Monogenic and Syndromic Obesity

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Disclosures

Speaker Bureau: Rhythm Pharmaceuticals

Learning Objectives

- Review the energy balance regulation pathway.
- To introduce rare disorders of obesity, also known as monogenic obesity.
- Review clinical features of syndromic genetic disorders that cause obesity

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- To introduce rare disorders of obesity, also known as monogenic obesity.
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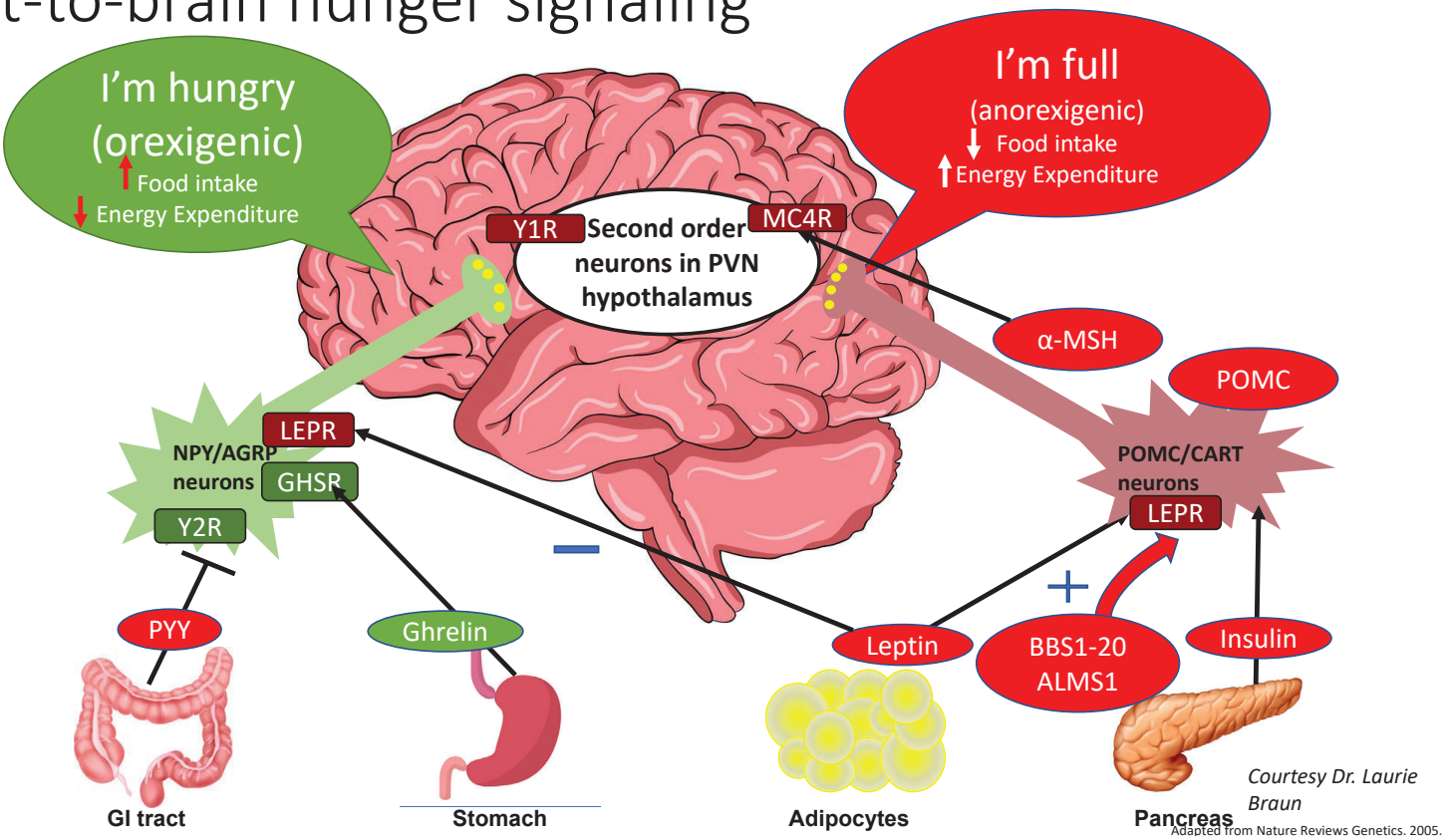
Gut-to-brain hunger signaling



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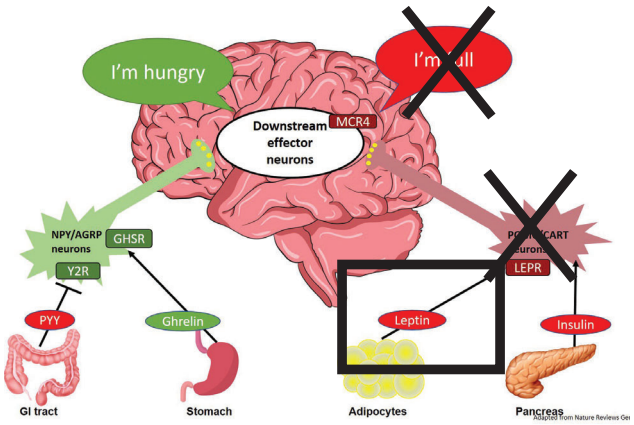
Monogenic Obesity



Congenital Leptin Deficiency

- **Cause**: mutations in gene for leptin (*LEP*)
- **Phenotype**: Hyperphagia with severe, early onset obesity, altered immune function and delayed puberty
- **Prevalence**: EXTREMELY RARE – only several case reports in consanguineous families*
- **Diagnostic test**: leptin level (undetectable), genetic testing
- **Treatment**: recombinant leptin

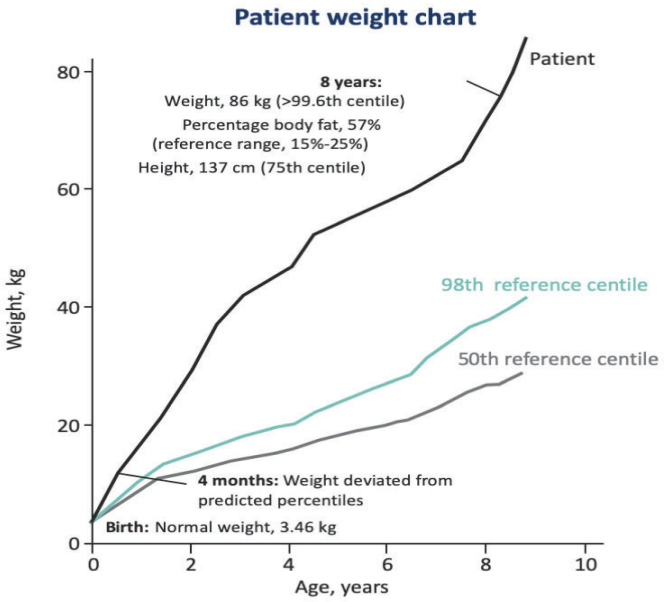
*Mostly found in consanguineous families.
Adapted from Bell CG, et al. *Nat Rev Genet*. 2005;6(3):221-34.

Leptin deficiency Case

- Female patient with rapid early onset weight gain at 4 months of age
- Hyperphagia (demanding food continuously, ate much more than siblings)
- Developed growth abnormalities in leg bones

  -corrective leg surgery

  -liposuction of lower limb fat to try to improve mobility



Montague et al Nature. 1997;387:903–908

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Leptin deficiency
Case continued..

- Endocrine tests
  - Serum Leptin undetectable
  - Insulin (Elevated markedly)
  - Proinsulin (4 times the ULN)
- Genetic tests:
  - Homozygous LEP frameshift mutation detected
  - Parents were heterozygous
- Eligible for treatment with recombinant human leptin replacement

Montague et al Nature. 1997;387:903–908

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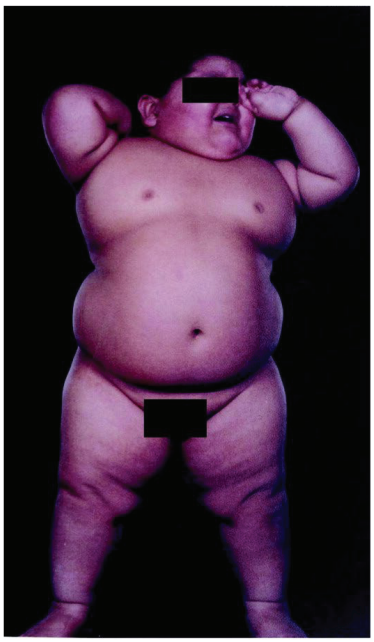
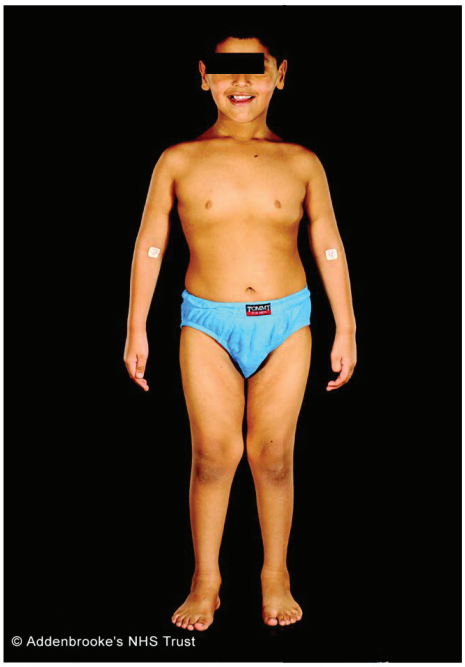


weight = 40kg, age 3yrs

BEFORE LEPTIN



weight = 29kg, age 6yrs

AFTER LEPTIN

Source: Endocrinology Reviews

Leptin treatment in Leptin deficiency

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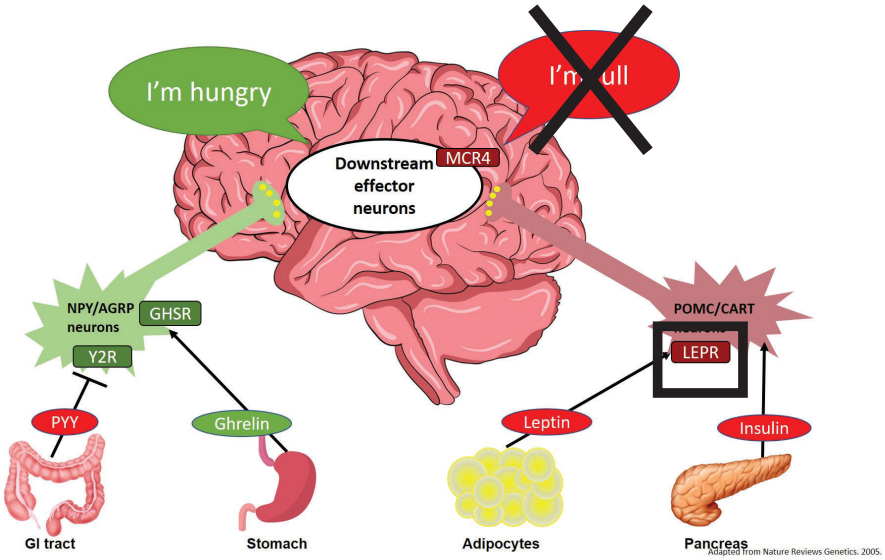
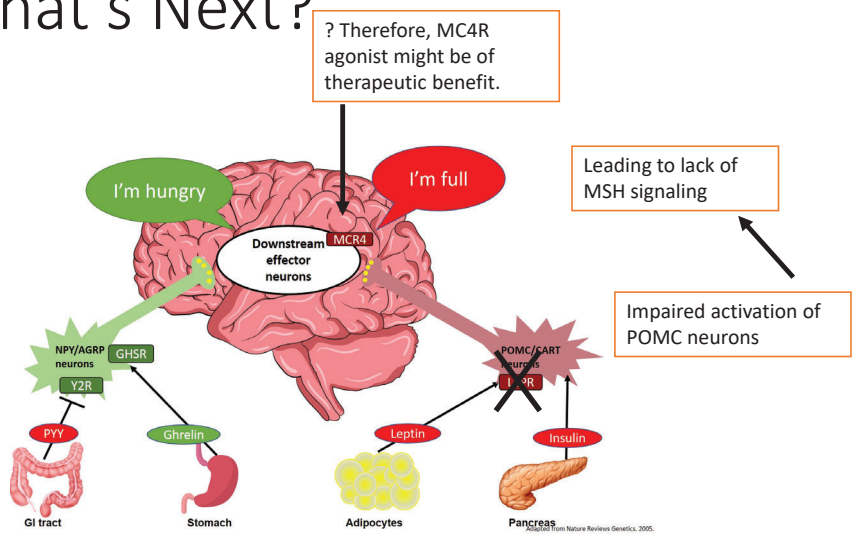
Monogenic Obesity:

Leptin receptor deficiency



- **Cause:** mutations in gene for leptin receptor (*LEPR*)
- **Phenotype:** Hyperphagia with severe, early-onset obesity and problems with sexual development [same as leptin deficiency]
- **Prevalence:** EXTREMELY RARE- only several case reports*
- **Diagnostic test:** leptin level [very high], genetic testing
- **Treatment:** none available, MC4R agonist in development

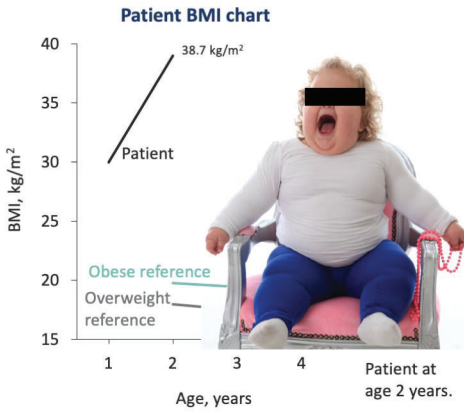
Leptin Receptor Deficiency: What's Next?



Adapted from Bell CG, et al. *Nat Rev Genet*. 2005;6(3):221-34.

LEPR Deficiency
Case 2

- 2-year-old female presents with progressive severe obesity from birth
- Consoled only by food
- Parents were unable to maintain nutritional plan owing to hyperphagia



Kleinendorst L, et al. *BMJ Case Rep*. 2017;2017:bcr-2017-221067.
Image reproduced from Kleinendorst L, et al. *BMJ Case Rep*. 2017;2017:bcr-2017-221067.

Case report: Leptin receptor deficiency

- No developmental delays or other abnormal clinical features present.
- Thyroid and cortisol levels normal
- Leptin levels elevated because of fat mass
- Sequenced MC4R and found no mutations

  -Subsequently sequenced 52 obesity related genes.
- Found compound heterozygous LEPR mutations

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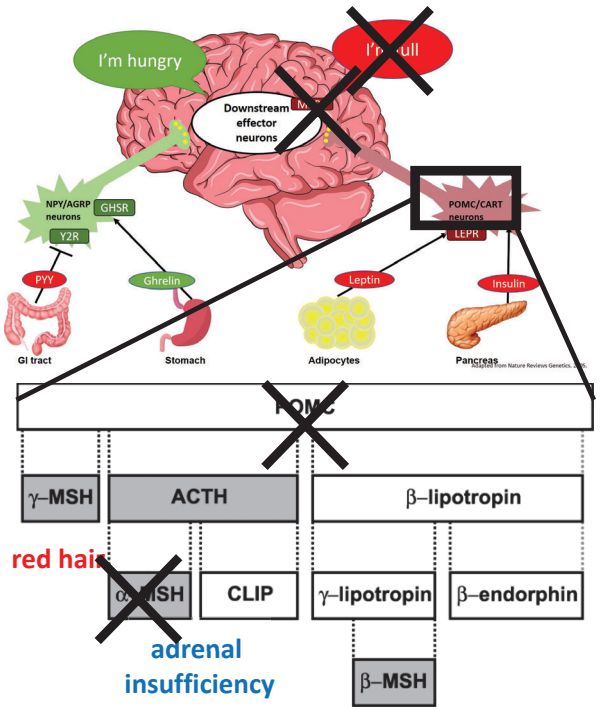
Monogenic Obesity:



POMC mutations

(Pro-opiomelanocortin)

- **Cause:** mutation in *POMC* gene
- **Phenotype:** early-onset obesity, **adrenal insufficiency**, **red hair**
- **Prevalence:** <1/1,000,000
- **Diagnostic test:** distinct phenotype, low cortisol, genetic testing
- **Treatment:**
  - Hydrocortisone replacement for adrenal insufficiency

Krude, Gruters, Trends in Endocrinology & Metabolism, 2000.

POMC Deficiency: Case Report

- 2-year-old Hispanic boy presents with early onset severe obesity

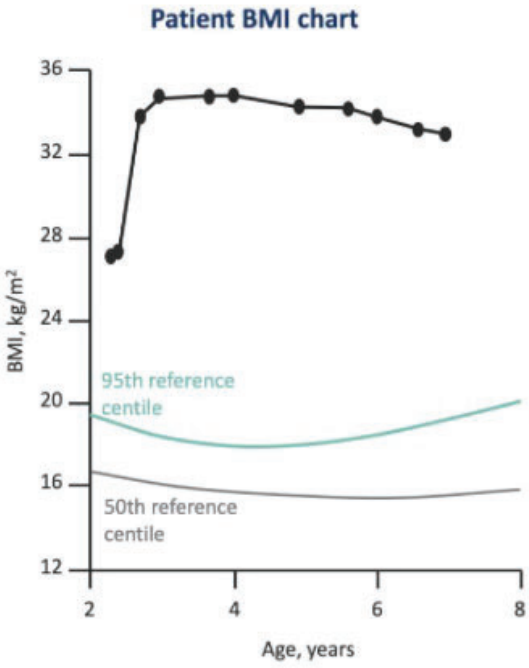
  -Neonatal Hypoglycemia

  -Frequent respiratory infections

  -Speech and motor delay
- Marked Hyperphagia
- Associated Adrenal Insufficiency and hypothyroidism

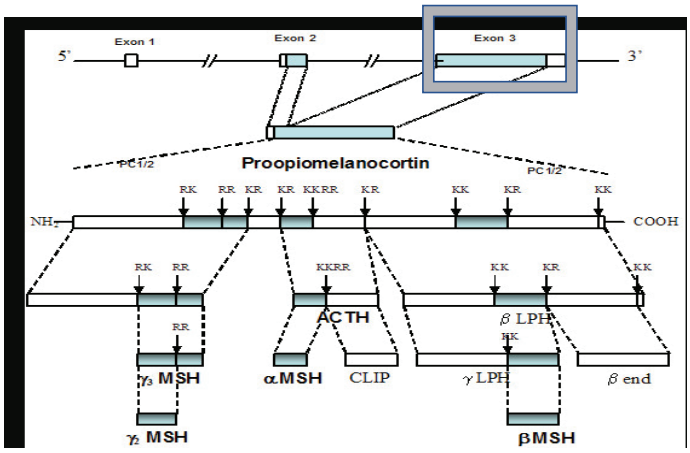
  -Hydrocortisone and levothyroxine replacement

Hilado and Randhawa.J Pediatric Endocrinol Metab.2018;31:815-819



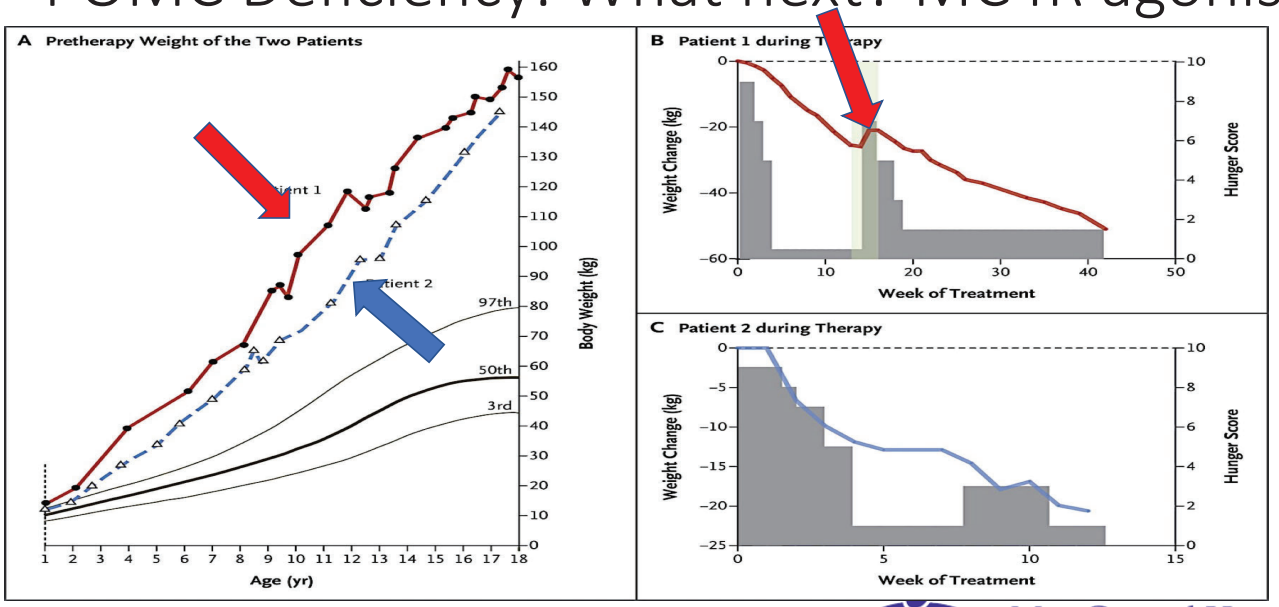
POMC Deficiency: Case 3 (cont'd)

- Negative testing for Prader-Willi syndrome
- Identified homozygous *POMC* mutation in exon 3
- Patient was treated with metformin
- Over a 3-year metformin treatment span, BMI decreased from 34.9 kg/m^2 to 32.9 kg/m^2



BMI = body mass index.
Millington GW. *Nutr Metab (Lond)*. 2007;4:18. Open Access.

POMC Deficiency: What next? MC4R agonists



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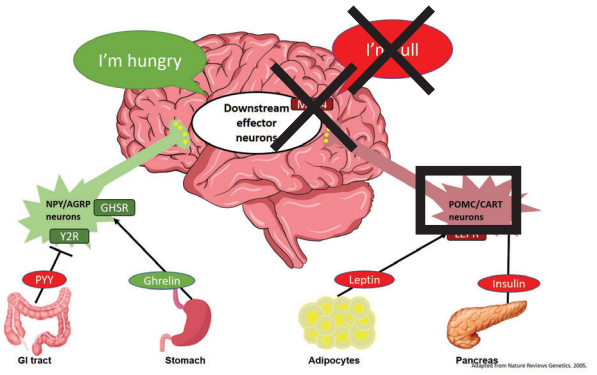
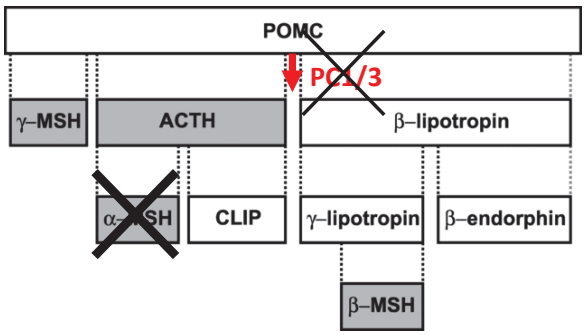
Monogenic Obesity:





PC1/3 mutations

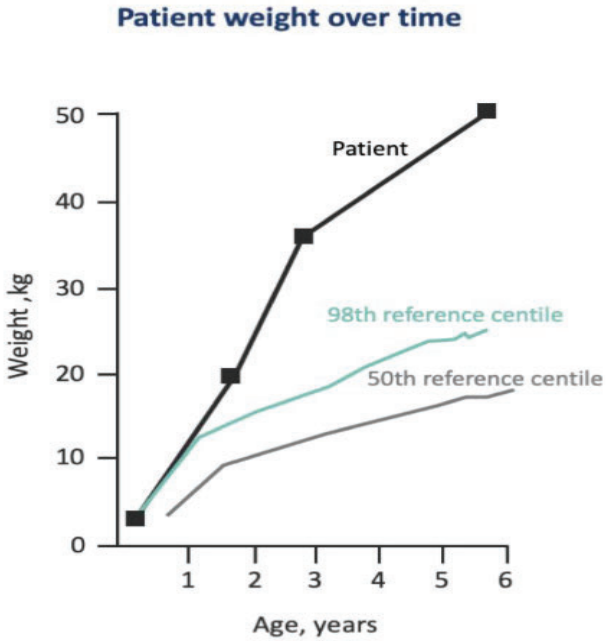
(Pro-hormone convertase)

- **Cause:** mutation in *PCSK1* gene
- **Phenotype:** severe obesity, low insulin, chronic diarrhea, problems with sexual development
- **Prevalence:** VERY rare- only several case reports*
- **Diagnostic test:** high pro-hormone levels, genetic testing
- **Treatment:**
  - Hormone replacement

PCSK1 Deficiency Case Report

- 6-year-old male with severe early onset obesity
- Malabsorptive diarrhea noted at the age of 8 days
- During first year of life required specialized formulas for weight gain
- Reported to be hyperphagic with food seeking behavior at the age of 2 .

Farooqi et al.JCEM 2007;92:3369-3373



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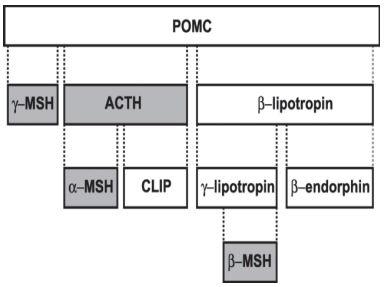
PCSK1 Deficiency
Case 4 (cont'd)

Clinical features of severe early onset obesity, abnormal Insulin/proinsulin ratio and sequencing diagnosed with prohormone convertase (PC) 1/3 deficiency

- Elevated ACTH precursor

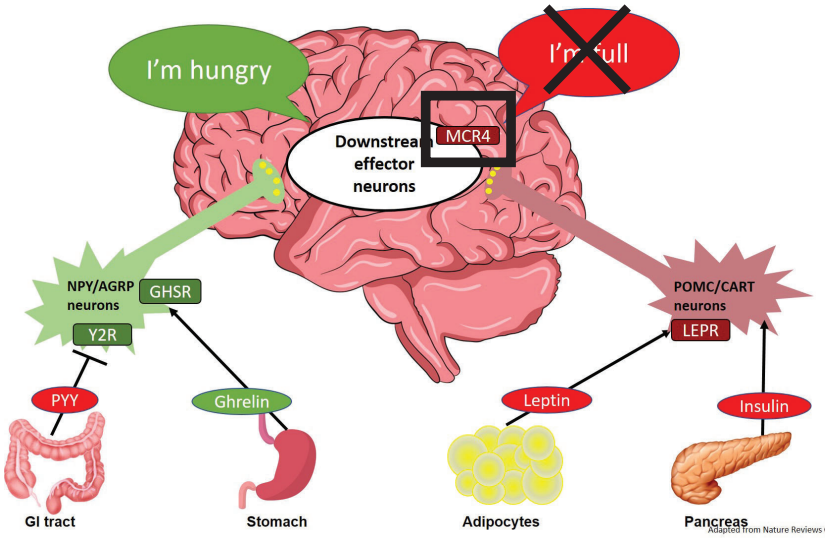
(549 pmol/l Ref range:78 pmol/l)

- Low free T_4



T_4 = thyroxine.
Farooqi IS, et al. *J Clin Endocrinol Metab.* 2007;92(9):3369-73.

Monogenic Obesity: MC4R mutations



Adapted from Nature Reviews Genetics. 2005.

- **Cause:** mutations in MC4R receptor (autosomal dominant)
- **Phenotype:** Normal mental status;
- Increased fat and lean mass with increased bone mineral density
- Accelerated linear growth(tall stature)
- Hyperinsulinemia
- **Prevalence:** General population at 1:2000
- Prevalence in patients with obesity :0.5 to 1%
- **Diagnosis :** genetic testing
- **Treatment:** *MC4R Agonist (Rhythm) in development*

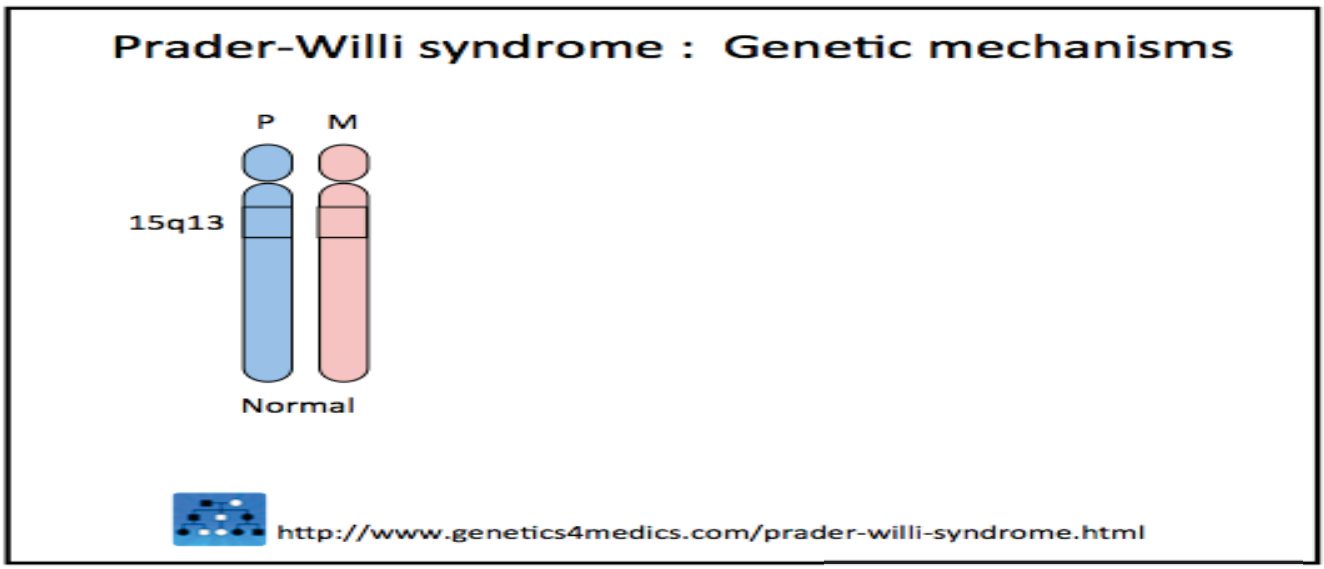
Learning Objectives

- Review the energy balance regulation pathway.
- To introduce rare disorders of obesity, also known as monogenic obesity.
- Review clinical features of syndromic genetic disorders that cause obesity

Syndromic obesity

- The most frequent forms of syndromic obesity are Prader-Willi and Bardet-Biedl syndrome.
- Not a single gene mutation but multiple genes are effected-- and have more features besides just obesity
- Mechanism of obesity is less well understood

Prader-Willi Syndrome



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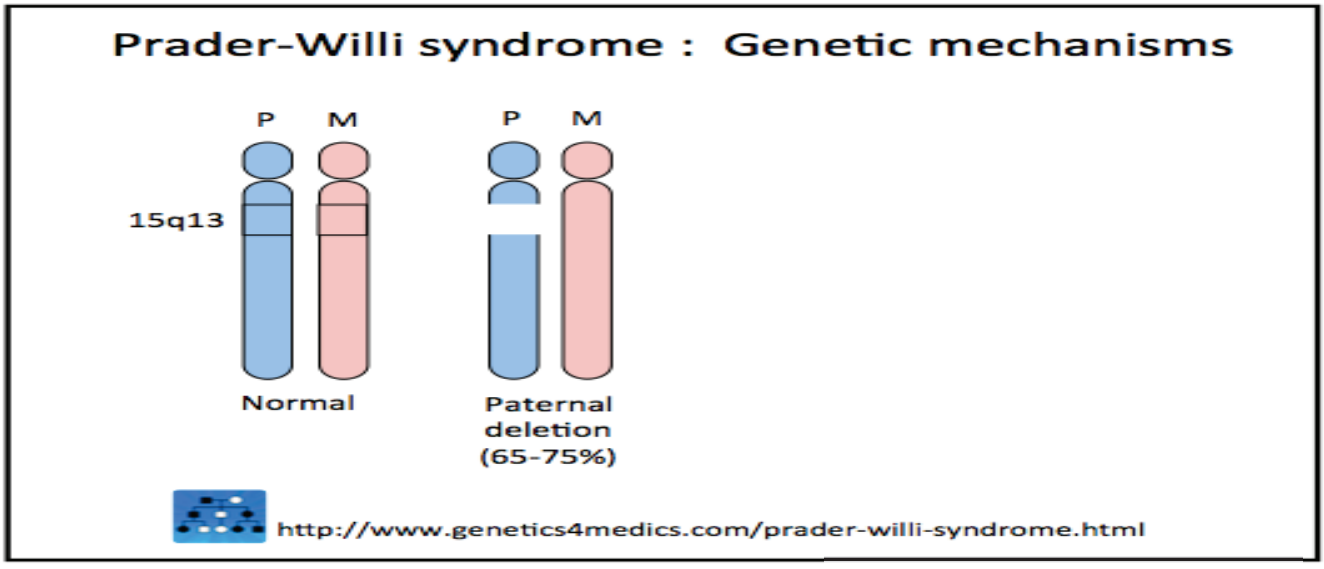
Prader-Willi Syndrome



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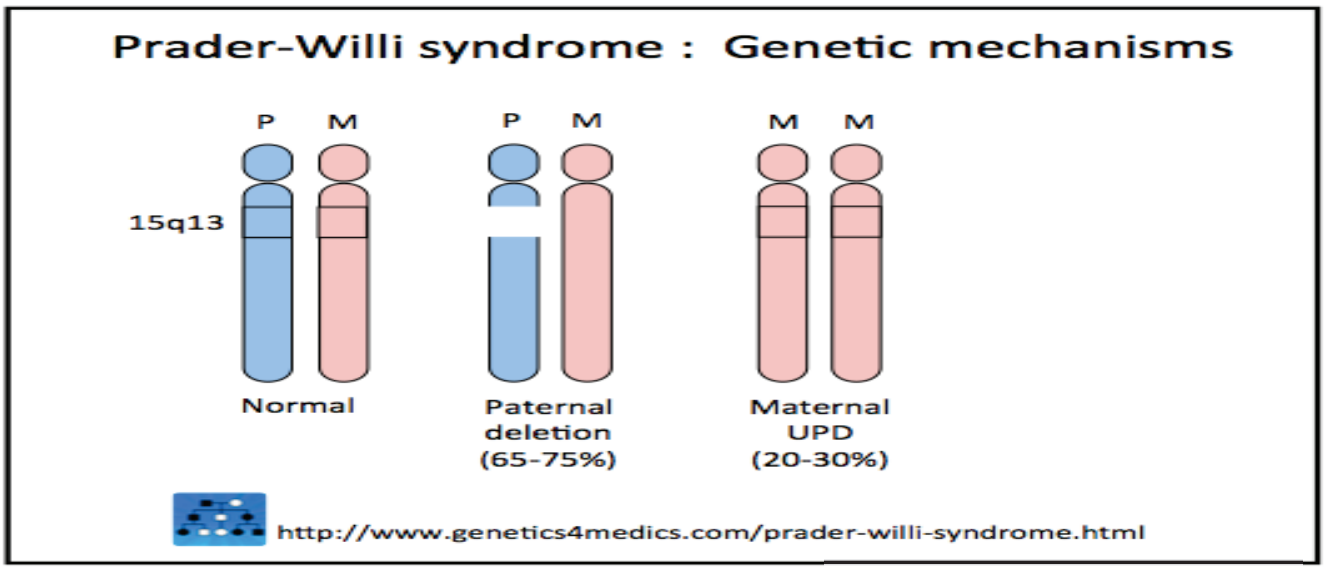
Prader-Willi Syndrome



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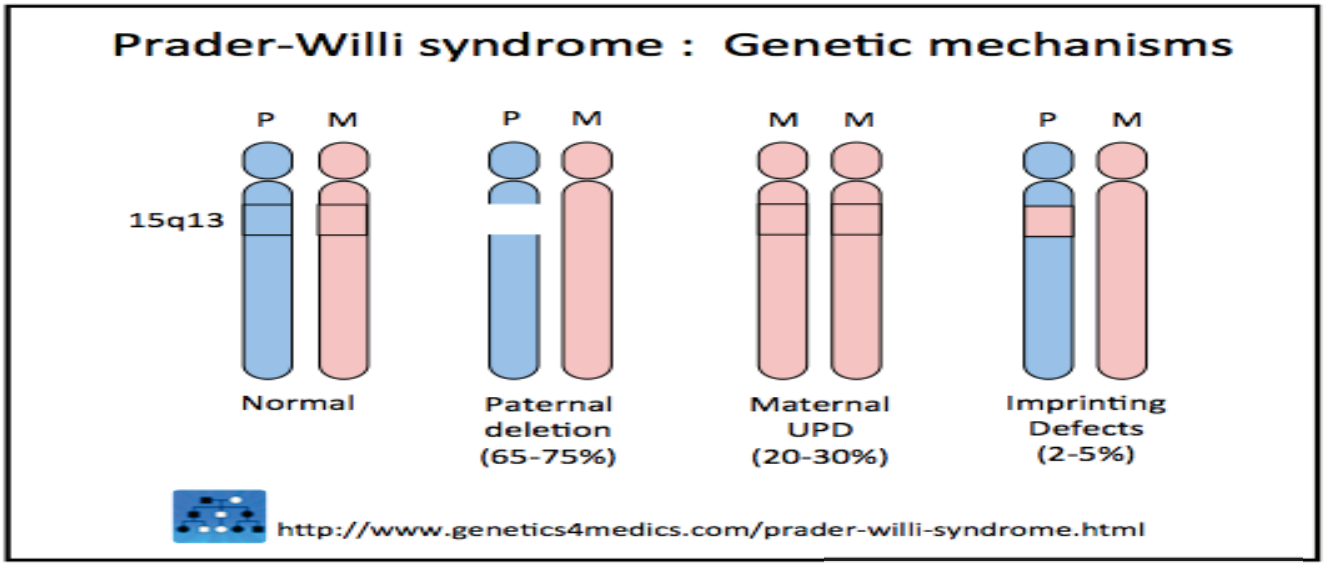
Prader-Willi Syndrome



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Clinical characteristics of Prader-Willi Syndrome

- Birth to 2 years :
  Hypotonia with poor suck
- 2–6 years
  Hypotonia with poor suck
  Global developmental delays
- 6–12 years :
  History of hypotonia with poor suck
  Global developmental delay
  Excessive eating
  (hyperphagia, obsession with food)
  Central obesity

Cassidy, S., & Driscoll, D. (2009). *EJHG, 17*(1), 3-13.

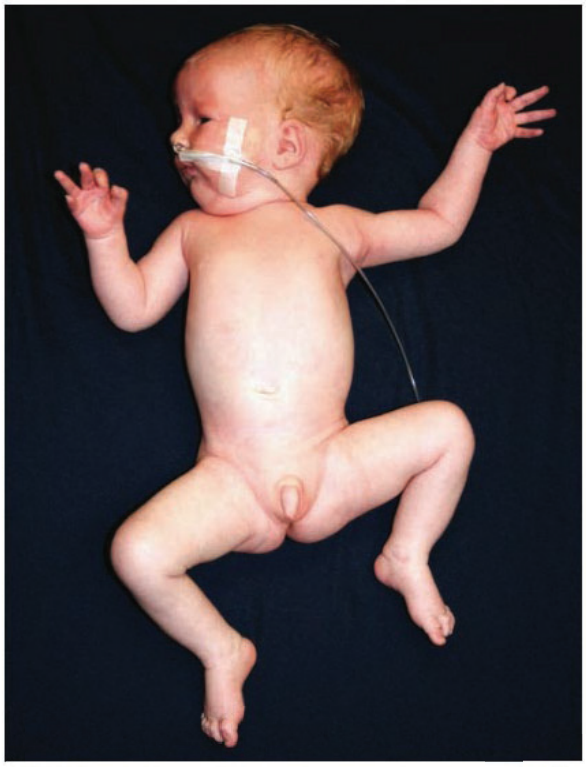
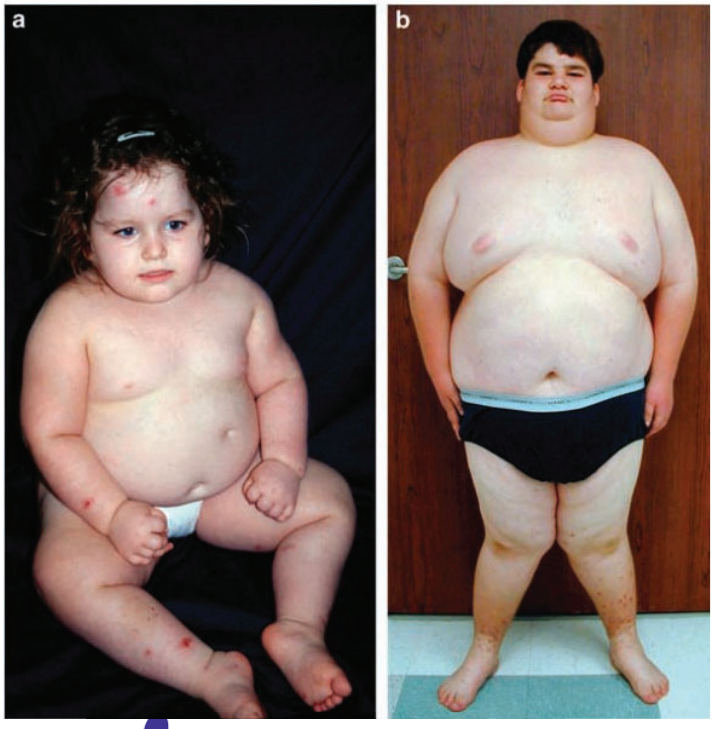


Figure 1 Hypotonia of infancy in a one-month-old male with PWS. Note frogleg position and need for a feeding tube. Also note dolichocephaly and hypoplastic, empty scrotum.

Clinical characteristics of Prader-Willi Syndrome

12 years through adulthood

Intellectual disability
Hyperphagia with central obesity
Hypothalamic hypogonadism
Typical behavior problems
(including temper tantrums and compulsive features)



Cassidy, S., & Driscoll, D. (2009). *EJHG, 17*(1), 3-13.

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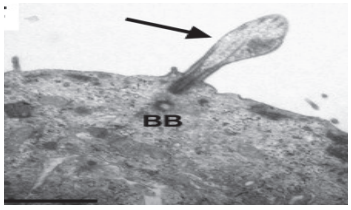
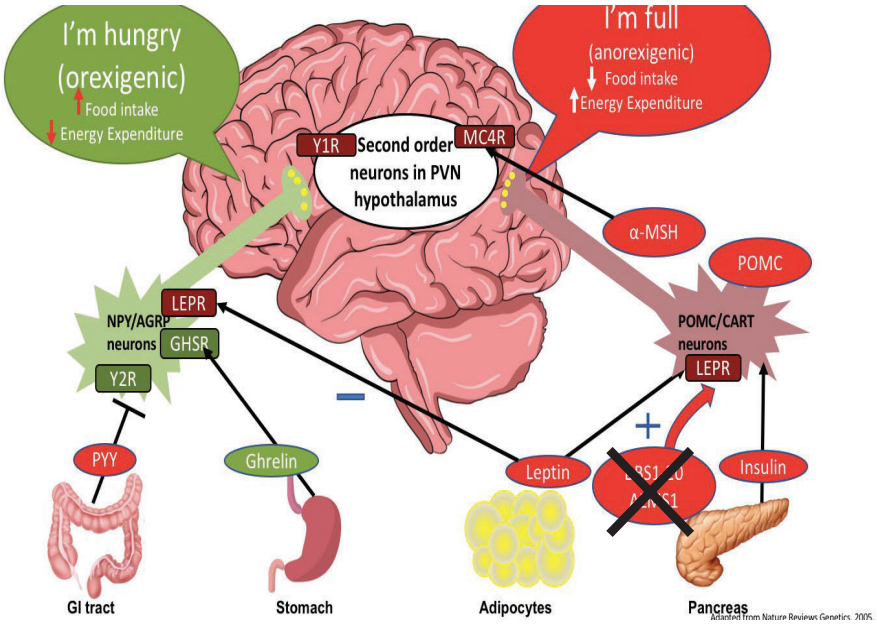
Bardet-Biedl Syndrome (BBS)

- Mutation in BBS genes
- BBS genes are involved in trafficking LEPR to the neuronal cell surface
- Also genetic defect in **cilia**

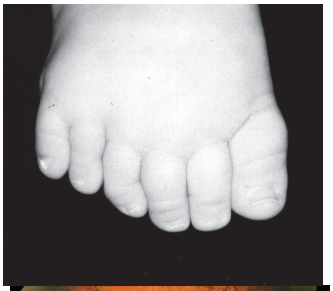


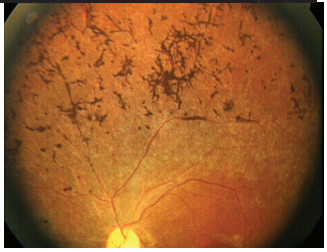


Clinical Characteristics

- Diagnostic criteria : 4 primary features
  OR 3 primary plus 2 secondary features

- Primary Criteria:
  -Rod cone dystrophy
  -Polydactyly
  -Obesity
  -Genital anomalies
  - Renal anomalies
  - Learning diabilities





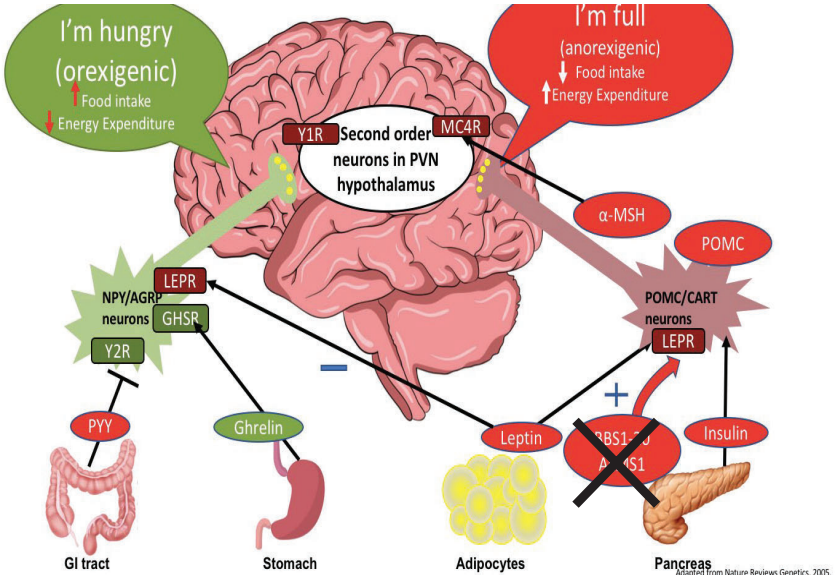
Forsythe and Beales.Eur J Hum genet.2013;21:8-13

Secondary Criteria:

- Speech delay
- Developmental delay
- Diabetes mellitus
- Dental anomalies
- Congenital Heart disease
- Brachydactyly
- Ataxia/Poor coordination
- Anosmia/Hyposmia

Alström syndrome: ALMS1 deficiency

- Mutation in ALMS1 gene.
- ALMS1 plays role in LEPR signaling and POMC neuron survival
- <1:1,000,000 (~900 cases)



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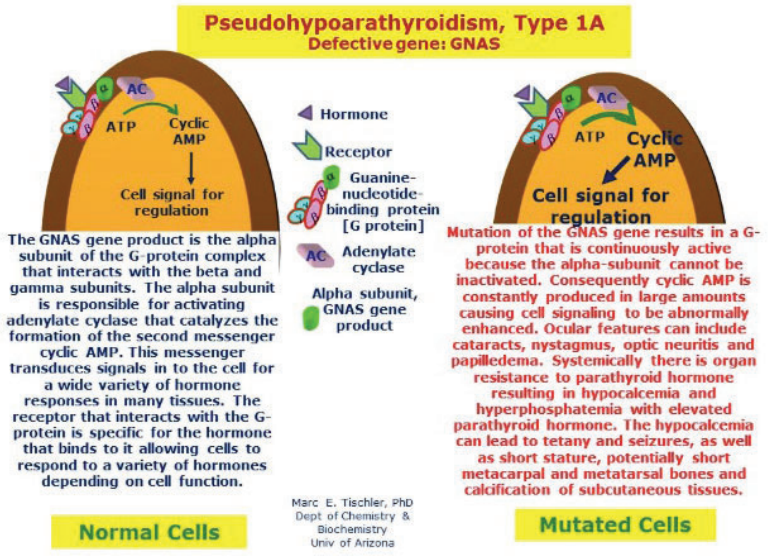
Alström syndrome: Clinical Characteristics

Diagnostic criteria: 2 major criteria, or 1 major criterion plus any 2 minor criteria[1]

Age, years	Major criteria	Minor criteria
<2	*ALMS1* mutation in 1 allele and/or family history of Alström syndrome • Vision (nystagmus, photophobia)	• Obesity Dilated cardiomyopathy with congestive heart failure
3-14	*ALMS1* mutation in 1 allele and/or family history of Alström syndrome • Vision (nystagmus, photophobia, decreased acuity, cone dystrophy [sometimes diagnosed as retinitis pigmentosa][2] by ERG)	• Obesity and/or insulin resistance • History of dilated cardiomyopathy with congestive heart failure • Hearing loss • Advanced bone age • Hepatic dysfunction • Renal failure
>15	*ALMS1* mutation in 1 allele and/or family history of Alström syndrome • Vision (legal blindness, history of nystagmus in infancy/childhood, cone and rod dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • History of dilated cardiomyopathy with congestive heart failure • Hearing loss • Hepatic dysfunction • Renal failure • Short stature • Male hypogonadism or female irregular menses and/or hyperandrogenism

Albright Hereditary Osteodystrophy

- Inactivating mutation in GNAS Inherited from the mother, can be associated with resistance to certain hormones, in particular the PTH. This is Pseudohypoparathyroidism type 1A.
- When inherited from father , no hormone resistance but an AHO phenotype .



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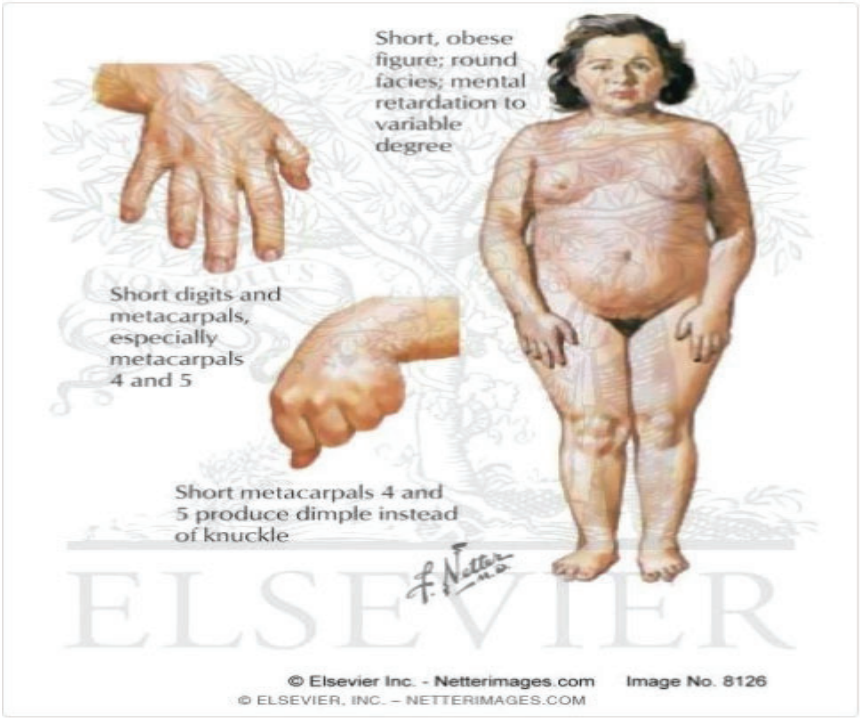
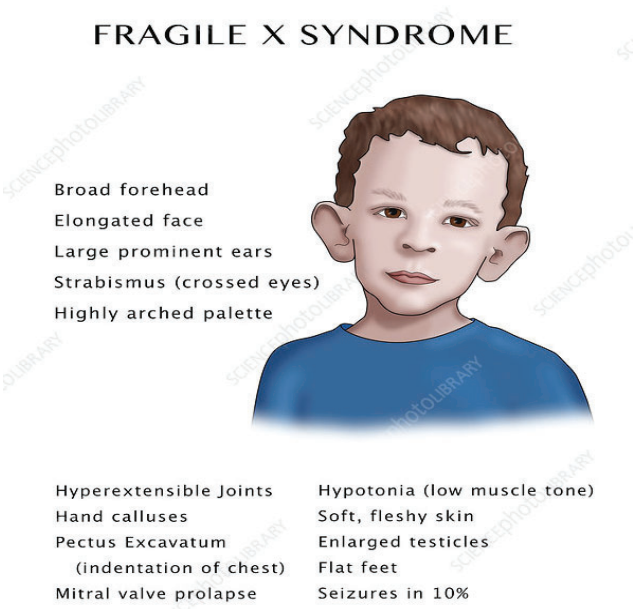
Albright Hereditary Osteodystrophy phenotype

- Developmental delay
- Short stature
- Round facies
- Short fourth and fifth metacarpals
- Brachydactyly
- Hypocalcemia (in PHP1 A)



Fragile X Syndrome

- Obesity in upto 60% of cases
- 1/2,500 births X-linked
- FMR1 gene (Xq27.3)
- Intellectual disability, hyperkinetic behavior, macroorchidism, large ears, prominent jaw



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Benefits of Identifying Genetic Cause

- Families relieved to know cause, feel less blame
- Anticipatory guidance and screening
- Social support groups provide community
- Management of hyperphagia as a physiologic medical condition
  - Distinct approach from traditional nutritional counseling for obesity
  - Food dosed and timed similar to prescription medications
  - In hypotonic conditions, 20% to 40% lower caloric needs due to decreased lean mass
    - Growth hormone therapy approved for PWS – increases muscle mass and tone, reduces truncal obesity, potential cognitive benefits when initiated early
- Genetic diagnosis → opportunity for targeted treatment

Styne DM, et al. *J Clin Endocrinol Metab.* 2017;102(3):709-57; Rubin DA, et al. *Food Nutr Res.* 2015;59:29427;
Goldstone AP, et al. *J Clin Endocrinol Metab*. 2008;93(11):4183-97.

Precision Medicine Based on Genetics

- Leptin replacement for leptin deficiency
- Melanocortin agonist (setmelanotide) under investigation for *LEPR, POMC, PCSK1, and CPE* mutations
- Targeted approaches being studied for other rare and common variants of leptin pathway genes

Farooqi IS, et al. *J Endocrinol*. 2014;223(1):T63-70.
Clement K, et al. *Nat Med*. 2018;24(5):551-5.
Kühnen P, et al. *N Engl J Med*. 2016;375(3):240-6.