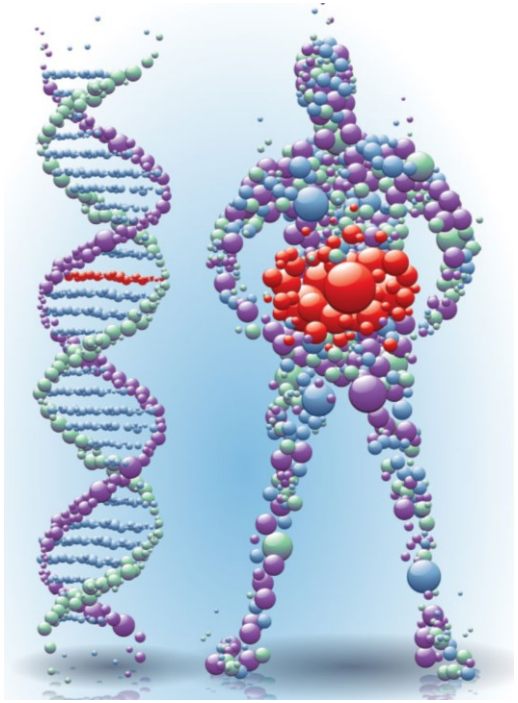
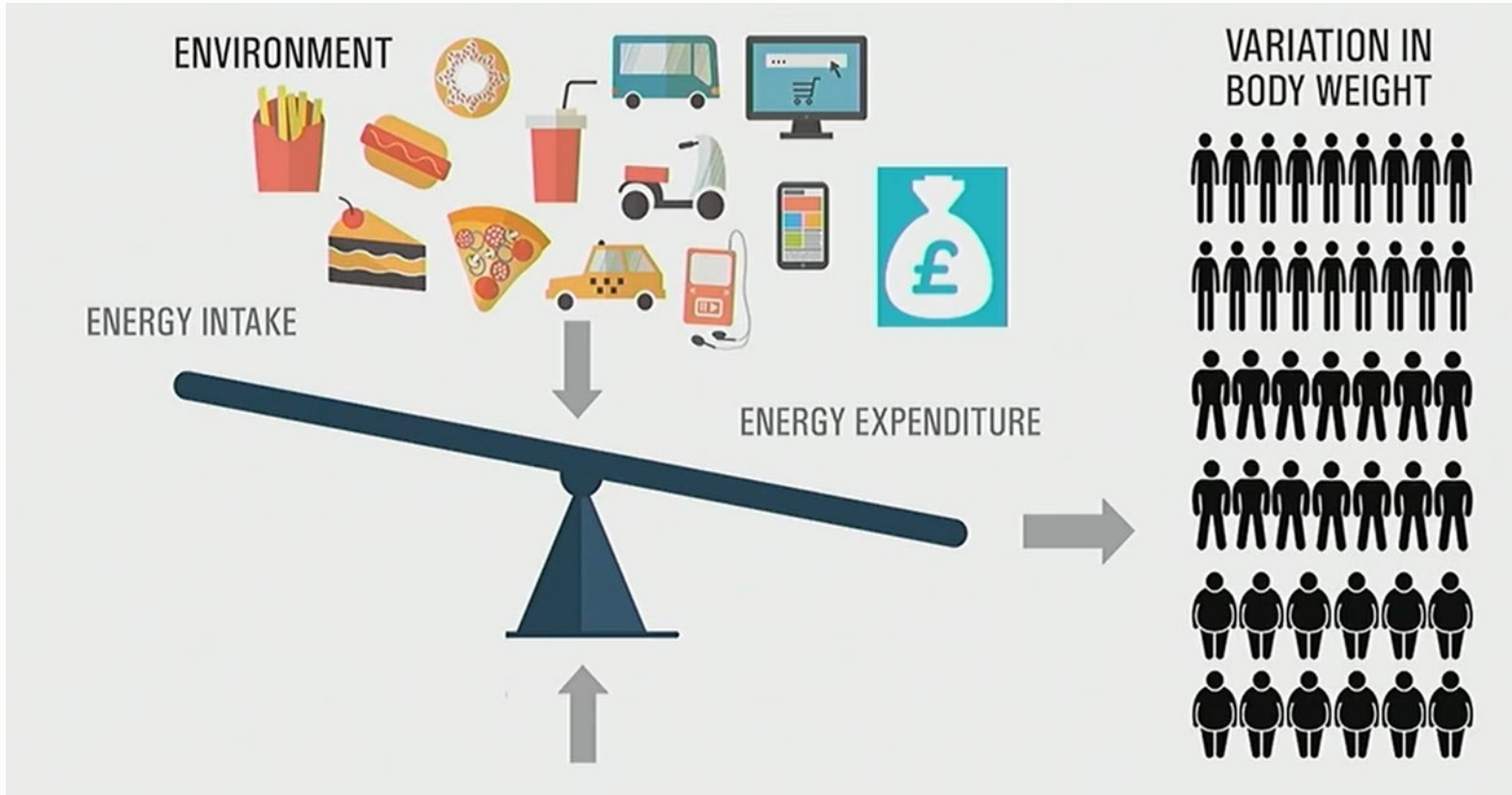
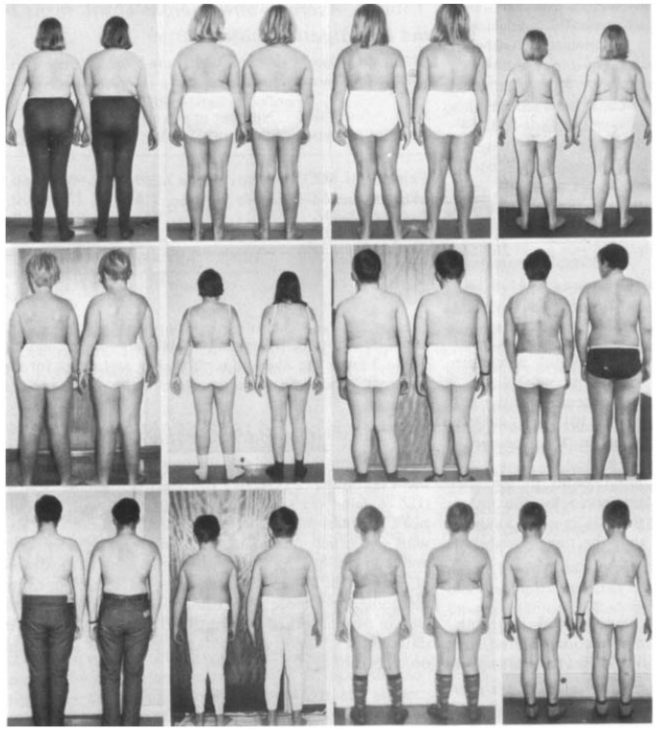
Monogenic Obesity - update



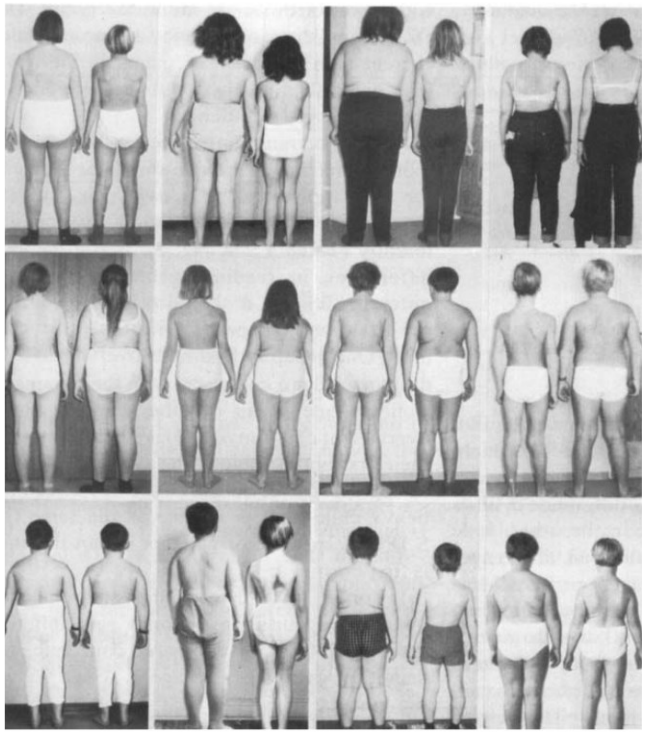
Gabriella Segal-Lieberman, MD
Head of the Israeli Center for Weight Management
Sheba Medical Center
Israel


ENVIRONMENT
ENERGY INTAKE
ENERGY EXPENDITURE
VARIATION IN BODY WEIGHT

Monozygotic twins



Dizygotic twins



Borjeson M, Acta Paediatr Scand 65: 279-287, 1976

- Identical twins - identical weight even if separated at birth *(Stunkard et al, NEJM 1990)*
- Weight of adopted children similar to biological parents *(Stunkard, Sorenson et al, NEJM 1986)*
- Identical twins gain similar amount of weight with overeating *(Bouchard et al, NEJM 1990)*
- **40-70% of difference in weight between 2 people, is due to differences in their genes**

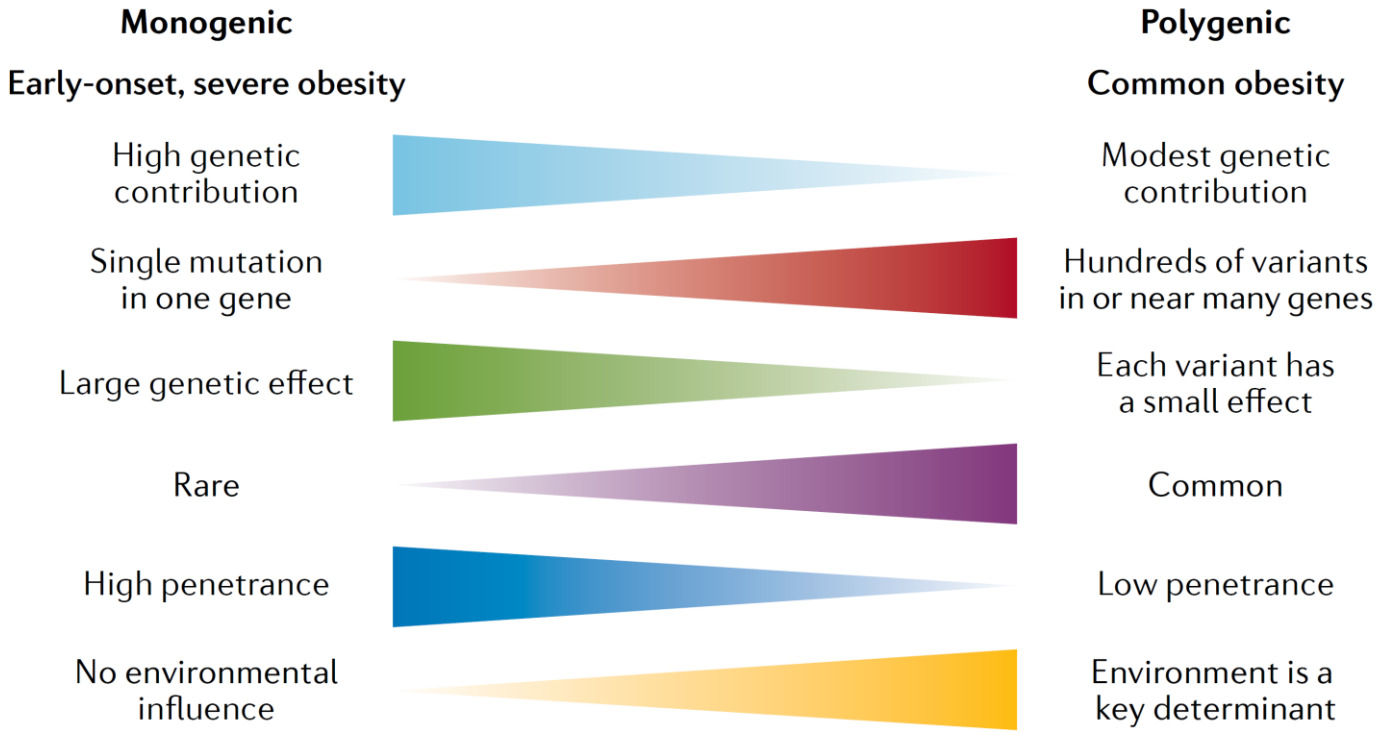
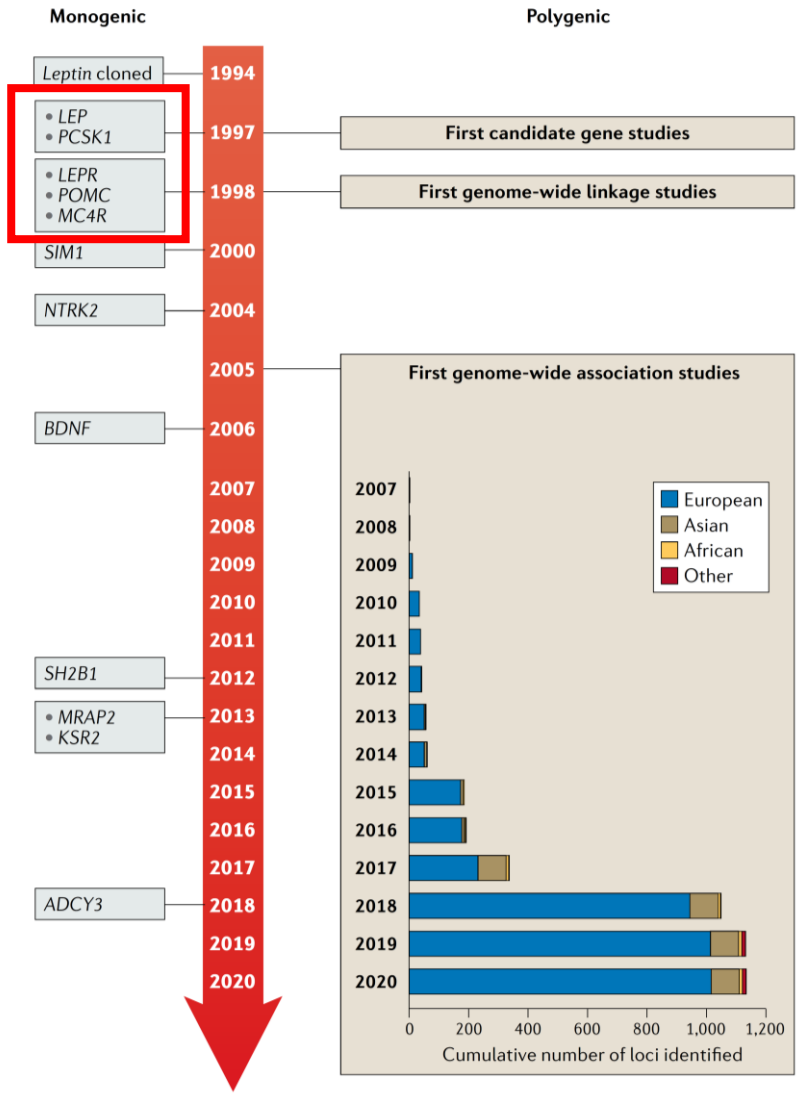
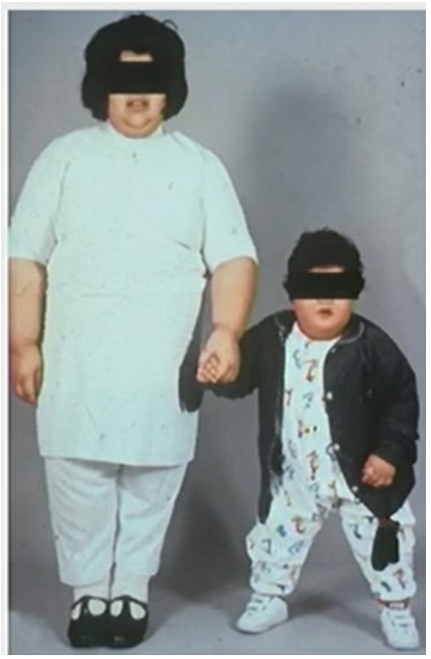


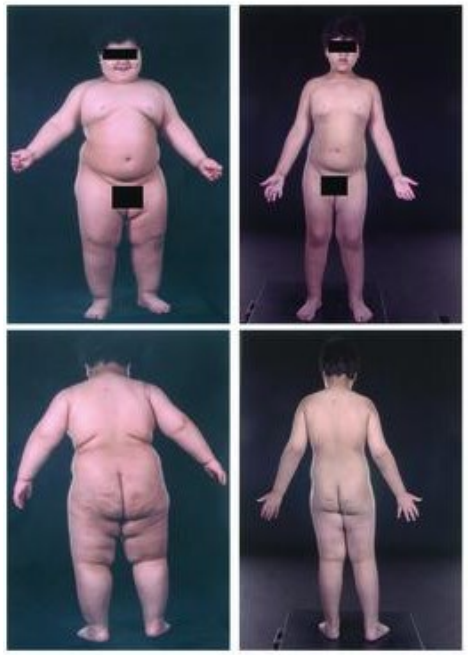
Fig. 2 | **Key features of monogenic and polygenic forms of obesity.**

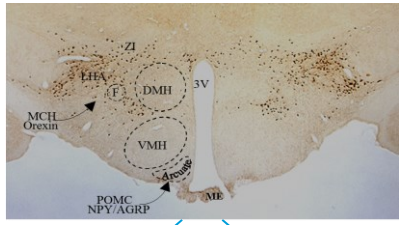


Loos RJF, Nature Reviews Genetics, September 2021

LEPTIN







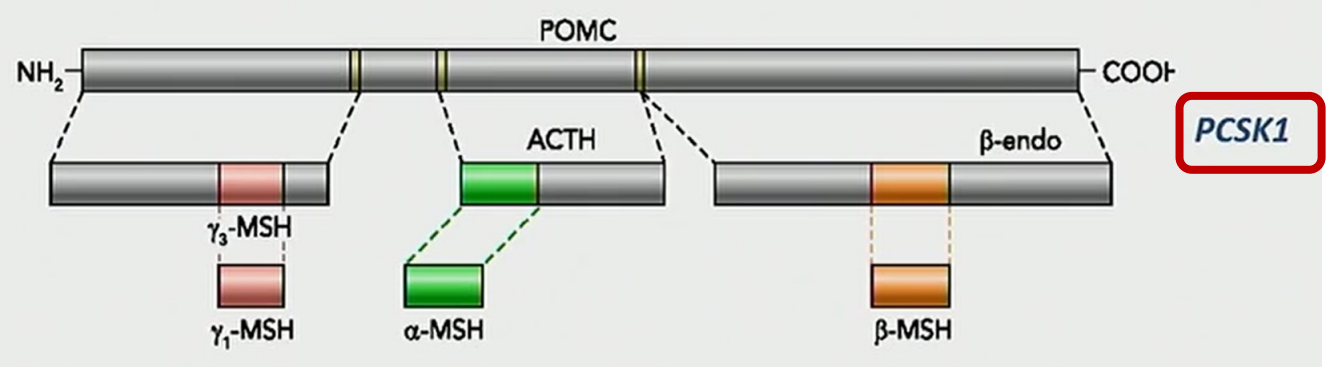
+ Leptin -

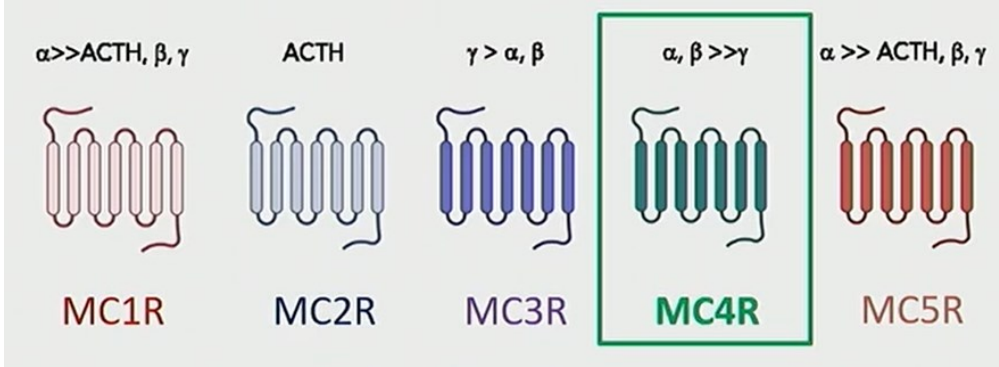
Anorexigenic
(Satiety signals)

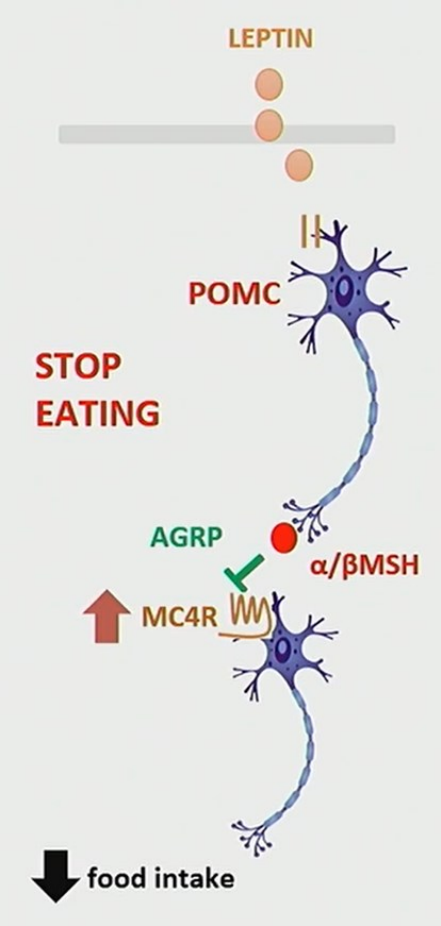
- POMC
- CART

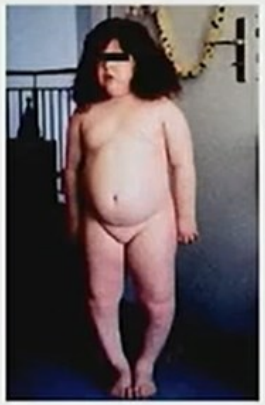
Orexigenic
(Hunger signals)

- NPY
- AgRP









b

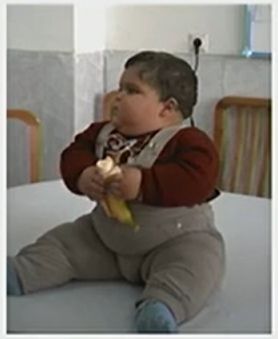
POMC deficiency
Obesity, isolated ACTH deficiency - low cortisol
Hypopigmentation

PCSK1 deficiency
Obesity, ACTH deficiency, multiple neuroendocrine abnormalities
Postprandial hypoglycaemia (high proinsulin)
Neonatal Enteropathy

Genetic disorders affect function of appetite-suppressing POMC neurons

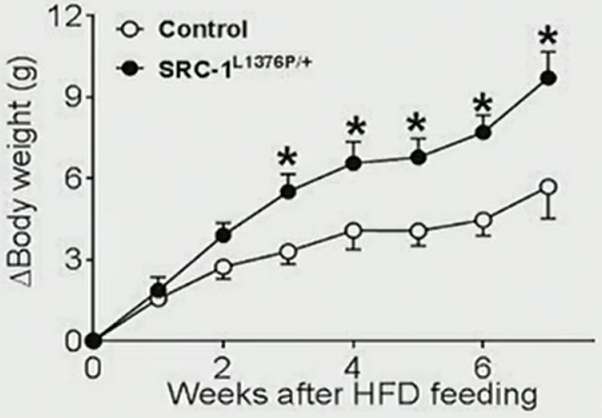
Genetics of Obesity Study (GOOS)

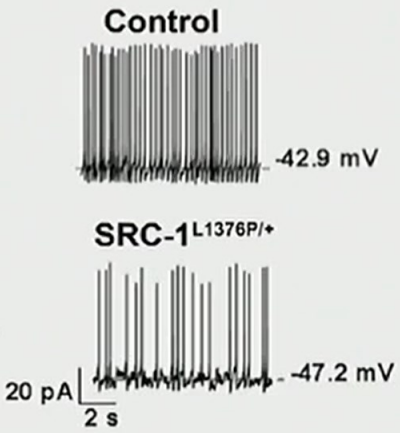
8,000 children with severe obesity

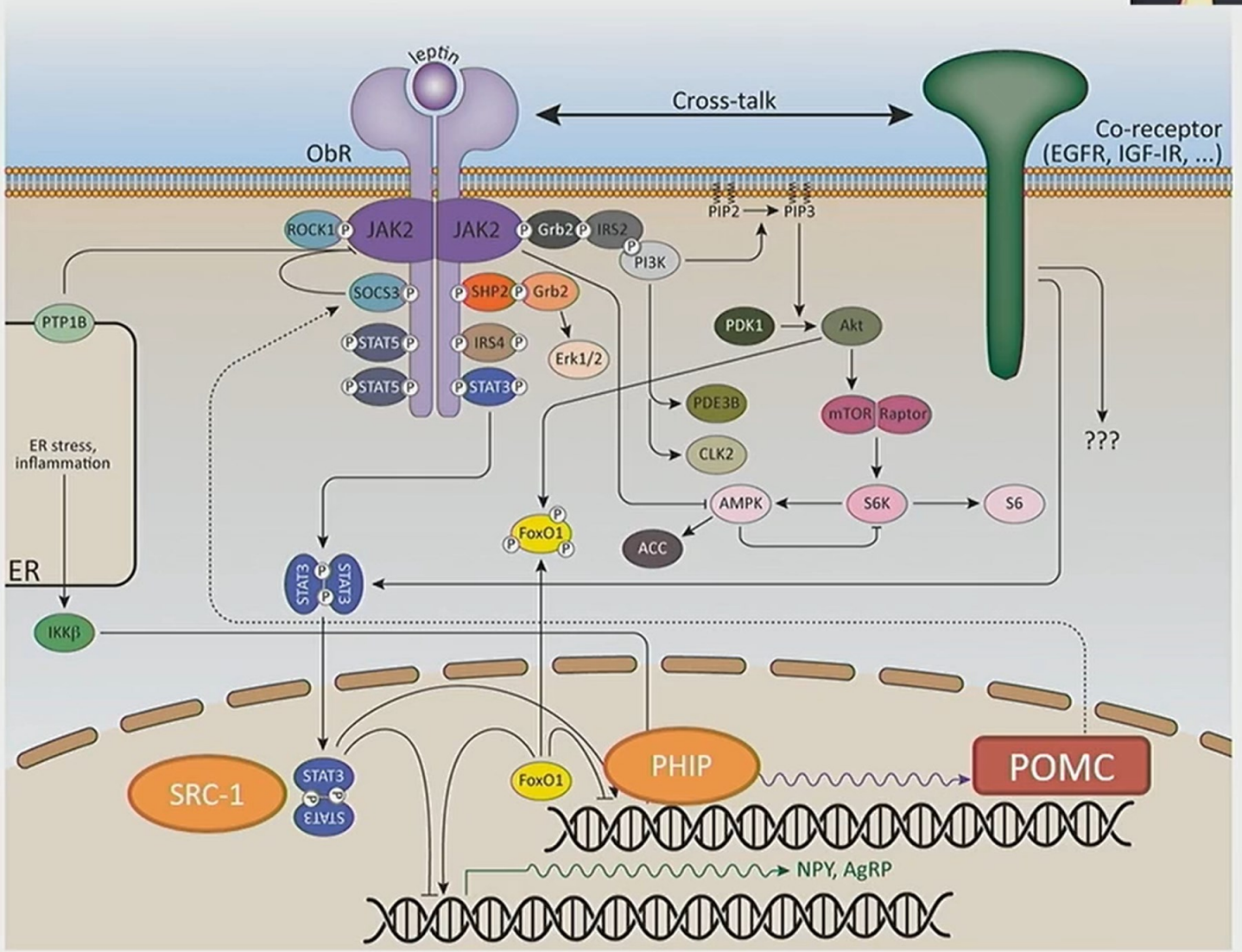


www.goos.org.uk

Rare variants in *SRC-1* modulate POMC transcription





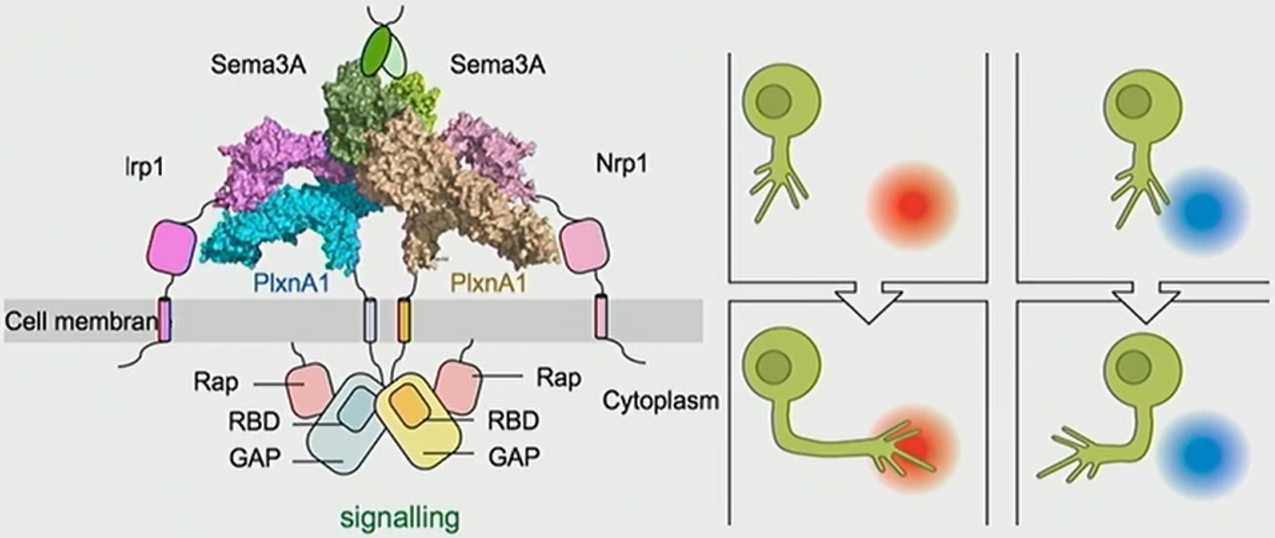


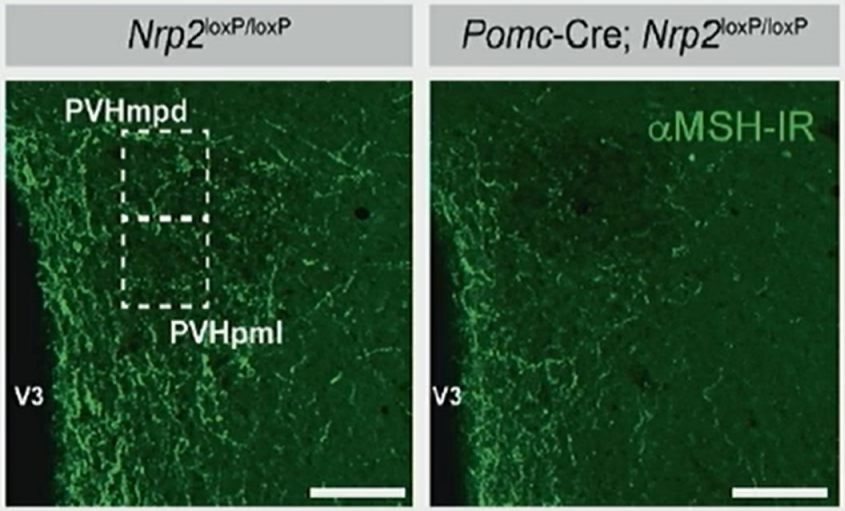
Yang, van der Klaauw, Zhu, Cacciottolo et al.
Nature Comms 2019; PMID: 30979869

Marenne et al. Cell Metabolism 2020; PMID: 32492392

Genetic disorders affect development of POMC and MC4R expressing neurons

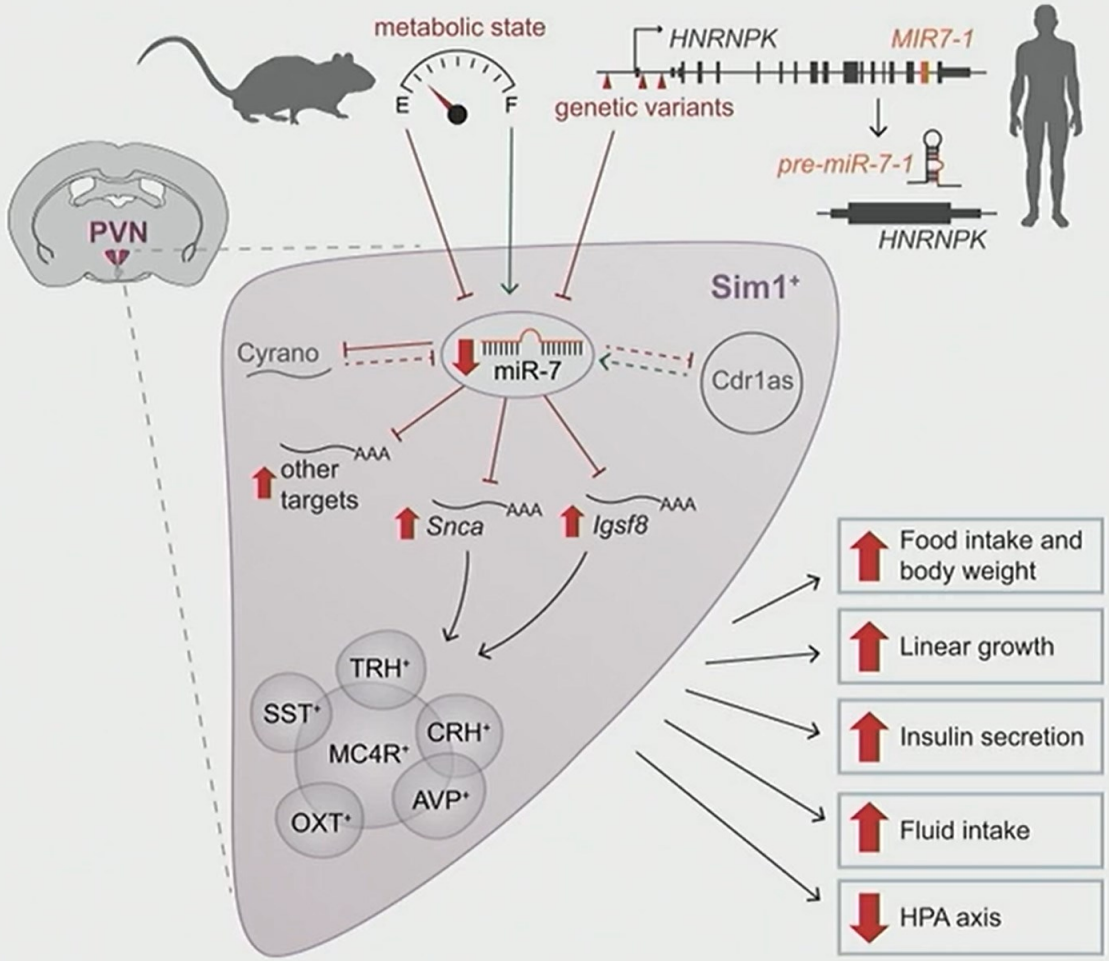
SEMA3s, PLEXINA1-4, NEUROPILIN 1 and 2
Rare variants in severely obese cases impair development of POMC projections





van der Klaauw, Croizier et al. Cell 2019; PMID: 30661757

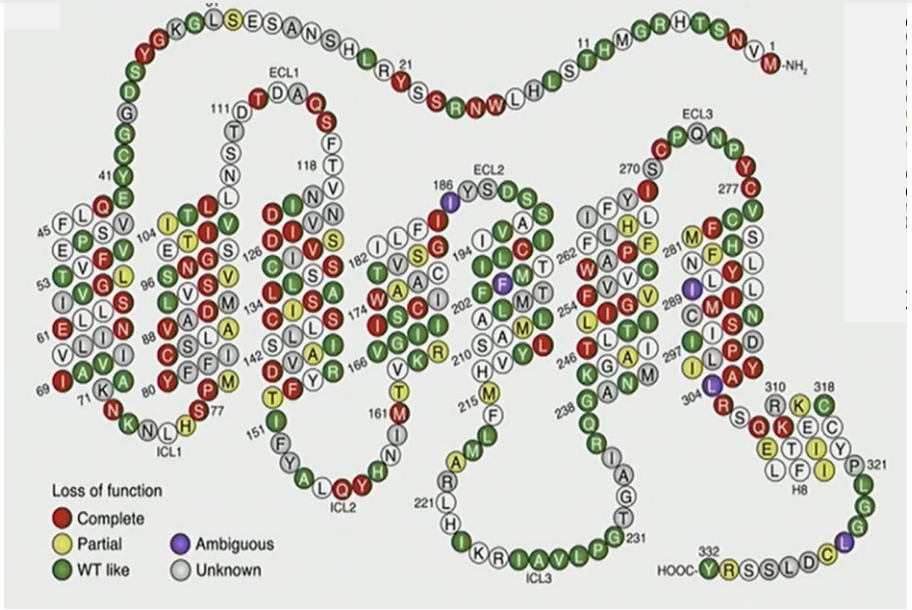
Common variants in HNRNPK (RNA binding protein) reduce expression of MicroRNA-7, which modulates function of MC4R expressing neurons



Le Pierre, Lawler, Stoffel et al. Nature Communications; PMID: 30661757

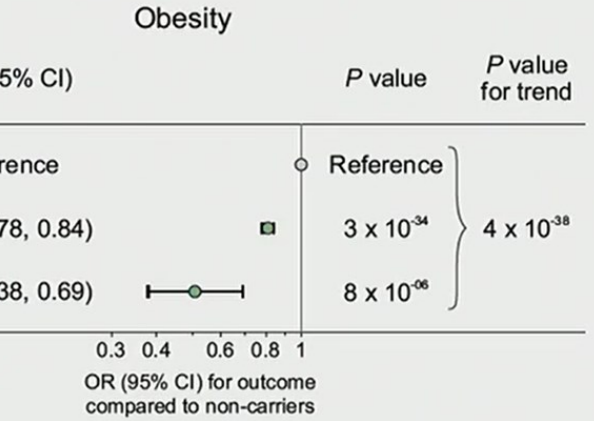
MC4R MUTATIONS

Heterozygous mutations in 5% of severely obese children (1-2% of obese adults)



Obesity

Carrier status for GoF β-arrestin biased alleles (N)	% with disease	OR (95% CI)	*P* value	*P* value for trend
Non-carriers (242,742)	42%	Reference	Reference	
Carriers of 1 allele (15,748)	38%	0.81 (0.78, 0.84)	3×10^{-34}	4×10^{-38}
Carriers of 2 alleles (231)	28%	0.51 (0.38, 0.69)	8×10^{-06}	

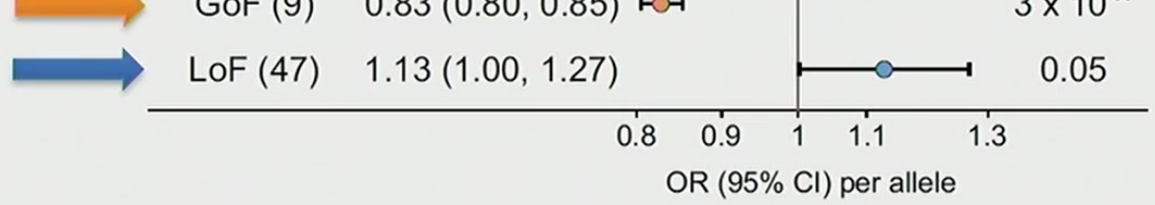


Carriers of 2 biased genes have 50% reduced risk of obesity & type 2 diabetes

Obesity

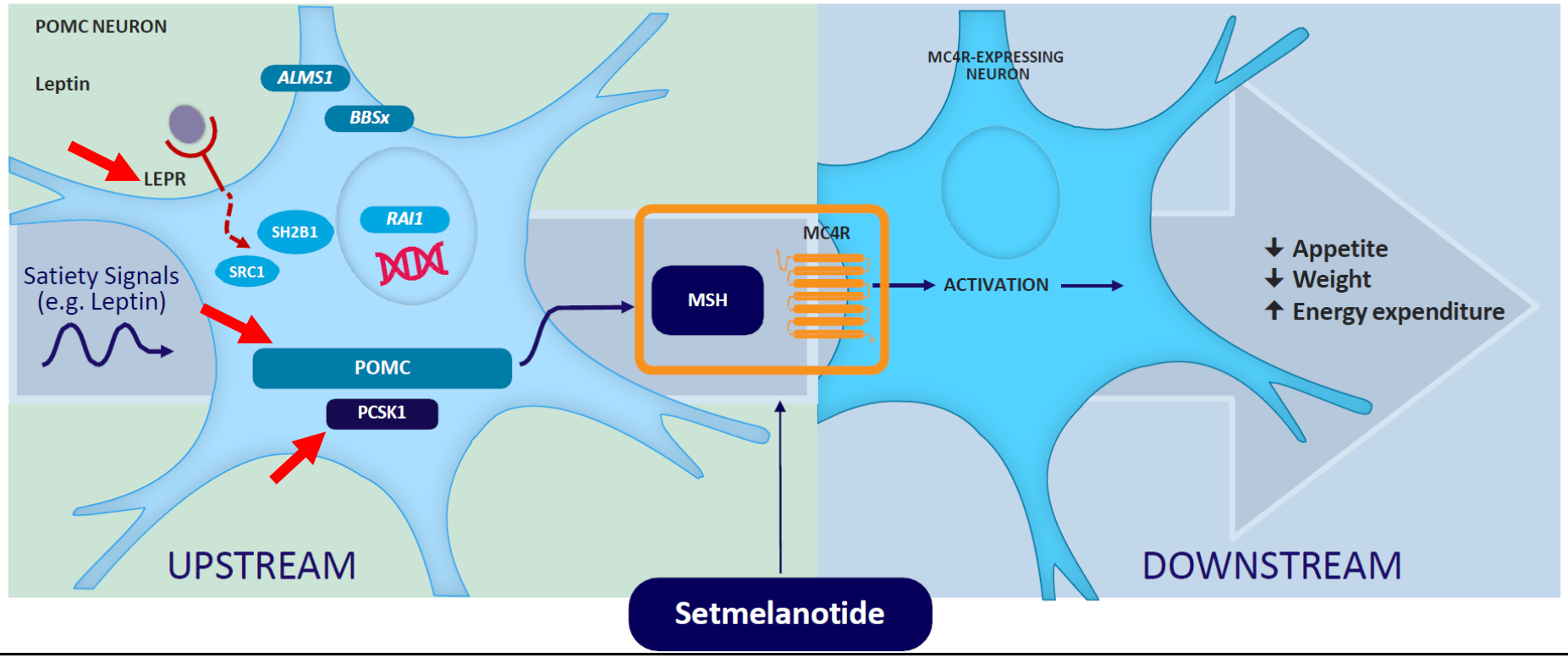
(Cases=109,139, Controls=149,605)

Class (n variants)	OR (95% CI)	*P* value
GoF (9)	0.83 (0.80, 0.85)	3×10^{-38}
LoF (47)	1.13 (1.00, 1.27)	0.05



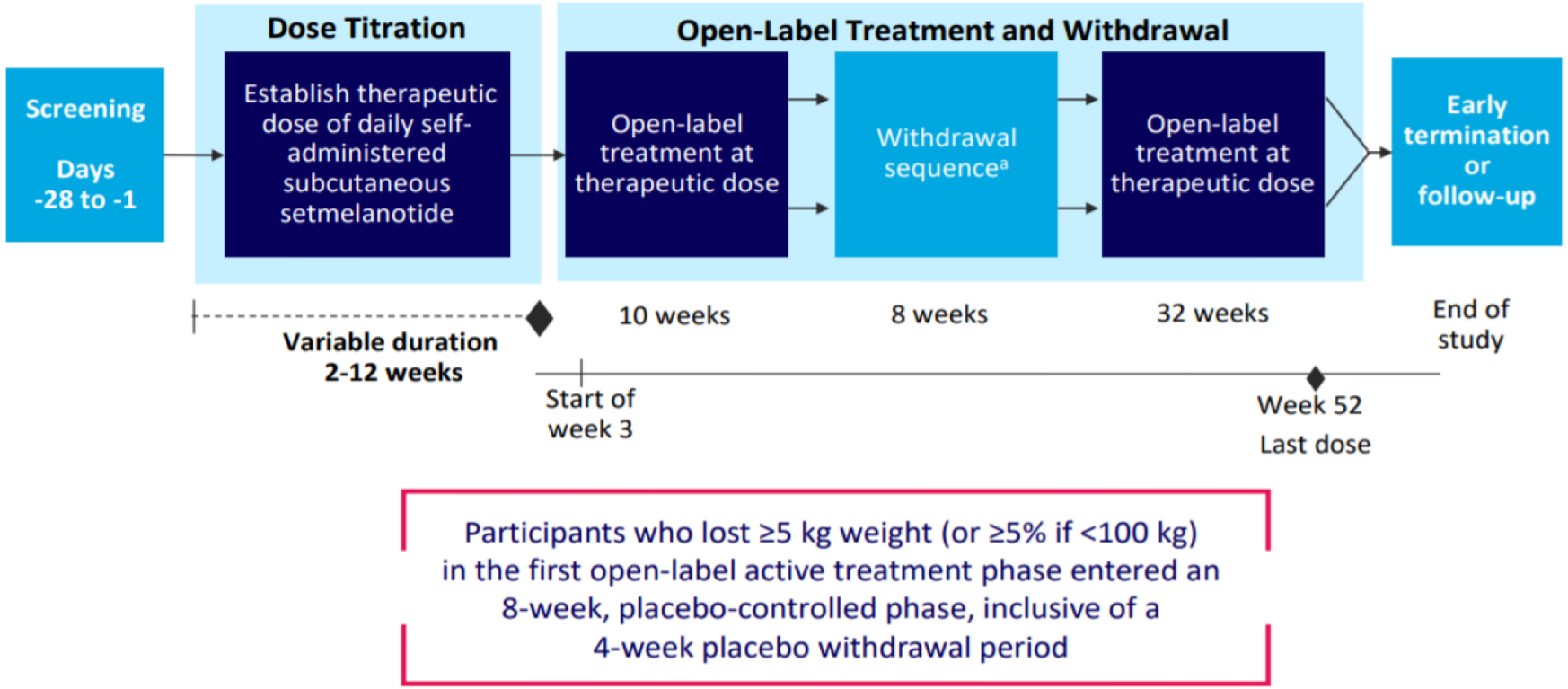
(Lotta, Mokrosinski, Mendes de Oliveira et al, Cell 2019)

• מנגנון פעולה: melanocortin 4 (MC4) receptor agonist



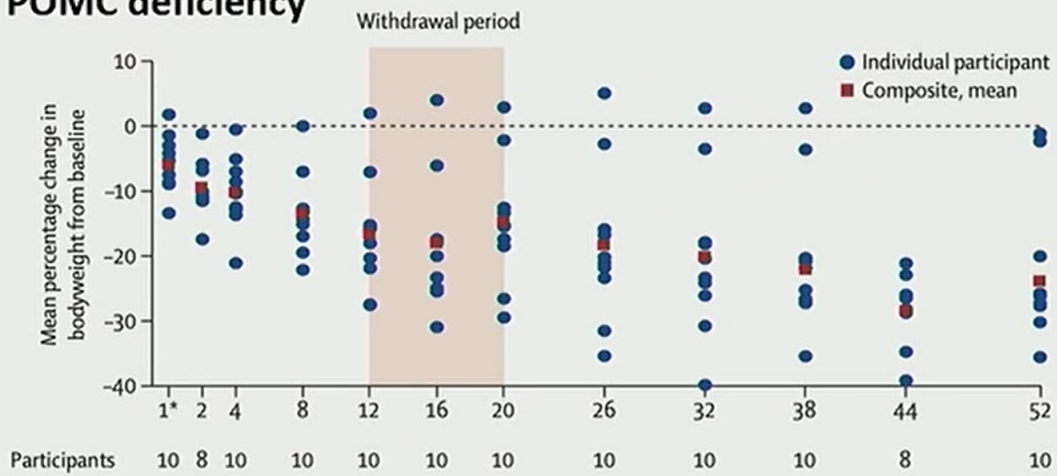
Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials

	POMC N=10	LEPR N=11
AGE	11-30	13-37
BMI	**40.4** (26.6-53.3)	**48.2** (35.8-64.6)

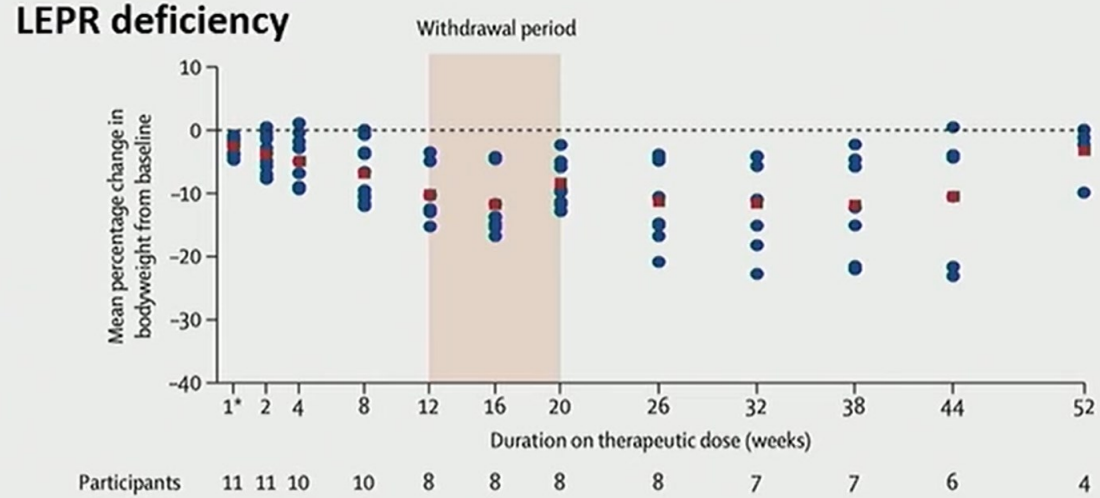


Clément, Karine, et al. *The Lancet Diabetes & Endocrinology* 8.12 (2020): 960-970.

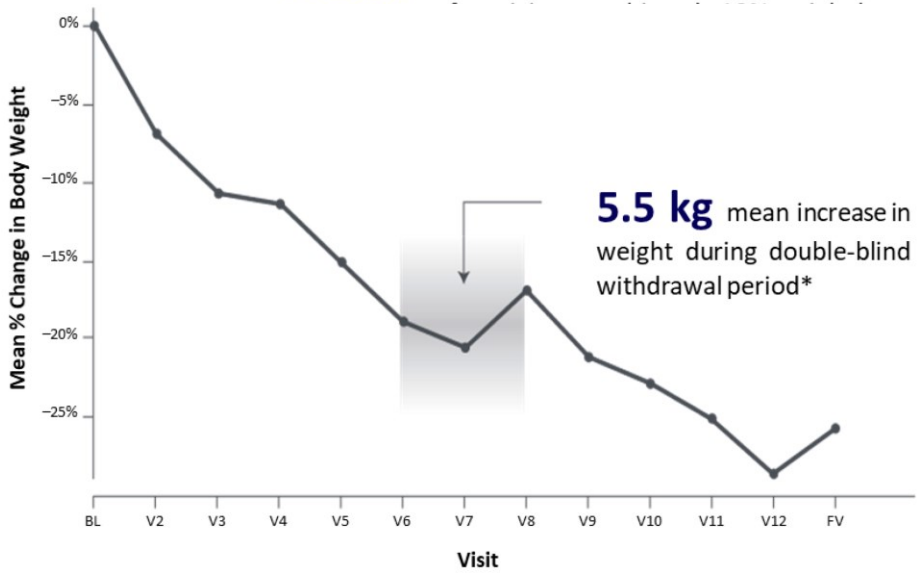
POMC deficiency



LEPR deficiency



POMC



POMC Phase 3 Topline Data* (n=10)

80% >10% weight loss

-25.4% mean weight reduction

-27.8% mean hunger score reduction

31.9kg / 70.2lbs mean weight loss in 1 year

LEPR Phase 3 Topline Data* (n=11)

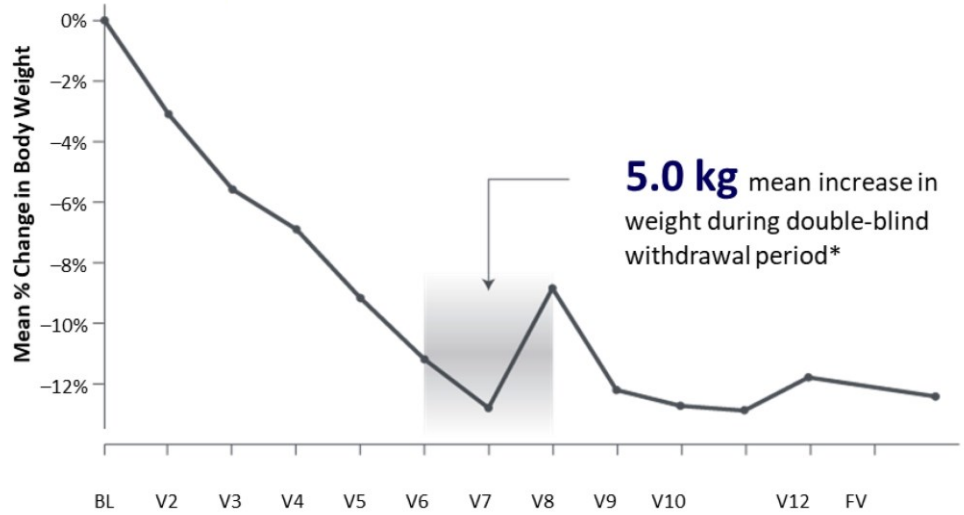
45.5% >10% weight loss

-12.5% mean weight reduction

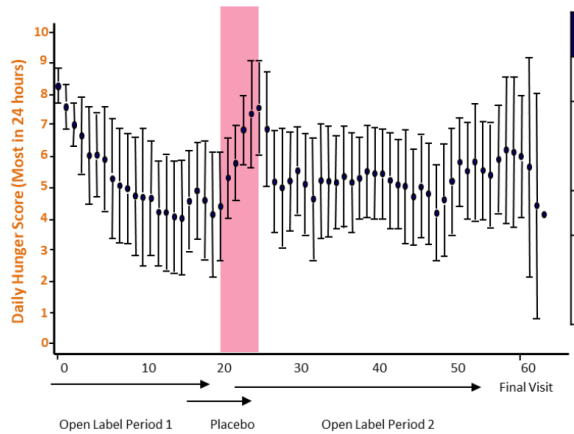
-41.9% mean hunger score reduction

16.7kg / 36.8lbs mean weight loss in 1 year

LEPR



Change in Hunger Score*†



During Placebo Period:	
Change in weight (kg)	
Mean	**+5.5**
Range	**1.5-10.5**
Change in hunger score	
Mean	**+2.2**
Range	**2.0 to 9.86**

	Participants with POMC deficiency obesity (n=10)	Participants with LEPR deficiency obesity (n=11)
Treatment-related adverse events	10 (100%)	11 (100%)
Injection site reaction	10 (100%)	11 (100%)
Skin and subcutaneous disorders related to hyperpigmentation	10 (100%)	5 (45%)
Skin hyperpigmentation	10 (100%)	4 (36%)
Pigmentation disorder	0	4 (36%)
Skin discolouration	0	2 (18%)
Nausea	5 (50%)	4 (36%)
Vomiting	3 (30%)	..
Serious adverse events	4* (40%)	3† (27%)
Serious treatment-related adverse events	0	0
Treatment-emergent adverse events leading to discontinuation	0	1 (9%)
Treatment-emergent adverse events leading to death	0	1 (9%)‡

Data are n (%). LEPR=leptin receptor. POMC=pro-opiomelanocortin.
*Serious adverse events were depression, major depression, acute adrenocortical insufficiency, pneumonia, and pleurisy. †Serious adverse events were cholecystitis, suicidal ideation, gastric banding reversal, and road traffic accident leading to death. ‡One participant died from injuries sustained during a car accident (not related to setmelanotide treatment).

Table 3: **Treatment-emergent adverse events in the safety analysis set**

Clément, Karine, et al. *The Lancet Diabetes & Endocrinology* 8.12 (2020): 960-970.

Efficacy and Safety of Open-Label Setmelanotide in Bardet-Biedl Syndrome: a Phase 3 Trial

Robert Haws,[1] Karine Clément,[2,3] Hélène Dollfus,[4] Andrea M. Haqq,[5] Gabriel Á. Martos-Moreno,[6] Wendy K. Chung,[7] Robert S. Mittleman,[8] Murray Stewart,[8] Matt Webster,[8] Guojun Yuan,[8] Jesús Argente[6,9]

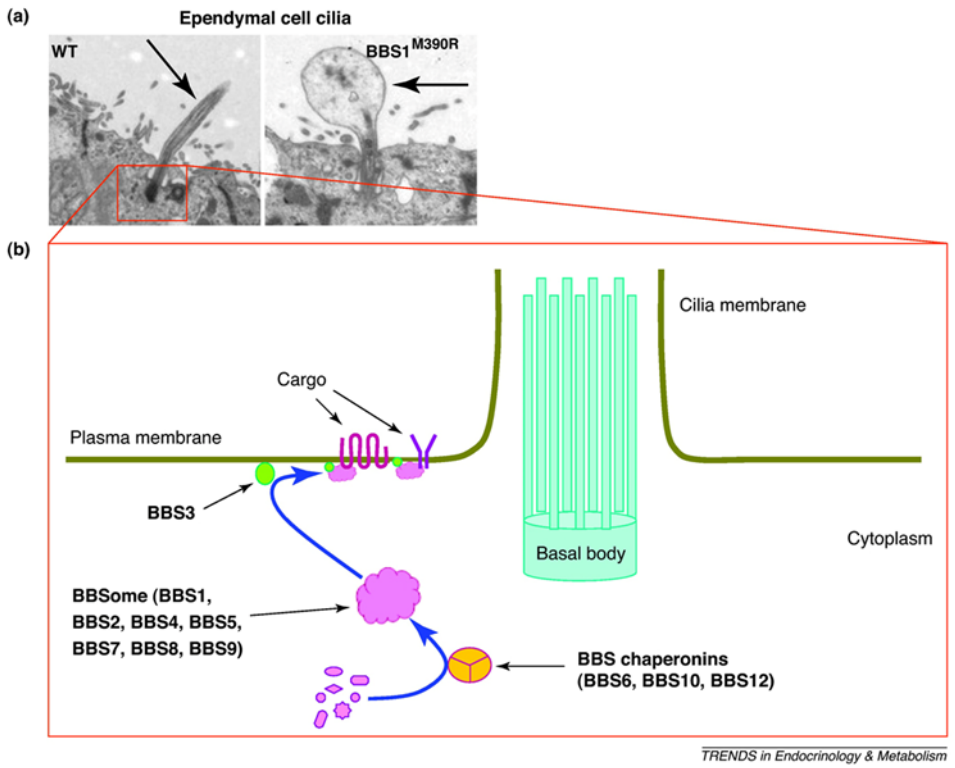
[1]Marshfield Clinic Research Institute, Marshfield, WI, USA; [2]Assistance Publique Hôpitaux de Paris, Nutrition Department, Pitié-Salpêtrière Hospital, Paris, France; [3]Sorbonne Université, INSERM, NutriOmics Research Unit, Paris, France; [4]Hôpitaux Universitaires de Strasbourg, CARGO and Department of Medical Genetics, Strasbourg, France; [5]Division of Pediatric Endocrinology, University of Alberta, Edmonton, AB, Canada; [6]Department of Pediatrics and Pediatric Endocrinology, Universidad Autónoma de Madrid, University Hospital Niño Jesús, CIBER "Fisiopatología de la obesidad y nutrición" (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain; [7]Division of Molecular Clinical Genetics, Department of Pediatrics, Columbia University, New York, NY, USA; [8]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [9]IMDEA Institute, Madrid, Spain

ObesityWeek® 2021 ● November 1-5, 2021 ● Virtual

Contemporary Clinical Trials Communications 22 (2021) 100780

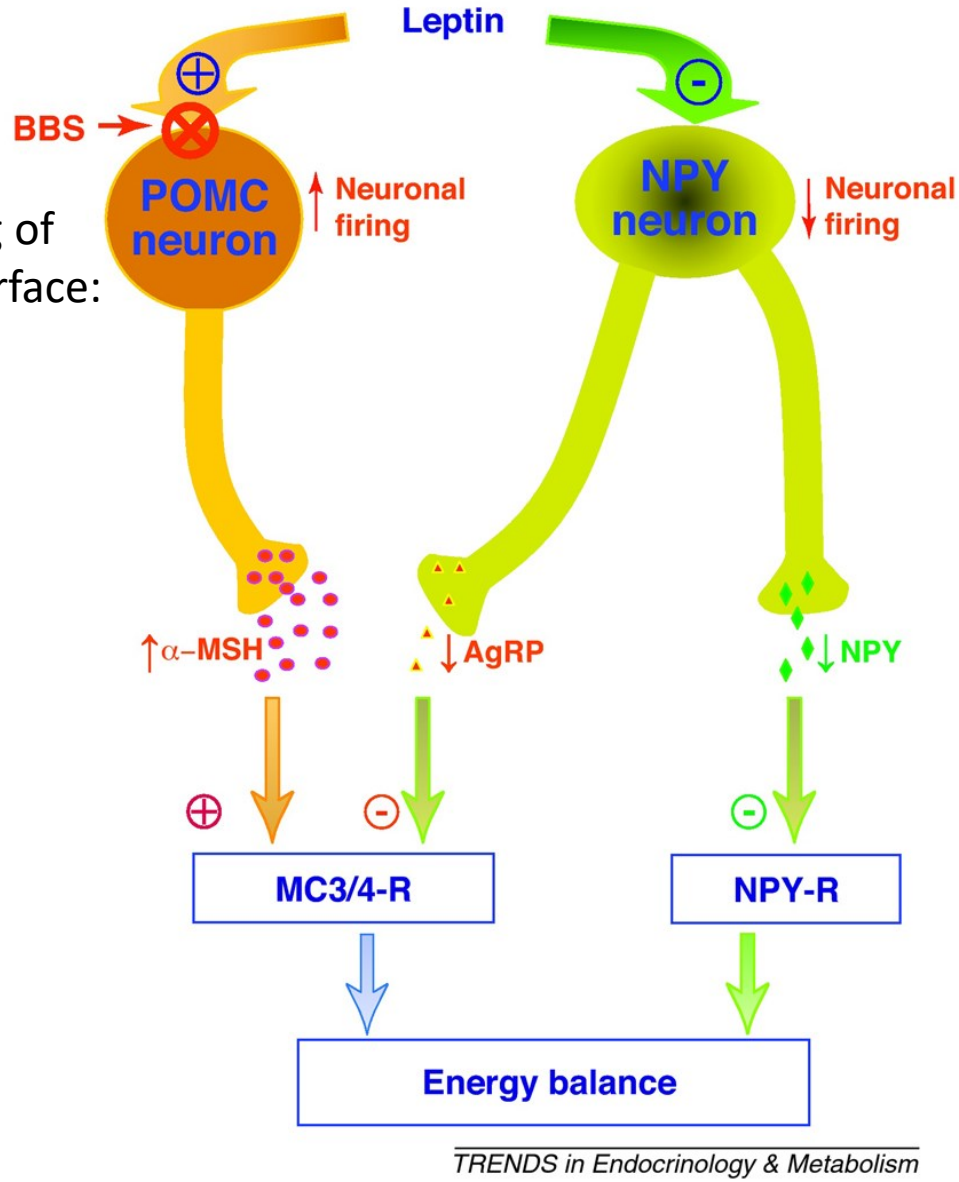
Bardet-Biedl Syndrome

- Highly pleiotropic autosomal recessive
- **Obesity**
- Retinitis pigmentosa
- polydactyly
- Learning disabilities
- Renal abnormalities
- 12 BBS genes (BBS 1-12) → **25**
- 1:125000-160000 (in middle east 1:13500) - La Reunion



Impaired trafficking of receptors to cell surface:

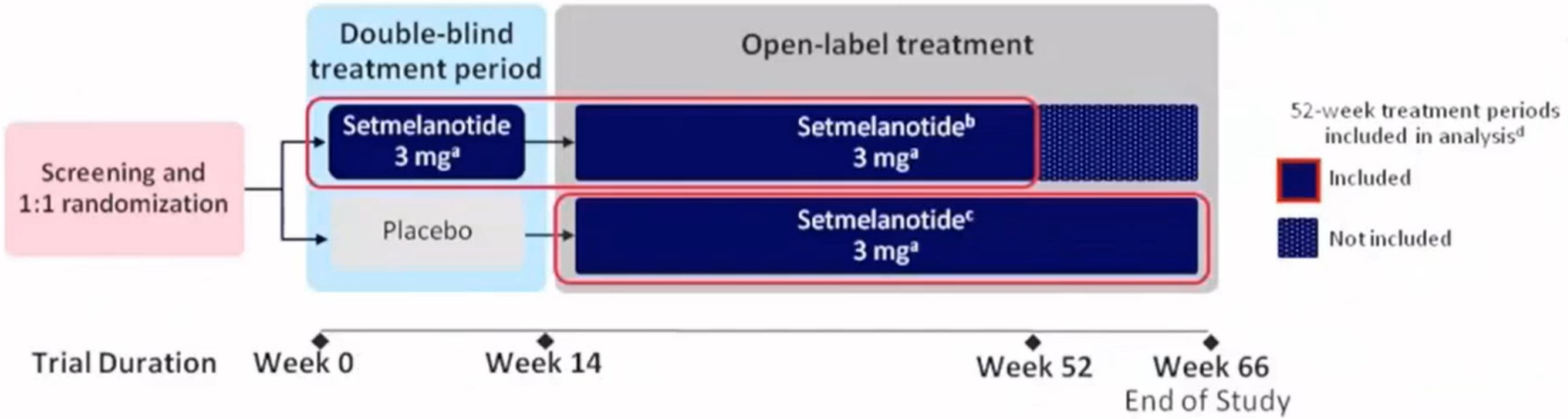
- **LepR**
- **Y2**
- **5-HT 2c**



Guo and Rahmouni, 22(7); 2011

Phase 3 Trial (NCT03746522) to Evaluate Setmelanotide in Patien With BBS

No specific guidance on diet and exercise given during the trial



Key inclusion criteria[1]

- Clinical diagnosis of BBS or Alström syndrome
- ≥6 years of age
- Obesity
  - ≥16 years: BMI ≥30 kg/m^2
  - 6–15 years: weight >97th percentile for age and sex

Key exclusion criteria

- Recent (within 2 months) intensive diet and/or exercise resulting in >2% weight loss
- Use of approved obesity medication within 3 months of randomization
- Prior gastric bypass resulting in >10% weight loss durably maintained
- Glomerular filtration rate <30 mL/min

[a]Dose escalation based on age up to 3.0 mg. [b]For patients who received >52 weeks of setmelanotide at the end of study, analysis was performed for 52 weeks of setmelanotide. [c]A multiple imputation model was used to impute data in patients who received <52 weeks of setmelanotide at the time of the analysis. [d]Efficacy outcomes were assessed at 52 weeks on active treatment for each study group (ie, Week 0 to 52 for the setmelanotide group and Week 14 to 66 for the group assigned to placebo during the double-blind treatment period).
BBS, Bardet-Biedl syndrome; BMI, body mass index.
1. Haws et al. *Contemp Clin Trials Commun*. 2021;22:100780.

Setmelanotide Treatment Was Associated With Clinically Significa Reduction in BMI in Patients With BBS

−9.1% mean change in BMI in patients ≥18 years old

−9.5% mean change in BMI in patients <18 years old

	Baseline	52 weeks on active treatment	Percent change from start of active treatment
Mean (SD) BMI in those ≥18 years old (n=15[a])	**46.4 kg/m²** (5.8)	**43.3 kg/m²** (7.2)	**−9.1** (6.8)
Mean (SD) BMI in those <18 years old (n=16[b])	**37.4 kg/m²** (9.4)	**34.2 kg/m²** (10.1)	**−9.5** (6.4)

[a]n=15 at baseline and 12 after 52 weeks on active treatment. [b]n=16 at baseline and 14 after 52 weeks on active treatment.
BBS, Bardet-Biedl syndrome; BMI, body mass index; SD, standard deviation.

Setmelanotide Treatment Was Associated With Significant Reduc Hunger in Patients With BBS ≥12 Years Old With No Cognitive Impairment

57.1% of patients with BBS ≥12 years old achieved a ≥25% reduction in maximal hunger score after 52 weeks of setmelanotide treatment (95% CI, 28.9%–82.3%; *P*<0.0001)

FDA approval of Setmelanotide for BBS on Sep. 2022

			t change from ctive treatment
Mean (SD) "most" hunger score (n=14)[a]	(1.9)	(2.5)	**–30.4** (26.5) ***P*=0.0004**

[a]Assessed using a numerical rating scale ranging from 0 to 10, where 0 = "not hungry at all" and 10 = "hungriest possible."
BBS, Bardet-Biedl syndrome; CI, confidence interval; SD, standard deviation.

Setmelanotide in hypothalamic obesity

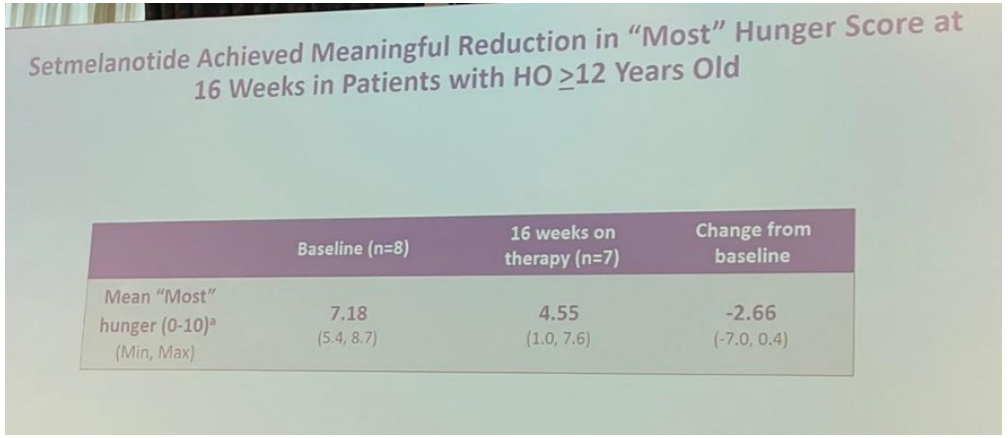
Phase 2 open-label trial designed to evaluate Setmelanotide's therapeutic effect in patients with hypothalamic obesity

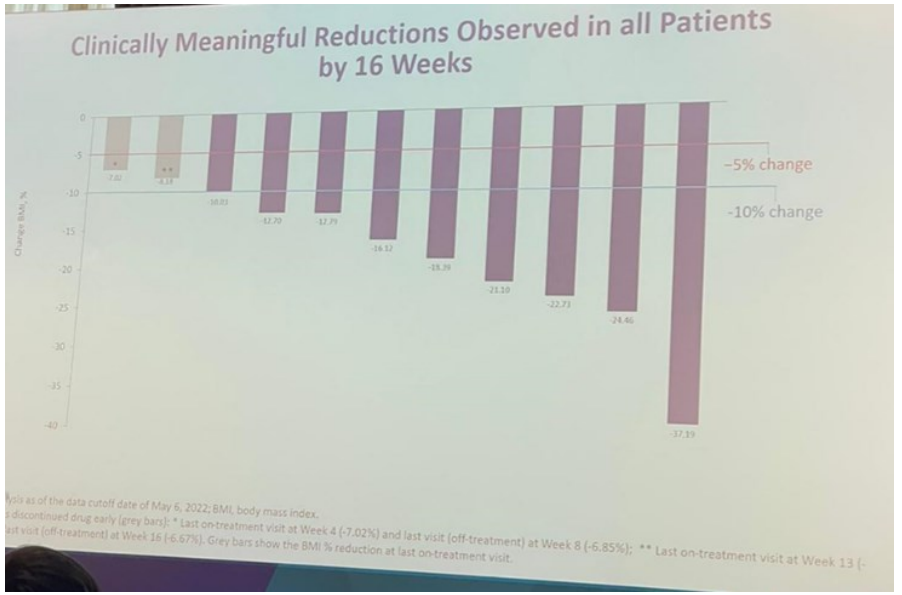
Ages 16-40

15.8% reduction in mean body weight (17.8% in completers 9/11) after 16 weeks

All patients lost at least 5% of their weight

Significant reduction in hunger score





- **שם התרופה:** IMCIVREE
- **שם גנרי:** SETMELANOTIDE
- **סטטוס רישום של ההתוויה המבוקשת בחו"ל :**
  - אישור FDA בנובמבר 2020 להתוויה הבאה:

Chronic weight management in adults and children aged 6 years and older with obesity associated with genetic testing for POMC, PCSK1, or LEPR deficiency

- **CHMP Positive Opinion מאי 2021**
- **התוויה מבוקשת לסל 2022:**
- טיפול בהשמנת יתר כרונית במבוגרים וילדים מגיל 6 ומעלה עקב חסר מוכח גנטית ב- POMC, PCSK1 או LEPR
  - התכשיר מבוקש להכללה בסל ביחד עם הבדיקה הגנטית הבאה:

Genetic testing for early onset (age 5) genetic obesity with hyperphagia

מינון ודרך מתן:

Dosage in Adults and Pediatric Patients 12 Years of Age and Older

- **Initial: 2 mg subcutaneous injection once daily** for 2 weeks, then adjust dosage if needed based on efficacy and tolerability

Dosage in Pediatric Patients 6 to less than 12 Years of Age

- **Initial: 1 mg subcutaneous injection once daily** for 2 weeks, then adjust dosage based on efficacy and tolerability

Maximum daily dose: 3 mg/day

Genetic testing now recommended in clinical guidelines worldwide

(Styne et al. JCEM 2017; PMID: 28359099)

- Early onset of obesity (age ≤ 6)
- Hyperphagia
- Family Hx.