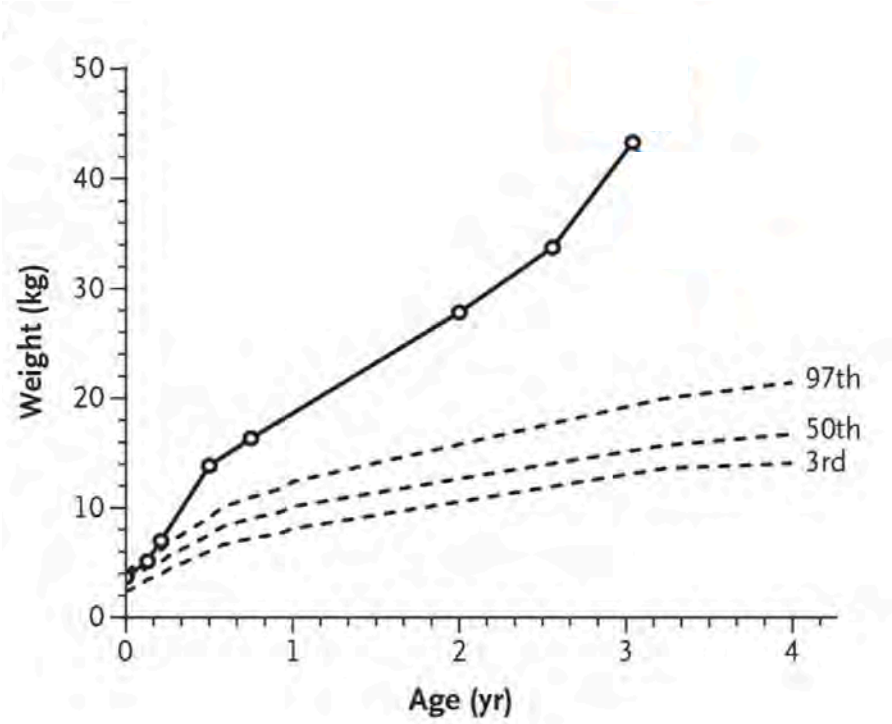
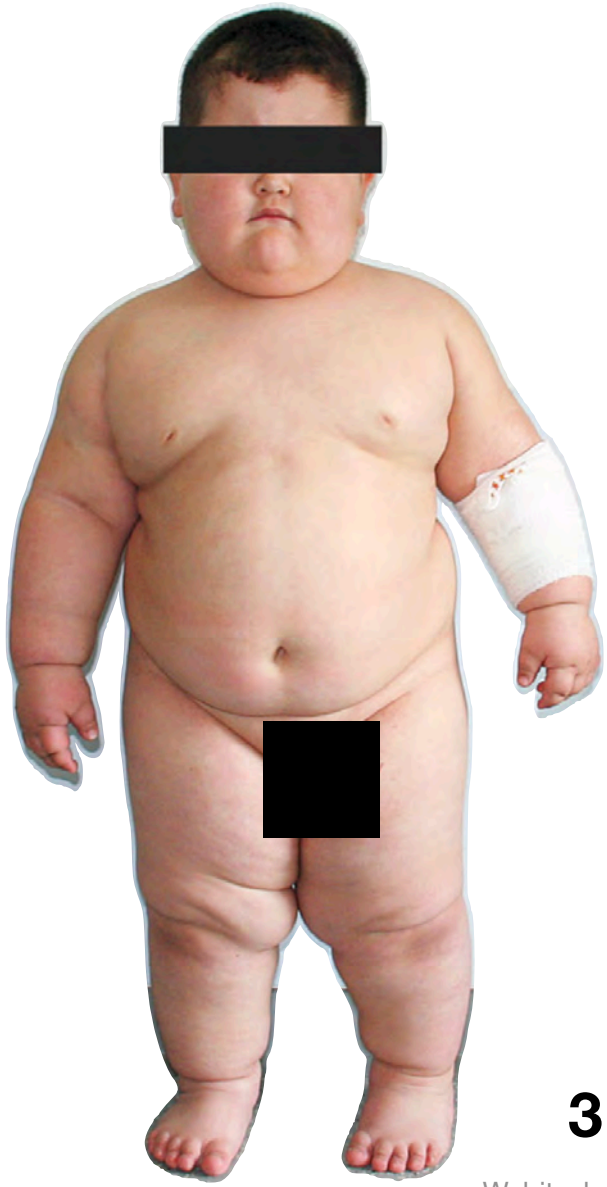
Monogenic and syndromic obesity

Prof Valérie Schwitzgebel
University of Geneva

Monogenic obesity

Leptin: Prevalence: <1 / 1 000 000

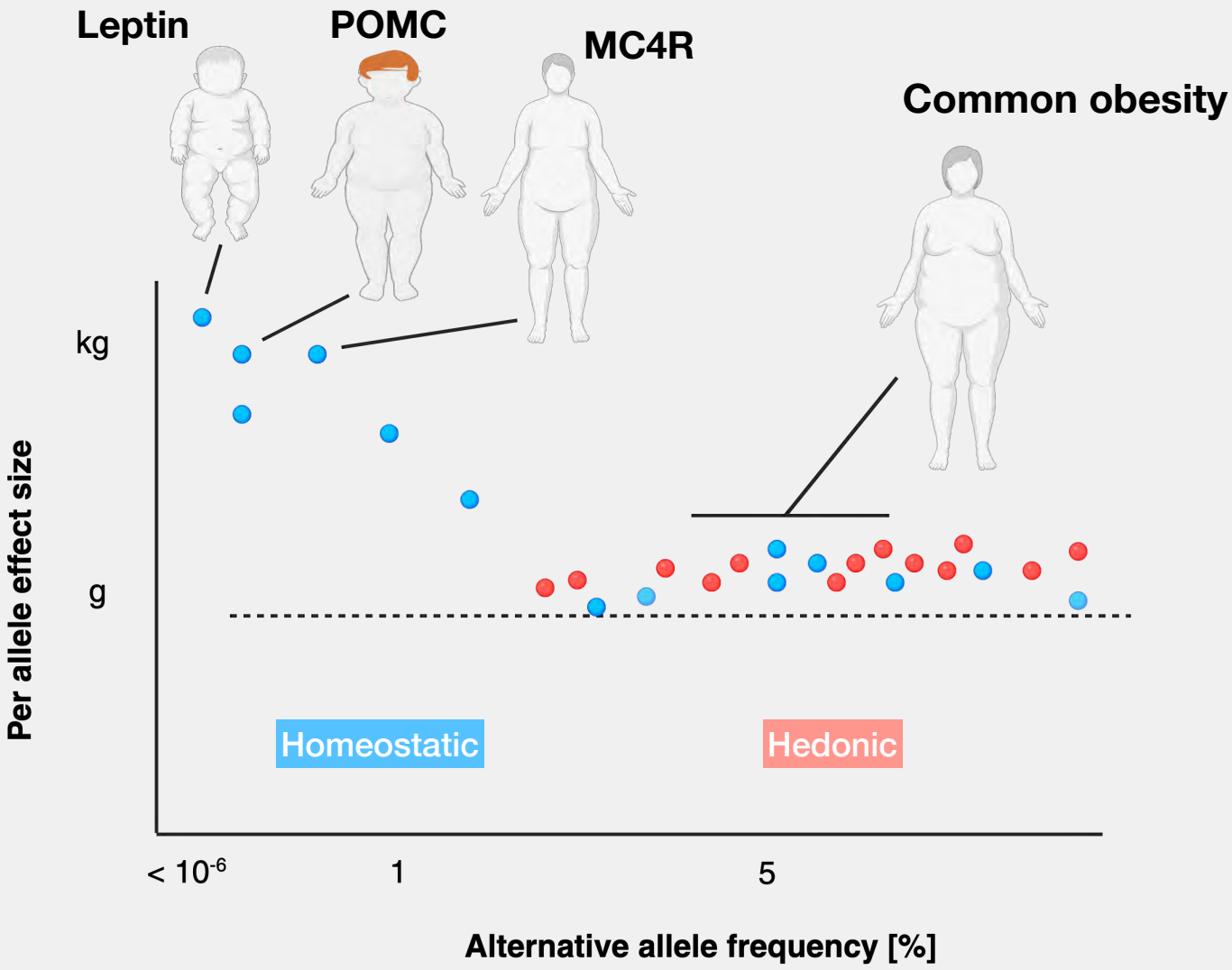




3 years

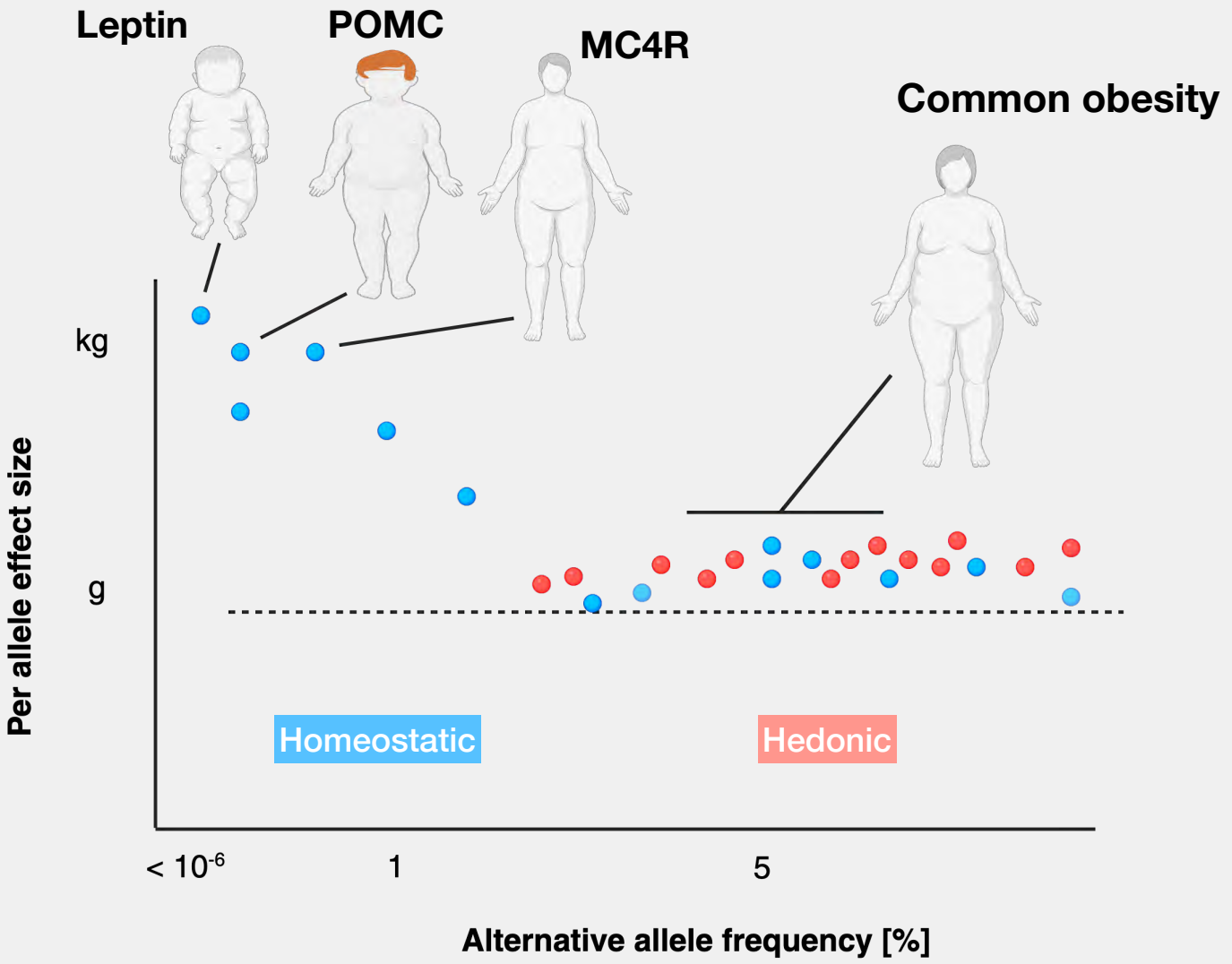
Wabitsch et al, JCEM 2015

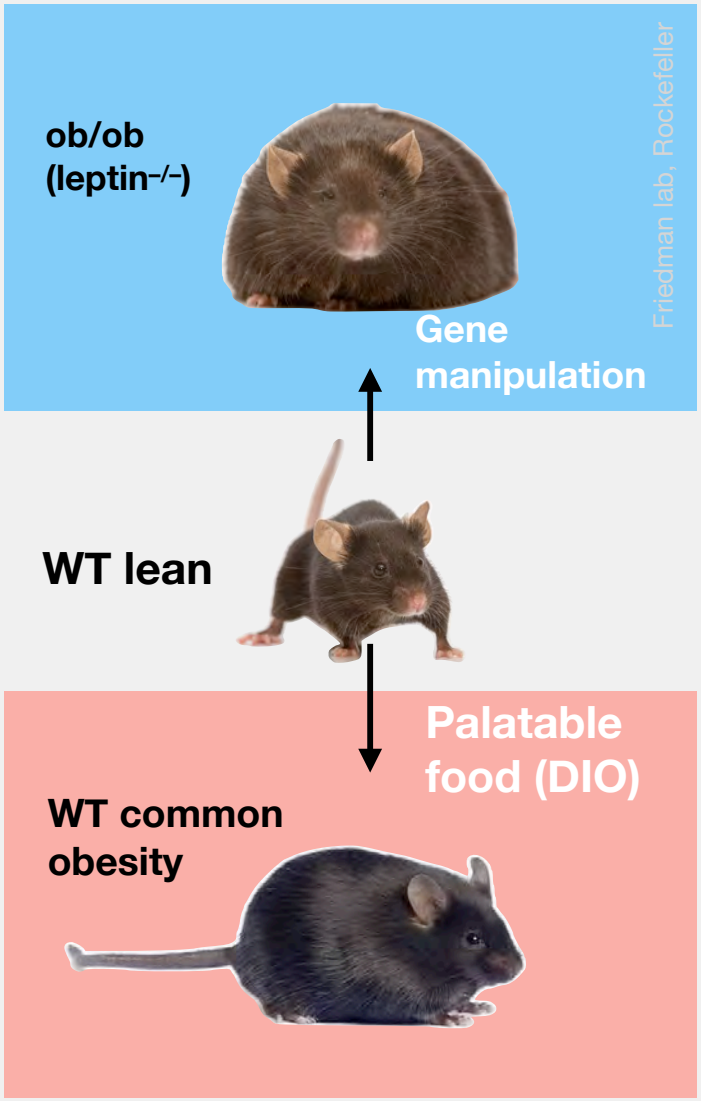
Mono *vs.* polygenic obesity



Schematics after Akbari et al. Science 2021
Stuber, Schwitzgebel & Luscher, Neuron 2025

Mono *vs.* polygenic obesity

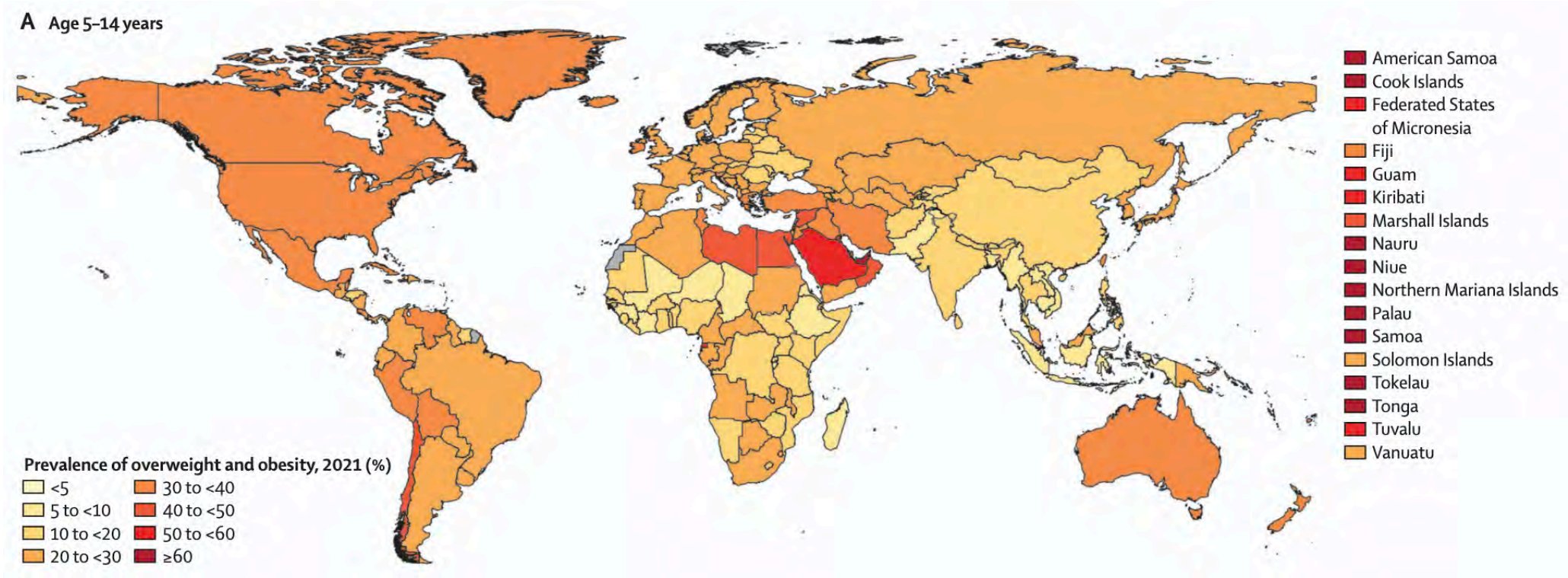




Epidemiology: Common obesity

For the first time in recorded history, children are more likely to be obese than underweight

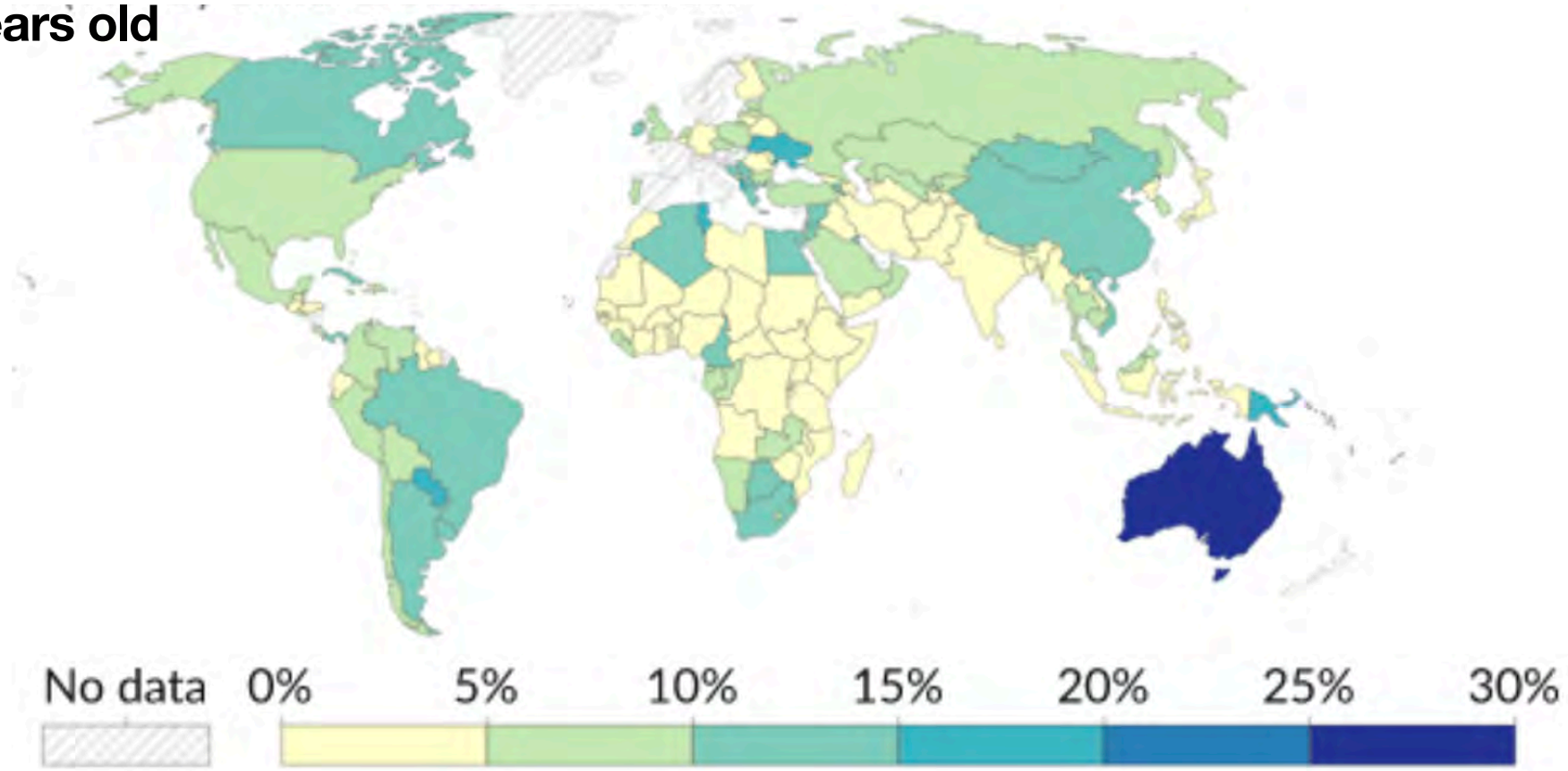
5-14 years old **Overall > 188 mio**



Adolescent BMI Collaborators, Lancet 2025

Epidemiology: Common obesity

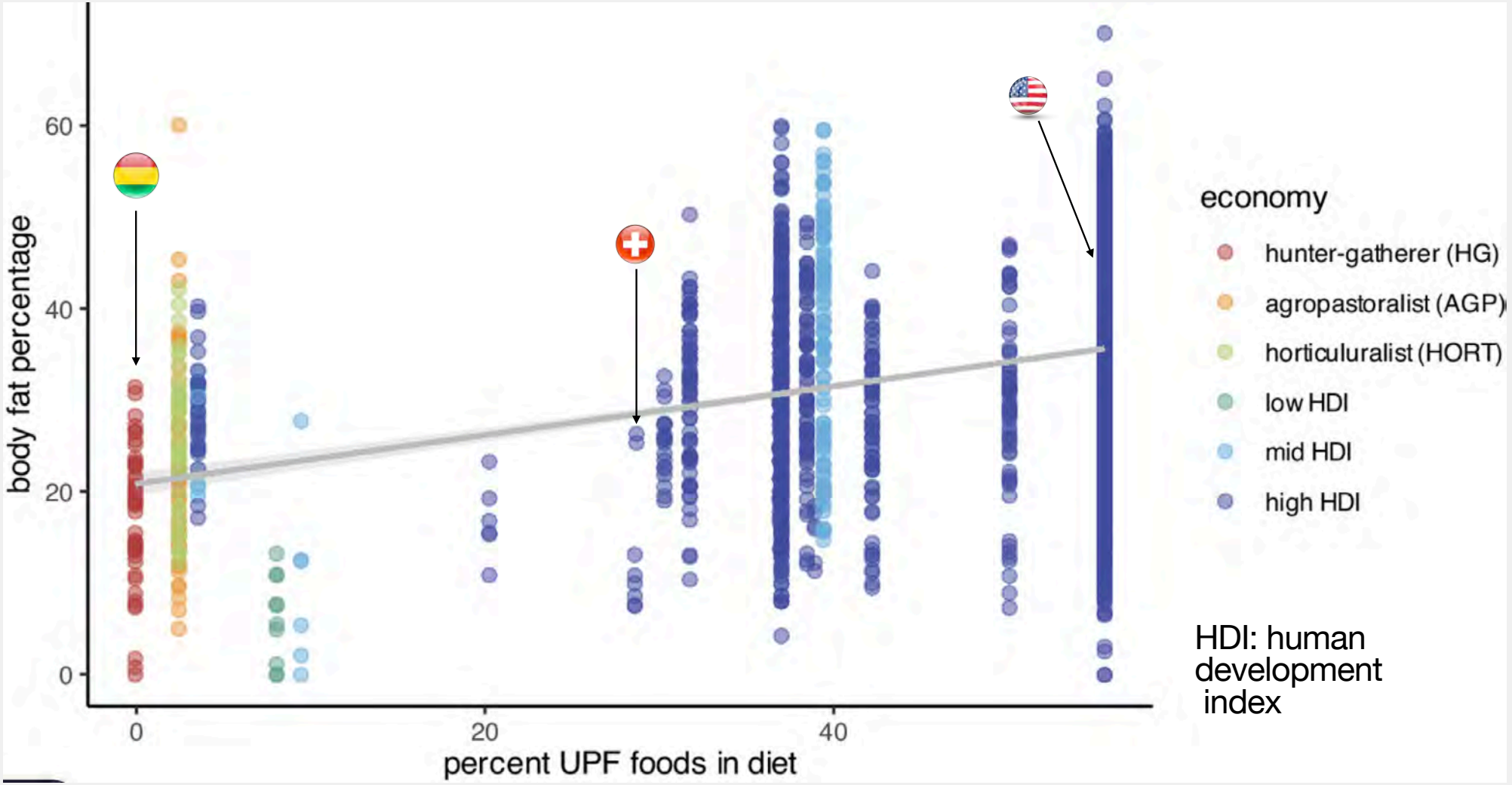
< 5 years old



McGrosky et al. PNAS 2025

Data source: WHO-Global Health Observatory 2025

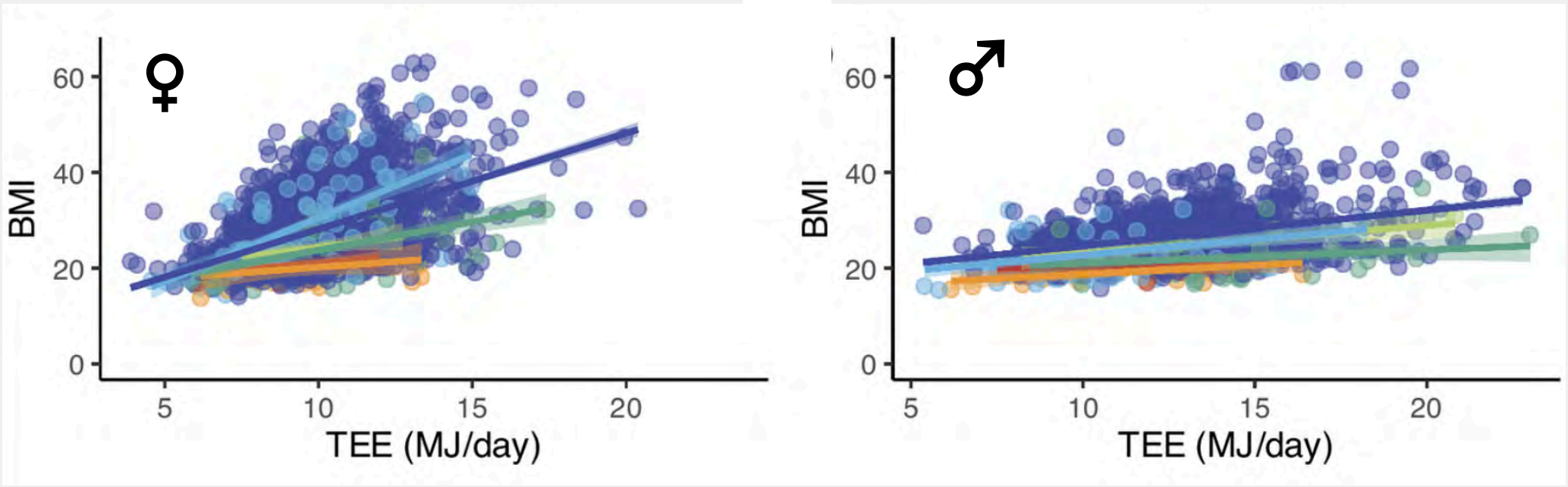
Ultra Processed Food (UPF) ~ BMI

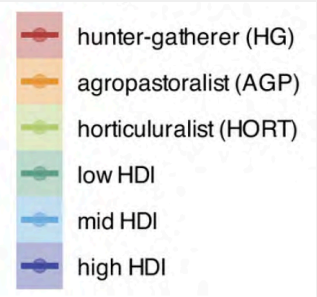


HDI: human development index

McGrosky et al. PNAS 2025

Energy expenditure correlates with BMI



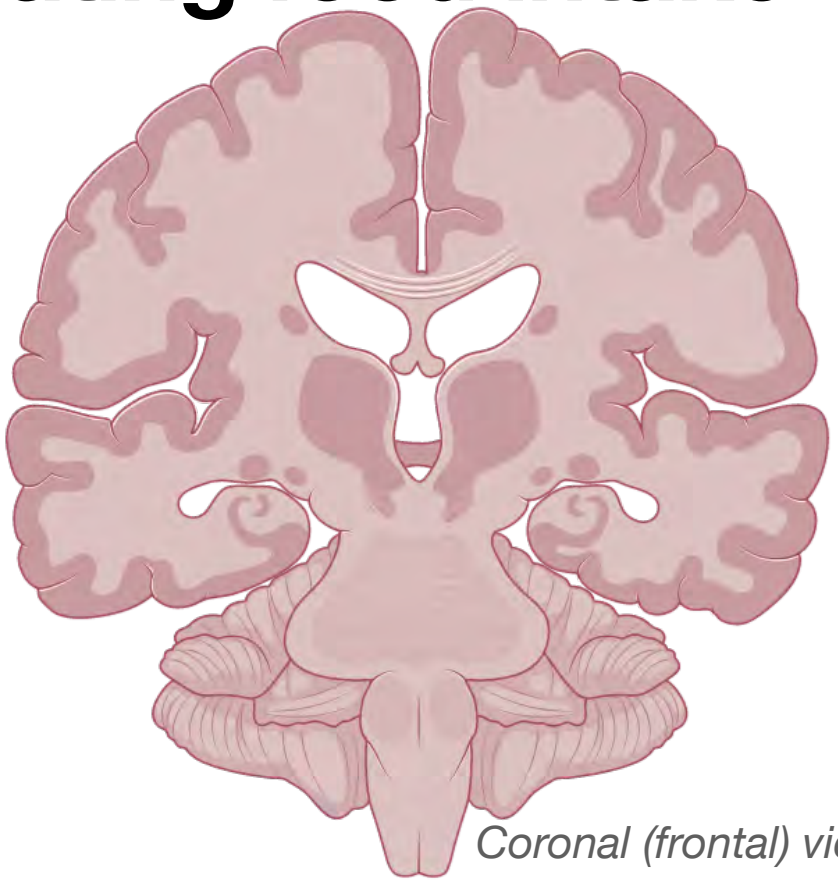


TEE: total energy expenditure

McGrosky et al. PNAS 2025

Systems regulating food intake

“Hunger”



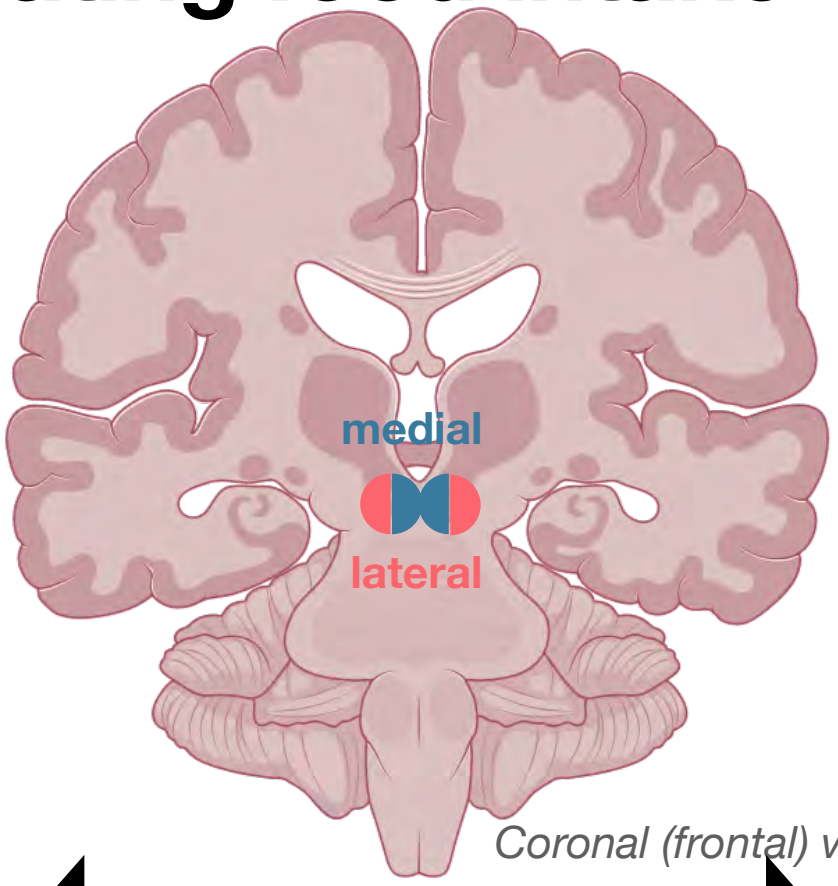
Coronal (frontal) view

“Eating beyond hunger”

Systems regulating food intake

"Hunger"

"Eating beyond hunger"



Coronal (frontal) view

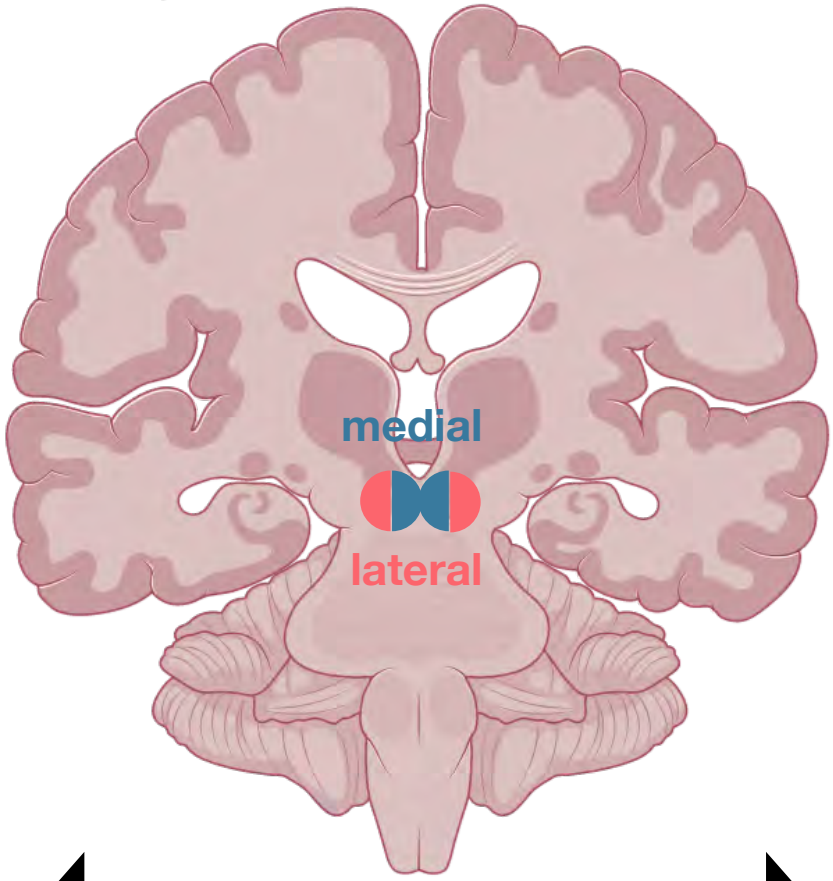
Homeostatic

Hedonic

Systems regulating food intake

Eating because hungry

Negative renforcement



Eating even without Hunger

Positive renforcement

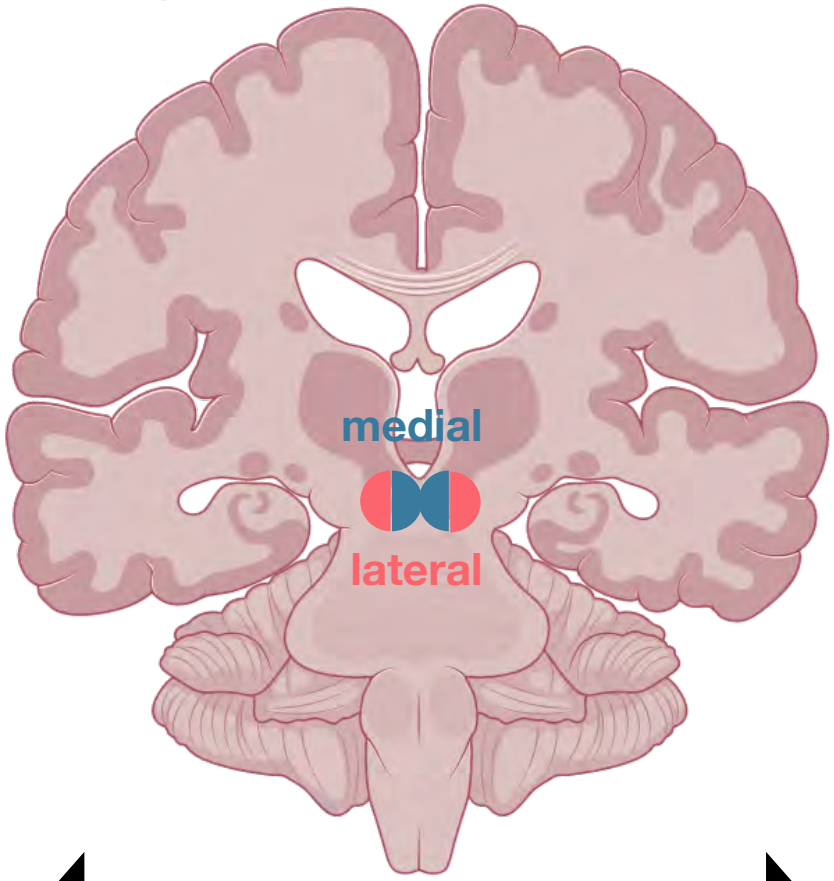
Homeostatic ⟷ **Hedonic**

Stuber, Schwitzgebel & Luscher, Neuron 2025

Systems regulating food intake

Eating because hungry

Negative renforcement



Eating even without Hunger

Positive renforcement

Homeostatic

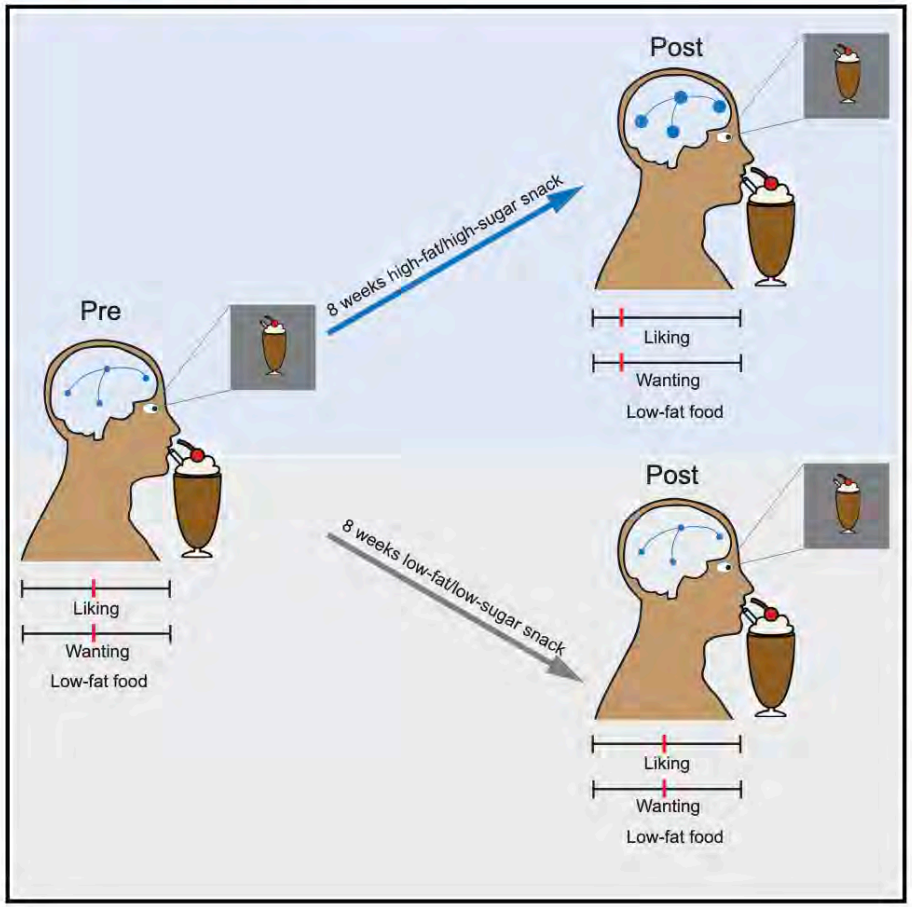
Reciprocal interaction

Hedonic

Stuber, Schwitzgebel & Luscher, Neuron 2025

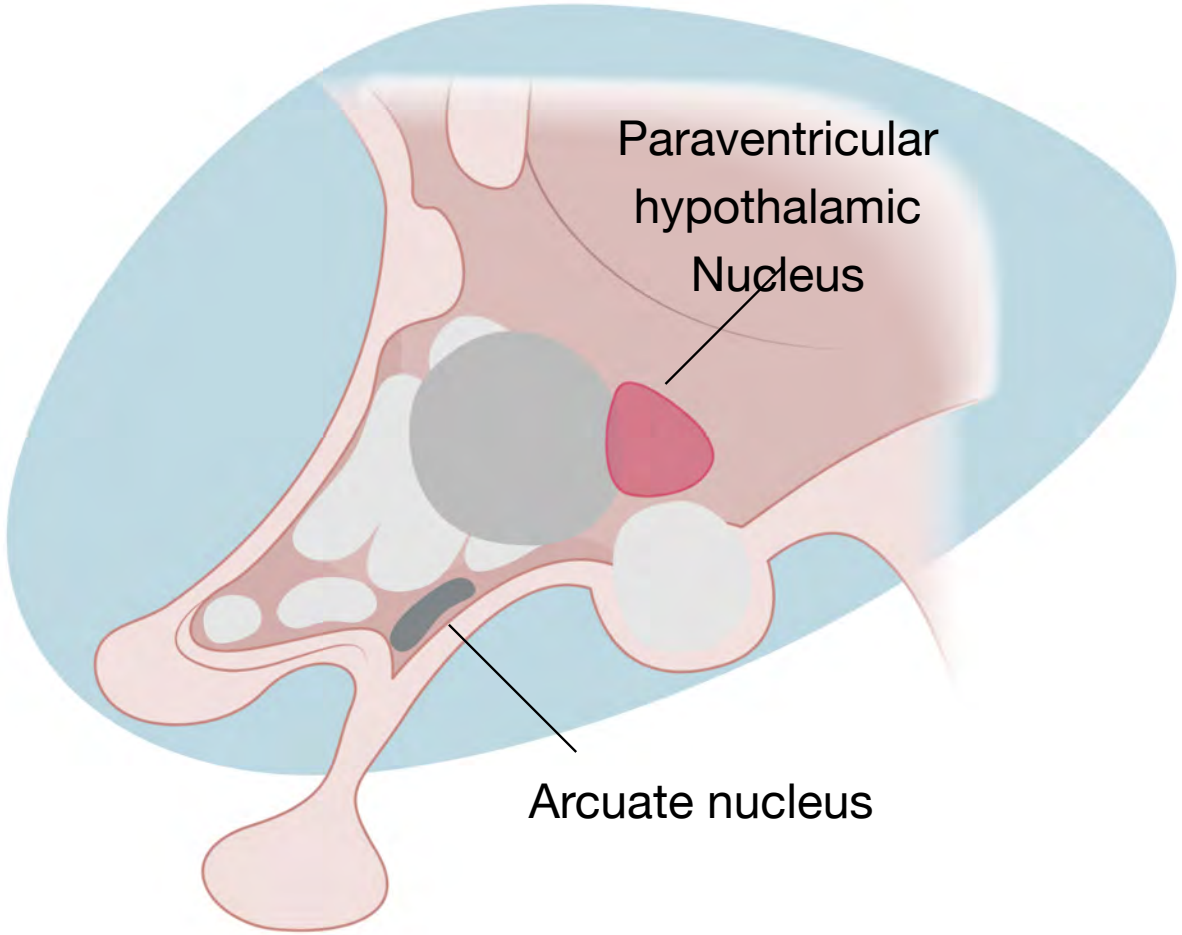
Daily intake of sweet and fatty snacks modulate reward processing

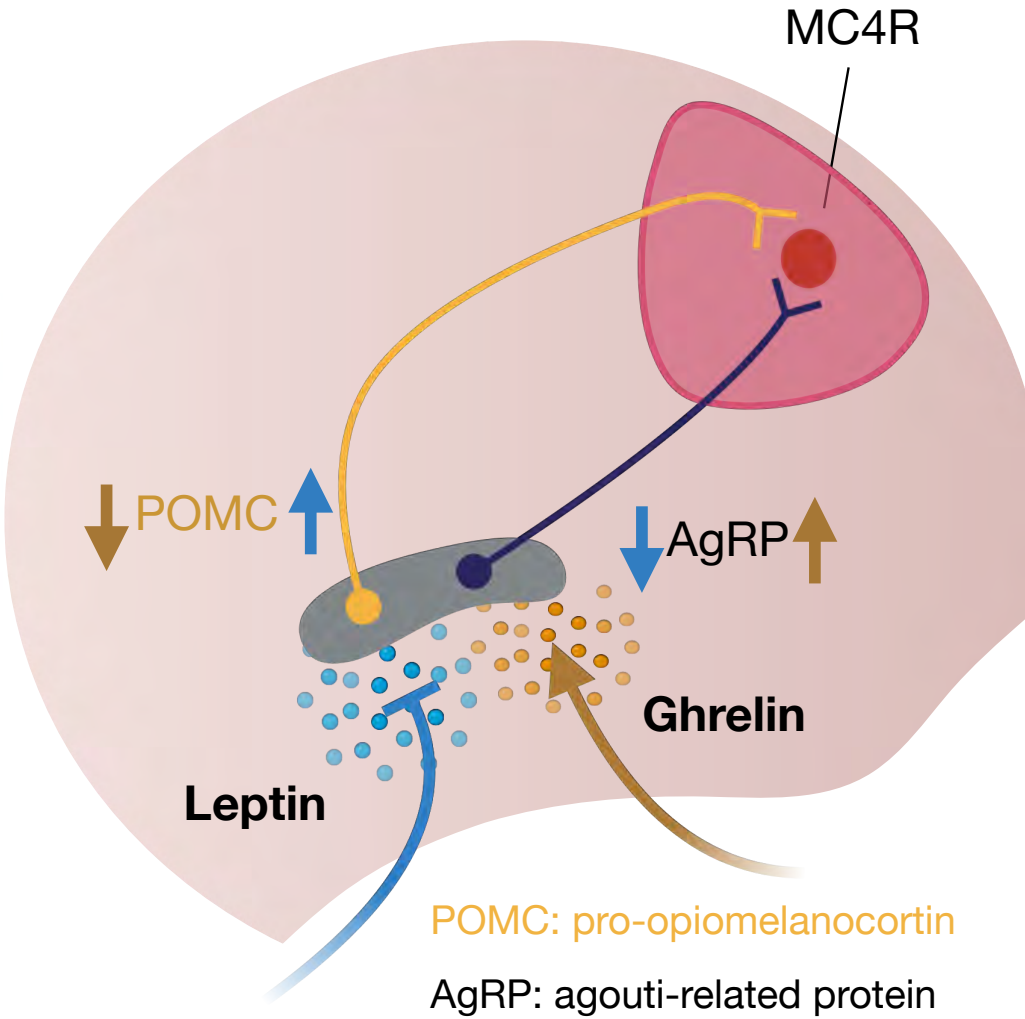
Hedonic pathway



Thanarajah et al., Cell Met 2023

Homeostatic pathway





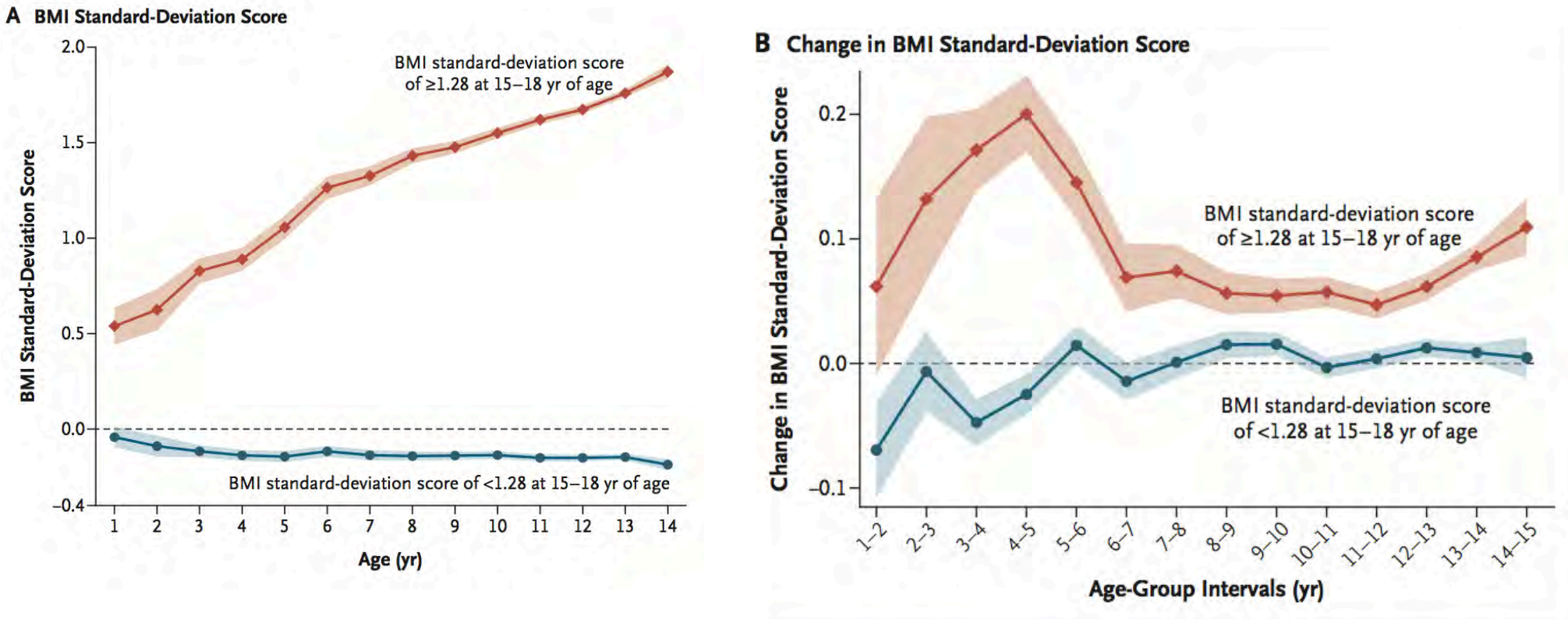
POMC: pro-opiomelanocortin

AgRP: agouti-related protein

Stuber, Schwitzgebel & Luscher, Neuron 2025
Collet & Schwitzgebel, Front Nutr 2024

Diagnosis: common obesity

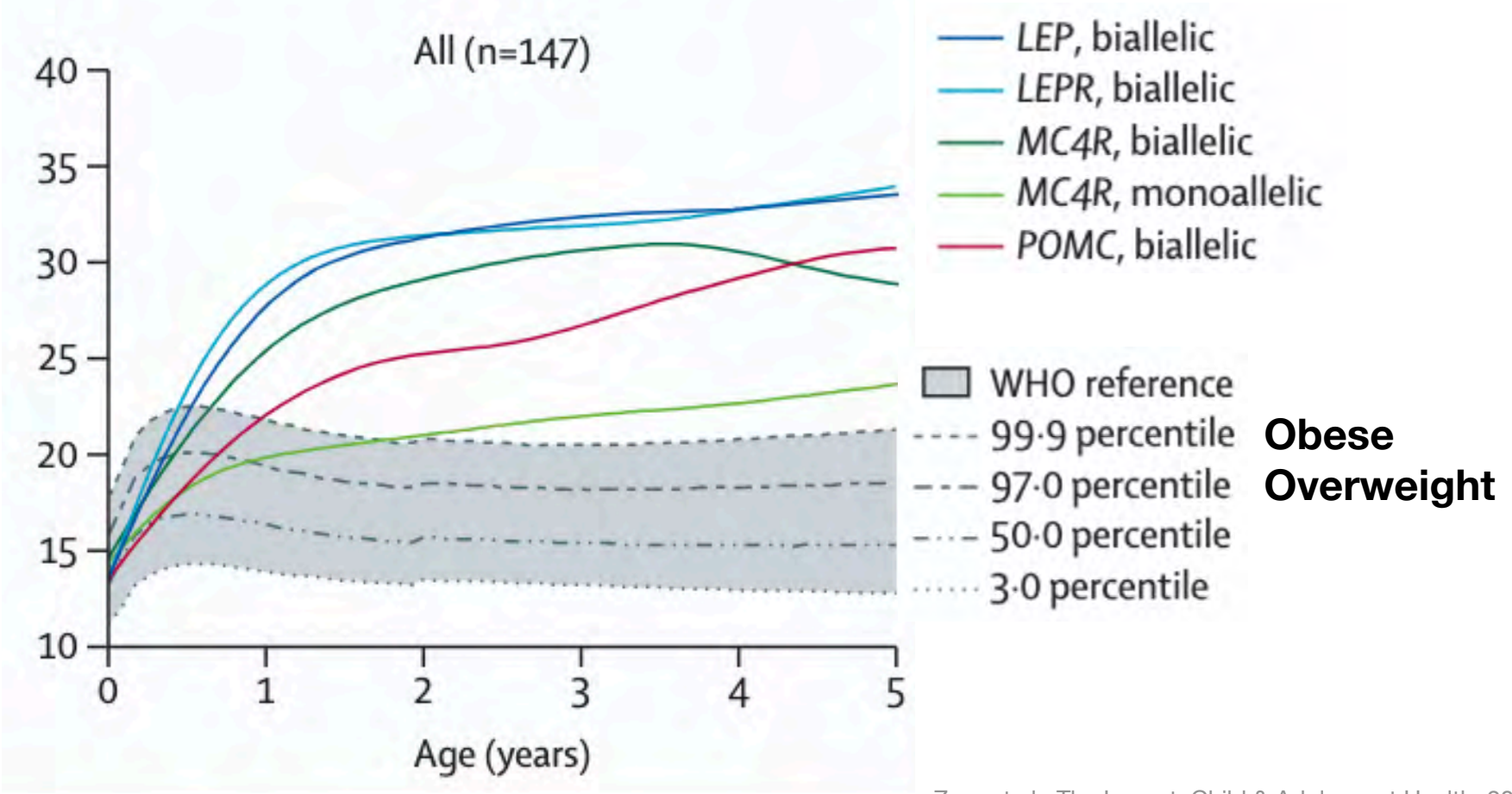
Dynamics of BMI changes in 34’196 children



Geserick et al, NEJM, 2018

Diagnosis: Monogenic obesity

BMI trajectory before age 5 years Cut-off: BMI 24 kg/m² at 2 years



Zorn et al., The Lancet, Child & Adolescent Health, 2025

Diagnosis: Monogenic obesity

Hyperphagia

- Insatiable hunger
- Food seeking behaviour
- Impaired satiety
- Emotional and behavioral consequences around food

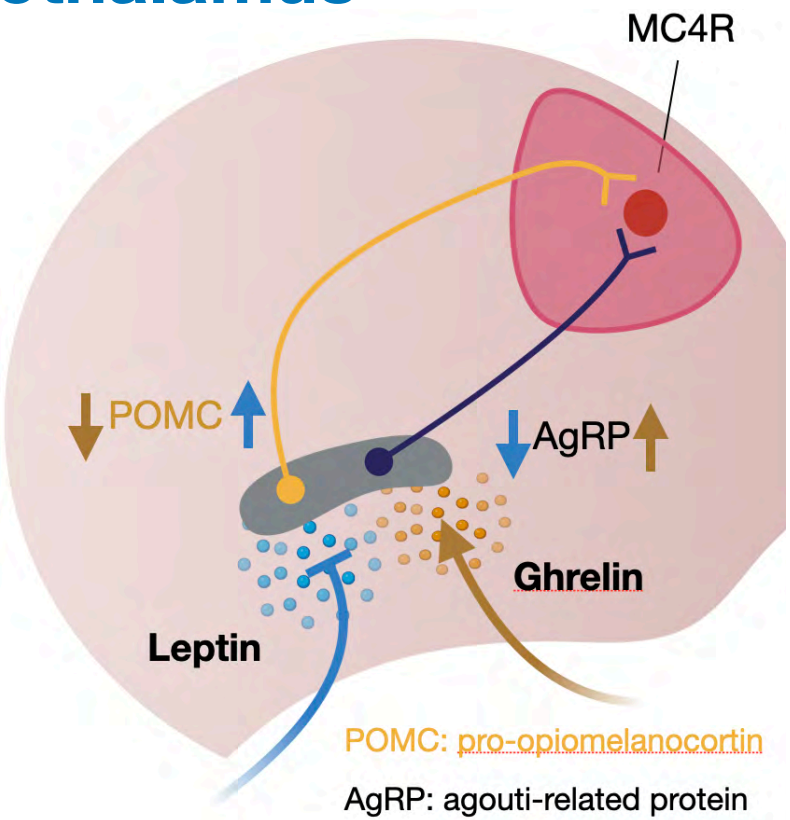
Item	0 Never	1 Rarely	2 Sometimes	3 Often	4 Always
1. My child seems constantly hungry even after a meal.	☐	☐	☐	☐	☐
2. My child talks about food frequently (e.g. asking what's for snack or next meal).	☐	☐	☐	☐	☐
3. My child appears preoccupied with thoughts of food.	☐	☐	☐	☐	☐
4. My child sneaks, steals or hides food.	☐	☐	☐	☐	☐
5. My child becomes upset or irritable if told "no" to food requests.	☐	☐	☐	☐	☐
6. My child will do almost anything to get food (e.g. tantrums, bargaining).	☐	☐	☐	☐	☐
7. My child forages through garbage or other people's food.	☐	☐	☐	☐	☐
8. My child eats faster than other children his/her age.	☐	☐	☐	☐	☐
9. My child's hyperphagic behavior interferes with daily life (family, school, social).	☐	☐	☐	☐	☐

Scoring:
– Sum all items (range 0–36).
– Higher scores indicate greater severity and impairment of hyperphagia.

Likert scale

MC4* receptor deficiency

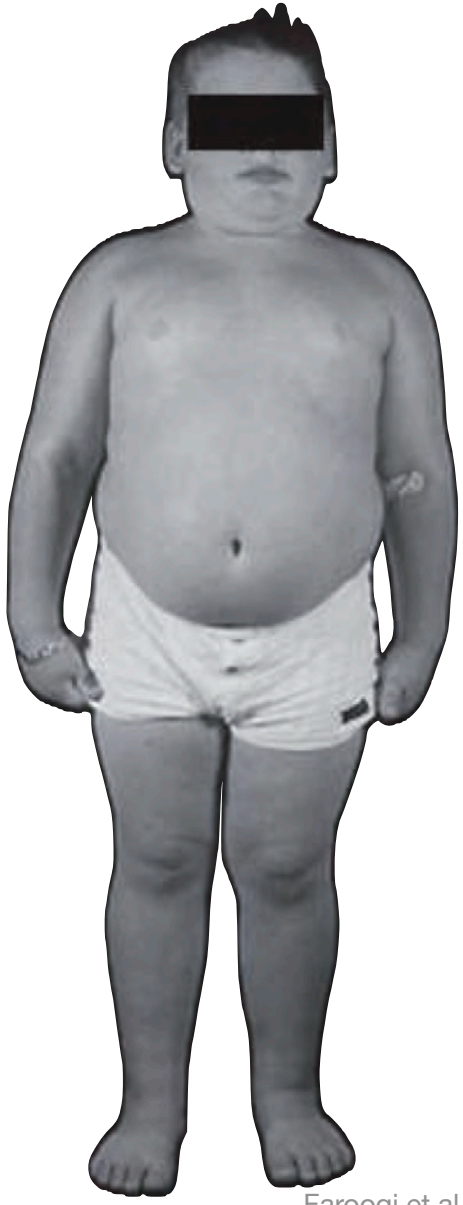
Hypothalamus



POMC: pro-opiomelanocortin

AgRP: agouti-related protein

***melanocortin**



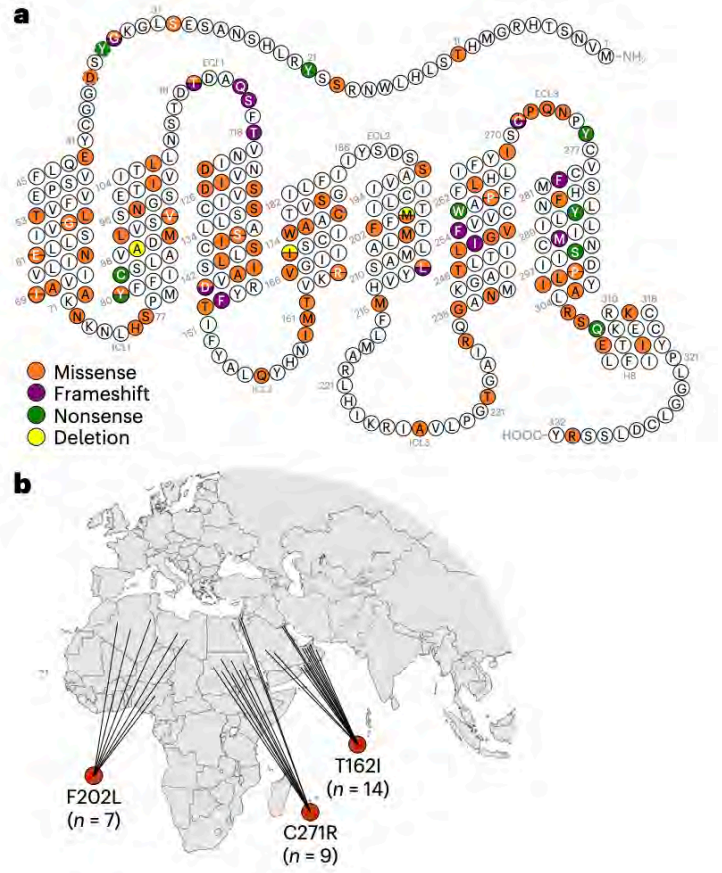
Farooqi et al, NEJM 2003

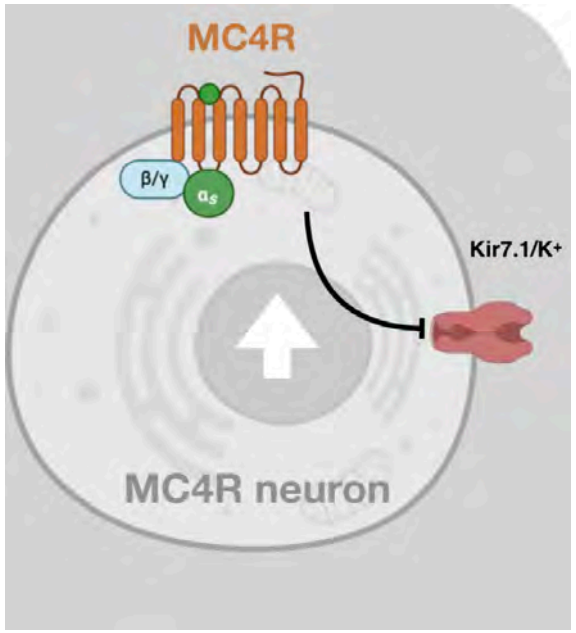
Collet & Schwitzgebel, Front Nutr 2024

MC4* receptor deficiency

7719 children: 4.1% pathogenic variants

3.2% het
0.7% hom
0.1% ch





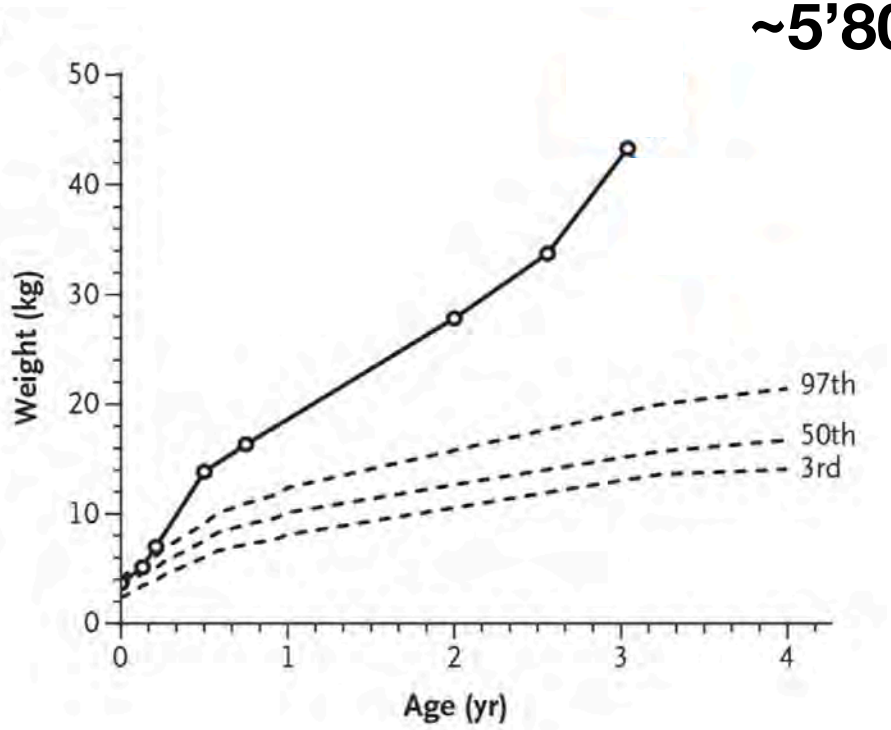
Seven-transmembrane receptor
G protein–coupled receptor (GPCR)

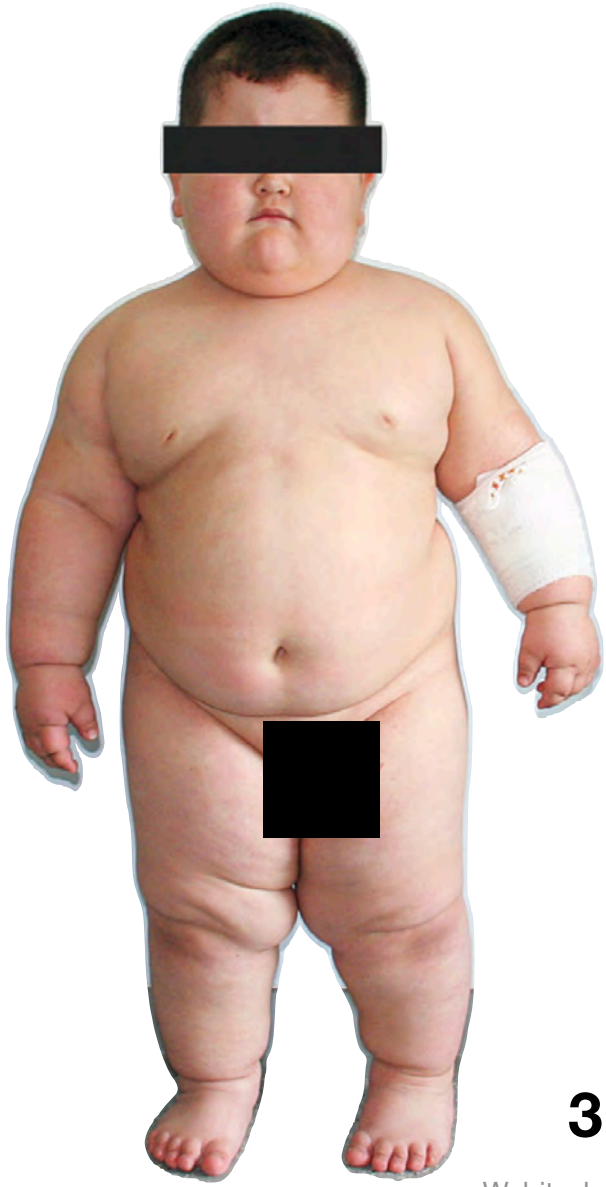
Zorn et al, Nat Med 2025
Stuber, Schwitzgebel & Luscher, Neuron 2025

Monogenic obesity

Leptin: Prevalence: <1 / 1 000 000

~5’800 kcal/d





3 years

Wabitsch et al, JCEM 2015

Homeostatic pathway

High morbidity and mortality in untreated leptin deficiency

A Retrospective Cross-sectional Study on Children with LEP, LEPR or MC4R deficiency from a Consanguineous Population

	LEP (*N=83*)	LEPR (*N=31*)	MC4R (*N=18*)
Onset of obesity and hyperphagia	< 1 year	< 1 year	~ 4 year
Mortality	26%	9%	NR
Delayed milestones	74%	60%	25%
Learning inability	77%	72%	25%
Aggressive behavior	84%	50%	NR
Attending school	22%	27 %	>75 %

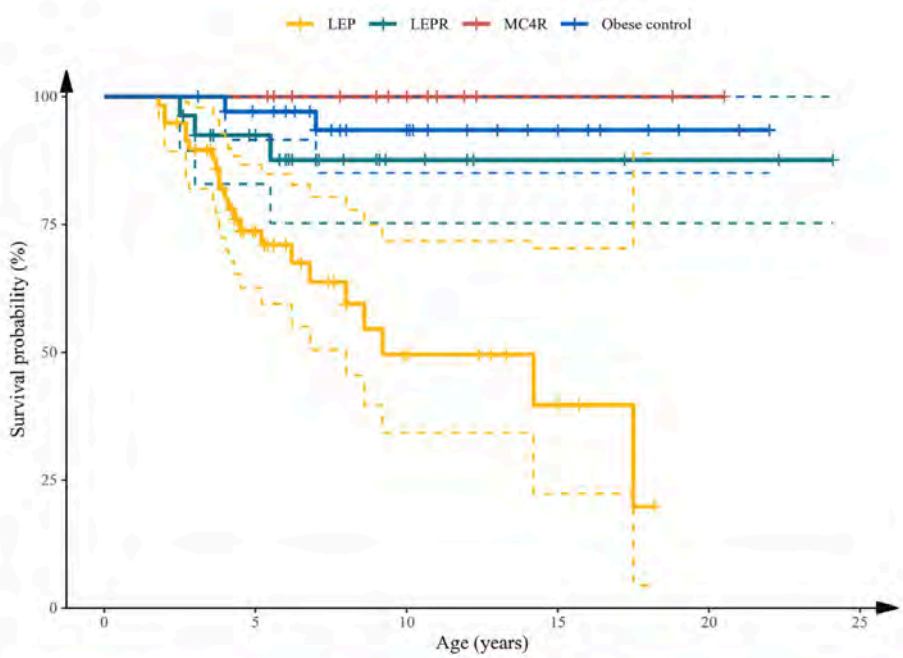


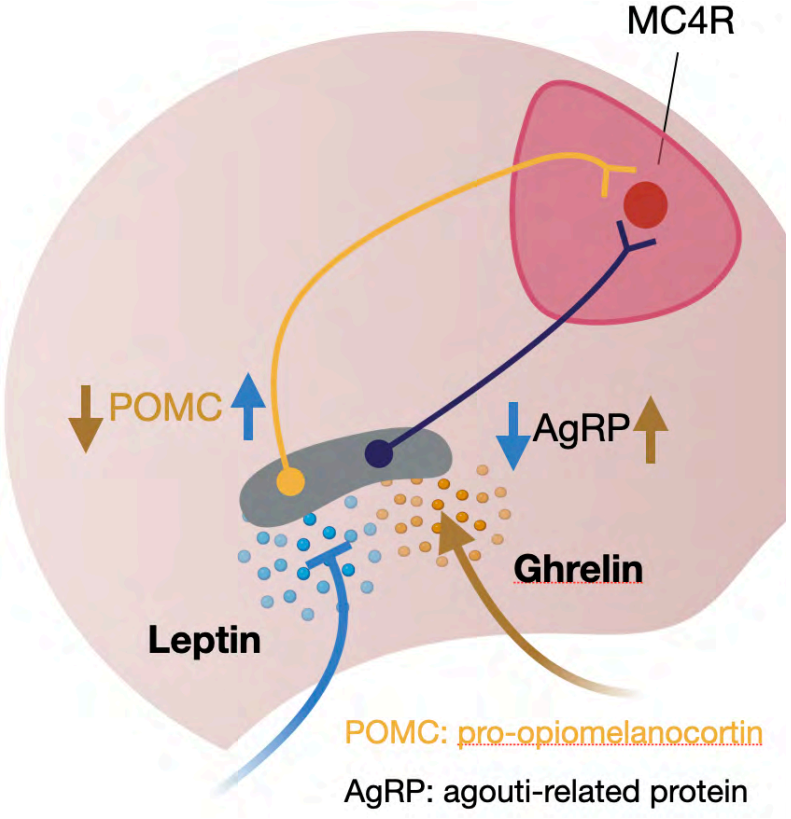
Figure 2. Survival curve of children with LEP, LEPR, and MC4R deficiencies and severely obese children negative for mutations in known obesity genes (obese controls)

Kaplan-Meier group log-rank $p < 0.05$.

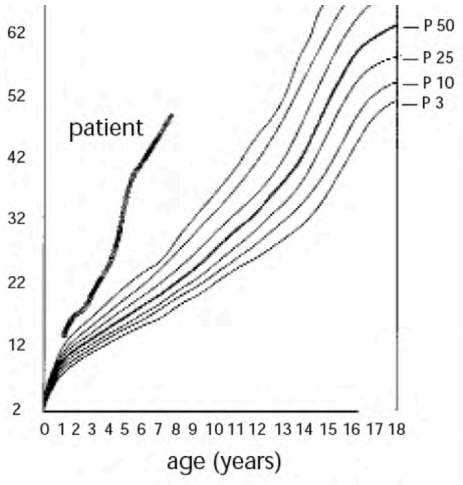
Saeed et al., Cell reports medicine 2023

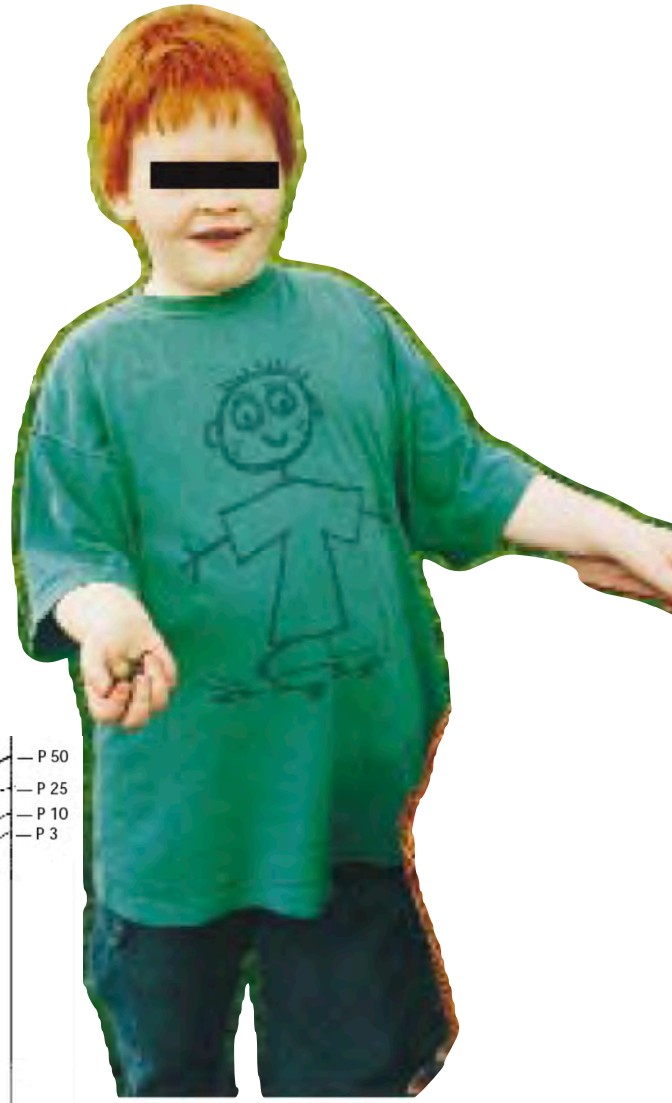
Absence of POMC*

POMC: Prevalence: 1-2 / 1 000 000



*proopiomelanocortin

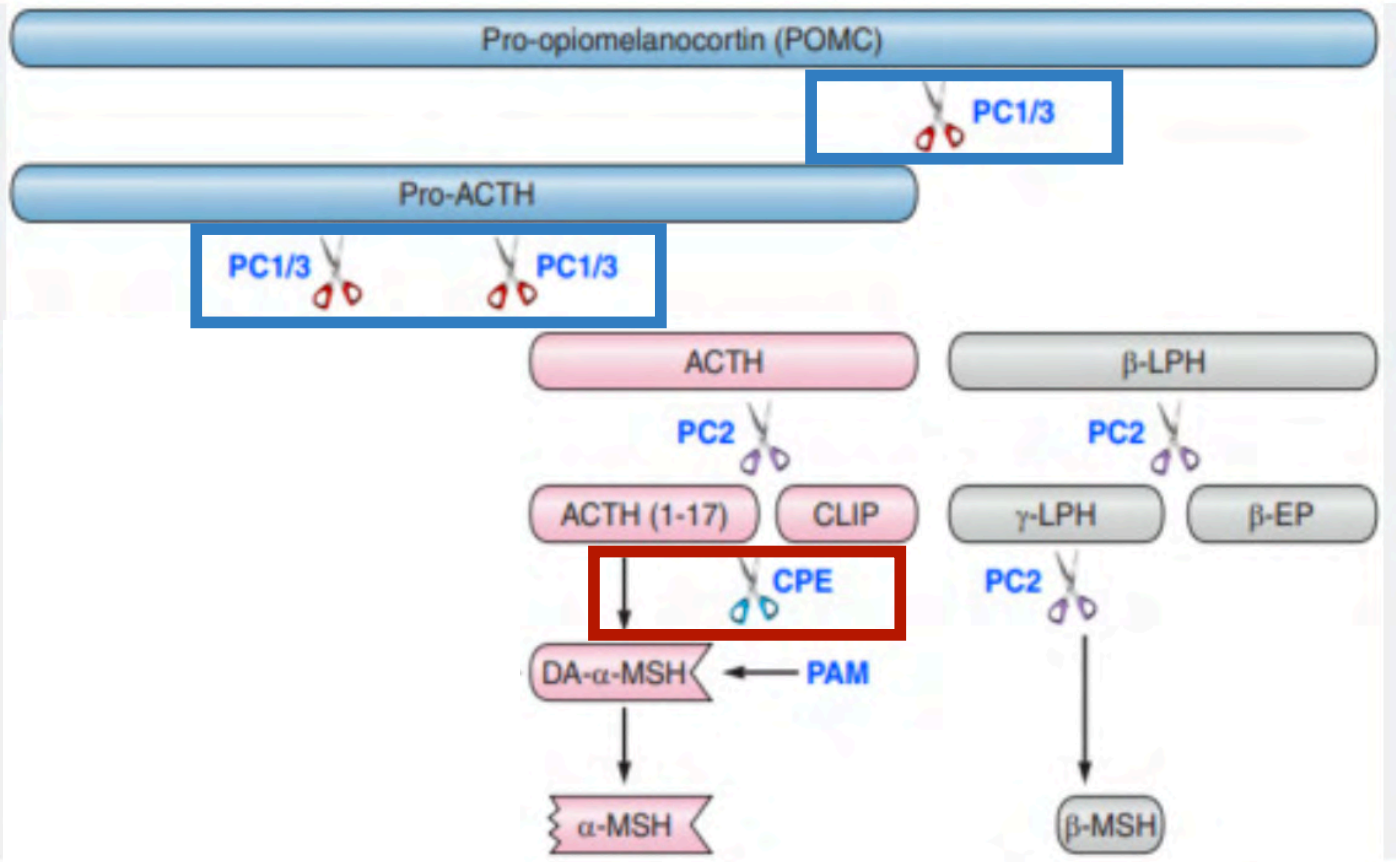




Krude et al, Nat Genetics 1998
Collet & Schwitzgebel, Front Nutr 2024

Pro-opiomelanocortin

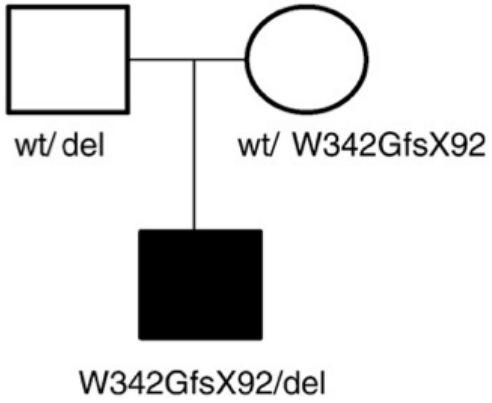
The dual role of α-MSH in regulating food intake and influencing hair pigmentation predicts that the phenotype associated with a defect in *POMC* function would include obesity, alteration in pigmentation and ACTH deficiency



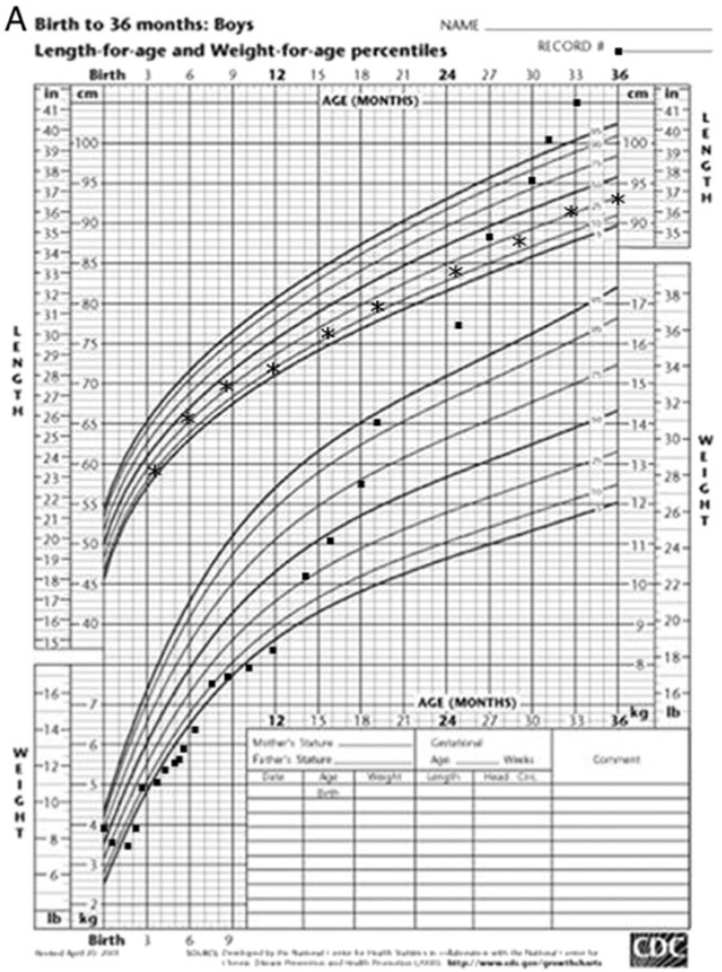
Fisher et al, Nutrient in the Prevention and Treatment of Disease, 2001

Absence of PCSK1*

PCSK1: Prevalence: 1-4 / 1 000 000



- Enteropathy
- Early obesity
- Diabetes insipidus
- Hypogonadism
- Central hypothyroidism
- ACTH deficiency

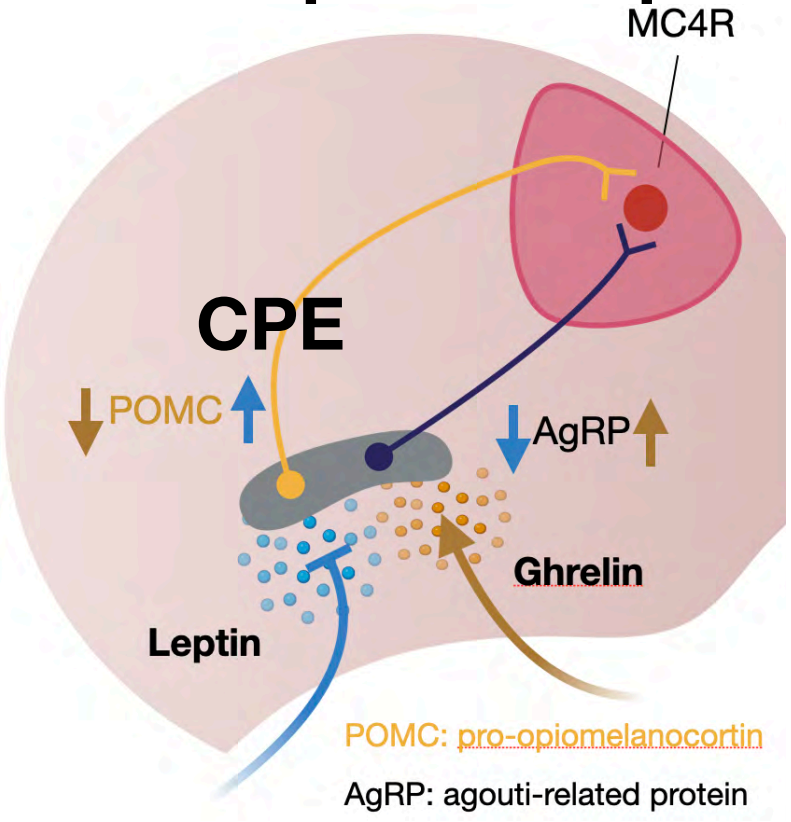


***Proprotein convertase, subtisiline/kexin-type 1**

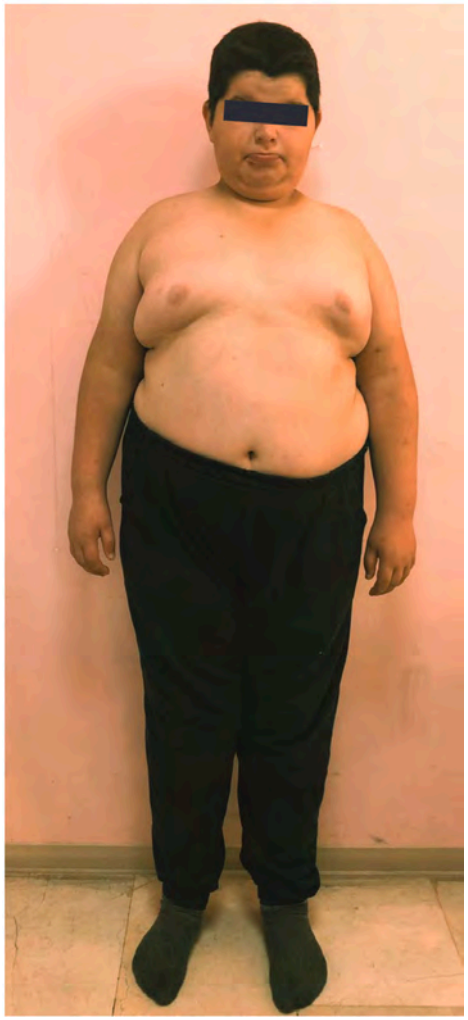
Frank, Farooqi, Mol Gen Met 2013

CPE* deficiency

No mature alpha MSH production



- Obesity
- Intellectual disability
- Hypogonadotropic hypogonadism

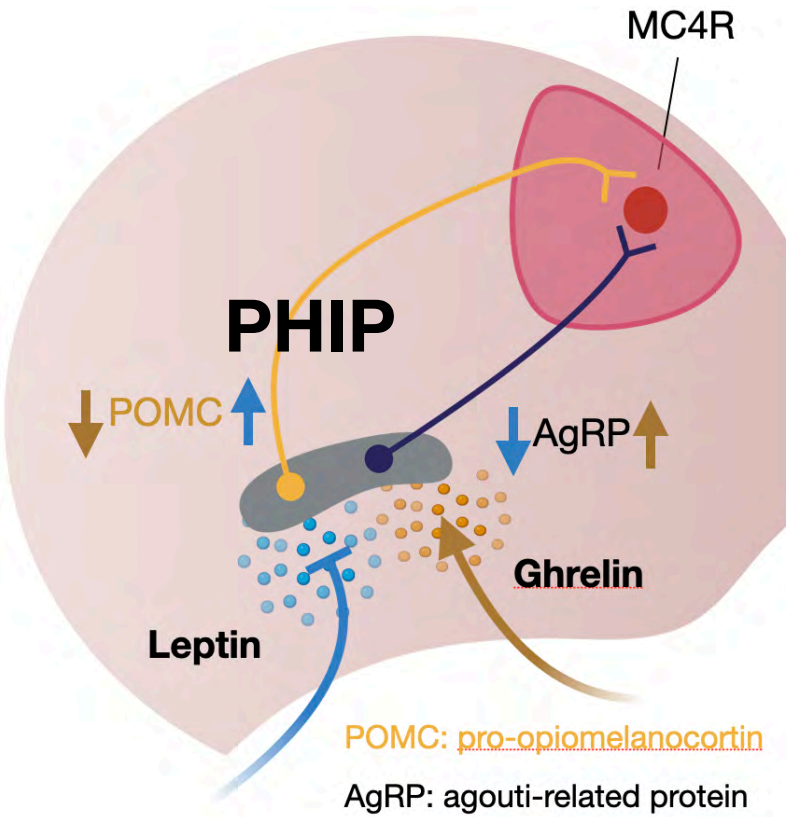


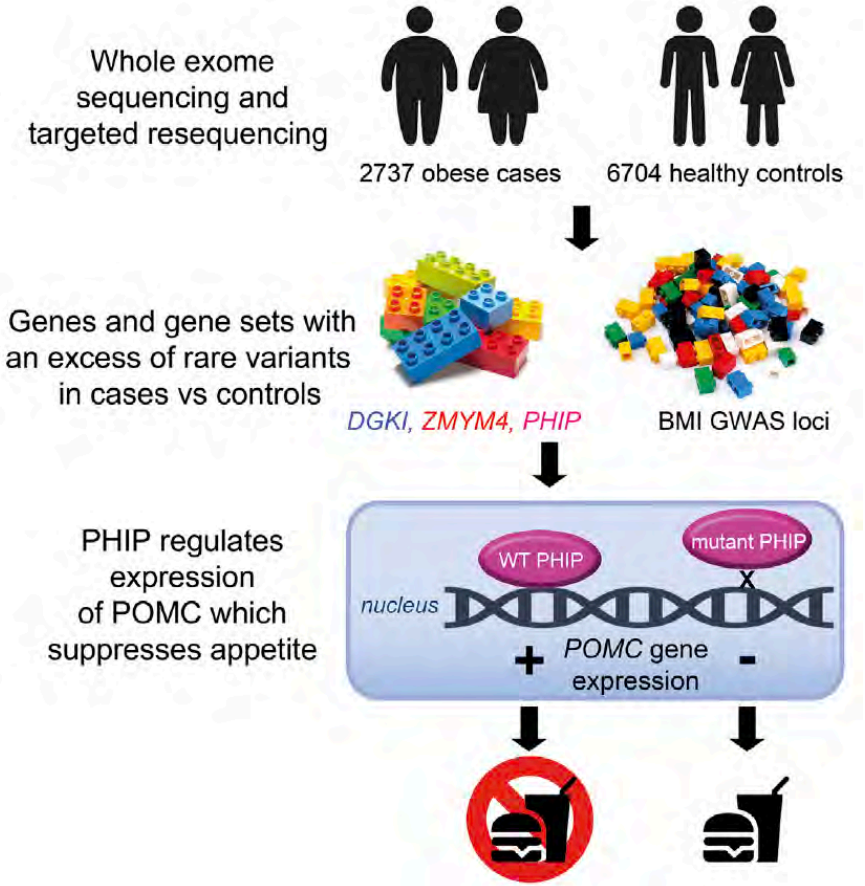
*Carboxypeptidase E

Durmaz et al, J Clin Res Pediatr Endocrinol 2021
Collet & Schwitzgebel, Front Nutr 2024

PHIP regulates expression of POMC

PHIP: Prevalence: <1 / 1 000 000





Marenne et al, Cell Met 2019
Collet & Schwitzgebel, Front Nutr 2024

PHIP regulates expression of POMC

PHIP: Prevalence: <1 / 1 000 000

Chung Jansen Syndrome

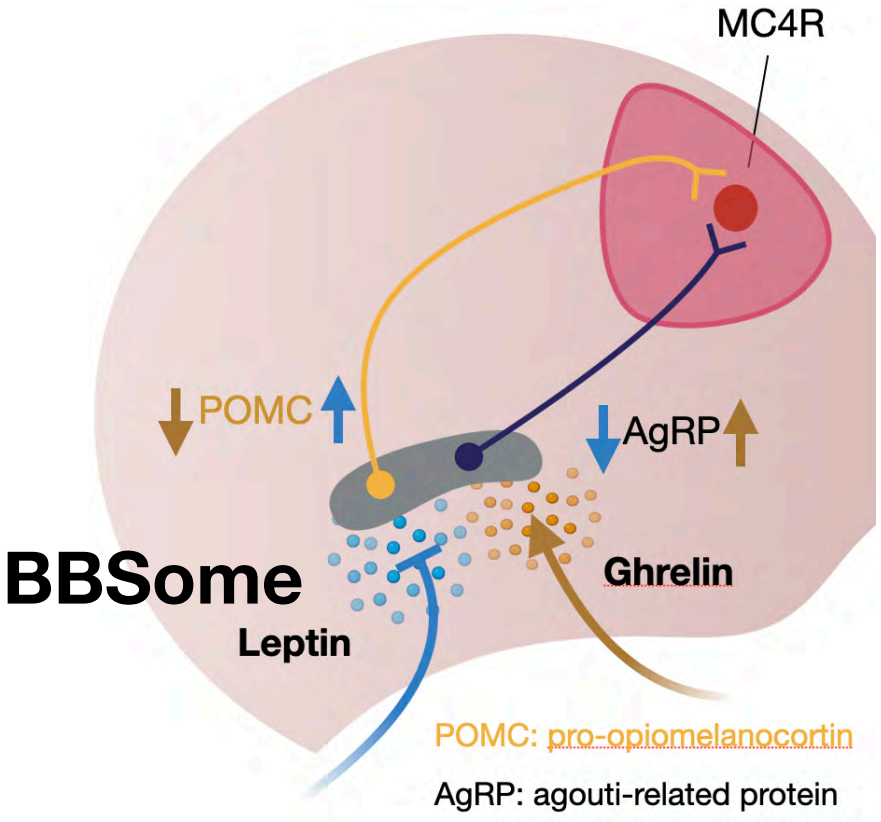
Severe neurodevelopmental syndrome with:

- Intellectual disability
- Autism/behavioral problems
- Hypotonia
- Dysmorphic features
- Obesity in 55 - 70%

Kampmeier et al, Front Cell Dev Bio 2023

Bardet Biedel Syndrome (BBS)

BBS: Prevalence: <1 / 100’000; ≥ 26 genes



Ciliopathy:

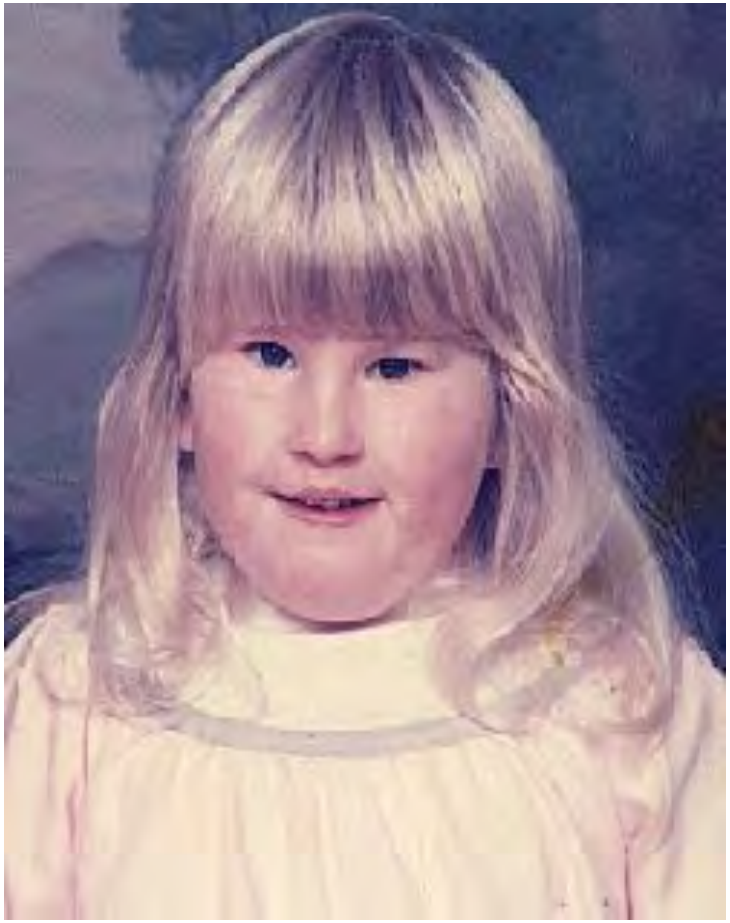
Maintaining LEPR localization at the cell surface requires intact primary cilia

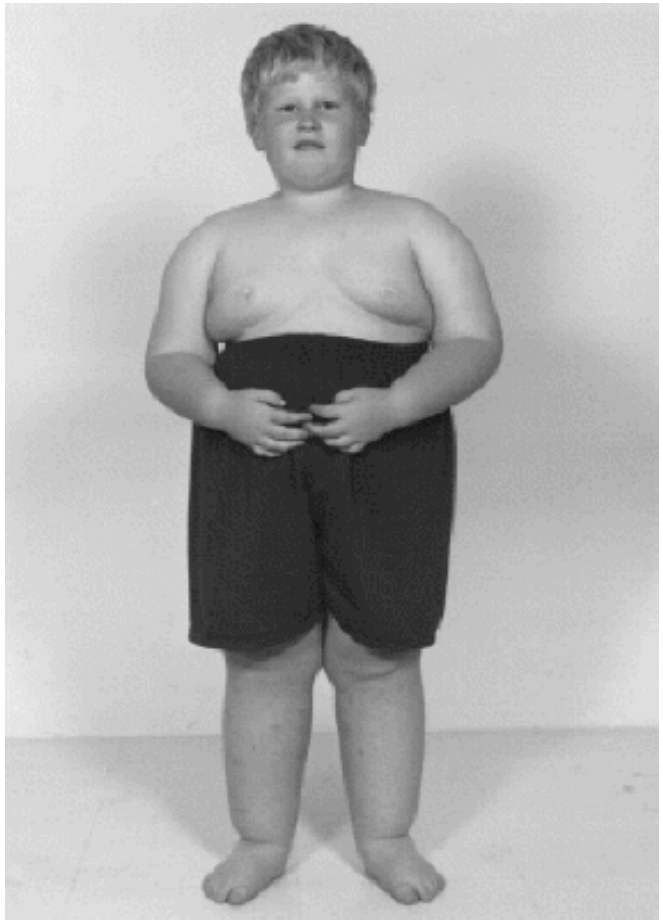
Forsythe E, et al. Eur J Hum Genet. 2013:21:8–13; 2. Forsythe E, et al. Front Pediatr 2018;6:1–8; 3; 3. Pomeroy J, et al. Pediatr Obes. 2021;16(2):e12703; 4. Poitou C, et al. Eur J Endocrinol. 2020;183;R149-R166; Dollfus, H. Eur J Hum Genet, 2024

Prader Willi Syndrome

PWS: Prevalence: 6 -7 / 100 000

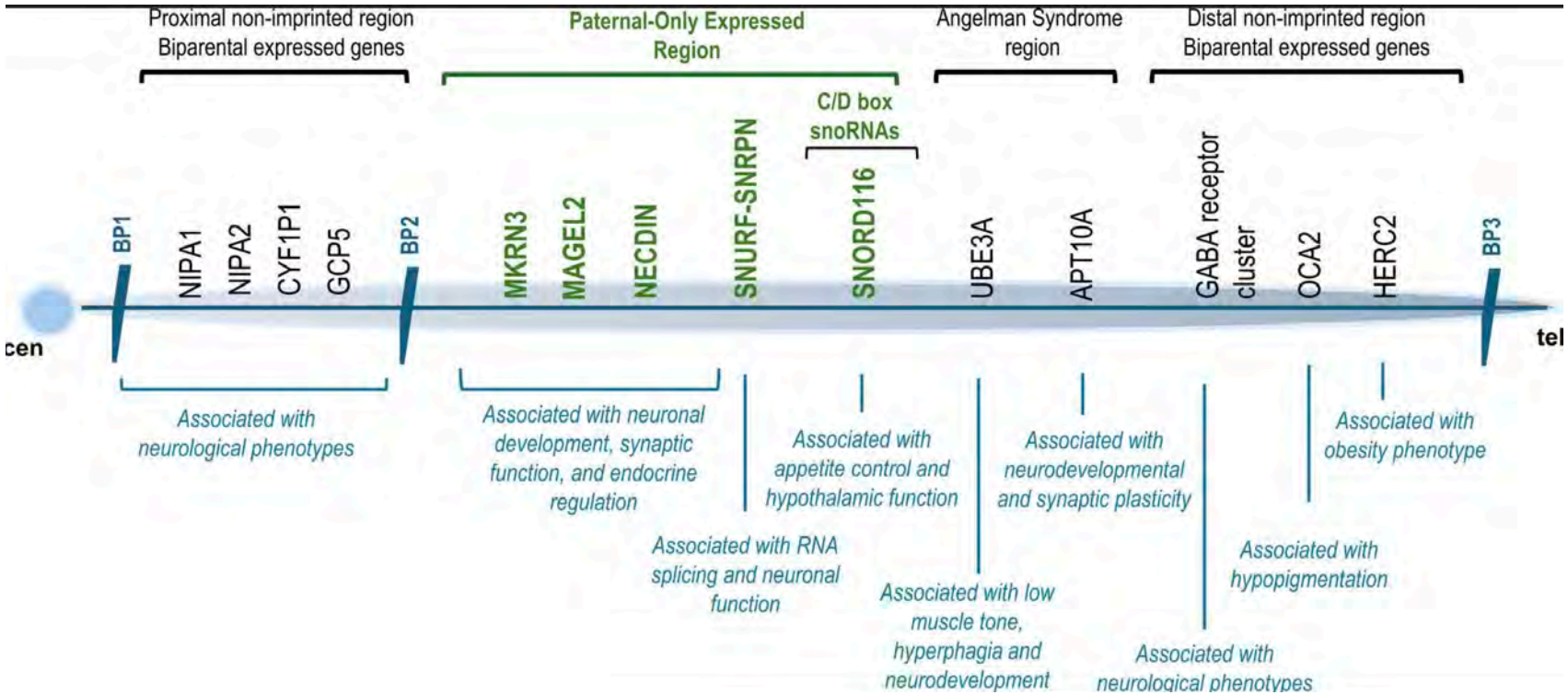
- Hyperphagia
- Obesity
- Hypogonadism
- Muscular hypotonia





Prader Willi Syndrome

Chromosome 15q11

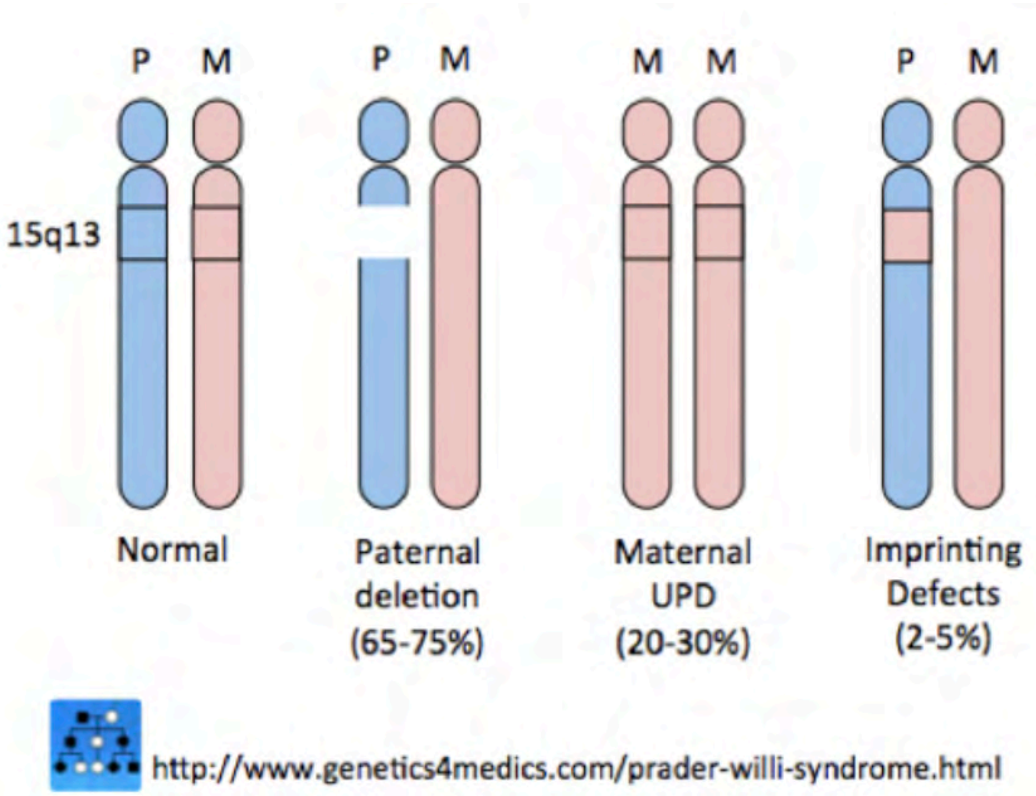


Hingar et al, Advances in Genetics 2025

Prader Willi Syndrome

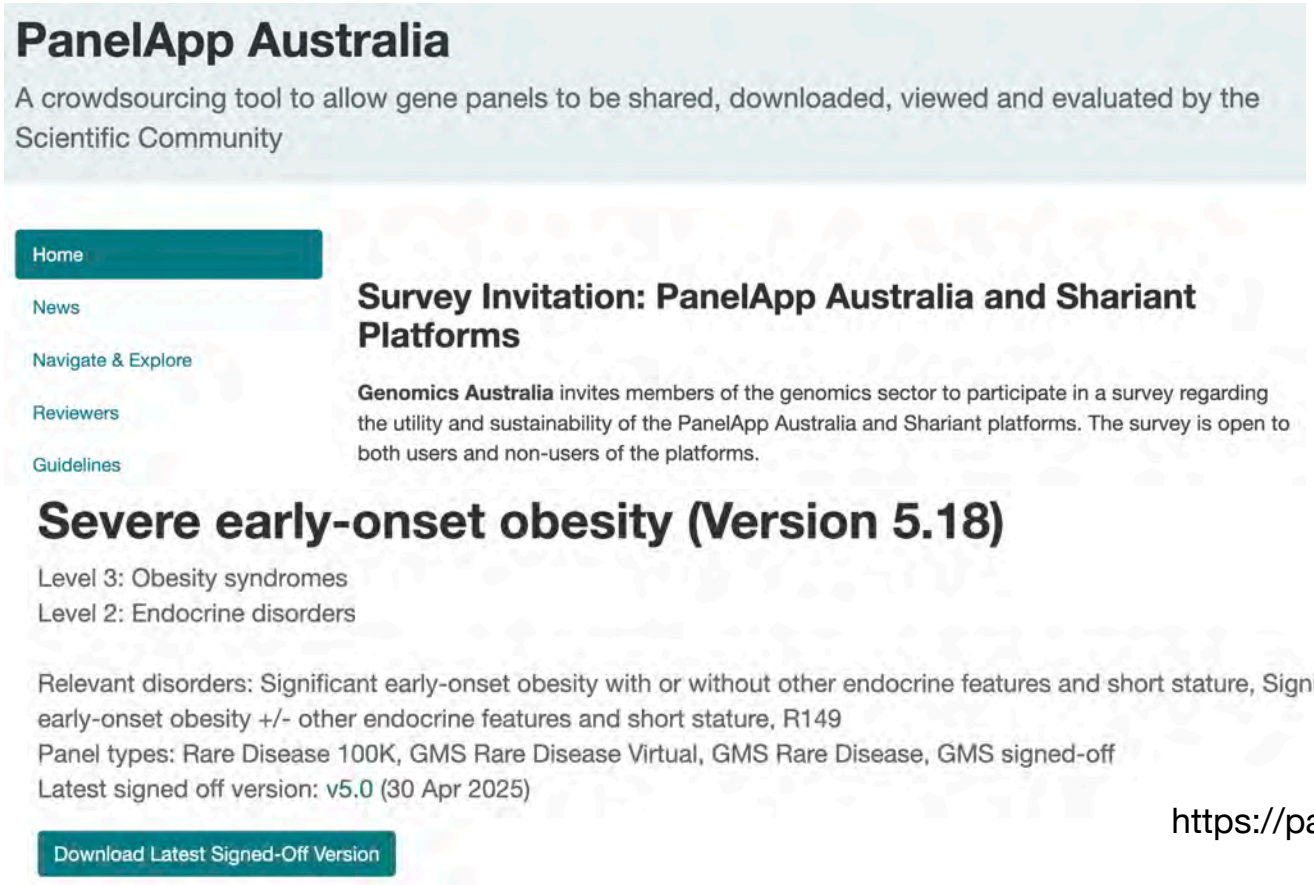
Genetics

- Deletion: more dysmorphism, cognitive impairment, obesity
- UPD: higher autism and psychosis risk
- Distinct neurodevelopmental profiles

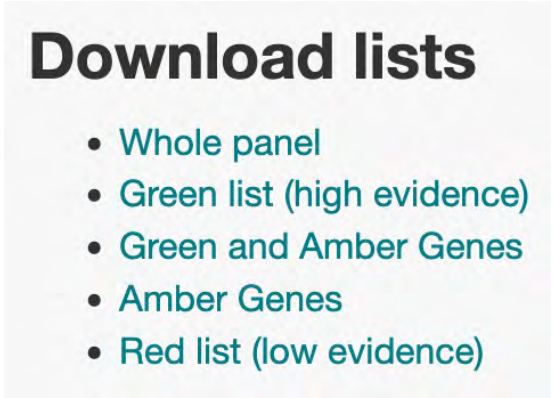


Genetic analysis

Whole exome sequencing



https://panelapp-aus.org/

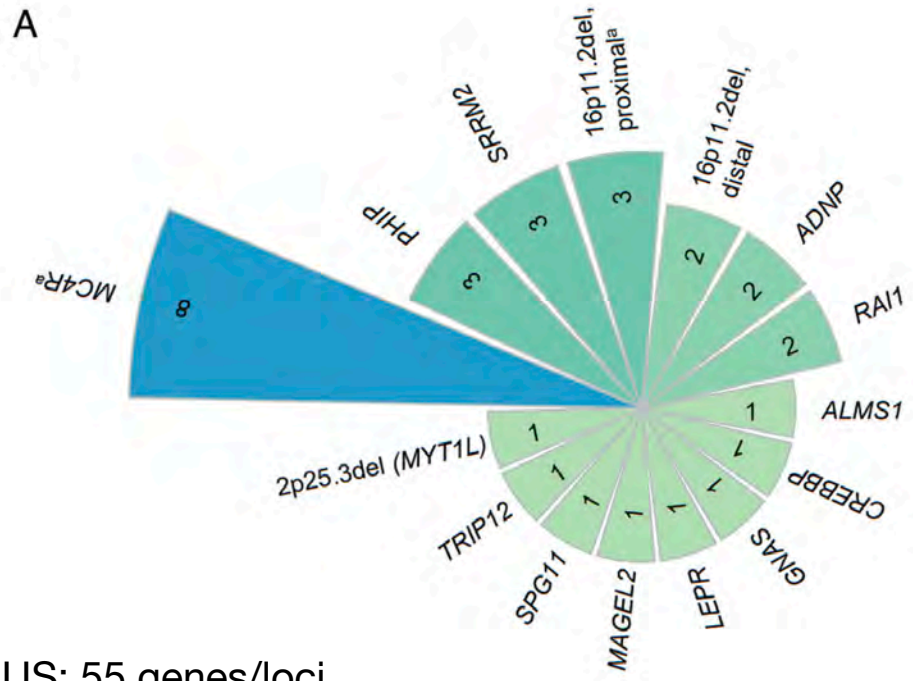


https://panelapp.genomicsengland.co.uk/panels/130/

Genetic analysis monogenic obesity

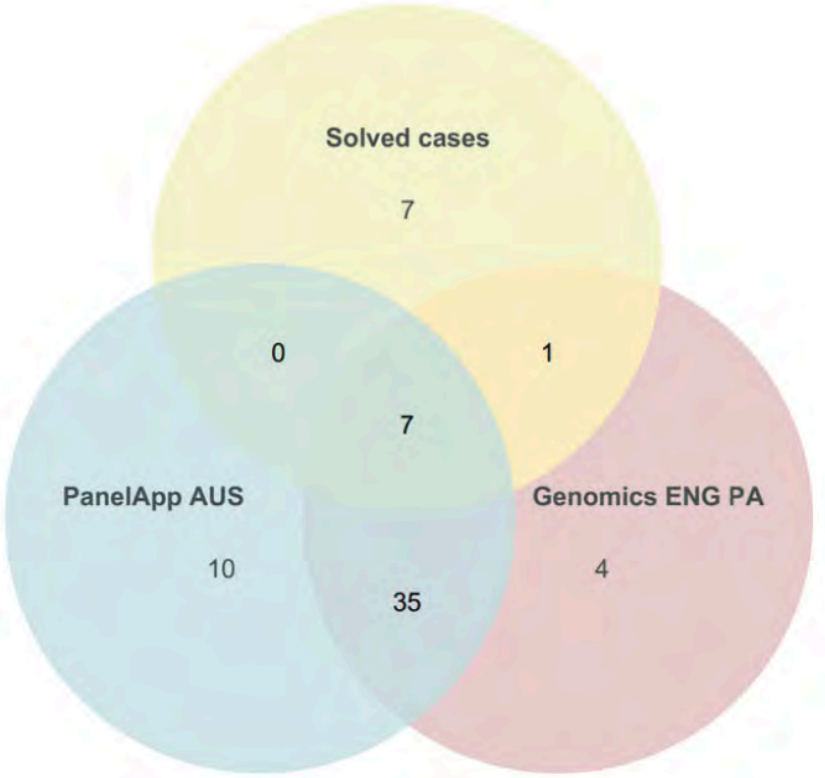
521 patients: 5.8% monogenic obesity, 7.1% potential obesogenic variant

40% of patients with monogenic obesity carried variants in genes not included in current obesity panels



AUS: 55 genes/loci
ENG: 52 genes/loci

Solved cases

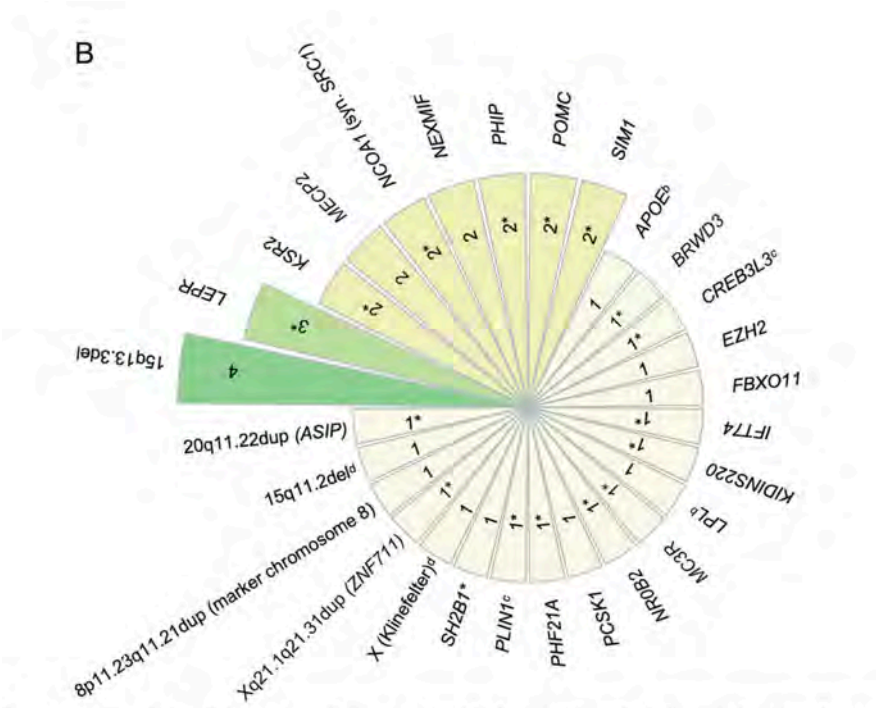


Künzel et al, Farooqi, Int Journal of Obesity 2025

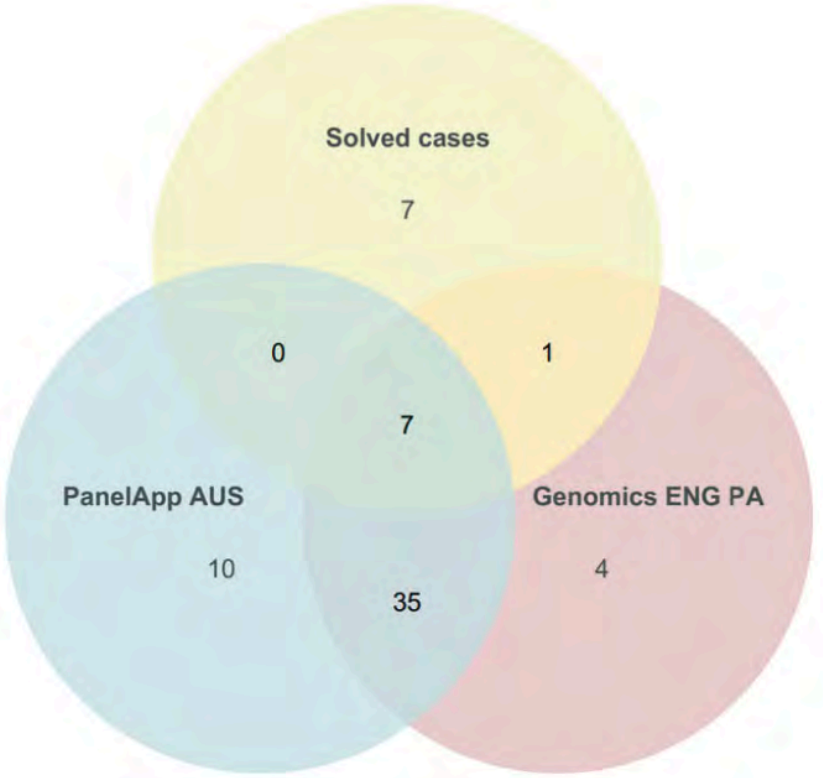
Genetic analysis monogenic obesity

521 patients: 5.8% monogenic obesity, 7.1% potential obesogenic variant

40% of patients with monogenic obesity carried variants in genes not included in current obesity panels

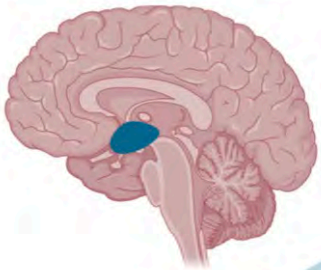


Potentially solved cases

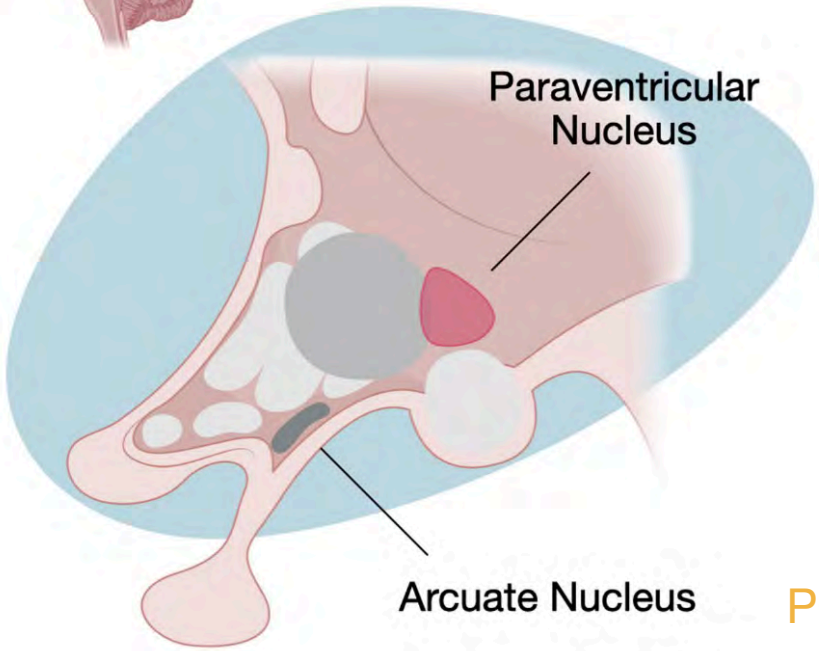


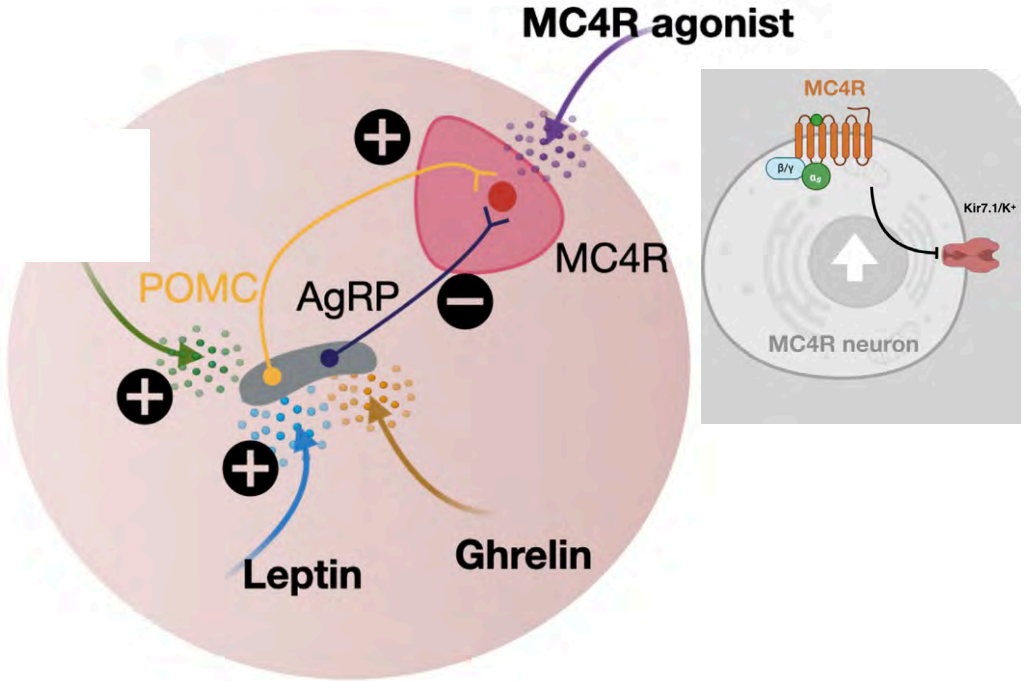
Künzel et al, Farooqi, Int Journal of Obesity 2025

Treatment options



Hypothalamus





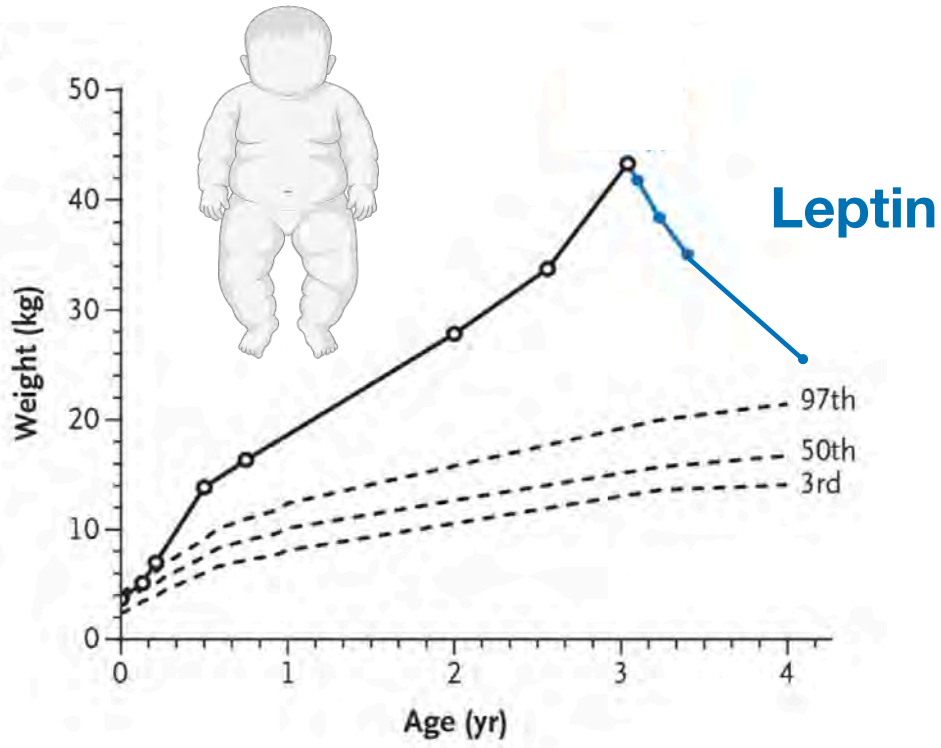
POMC: pro-opiomelanocortin

AgRP: agouti-related protein

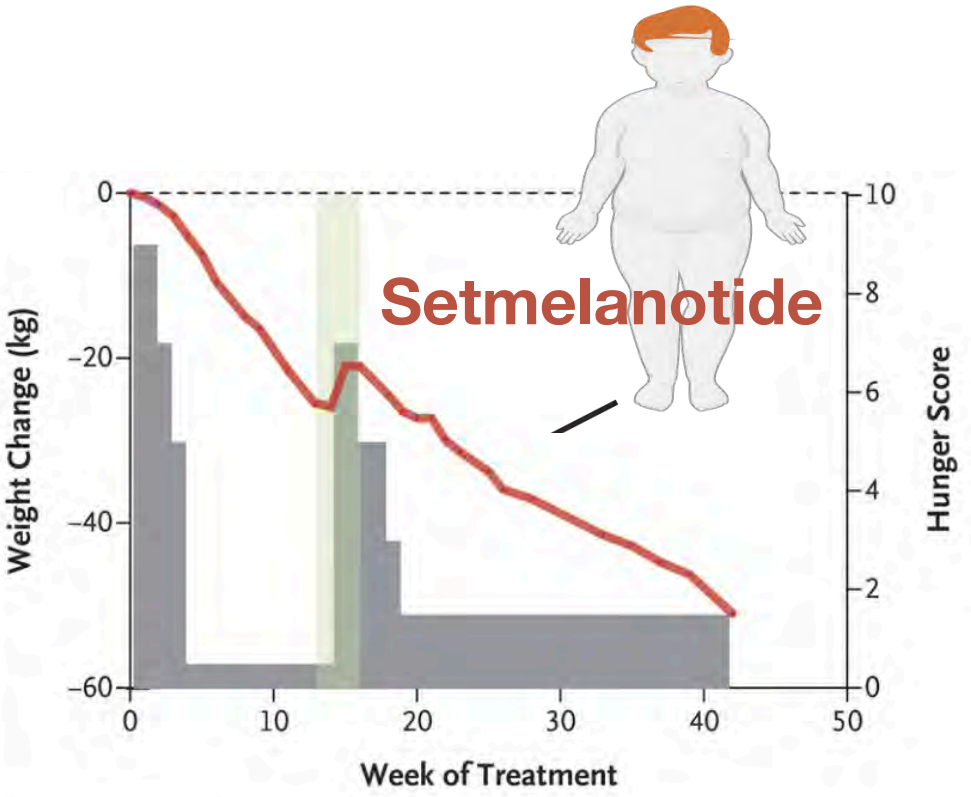
Collet & Schwitzgebel, Front Nutr 2024
Stuber, Schwitzgebel & Luscher, Neuron 2025

Precision treatment

Leptin deficiency



POMC deficiency



Kühnen et al., NEJM 2016
Farooqi et al., NEJM 2017

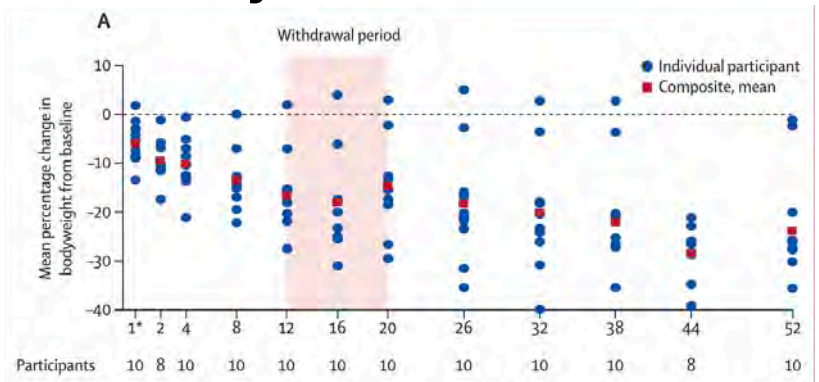
Efficacy of Setmelanotide

	Participants with POMC deficiency obesity (n=10†)	Participants with LEPR deficiency obesity (n=11)
Age, years	18·4 (6·2; 11·0–30·0)	23·7 (8·4; 13·0–37·0)
Sex		
Male	5 (50%)	3 (27%)
Female	5 (50%)	8 (73%)
Genotype		
Compound heterozygous	2 (20%)	6 (55%)
Homozygous	8 (80%)	5 (45%)
Ethnicity		
Hispanic or Latino	1 (10%)	0
Not Hispanic or Latino	8 (80%)	11 (100%)
Unknown	1 (10%)	0
Race		
White	7 (70%)	10 (91%)
Other	3 (30%)	1 (9%)
Bodyweight, kg	118·7 (37·5; 55·9–186·7)	133·3 (26·0; 89·4–170·4)
BMI, kg/m²	40·4 (9·0; 26·6–53·3)	48·2 (10·4; 35·8–64·6)
Most hunger score‡	8·0 (0·8; 7·0–9·0)	7·1 (1·0; 5·0–8·0)

Data are mean (SD; range) and n (%). LEPR=leptin receptor. POMC=pro-opiomelanocortin. *Data shown are for the safety analysis set, except where otherwise indicated. †Includes nine participants with variants in *POMC* and one with a variant in *PCSK1*. ‡The most hunger score assessed in participants aged 12 years or older in the full analysis set is based on an 11-point Likert-type scale, where 0 indicates not hungry at all, and 10 indicates hungriest possible.

Table 1: **Baseline characteristics***

POMC deficiency



LEPR deficiency

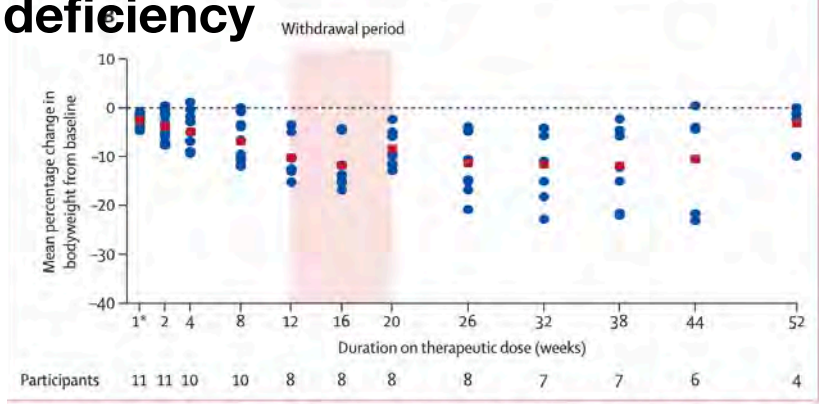


Figure 2: **Effect of setmelanotide on weight loss in participants with POMC (A) or LEPR (B) deficiency obesity in the full analysis set**
Values from baseline to before the final 2 weeks of the dose titration phase are not shown. LEPR=leptin receptor. POMC=pro-opiomelanocortin. *Start of therapeutic dose.

Clément et al., Lancet Diabetes Endocrinology 2020

Treatment options

Real-life Evaluation of WEGOVY (Semaglutide) Treatment in Adults With Monogenic Obesity (ObGeSema) (ObGeSema)

ClinicalTrials.gov ID NCT06380426

Sponsor Assistance Publique - Hôpitaux de Paris

Information provided by Assistance Publique - Hôpitaux de Paris (Responsible Party)

Last Update Posted 2025-08-07

Summary

- Increasing obesity pandemic
- Homeostatic - Hedonic pathways
- Highlighted monogenic and syndromic obesity
- Diagnosis - clinical - genetic to be improved
- Precision treatment:
  - Leptin LEP
  - MC4R agonist: BBS, biallelic POMC, PCSK1, LEPR