Congenital Hypopituitarism

Laura Jacobsen, MD

Joint NICU-Endo Lecture

March 9, 2023

What is the first word that comes to mind when you hear "congenital hypopituitarism"?

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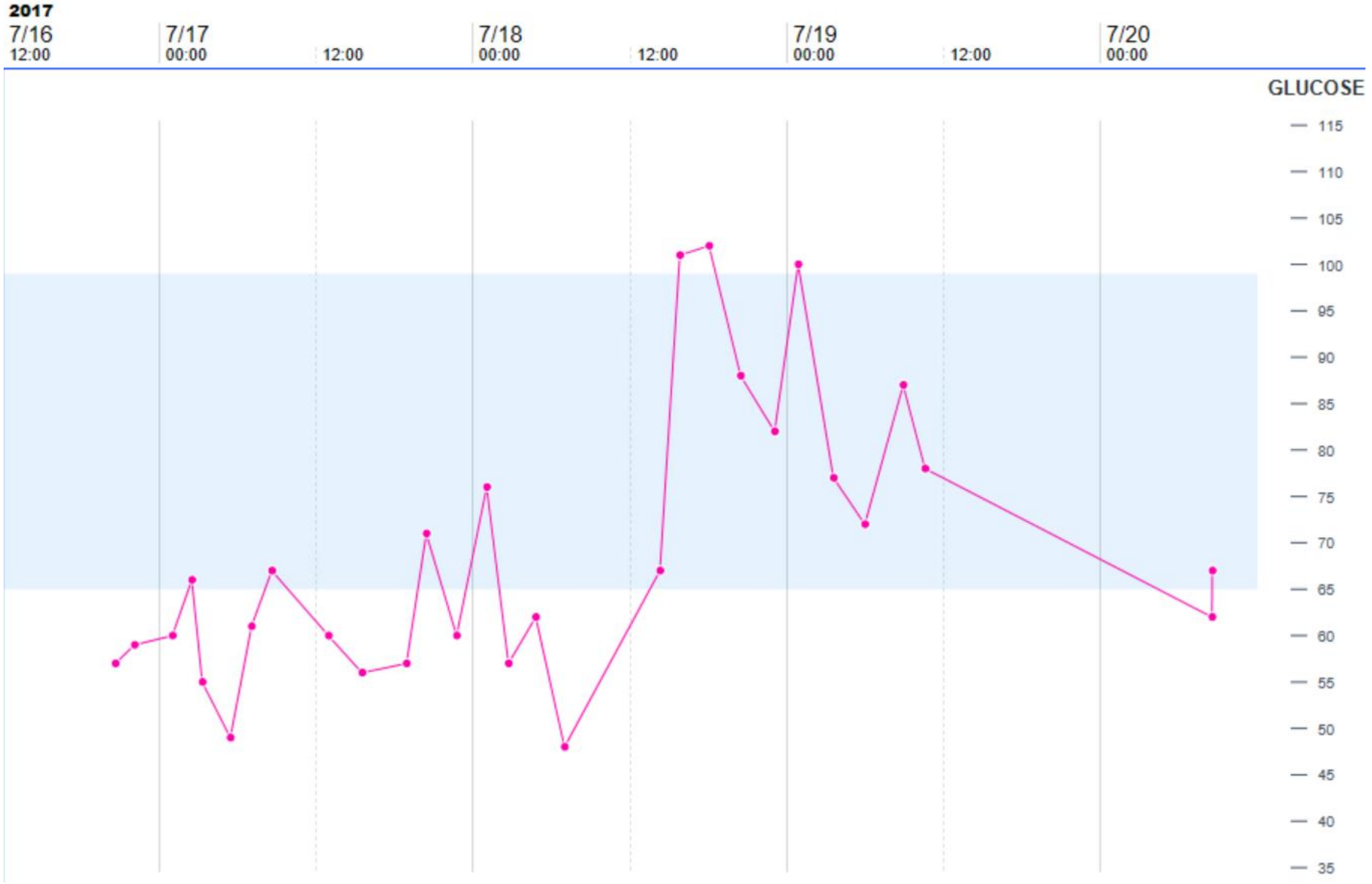
Learning Objectives

1. Review normal **development** of the pituitary gland.
2. Identify **gene defects** involved in congenital hypopituitarism and the resultant **hormone deficiencies**.
3. Recognize **signs and symptoms** of neonatal hypopituitarism and optic nerve hypoplasia (septo-optic dysplasia).
4. Evaluate how **imaging** may or may not aid in diagnosis and prediction.

Case #1

- 9 day old M admitted to Shands for fever (101.3 F) and found to have a UTI
- POC BG 59 mg/dL
- BMP glucose 42 mg/dL



Case #1 Birth History

- Born at 40 3/7 weeks gestation via SVD at OSH
- Initial BG 57 mg/dL but “lethargic” and taken to NICU
- Per mother had BG of 10 mg/dL and given IV fluids for 3 days
- Clinically jaundiced with **mixed** hyperbilirubinemia

7/14/17 16:25
Bilirubin, Direct: 1.9 (H)
Total Bilirubin: 18.7 (HH)

- PCP noted micropenis 1.4 cm SPL

Congenital Hypopituitarism is Infrequent

1:4000 - 10,000 live births

Mutations in genes involved in pituitary development

Isolated or combined pituitary hormone deficiencies

Life-threatening if untreated

52% of neonates with hypopituitarism present postnatally with associated complications, only 23% are diagnosed in the neonatal period

Think Congenital Hypopituitarism If…

- Persistent hypoglycemia in infancy
- Persistent jaundice
- Micropenis in infancy
- Midline defects
- Multiple pituitary hormone deficiencies

Development of the Pituitary Gland

- Pituitary develops from 2 embryonic tissues

Rathke's pouch from the primitive oral cavity --- visible by 5 weeks gestation

Adenohypophysis
Anterior pituitary

Neural component from floor of primitive forebrain (diencephalon)

Neurohypophysis
Posterior pituitary

- Morphologically mature pituitary gland by 13-15 weeks gestation

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Which is larger by weight?

Anterior pituitary

Posterior pituitary

Total Results: 0

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Which is larger by weight?

Anterior pituitary

Posterior pituitary

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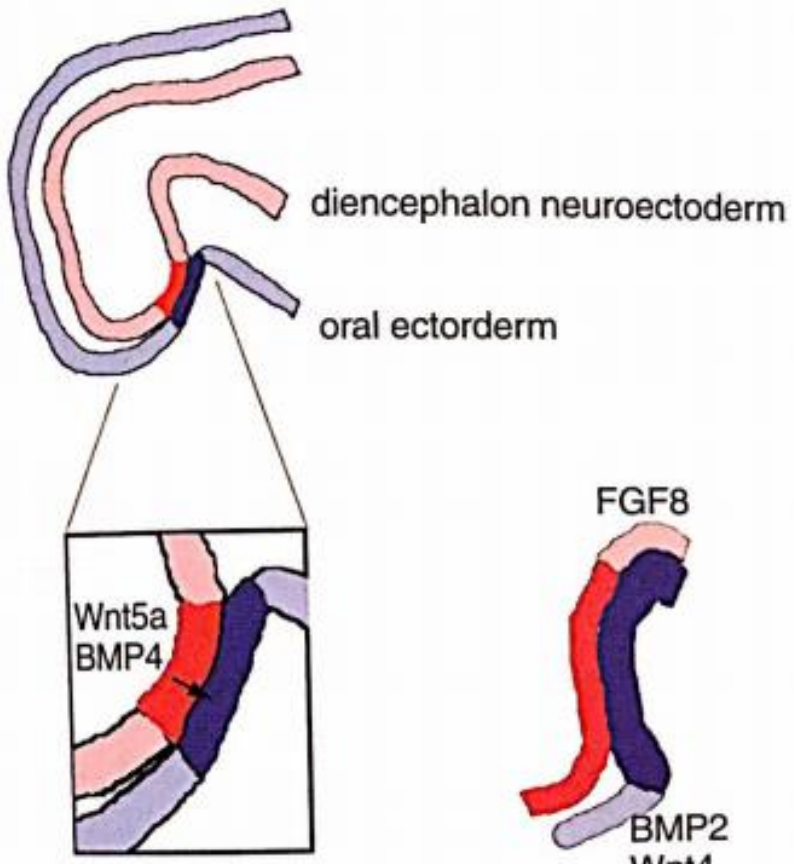
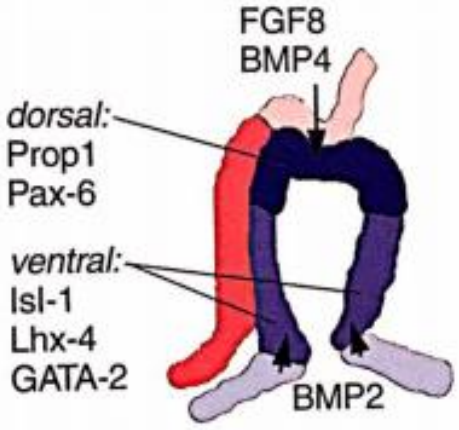
1. **Somatotrophs 45% of total cell mass**
2. **Lactotrophs 15%**
3. **Gonadotrophs 10%**
4. **Thyrotrophs 15%**
5. **Corticotrophs 15%**

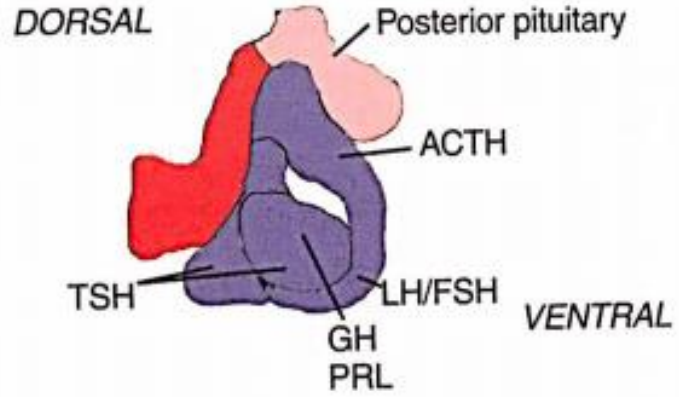


Pituitary Placode

Rudimentary Rathke's Pouch

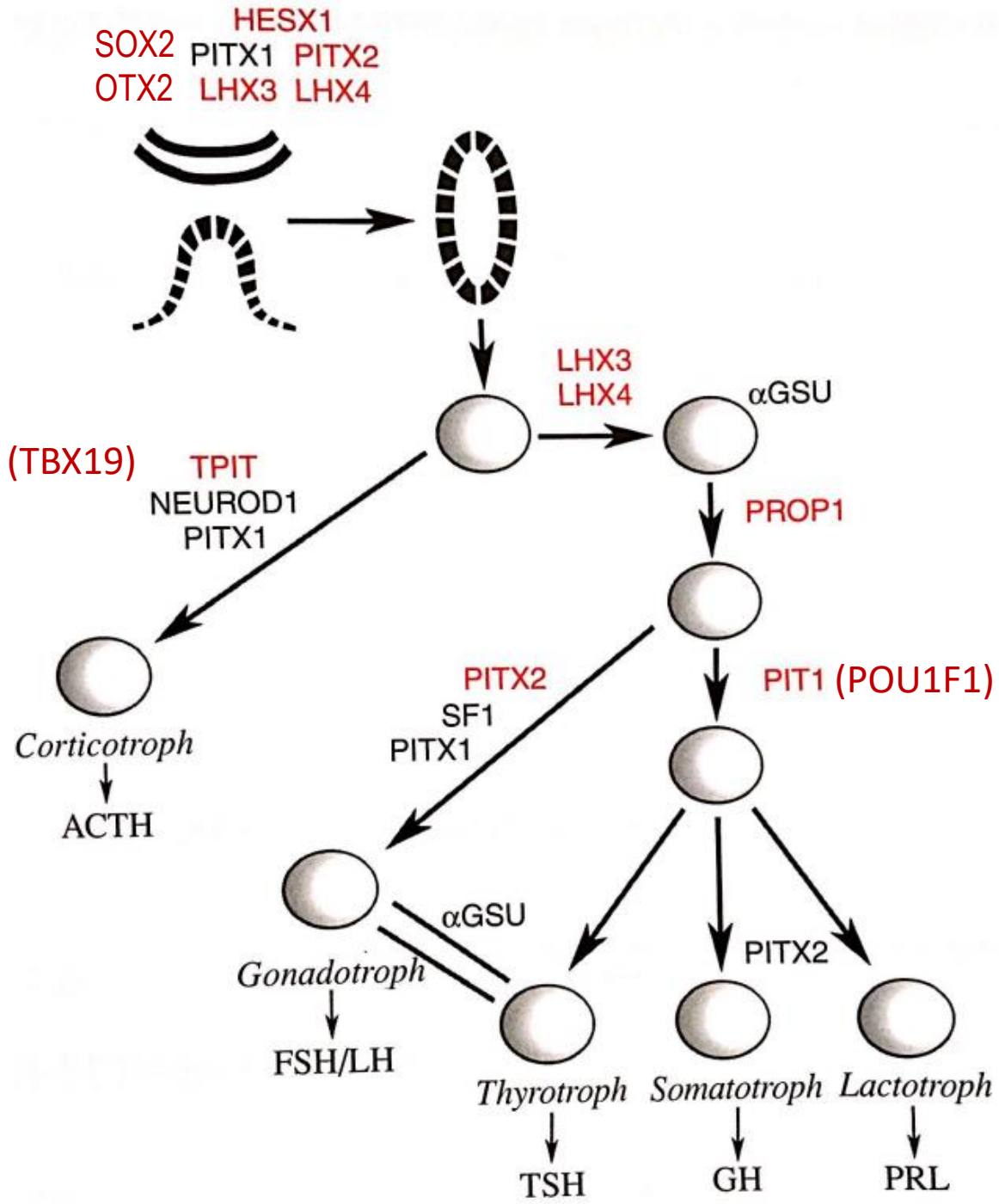


Definitive Rathke's Pouch



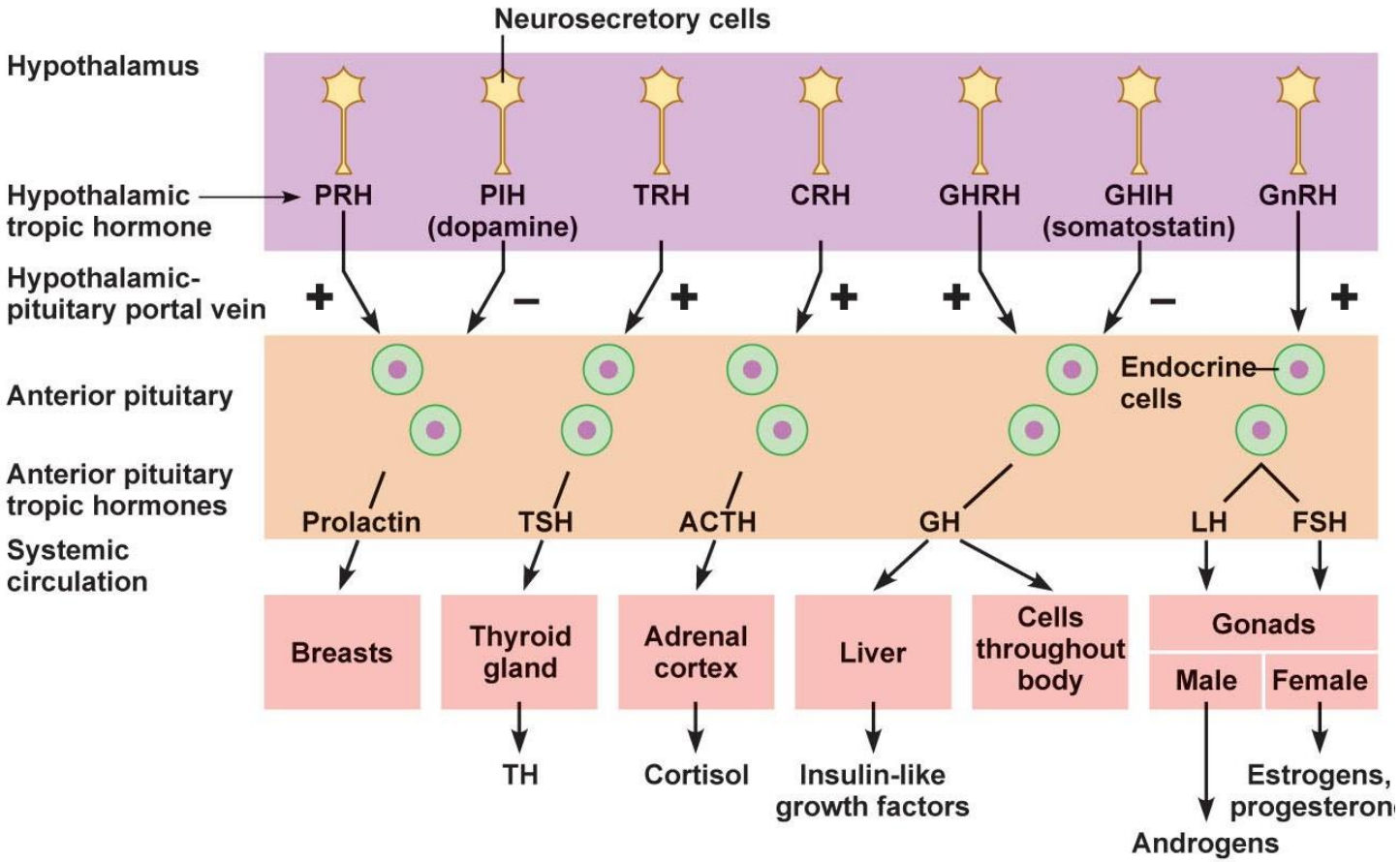
Mature Pituitary Gland

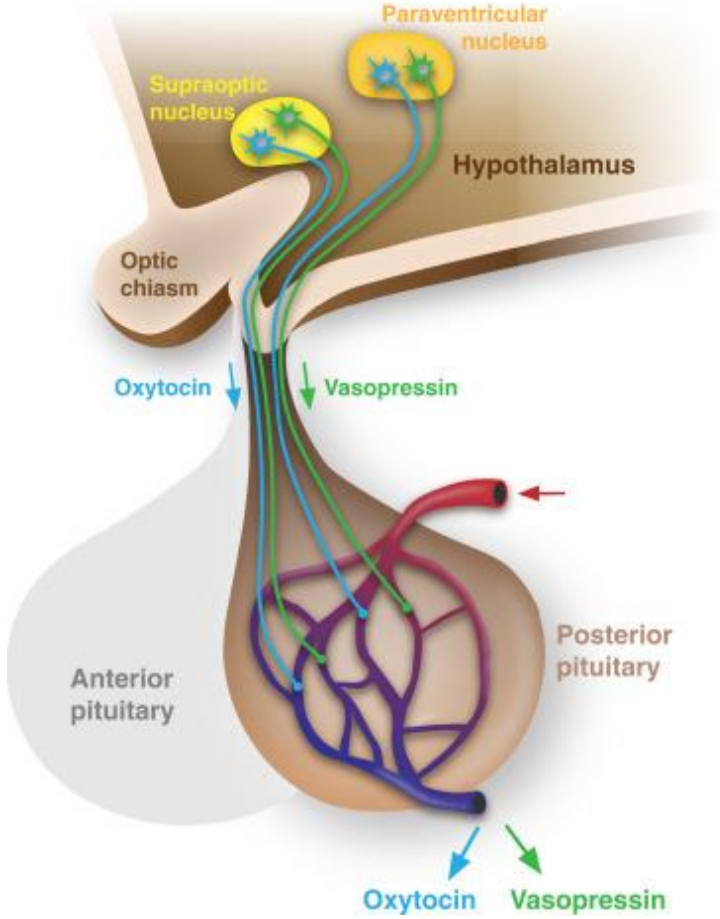
Ventral



Dorsal

Multiple Points Along the Hypothalamic-Pituitary Pathway Can Lead to Congenital Hypopituitarism





Gene Affected

Hormone Deficiency

HESX1 (RPX), SOX2, OTX2

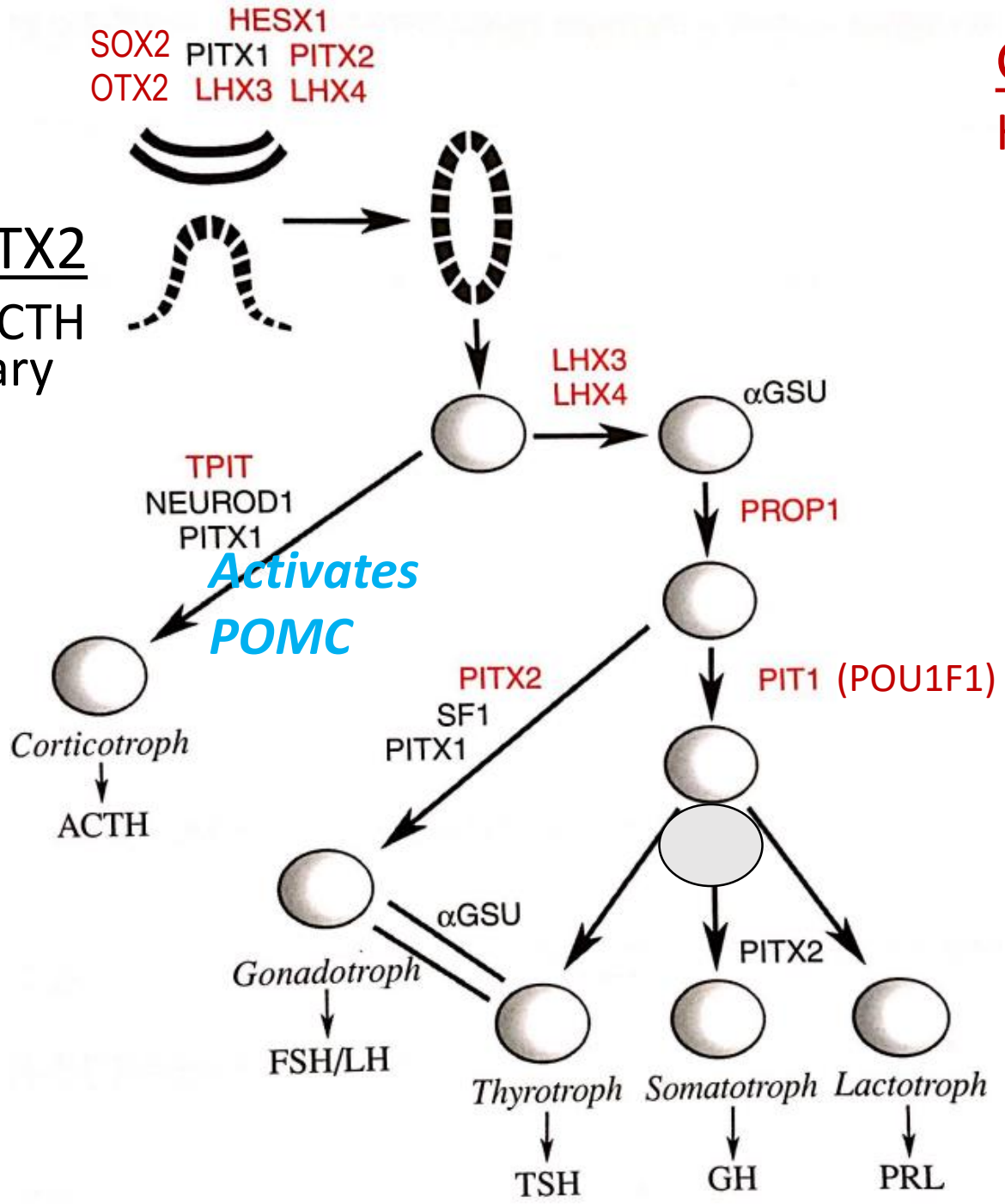
GH ± TSH, PRL, LH/FSH, ACTH ± ectopic posterior pituitary (± ADH)

TPIT

ACTH

PITX2

GH, LH/FSH



LHX3

GH, TSH, PRL, LH/FSH ± ACTH

LHX4

GH, TSH, PRL, ACTH, LH/FSH

PROP1

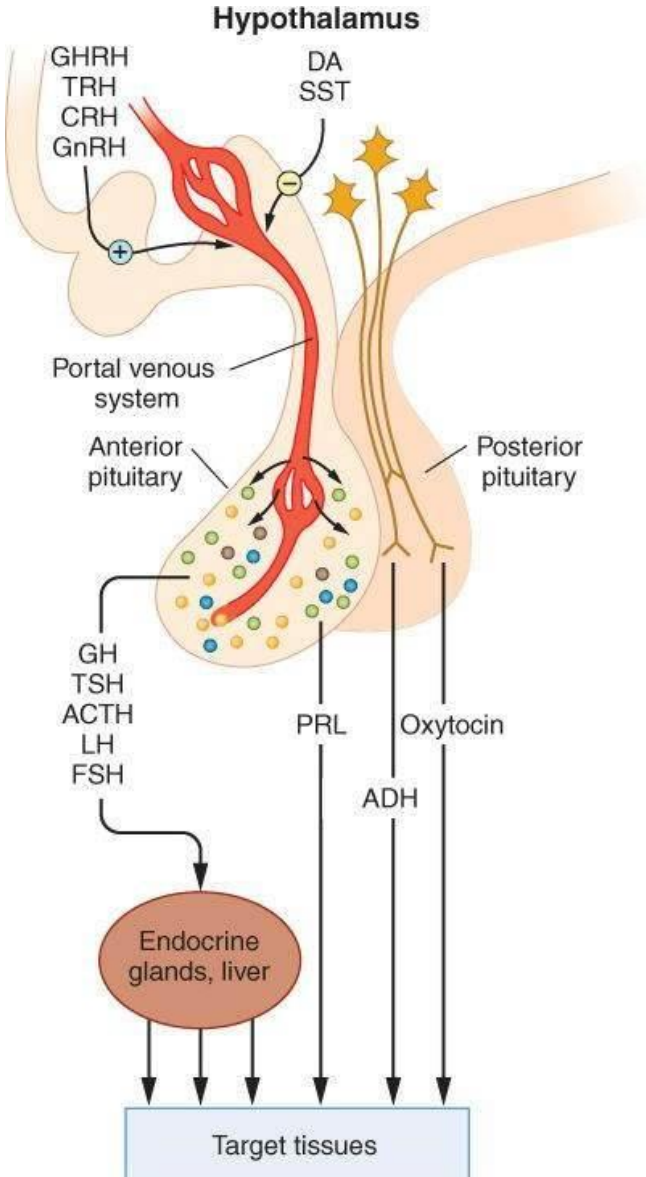
GH, TSH, PRL, LH/FSH ± evolving ACTH

PIT1

GH, TSH, PRL

Gene	Endocrine Deficiency	Other Clinical Features	Inheritance	Prevalence
Optic Nerve Hypoplasia (Septo-optic dysplasia)				
HESX1, SOX2, OTX2	Isolated GH def or combined def	Eye abnormalities (ONH), midline brain deformities	Any	1:10,000 (incidence)
Combined Pituitary Hormone Deficiencies (CPHD)				
LHX3	Anterior pituitary hormone def (APHD)	Limitation of neck rotation, short/rigid cervical spine, SNHL	AR	Rare
LHX4	APHD	± Cerebellar abnormalities	AD	Rare
PROP1	APHD		AR	3% sporadic 30-50% familial
PIT1	GH, TSH, PRL	± Severe hypothyroidism	Any	1-3% sporadic 30% familial
Axenfeld–Rieger Syndrome				
PITX2	GH, LH/FSH	Eye/dental abnormalities, protuberant umbilicus	AD	Rare
Congenital Isolated Adrenocorticotrophin Deficiency				
TPIT	ACTH	± Profound hypoglycemia	Any	Rare

Isolated Pituitary Hormone Deficiencies



Growth Hormone (GH)

- GH1
  - growth hormone gene
- GHRHR
  - growth hormone releasing hormone receptor

Thyroid Stimulating Hormone (TSH)

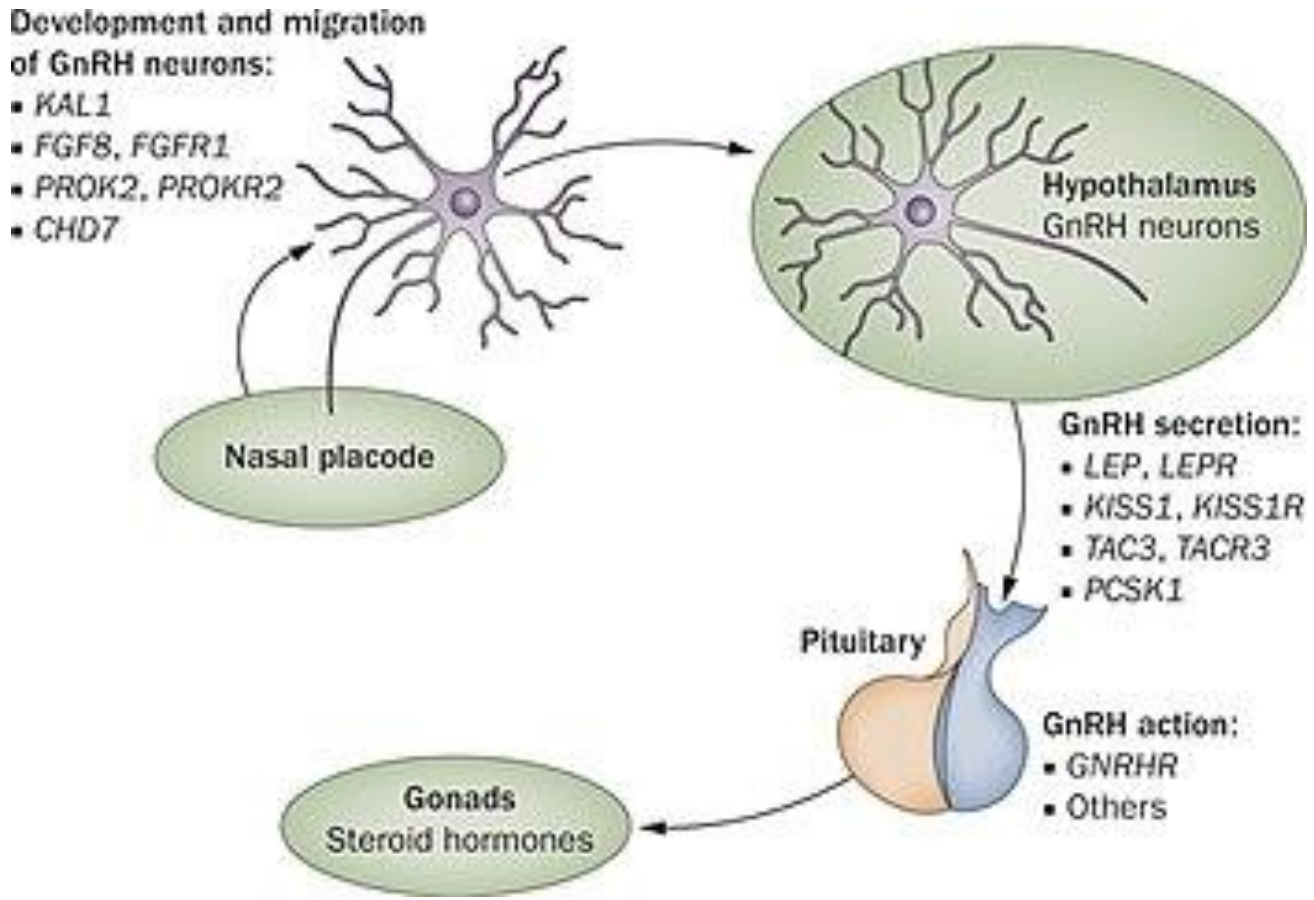
- TSHβ
  - TSH beta subunit gene
- TSHR
  - TSH receptor

Adrenocorticotropin Hormone (ACTH)

- PC1
  - Prohormone convertase 1
- POMC
  - pro-opiomelanocortin
- CRH
  - corticotropin-releasing hormone

Isolated Pituitary Hormone Deficiency of Gonadotropins (LH/FSH)

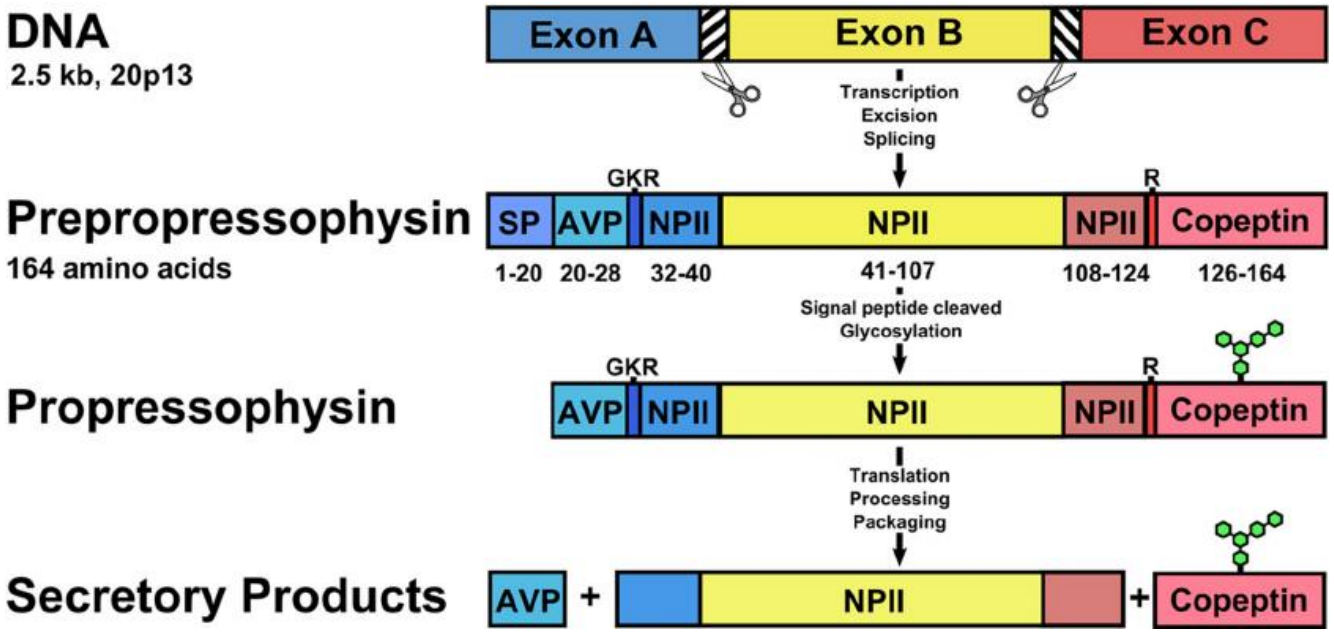
- Kallman syndrome
- Idiopathic hypogonadotrophic hypogonadism (IHH)



Congenital Posterior Pituitary Disorder

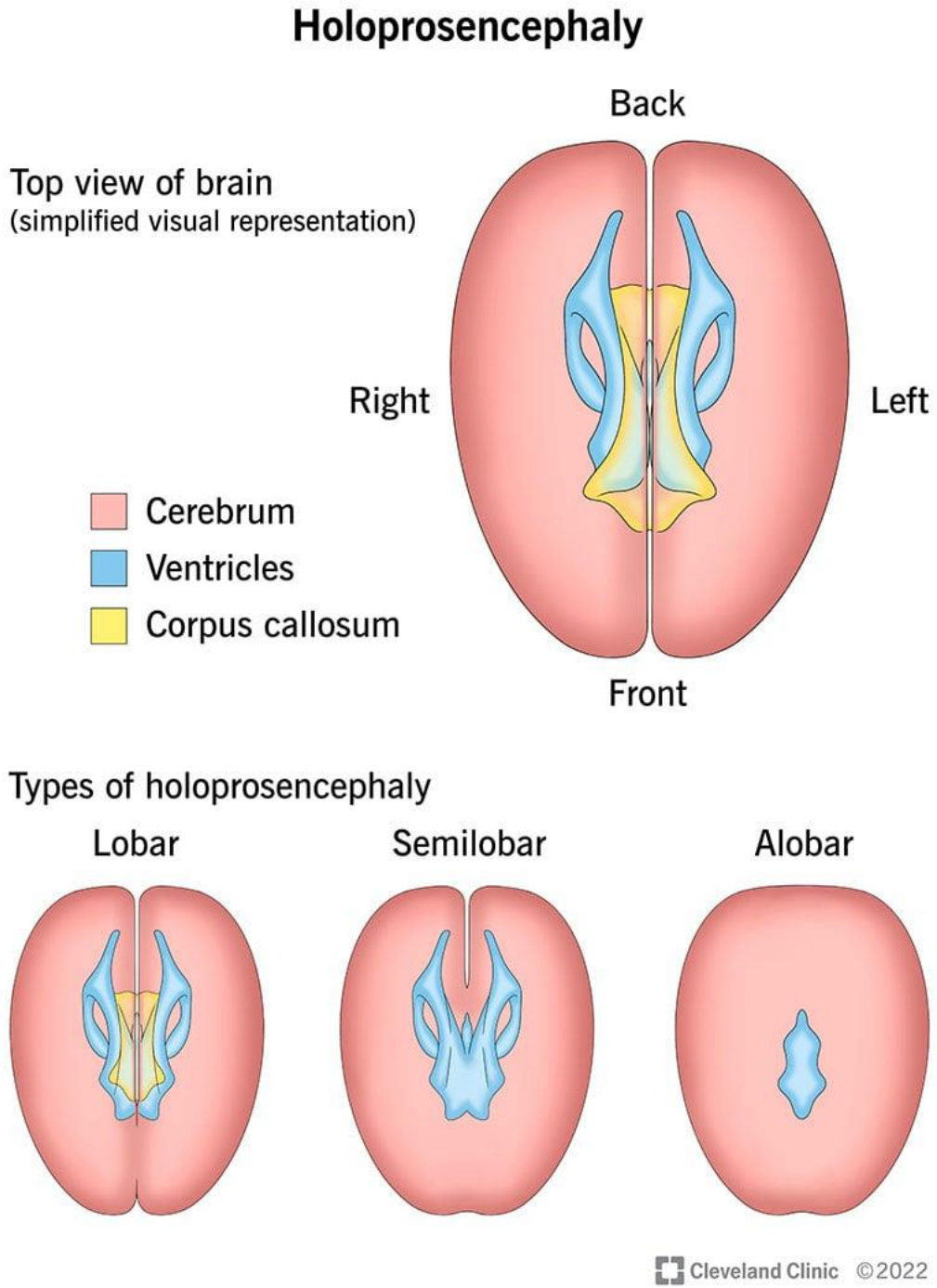
<u>Familial antidiuretic hormone (ADH) deficiency</u>

- Rare (acquired more common)
- Central diabetes insipidus
- Mutations of the **arginine vasopressin (AVP)-neurophysin II gene**
- Autosomal dominant
- Signs and symptoms usually become apparent in childhood and worsen over time



Holoprosencephaly

- Encompasses a number of structural midline forebrain abnormalities
- Trisomy 13, **SHH**, SIX3, TGIF1, ZIC2, PTCH1, FOXH1, NODAL, CDON, **FGF8**, and **GLI2**
- Deficient ADH in up to 70% of patients
  - With/without hypopit/IGHD



Genetic Testing

- Majority of children with isolated GH or combined pituitary hormone deficiencies do not have identified mutations
  - Sporadic or yet to be identified mutations or genes
- Suggested that patients with IGHD or CPHD associated **with** abnormalities of pituitary development undergo genetic testing
  - Evolution of disease
  - Genetic counseling

Prevention Genetics: Combined Pituitary Hormone Deficiency (CPHD) Panel

- *GLI2*
- *HESX1*
- *LHX3*
- *LHX4*
- *OTX2*
- *POU1F1*
- *PROP1*
- *SOX2*
- *SOX3*

GeneDx:

HESX1

Invitae: Septo-optic Dysplasia Panel

- ✓ GLI2
- ✓ HESX1
- ✓ OTX2
- ✓ PAX6
- ✓ PROP1
- ✓ SOX2
- ✓ SOX3
- ✓ TAX1BP3

Relationship between symptoms and specific hormone deficiencies

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In congenital hypopituitarism, hypoglycemia is caused by a deficiency of:

- GH
- TSH
- LH/FSH
- ACTH
- ADH

Total Results: 0

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Signs and Symptoms of Neonatal Hypopituitarism - Hypoglycemia

- Growth hormone deficiency
  - Fasting hypoglycemia with mild ketosis
  - Needed for gluconeogenesis
  - Poor response to glucagon (because of above and this is not hyperinsulinism)
  - GH is a counter-regulatory hormone

- Adrenal insufficiency
  - Cortisol is a counter-regulatory hormone

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In congenital hypopituitarism, micropenis is caused by a deficiency of:

- GH
- TSH
- LH/FSH
- ACTH
- ADH

Total Results: 0

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Signs and Symptoms of Neonatal Hypopituitarism - Micropenis

- Hypogonadotropic hypogonadism: low LH → low T → low DHT → less phallus growth

- GH deficiency: less tissue growth

- Undescended testes
- Lack of puberty
- Infertility

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In congenital hypopituitarism, jaundice is caused by a deficiency of:

- GH
- TSH
- LH/FSH
- ACTH
- ADH

Total Results: 0

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ADH

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Signs and Symptoms of Neonatal Hypopituitarism - Jaundice

- Hypothyroidism: **Indirect** – prolonged physiological jaundice
- Adrenal insufficiency: **Direct** - cortisol increases bile flow and aids bile acid synthesis and transport
  - TPIT mutation; improved hepatobiliary function following hydrocortisone replacement (before levothyroxine or growth hormone replacement started)
- Growth hormone deficiency: animal studies identified this as a mechanism of hyperbilirubinemia, but it has not been seen in isolated GH deficiency in humans, thus it is still controversial
- Neonatal giant cell hepatitis (NGCH) – multinuclear giant cells develop from liver injury
  - Liver biopsy may occur earlier than a diagnosis of hypopituitarism

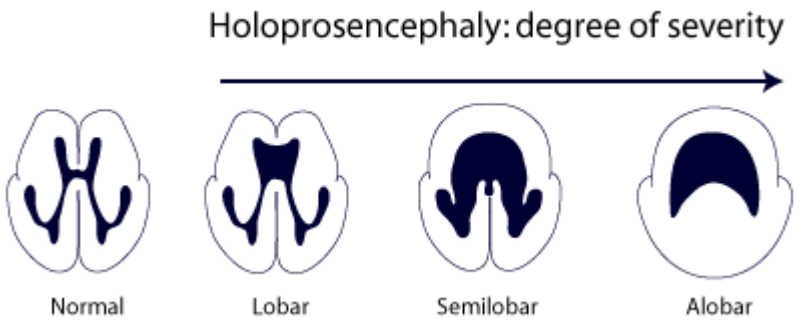
Signs and Symptoms of Optic Nerve Hypoplasia (ONH), also called Septo-Optic Dysplasia (SOD)

- **Optic nerves** are abnormally small and with fewer connections between the eyes and brain
- Impaired vision in one or both eyes
- Nystagmus
- Abnormal development of structures separating the right and left hemispheres of the **brain**
  - Corpus callosum, septum pellucidum
  - Depending on which structures are affected +/- intellectual disability and other neurological problems
- **Pituitary** hypoplasia/varying degree of hypopituitarism

Younger maternal age (+/- maternal substance abuse)

“Midline Defects”

- Single central incisor
- Cleft lip and/or palate
- Optic nerve hypoplasia/aplasia
- Absent or hypoplastic septum pallucidum and/or corpus callosum
- Holoprosencepahly



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sm, Second Edition: www.accesspediatrics.com
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Likelihood of Hypothalamic/Pituitary Dysfunction in ONH (SOD)

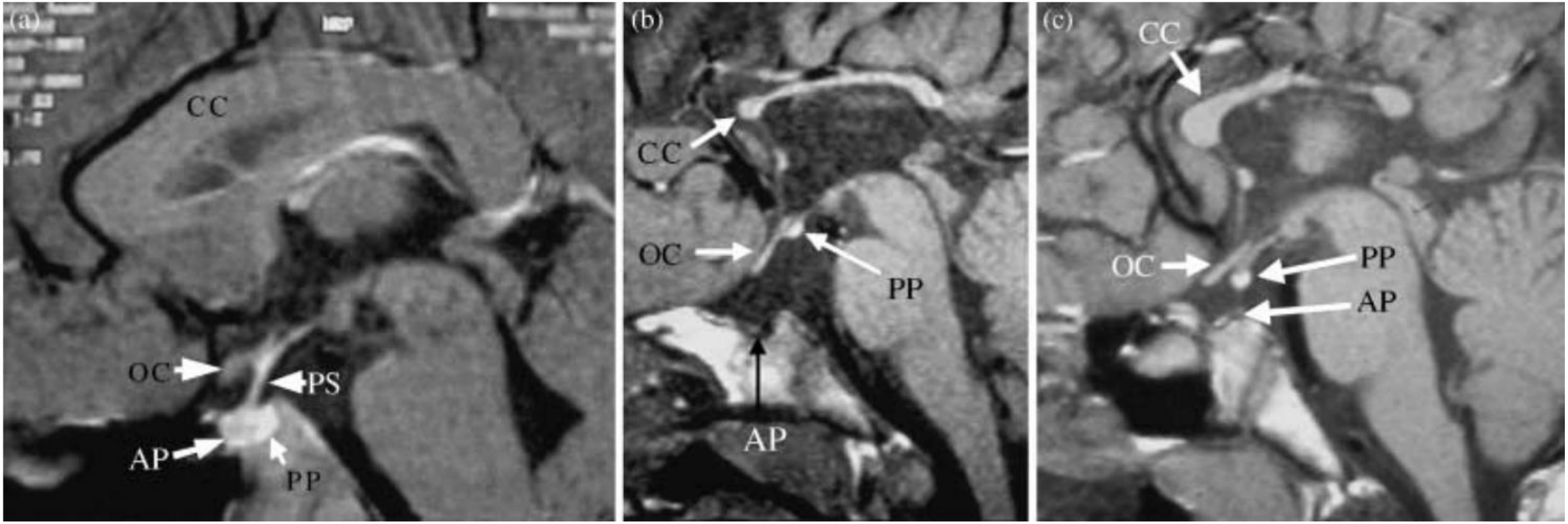
Endocrinopathy affect most regardless of laterality or neuroradiographic abnormalities	Hypopituitarism in 75 %	GHD was the most common 70%	Central hypothyroidism 43%
ACTH deficiency 27%	Diabetes insipidus 5%	Delayed or precocious puberty	Evolving pituitary dysfunction has been documented but is poorly understood

Garcia-Filion & Borchert. Curr Treat Options Neurol. 2013;15(1):78-89

Does Imaging Aid in Diagnosis or Prediction?

- Ectopic posterior pituitary (EPP)
  - More common in multiple pituitary hormone deficiencies (up to 87% of cases in one study) than in isolated GHD (only 10% of cases)
  - May be a marker of permanent GH deficiency
- Hypoplastic adenohypophysis – is it helpful (eh, depends on the study)
- Pituitary abnormalities
  - In 80% with isolated GHD
  - In 93% with combined pituitary hormone deficiencies
- If peak GH < 3 ng/mL, higher frequency of MRI abnormalities (irrespective of number of pituitary deficiencies)
  - 90% with GH < 3 ng/mL had MRI findings compared with 39% with GH ≥ 3 ng/mL

Alyahyawi et al. Horm Res Paediatr 2018;89:22–30.
Garel C, Leger J. Horm Res 2007;67:194–202.
Hamilton et al. Am J Neuroradiol. 1998;19:1609-1615.



- Pituitary height is thought to be directly related to GH levels (and pubertal status)
- However, no correlation has been found between the size of the pituitary gland and the severity of the endocrine defect

Gene	Endocrine Deficiency	Other Clinical Features
Optic Nerve Hypoplasia (Septo-optic dysplasia)		
HESX1, SOX2, OTX2	Isolated GH def or combined def	Ectopic posterior pituitary, small anterior pituitary, empty sella
Combined Pituitary Hormone Deficiencies (CPHD)		
LHX3	Anterior pituitary hormone def (APHD)	Pituitary hypoplasia, enlarged anterior pituitary, possible microadenoma
LHX4	APHD	Ectopic posterior pituitary, small sella and anterior pituitary, abnormal cerebellar tonsils
PROP1	APHD	Small anterior pituitary, intrasellar or suprasellar mass (mechanism unknown)
PIT1	GH, TSH, PRL	Small anterior pituitary
Axenfeld–Rieger Syndrome		
PITX2	GH, LH/FSH	Empty sella
Congenital Isolated Adrenocorticotrophin Deficiency		
TPIT	ACTH	Normal or hypoplastic pituitary

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What cells are the most abundant cell in the pituitary gland?

- TSH-secreting cells
- ADH-secreting cells
- ACTH-secreting cells
- GH-secreting cells
- LH/FSH-secreting cells

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Case #1 Follow Up

Low cortisol (<3 mcg/dL) x2 critical sample & during low-dose ACTH stimulation test

Free T4 low for age* (0.7 ng/dL)

GH suboptimal during critical sample (<7 mU/L)

Stress dose hydrocortisone then levothyroxine started

Since BGs maintained, growth hormone (GH) not started inpatient

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ⓘ Do not include PHI or patient-specific data in SmartPhrases.

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TSH (mU/L)

1-6 days of life: 0.71-57.2

7-90 days of life: 0.99-10.9

3-12 months: 0.61-10.7

1-3 years: 0.6-5.8

3-5 years: 0.63-5.63

6-8 years: 0.76-5.35

9-11 years: 1.04-5.61

12-15 years: 0.51-4.6

16-20 years: 0.38-3.47

Free T4 (ng/dL)

1-6 days of life: 0.85-2.68

7-90 days of life: 0.99-2.33

3-12 months: 0.96-1.83

1-3 years: 1.08-1.66

3-5 years: 1.03-1.58

6-8 years: 1.06-1.69

9-11 years: 1.03-1.68

12-15 years: 0.93-1.7

16-20 years: 0.95-1.7

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Thyroid Function Test Ranges for Premature Infants +/- 2 SD

Gestation (wk)	Cord Conversion		d7 Conversion		d14 Conversion		d28 Conversion	
T4	Lower (mcg/dL)	Upper (mcg/dL)	Lower (mcg/dL)	Upper (mcg/dL)	Lower (mcg/dL)	Upper (mcg/dL)	Lower (mcg/dL)	Upper (mcg/dL)
23-27	1.399	9.479	0.466	7.615	0*	9.868	1.476	10.800
28-30	2.253	10.334	2.098	10.490	2.098	11.111	2.797	12.121
31-34	3.108	12.121	2.564	16.239	1.943	16.239	3.030	14.841
>=37	5.284	13.054	6.915	18.415	7.925	13.520	5.361	14.064
FT4	Lower (ng/dL)	Upper (ng/dL)	Lower (ng/dL)	Upper (ng/dL)	Lower (ng/dL)	Upper (ng/dL)	Lower (ng/dL)	Upper (ng/dL)
23-27	0.458	2.106	0.350	2.587	0.435	2.455	0.645	2.354
28-30	0.591	2.300	0.497	3.139	0.777	2.517	0.855	2.564
31-34	0.824	2.160	0.995	3.294	1.103	2.813	0.963	2.797
>=37	0.629	2.183	1.562	3.831	1.469	2.587	0.963	2.331
TBG	Lower (mg/L)	Upper (mg/L)	Lower (mg/L)	Upper (mg/L)	Lower (mg/L)	Upper (mg/L)	Lower (mg/L)	Upper (mg/L)
23-27	7.4	30.2	9.1	25.1	8.5	29.3	10.8	34.8
28-30	9.4	29.8	10.4	30	10.7	31.5	9.8	34.2
31-34	7.6	40.4	8.6	40.2	7.6	39.2	7.9	38.3
>=37	18	40.4	12.1	54.9	19.9	35.1	0*	161.3
TSH	Lower (mU/L)	Upper (mU/L)	Lower (mU/L)	Upper (mU/L)	Lower (mU/L)	Upper (mU/L)	Lower (mU/L)	Upper (mU/L)
23-27	1	12.6	0*	8.7	0*	9.3	0*	13.2†
28-30	0*	14.4	0*	8.6	0*	27.3†	0*	8.6
31-34	0*	18.3	0*	13.2†	0*	22.4†	0*	10.3†
>=37	0*	16.3	0*	6.2	0*	6.5	0*	3.6
T3	Lower (ng/dL)	Upper (ng/dL)	Lower (ng/dL)	Upper (ng/dL)	Lower (ng/dL)	Upper (ng/dL)	Lower (ng/dL)	Upper (ng/dL)
23-27	0*	49.48	0*	72.91	0*	90.49	8.46	117.83
28-30	0*	70.31	7.81	104.16	16.28	128.25	24.74	149.73
31-34	0*	82.03	20.18	163.40	27.34	191.39	39.06	200.51
>=37	0*	128.90	47.52	248.03	104.81	229.80	111.97	239.57
rT3	Lower (ng/dL)	Upper (ng/dL)	Lower (ng/dL)	Upper (ng/dL)	Lower (ng/dL)	Upper (ng/dL)	Lower (ng/dL)	Upper (ng/dL)
23-27	39.06	716.10	6.51	162.75	13.02	143.22	19.53	123.69
28-30	45.57	592.41	13.02	195.30	26.04	130.20	6.51	136.71
31-34	52.08	546.84	6.51	214.83	19.53	149.73	6.51	136.71
>=37	78.12	364.56	19.53	201.81	13.02	143.22	6.51	110.67

Williams, et al. Developmental Trends in Cord and Postpartum Serum Thyroid Hormones in Preterm Infants. J Clin Endocrinol Metab. 2004;89:5314–5320

**Limited numbers and sample variability prevent lower range determination.*

†Additional literature conclude that TSH should be < 10 mU/L in the first 12 months of life.

Conversion table provided by students MaryBeth, Reesa and Raquel

11/1/2016 UF Peds Endo

Case #1 Follow Up

Sodium levels normal (<145 mmol/L), without excessive urination (<5 ml/kg/hr)

Sella MRI: hypoplasia of adenohypophysis, ectopic posterior pituitary bright spot; normal optic nerves (MRI and Ophthalmology eval)

Hyperbilirubinemia resolved without need for phototherapy

Gonadotropins 'low' (not at pubertal levels) during 'mini-puberty' (in boys 2 weeks – 6 months old)

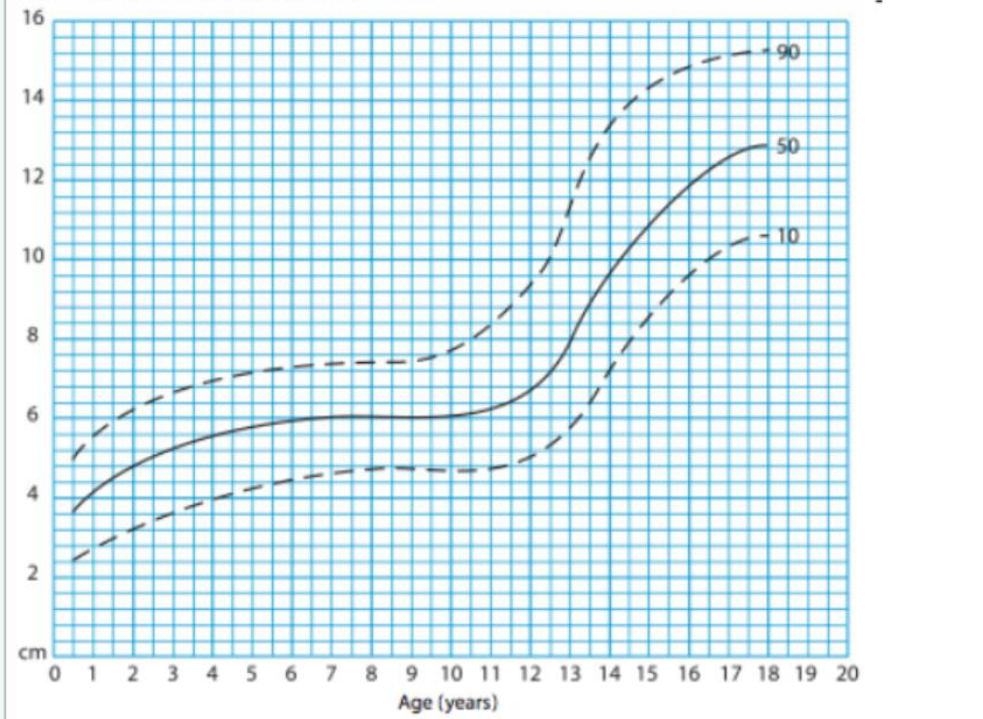
Treated with 3 months of IM testosterone for micropenis (SPL<2.5cm*) with increased phallus size

User SmartPhrase – LJPENILELENGTHINFANTNORMS [258363]

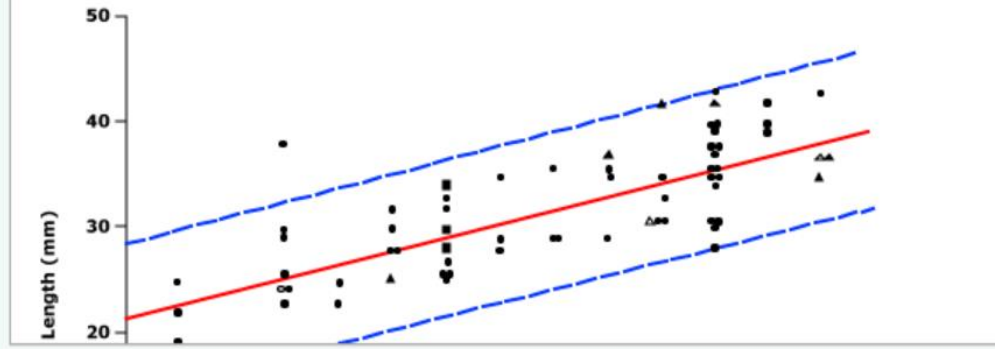
Do not include PHI or patient-specific data in SmartPhrases.

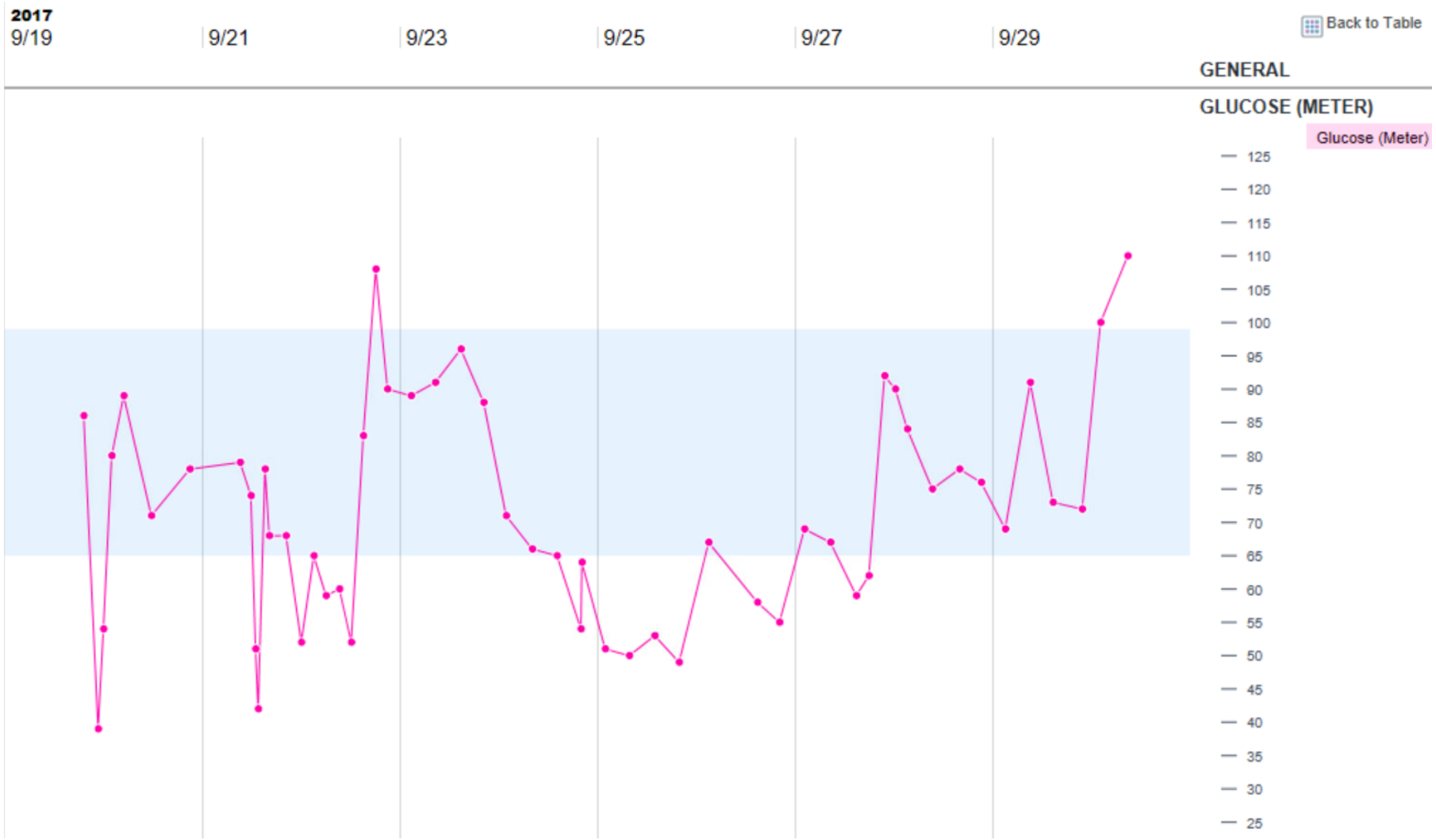
Insert SmartText | Insert SmartList

Stretched penile length growth chart:



Reproduced from Shonfeld & Beebe. 1942, Journal of Urology, 48, 759-777.





Case #2

- 7 day old F, GA 39 wks, BW 2890g
- At outside nursery, had hypothermia and persistent hypoglycemia: BG 35 mg/dL during episode of clonic movements and eye deviation

Case #2

- Brain (sella) MRI: septum pellucidum not visualized, hypoplastic corpus callosum, pituitary gland visualized, pituitary stalk not discretely visualized, optic chiasm visualized
- Ophthalmology examination: bilateral optic nerve hypoplasia with no pupillary responsiveness and poor to no vision predicted

When poll is active, respond at **pollev.com/laurajacobsen568**

Select all features that can be associated with hypopituitarism

- Persistent hypoglycemia
- Persistent jaundice
- Micropenis
- SGA
- Central incisor
- Congenital hearing loss

Total Results: 0

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Select all features that can be associated with hypopituitarism

- Persistent hypoglycemia
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Summary, Think Congenital Hypopituitarism if…

- Persistent hypoglycemia in infancy
- Persistent jaundice
- Micropenis in infancy
- Midline defects
- Multiple pituitary hormone deficiencies

- Pituitary development controlled by several key genes
  - HESX1, SOX2, OTX2, LHX3, LHX4, PROP1, PIT1, PITX2, TPIT
- Imaging is necessary but with limitations in diagnosis and prediction
- Most will **not** have confirmed mutations, but genetic testing MAY provide insight into evolution of disease and heredity if positive