Genetic of Obesity

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Obesity: Physiology, Health and Diseases
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In 2015, 107.7 million children and overall prevalence of obesity in children 5%
Prevalence of Obesity in Thailand

Our Super-Sized Kids

It's not just genetics and diet. An in-depth look at how our lifestyle is creating a juvenile obesity epidemic—and the scoop on how to cure it.
Genetic obesity

- Rare cause (7%) of childhood obesity
- Clues:
  - Early-onset/severe obesity
  - Hyperphagia*
  - Dysmorphic features
  - Cognitive impairment
- Monogenic obesity
  - Mutation in single gene resulting in obesity
- Syndromic obesity
  - Obesity associated with dysmorphic features

Hx and PE

Obesity

Growth failure

Onset of obesity

< 2-5 years

- Monogenic obesity
  - Leptin deficiency
  - Leptin receptor deficiency
  - MC4R deficiency
  - POMC deficiency
  - PC-1 deficiency

> 5 years

- Exogenous obesity

Syndromic obesity

- PWS
- BBS
- Alstrom syndrome
- Cohen syndrome
- Carpenter syndrome
- AHO

Delayed development

- Endocrine causes
  - Cushing syndrome
  - Hypothyroidism
  - GH deficiency

PWS: Prader Willi syndrome
BBS: Bardet-Biedl syndrome
AHO: Albright hereditary osteodystrophy
Monogenic obesity

- Mutation in single gene resulting in obesity
- Gene involving energy balance or hypothalamus development → defect in control food intake and energy expenditure

**Clues:**
- Rapid weight gain in the first year of life
- Hyperphagia
- Normal growth and development
The homeostatic pathway of energy balance
The leptin-melanocortin pathway

The homeostatic pathway of energy balance

The leptin-melanocortin pathway

- Leptin (LEP)
- Leptin receptor (LEPR)
- Melanocortin receptor 4 (MC4R)
- Proopiomelanocortin (POMC)
- Prohormone convertase-1 (PC-1)

Hypothalamus

- POMC
- PC-1
- α-MSH
- MC4-R
- Leptin receptor

Adipose tissue

Food Intake

Energy storage
Leptin deficiency

- Normal weight at birth
- Rapidly hyperphagia resulting in severe obesity
- Hypogonadotrophic hypogonadism
- Hypercortisolemia
- Hyperinsulinaemia and insulin resistance

ob/ob mouse

Leptin deficiency

- First report of human in 1997
- Two children (OB1 and OB2) from highly consanguineous family of Pakistani origin

Clinical manifestations:
- Normal birth weight: 3.46 kg and 3.53 kg
- Severe and intractable obesity since early age and marked hyperphagia
- High percentage body fat: 57% at age of 8 and 53% at age of 2
- Very low serum leptin: 0.11 and 0.38 ng/mL
- Hyperinsulinemia, elevation of TSH

Homozygous frame-shift mutation in LEP (c.398delG)

Leptin deficiency

- 43 patients reported worldwide
- Additional features:
  - Recurrent infection due to abnormal T cell number and function
  - Central hypothyroidism and hypogonadotrophic hypogonadism

Funcke et al. Molecular and Cellular Pediatrics 2014, 1:3
Leptin receptor mutation

- Three severely obese adult siblings from consanguineous family
- Central hypothyroidism
- Normal puberty
- High serum leptin

G→A base substitution in the splice donor site of exon 16 of LEPR

Congenital Deficiency of the Leptin Receptor

- Sequenced LEPR in 300 subjects with hyperphagia and severe early-onset obesity
- 8/300 (3%) had nonsense or missense LEPR mutations (homozygotes = 7 and compound heterozygote = 1)
- Alterations in immune function
- Hypogonadotropic hypogonadism
- Normal serum leptin levels (appropriated with fat mass)
- Clinical features were less severe than congenital leptin deficiency
Effect of rh-leptin

- Sustained weight loss due to loss of fat mass
- Decrease energy intake
- Reduce serum insulin, cholesterol, triglycerides, LDL cholesterol and increase serum HDL cholesterol
- Gradual increase in gonadotropins and estradiol
- Improved in central hypothyroidism
- Increase CD4+ T cell number and normalizes CD4+/CD8+ T cell ratio
Obesity from Leptin pathway

- Autosomal recessive disorder

- Mutation in *LEP* (Leptin deficiency or bioinactive leptin) and *LEPR* (Leptin receptor defect)

- Clinical presentations:
  - Normal birth weight
  - Early weight gain/severe obesity from hyperphagia
  - Increase fat mass
  - Frequent infection, central hypothyroidism, HH, hyperinsulinemia

- Genetic testing for *LEP* and *LEPR*

- Treatment: recombinant human leptin
Melanocortin-4 receptor (MC4R)
MC4R deficiency

- First described in 1998
- Index case: A 4-years-old boy
  - Weight 32 kg and BMI 28 kg/m²
  - Normal birthweight 3.8 kg
  - Hyperphagia and progressive weight gain from the age of 4 months
- The father: 30 year old
  - Weight 139 kg and BMI 41 kg/m²
  - Normal birth weight, but obesity since 6 months of age

MC4R deficiency

Heterozygous for a 4-nt ‘CTCT’ deletion at codon 211, resulting in frameshift that introduces a top codon.
**MC4R deficiency**

- **Most common form of monogenic obesity:**
  - Prevalence 0.5% of obese adults to 6% of severe obese children\(^1\)
  - 2.5% of people with a BMI > 30\(^2\), 4% of people with a BMI > 35\(^3\)

- **Autosomal dominant**

- **Clinical features:**
  - Hyperphagia in the first year of life
  - Increase in both fat and lean mass
  - Marked increase in bone mineral density: ‘big-boned’
  - Hyperinsulinemia

- **No specific therapy**

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Proopiomelanocortin (POMC)

- Hypothalamus
  - MC4-R
  - PC-1
  - α-MSH
- Leptin receptor
- Leptin
- Adipose tissue

Food Intake

Energy storage

ACTH

PC1/3 (Hypothalamus, skin and pituitary)

PC2 (Hypothalamus and skin only)

γ-MSH  α-MSH

β-MSH  β-endorphin
POMC deficiency

- Adrenal crisis due to ACTH deficiency since neonatal period
- Pale skin, red hair
- Treatment: long term steroid replacement

PCS are endoproteases that cleave inactive hormone precursors into biologically active peptides.

**PC1/3 and PC2**: ProTRH, proinsulin, proglucagon, Pro-GHRH, POMC, pro-neuropeptide Y and pro-cocaine-amphetamine-related transcript.

![Diagram of Prohormone Convertases (PCs)](image)
PC-1 deficiency

- Hyperphagia and early-onset obesity (abnormal processing of POMC to α-MSH)
- Mild hypocortisolism (partial ACTH deficiency)
- Malabsorption and small bowel dysfunction, variable severity (Abnormal processing of proglucagon to GLP-2)
- Postprandial hyperglycemia and reactive hypoglycemia (abnormal processing of proinsulin to insulin)
- Hypogonadotrophic hypogonadism (impaired proGHRH processing)
- Central hypothryroidism (impaired proTRH processing)

Syndromic obesity

- 30 Mendelian disorder with obesity
- Unclear pathophysiology of obesity

Clues:
- Dyshomorphic features
- Growth failure
- Cognitive impairment
- Obesity typically occurs after infancy

- No specific treatment
Prader-Willi syndrome (PWS)
Prader-Willi syndrome (PWS)

- Most common cause of syndromic obesity
- Incidence 1/16,000 live births
- Loss of function in paternally derived 15q11-q13
  - Deletion (70-75%)
  - Uniparental disomy (UPD) (20-25%)
  - Imprinting (2-5%) or unbalanced translocations (1%)
Hypotonia ‘floppy child’, feeding problems and failure to thrive in early infancy followed by hyperphagia leading to obesity from 9 months to adult.

Growth delay, learning difficulties, behavioural problems, sleep abnormalities and hypogonadism.

Short stature, small hands and feet, narrow nasal bridge, almond-shaped palpebral fissures, thin upper lip, narrow bifrontal diameter, scoliosis, eye abnormalities and hypopigmentation.
Mechanism of obesity in Prader-Will syndrome

- **Arcuate Nucleus**
  - POMC
  - POMC $\downarrow$ αMSH $\beta$MSH
  - NPY $\downarrow$
  - AGRP $\downarrow$

- **Paraventricular Nucleus**
  - MCR-4

- **Ventromedial Nucleus**
  - TKR

- **Loss of feedback mechanism**

- **Leptin $\downarrow$**
  - Adipose tissue
  - Long term control of food intake

- **Insulin $\downarrow$**
  - Pancreas

- **PYY $\downarrow$**
  - Short term control of food intake

- **Ghrelin $\uparrow$**

- **GH $\downarrow$**
  - TRH-TSH Axis

- **Growth delay**, **$\downarrow$EE, $\downarrow$BMR**

- **Fat mass**, **$\uparrow$ Muscle mass**

- **$\downarrow$ Energy Expenditure**

- **$\uparrow$ food intake**

**Delayed sense of fullness**
**Early loss of appetite**
Bardet–Beidl syndrome (BBS)
Bardet–Beidl syndrome (BBS)

- Autosomal recessive syndrome

- 6 primary features: rod-cone dystrophy, polydactyly, obesity, genital abnormalities, renal defects and learning difficulties

- Secondary features: developmental delay, speech deficit, brachydactyly or syndactyly, dental defects, ataxia or poor coordination, olfactory deficit, diabetes mellitus and congenital heart disease

Diagnosis:
- At least 4 of primary features
- 3 primary features + 2 secondary features

Age 7 years with truncal obesity

Broad hands with stubby fingers and brachydactyly

Pes planus

Clinical findings in Alström syndrome

Main clinical features

- Photoreceptor dystrophy
- Nystagmus and photophobia
- Sensorineural hearing loss
- Truncal obesity
- Type 2 diabetes mellitus
- Dilated cardiomyopathy

Other features

- Acanthosis nigricans
- Hypertriglyceridemia
- Endocrine anomalies (GHD, hypothyroidism, hypogonadism)
- Hepatic, renal, and pulmonary pathology
- Cognitive impairment and developmental delay
- Scoliosis and kyphosis
- Flat feet

Take home message

- Genetic obesity is a rare condition

- Monogenic obesity:
  - Severe obesity since 1\textsuperscript{st} year of life, hyperphagia, normal growth and development
  - Most common cause is MC4R (big bone)

- Syndromic obesity: obesity after 1\textsuperscript{st} few years of life, dysmorphic feature, growth failure and delay development

- Treatment available only in leptin deficiency