Dpysl5</i>	<i>Dihydropyrimidinase-like 5</i>	<i>Itga6</i>	<i>Integrin alpha 6</i>
<i>Efnb1</i>	<i>Ephrin B1</i>	<i>Itgb1</i>	<i>Integrin beta 1</i>
<i>Efnb3</i>	<i>Ephrin B3</i>	<i>Itgb5</i>	<i>Integrin beta 5</i>
<i>Ephb2</i>	<i>Eph receptor B2</i>	<i>Nid1</i>	<i>Nidogen 1</i>
<i>Foxd1</i>	<i>Forkhead box D1</i>	<i>Nid2</i>	<i>Nidogen 2</i>
<i>Linc</i>	<i>Lung-inducible neuralized-related C3HC4 RING domain protein</i>	<i>Pxn</i>	<i>Paxillin</i>
<i>Ngfr</i>	<i>Nerve growth factor receptor</i>	<i>RhoA</i>	<i>ras homolog gene family, member A</i>
<i>Ntn1</i>	<i>Netrin 1</i>	<i>Sirpa</i>	<i>Signal-regulatory protein alpha</i>
<i>Vasp</i>	<i>Vasodilator-stimulated phosphoprotein</i>	<i>Zfp488</i>	<i>Zinc finger protein 488</i>
Axon choice point recognition		Focal adhesion formation	
<i>Efnb3</i>	<i>Ephrin B3</i>	<i>Pxn</i>	<i>Paxillin</i>
Glial cell migration			
<i>Cspg4</i>	<i>Chondroitin sulfate proteoglycan 4</i>		

* This table lists mouse genes. For human orthologues refer to <http://www.informatics.jax.org/>

Table 2b

Genes identified with relationships to cell apoptosis and proliferation*

GO Terminology and Gene Symbol	Gene Name	GO Terminology and Gene Symbol	Gene Name
Regulation of apoptosis		Cell Proliferation	
<i>Ank2</i>	<i>Ankyrin 2, brain</i>	<i>Anxa7</i>	<i>Annexin A7</i>
<i>Apaf1</i>	<i>Apoptotic peptidase activating factor 1</i>	<i>Btc</i>	<i>Betacellulin, epidermal growth factor family member</i>
<i>Bad</i>	<i>Bcl-associated death promoter</i>	<i>Btg1</i>	<i>B-cell translocation gene 1, anti-proliferative</i>
<i>Bag1</i>	<i>Bcl2-associated athanogene 1</i>	<i>Cdk9</i>	<i>Cyclin-dependent kinase 9</i>
<i>Bat3</i>	<i>HLA-B-associated transcript 3</i>	<i>Chrd</i>	<i>Chordin</i>
<i>Bax</i>	<i>Bcl2-associated X protein</i>	<i>Cops2</i>	<i>COP9 (constitutive photomorphogenic) homolog, subunit 2</i>
<i>Bcl2</i>	<i>B-cell leukemia/lymphoma 2</i>	<i>Cspg4</i>	<i>Chondroitin sulfate proteoglycan 4</i>
<i>Bcl2l11</i>	<i>BCL2-like 11 (apoptosis facilitator)</i>	<i>Cul1</i>	<i>Cullin 1</i>
<i>Bcl2l12</i>	<i>BCL2-like 12</i>	<i>Fgf1</i>	<i>Fibroblast growth factor 1</i>
<i>Bcl2l2</i>	<i>Bcl2-like 2</i>	<i>Gpr157</i>	<i>G protein-coupled receptor</i>
<i>Bid</i>	<i>BH3 interacting domain death agonist</i>	<i>Gspt2</i>	<i>G1 to S phase transition 2</i>
<i>Bmf</i>	<i>Bcl2 modifying factor</i>	<i>lfrd2</i>	<i>Interferon-related developmental regulator 2</i>
<i>Bnip31</i>	<i>BCL2/adenovirus E1B interacting protein 3-like</i>	<i>Igf2</i>	<i>Insulin-like growth factor 2</i>
<i>Casp2</i>	<i>Caspase 2</i>	<i>Kit</i>	<i>kit oncogene</i>
<i>Casp9</i>	<i>Caspase 9</i>	<i>Mdk</i>	<i>Midkine</i>
<i>Cul7</i>	<i>Cullin 7</i>	<i>Ovca2</i>	<i>Candidate tumour suppressor OVCA2</i>
<i>Dap3</i>	<i>Death associated protein 3</i>	<i>Park7</i>	<i>Parkinson disease (autosomal recessive, early onset) 7</i>

<i>Dedd</i>	Death effector domain-containing	<i>Prkar1a</i>	Protein kinase, cAMP dependent regulatory, type I, alpha
<i>Fadd</i>	Fas (TNFRSF6)-associated via death domain	<i>Prkar2b</i>	Protein kinase, cAMP dependent regulatory, type II beta
<i>Gga2</i>	Golgi associated, gamma adaptin ear containing, ARF binding protein 2	<i>Rps27</i>	Ribosomal protein S27
<i>Hif1a</i>	Hypoxia inducible factor 1, alpha subunit	<i>Tgfb2</i>	Transforming growth factor, beta 2
<i>Ift57</i>	Intraflagellar transport 57 homolog	<i>Tnfrsf1b</i>	Tumour necrosis factor receptor superfamily, member 1b
<i>Irak2</i>	Interleukin-1 receptor-associated kinase 2	<i>Tspan5</i>	Tetraspanin 5
<i>Kbtbd10</i>	Kelch repeat and BTB (POZ) domain containing 10	<i>Uhrf1</i>	Ubiquitin-like, containing PHD and RING finger domains, 1
<i>Mnt</i>	Max binding protein	Regulation of cell proliferation	
<i>Moap1</i>	Modulator of apoptosis 1	<i>Anxa1</i>	Annexin A1
<i>Pea15</i>	Phosphoprotein enriched in astrocytes 15	<i>Cdk4</i>	Cyclin-dependent kinase 4
<i>Thoc1</i>	THO complex 1	<i>Cfdp1</i>	Craniofacial development protein 1
<i>Usp14</i>	Ubiquitin specific peptidase 14	<i>Ctnnb1</i>	Catenin (cadherin associated protein), beta 1
Induction of apoptosis		<i>E2f4</i>	E2F transcription factor 4
<i>Bax</i>	Bcl2-associated X protein	<i>Fanc1</i>	Fanconi anaemia, complementation group L
<i>Bbc3</i>	Bcl-2 binding component 3	<i>Fanca</i>	Fanconi anaemia, complementation group A
<i>Bnpl</i>	BCL2/adenovirus E1B 19kD interacting protein like	<i>Foxo1</i>	Forkhead box O1
<i>Casp2</i>	Caspase 2	<i>Kctd11</i>	Potassium channel tetramerization domain containing 11

<i>Dffa</i>	DNA fragmentation factor, alpha subunit	<i>Mafg</i>	<i>v-maf musculoaponeurotic fibrosarcoma oncogene family, protein G</i>
<i>Ngfr</i>	Nerve growth factor receptor (TNFR superfamily, member 16)	<i>March9</i>	Membrane-associated ring finger (C3HC4) 9
<i>Ngfrap1</i>	Nerve growth factor receptor (TNFRSF16) associated protein 1	<i>Mif</i>	Macrophage migration inhibitory factor
<i>Plagl2</i>	Pleomorphic adenoma gene-like 2	<i>Mina</i>	myc induced nuclear antigen
<i>Pten</i>	Phosphatase and tensin homolog	<i>Pin1</i>	Protein (peptidyl-prolyl cis/trans isomerase) NIMA-interacting 1
<i>Serinc3</i>	Serine incorporator 3	<i>Ranbp1</i>	RAN binding protein 1
<i>Sh3glb1</i>	SH3-domain GRB2-like B1 (endophilin)	<i>Stat6</i>	Signal transducer and activator of transcription 6
<i>Stkl7b</i>	Serine/threonine kinase 17b (apoptosis-inducing)	<i>Tgfb2</i>	Transforming growth factor, beta receptor II
<i>Trim35</i>	Tripartite motif-containing 35	<i>Trp53</i>	Transformation related protein 53 inducible nuclear protein 2
Positive regulation of apoptosis		Positive regulation of cell proliferation	
<i>B3gnt4</i>	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 4	<i>Ciao1</i>	Cytosolic iron-sulfur protein assembly 1 homolog
<i>Bcl2l11</i>	BCL2-like 11 (apoptosis facilitator)	<i>Cnbp</i>	cellular nucleic acid binding protein
<i>Bclaf1</i>	BCL2-associated transcription factor 1	<i>Col18a1</i>	Procollagen, type XVIII, alpha 1
<i>Bid</i>	BH3 interacting domain death agonist	<i>D17Wsu104e</i>	DNA segment, Chr 17, Wayne State University 104, expressed
<i>Ccar1</i>	Cell division cycle and apoptosis regulator 1	<i>Ddr2</i>	Discoidin domain receptor family, member 2
<i>Col18a1</i>	Procollagen, type XVIII, alpha 1	<i>E2f3</i>	E2F transcription factor 3
<i>Cyts</i>	Cytochrome c, somatic	<i>Edg3</i>	Endothelial differentiation, sphingolipid G-protein-coupled receptor, 3

<i>Diablo</i>	Diablo homolog	<i>Fgf10</i>	Fibroblast growth factor 10
<i>Inpp5d</i>	Inositol polyphosphate-5-phosphatase D	<i>Fgfr2</i>	Fibroblast growth factor receptor 2
<i>Pou4f1</i>	POU domain, class 4, transcription factor 1	<i>Pdgfc</i>	Platelet-derived growth factor, C polypeptide
<i>Uaca</i>	Uveal autoantigen with coiled-coil domains and ankyrin repeats	<i>Pura</i>	Purine rich element binding protein A, transcript variant 3
Positive regulation of non-apoptotic cell death		<i>Rogdi</i>	Rogdi homolog
<i>Cdkn1a</i>	Cyclin-dependent kinase inhibitor 1A (P21)	<i>Tspan31</i>	Tetraspanin 31
Negative regulation of apoptosis		Negative regulation of cell proliferation	
<i>Akt2</i>	Thymoma viral proto-oncogene 2	<i>Bap1</i>	Brca1 associated protein 1
<i>Birc4</i>	Baculoviral IAP repeat-containing 4	<i>Btg1</i>	B-cell translocation gene 1, anti-proliferative
<i>Casp2</i>	Caspase 2	<i>Cav1</i>	Caveolin, caveolae protein 1
<i>Cdkn1a</i>	Cyclin-dependent kinase inhibitor 1A (P21)	<i>Cdkn1a</i>	Cyclin-dependent kinase inhibitor 1A (P21)
<i>Pik3r1</i>	Phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)	<i>E2f7</i>	E2F transcription factor 7
<i>Trp53</i>	Transformation related protein 53	<i>Frk</i>	fyn-related kinase
Apoptotic Program		<i>Glmn</i>	Glomulin, FKBP associated protein
<i>Acin1</i>	Apoptotic chromatin condensation inducer 1	<i>Ifitm3</i>	Interferon induced transmembrane protein 3
<i>Fadd</i>	Fas (TNFRSF6)-associated via death domain	<i>Ppp2r3a</i>	Protein phosphatase 2 (formerly 2A), regulatory subunit B, alpha
<i>Scotin</i>	Scotin gene	<i>Prkrir</i>	Protein-kinase, interferon-inducible double stranded RNA dependent inhibitor, repressor of (P58 repressor)

<i>Sh3glb1</i>	SH3-domain GRB2-like B1 (endophilin)	<i>Smarca2</i>	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 1
Caspase activation		<i>Tax1bp3</i>	Tax1 (human T-cell leukaemia virus type I) binding protein 3
<i>Apaf1</i>	Apoptotic peptidase activating factor 1	<i>Tsg101</i>	Tumour susceptibility gene 101
<i>Cd8b1</i>	CD8 antigen, beta chain 1	Regulation of progression through embryonic mitotic cell cycle	
<i>Ift57</i>	Intraflagellar transport 57 homolog	<i>E4f</i>	E4F transcription factor 1
<i>Rbx2</i>	Similar to RING-box protein 2	Inner cell mass cell proliferation	
<i>Rnf7</i>	Ring finger protein 7	<i>Ncapg2</i>	Non-SMC condensin II complex, subunit G2
Caspase activation via Cytochrome C		<i>Setdb1</i>	SET domain, bifurcated 1
<i>Bax</i>	Bcl2-associated X protein	Negative regulation of endothelial cell proliferation	
<i>Cyts</i>	Cytochrome c, somatic	<i>Cav1</i>	Caveolin, caveolae protein 1
DNA fragmentation during apoptosis		Neuroblast proliferation	
<i>Aifm1</i>	Apoptosis-inducing factor, mitochondrion-associated 1	<i>Hhip</i>	Hedgehog-interacting protein
<i>Dffa</i>	DNA fragmentation factor, alpha subunit	Negative regulation of fibroblast proliferation	
<i>Sod1</i>	Superoxide dismutase 1, soluble	<i>Bax</i>	Bcl2-associated X protein
Nuclear fragmentation		<i>Pmaip1</i>	Phorbol-12-myristate-13-acetate-induced protein 1
<i>Bax</i>	Bcl2-associated X protein	<i>Trp53</i>	Transformation related protein 53
Apoptotic mitochondrial changes		T cell proliferation	
<i>Aifm1</i>	Apoptosis-inducing factor, mitochondrion-associated 1	<i>Cxcl12</i>	Chemokine (C-X-C motif) ligand 12
<i>Akt2</i>	Thymoma viral proto-oncogene 2	Negative regulation of T cell proliferation	
<i>Bax</i>	Bcl2-associated X protein	<i>Cd276</i>	CD276 antigen

<i>Dap3</i>	Death associated protein 3	B cell proliferation	
<i>Pim2</i>	Protein-serine/threonine kinase	<i>Prkcd</i>	Protein kinase C, delta
<i>Rbx2</i>	Similar to RING-box protein 2	Positive regulation of B cell proliferation	
<i>Rnf7</i>	Ring finger protein 7	<i>Cdkn1a</i>	Cyclin-dependent kinase inhibitor 1A (P21)
Release of Cytochrome C from mitochondria		Negative regulation of B cell proliferation	
<i>Bax</i>	Bcl2-associated X protein	<i>Inpp5d</i>	Inositol polyphosphate-5-phosphatase D
<i>Bcl2</i>	B-cell leukaemia/lymphoma 2		
<i>Pmaip1</i>	Phorbol-12-myristate-13-acetate-induced protein 1		
Protein insertion into mitochondrial membrane during induction			
<i>Bax</i>	Bcl2-associated X protein		
<i>Pmaip1</i>	Phorbol-12-myristate-13-acetate-induced protein 1		
Regulation of retinal programmed cell death			
<i>Zfp91</i>	Zinc finger protein 91		
Anti-apoptosis			
<i>Api5</i>	Apoptosis inhibitor 5		
<i>Bcl2</i>	B-cell leukaemia/lymphoma 2		
<i>Bfar</i>	Bifunctional apoptosis regulator		
<i>Birc4</i>	Baculoviral IAP repeat-containing 4		
<i>Birc5</i>	Baculoviral IAP repeat-containing 5		
<i>Birc6</i>	Baculoviral IAP repeat-containing 6		
<i>Cfdp1</i>	Craniofacial development protein 1		
<i>Ciapi1</i>	Cytokine induced apoptosis inhibitor 1		
<i>Dad1</i>	Defender against cell death 1		

<i>Hells</i>	Helicase, lymphoid specific		
<i>Mapk8ip1</i>	Mitogen activated protein kinase 8 interacting protein 1		
<i>Pim2</i>	Proviral integration site 2		
<i>Prdx2</i>	Peroxiredoxin 2		
<i>Qars</i>	GlutaminyI-tRNA synthetase		
<i>Rbx2</i>	Similar to RING-box protein 2		
<i>Rnf7</i>	Ring finger protein 7		
<i>Sgk3</i>	Serum/glucocorticoid regulated kinase 3		
<i>Stambp</i>	Stam binding protein		
<i>Tsc22d3</i>	TSC22 domain family 3		
<i>Zc3hc1</i>	Zinc finger, C3HC type 1		

* This table lists mouse genes. For human orthologues refer to <http://www.informatics.jax.org/>

Table 3**CLINICAL AND THERAPEUTIC IMPLICATIONS**

***Mouse mutants can model human-pituitary disease**

- * PROP1 and POU1F1 are mutated in some patients with hypopituitarism
- * PTTG mutations cause genomic instability in human adenoma

***Tumor suppressors and oncogenes mutated in familial pituitary adenoma syndromes are expressed in early mouse pituitary development, suggesting roles in normal pituitary growth regulation.**

- * Menin (Multiple endocrine neoplasia)
- * PRKAR1A (Carney Complex),
- * GNAS1 (McCune Albright),
- * AIP (somatotropinomas and prolactinomas)

***Gene discovery with mouse mutants reveals new candidates for functional tests and human screening**

- * AES is a candidate for growth insufficiency
 - * Developmentally expressed genes in several biological process categories are candidates for adenoma risk
 - * apoptosis (N=79)
 - * cell proliferation (N=77)
 - * migration (N=40)
-