# How We Understand Hyperphagia in PWS


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Project ECHO®

IPWSO International Prader-Willi Syndrome Organisation

ICE Imperial Centre for Endocrinology

Imperial College London

Neuropsychopharmacology Unit

# Disclosures

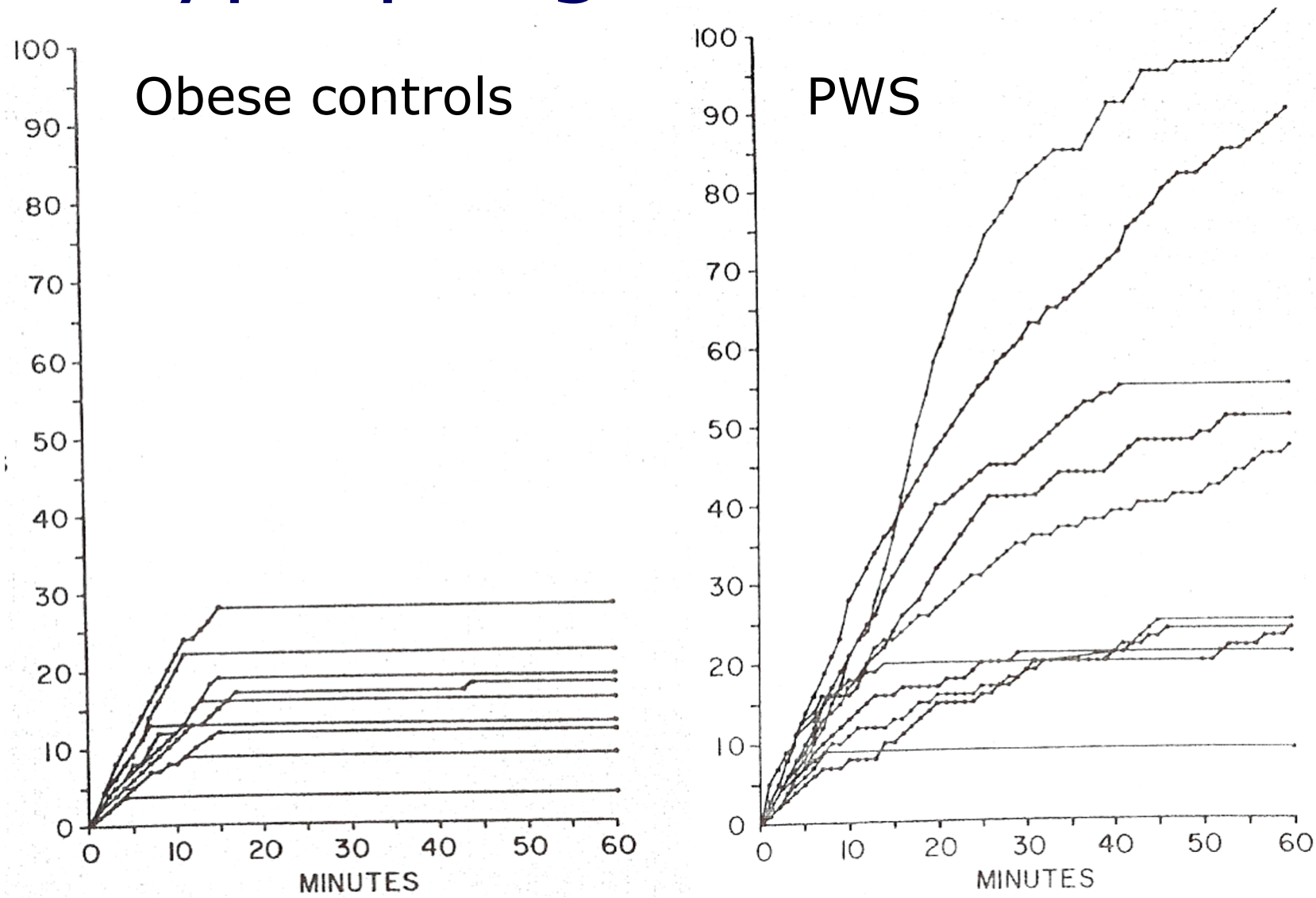
- Novo Nordisk (Data Safety Monitoring Committee, speaker honorarium)
- Millendo Therapeutics (Medical Advisory Board)
- Soleno Therapeutics (consultant)
- Helsinn Healthcare S.A. (consultant)
- Evidera / Rhythm Pharmaceuticals (consultant)
- Radius Health (consultant)
- Pfizer (research grant support)
- Janssen (speaker honoraria)
- Merck (speaker honorarium)

# Learning Objectives

- An understanding of the nature of hyperphagia and overeating in PWS.
- An understanding of the importance of control of the food environment in management of hyperphagia in PWS.
- An understanding of the current situation regarding potential new treatments for hyperphagia in PWS

# Hyperphagia in PWS

**Sandwich quarters**




Zipf & Bentson *Am J Clin Nutr 46:277-281, 1987*

# Hyperphagia

- upset when denied a desired food
- bargain or manipulate to get more food at meals
- forage through trash for food
- eating rotten food
- eating non-food items
- get up at night to food seek
- persistent in asking or looking for food after being told no
- spending lot of time asking or talking about food
- try to sneak or steal food
- distressed when others tried to stop them asking about food
- food-related behaviour interferes with normal daily activities
  e.g. self-care, recreation, school or work

Dykens EM et al. Obesity 15:1816, 2007

# Nutritional Phases

0) Reduced birth weight (15-20%)

1a) Hypotonia with difficulty feeding (0-9 mo)

*- may also have FTT despite adequate calories*

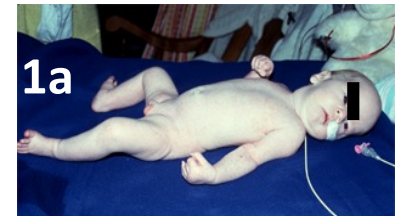
1b) No difficulty feeding, growing on curve (9-25 mo)

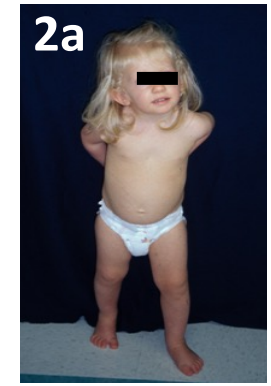
2a) Weight ↑ without ↑ in calories (2.1-4.5 y)

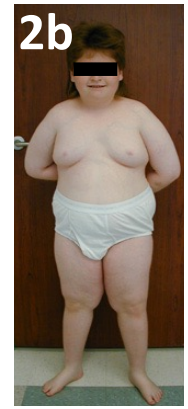
2b) Weight ↑ with ↑ in calories (4.5-8 y)

3) Hyperphagic, reduced satiety (>8 y)

4) Prev. 3), but appetite is less *now (adulthood)*



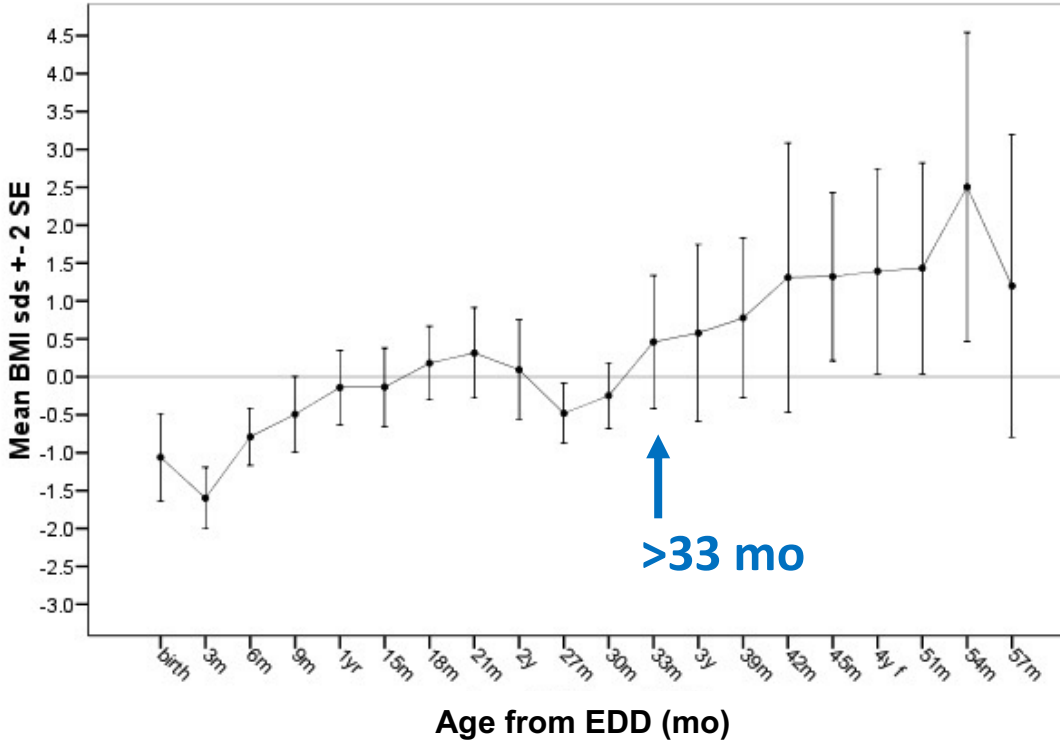





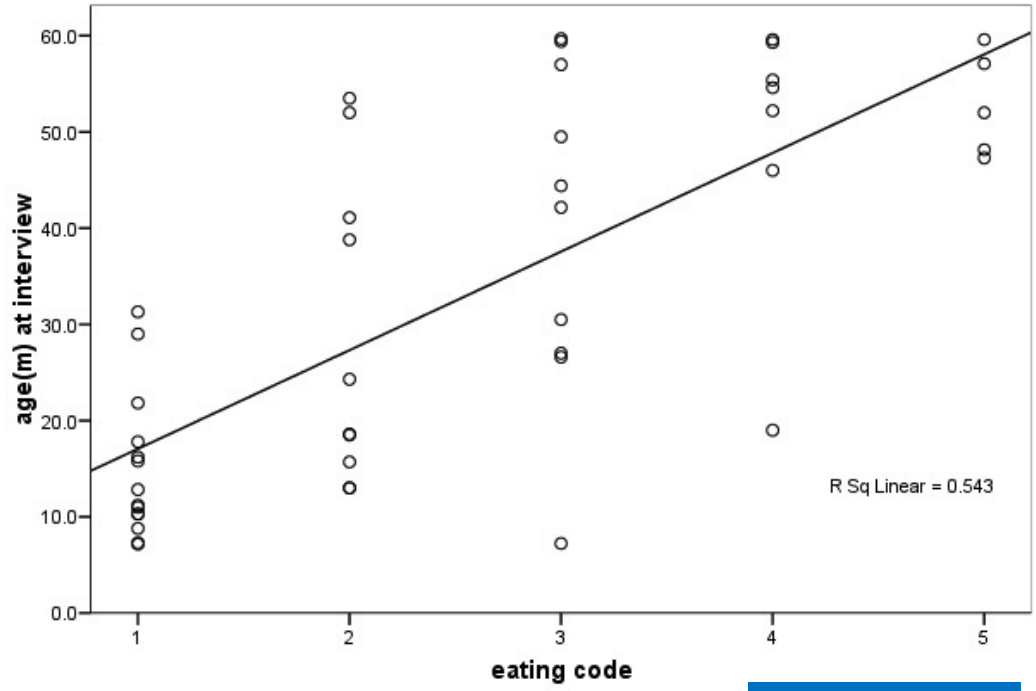
Miller JL et al. Am J Med Genet 2011

# Natural History of Obesity and Hyperphagia

## BMI SDS vs. Age




## Age vs. Eating Code




**Hyperphagia**

**>40 mo**

Butler, Holland & Goldstone. *Dev Med Child Neurology 2009*

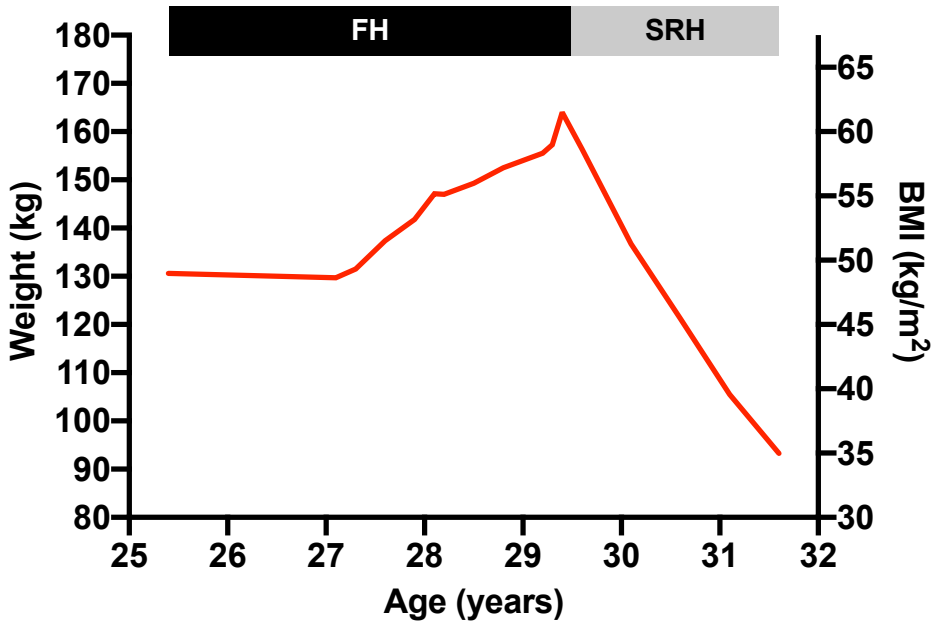
# Obesity Management

- Early diagnosis allows early institution of low-calorie, well-balanced diet
- Appropriate psychological and behavioural counselling of patient and family
- Early, repeated discussion of inevitability of hyperphagia (even in infancy)
- Rigorous supervision & control of food environment
- Restriction of access to food & money with appreciation of legal & ethical obligations
- Regular exercise
- GH helps body composition (no effect on hyperphagia known)
- Previous licensed anorexigenic agents not successful to date
- Several trial drugs have potential
- Bariatric surgery not recommended, complications +++, poor long term data

Goldstone et al. J Clin Endo Metab 93:4183-97, 2008

# Case Report #2

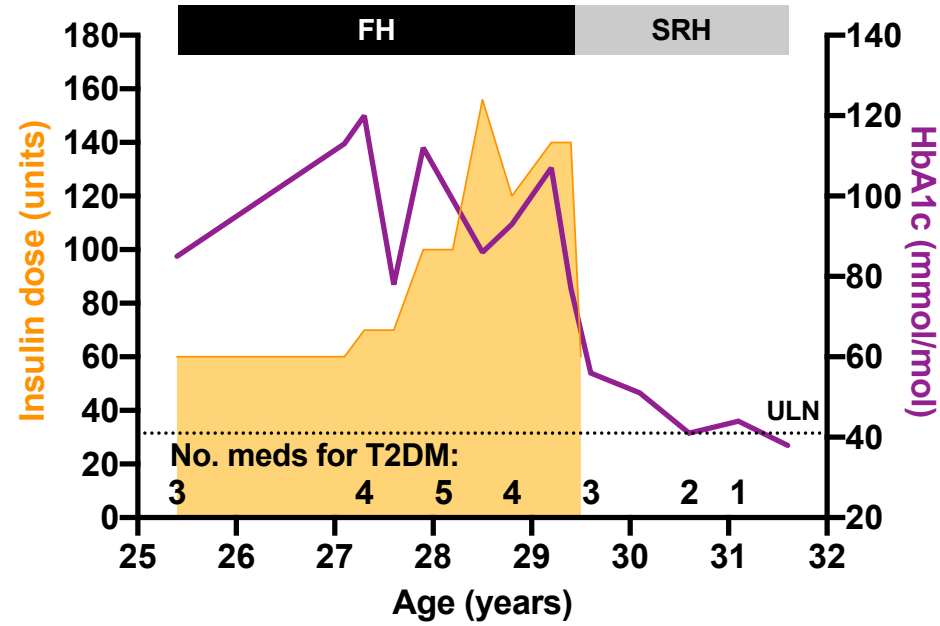
## Benefits Specialist PWS Residental Home for Weight




T2DM since 19yo

**Weight loss only once in specialist PWS residential home**

## Benefits Specialist PWS Residental Home for Diabetes

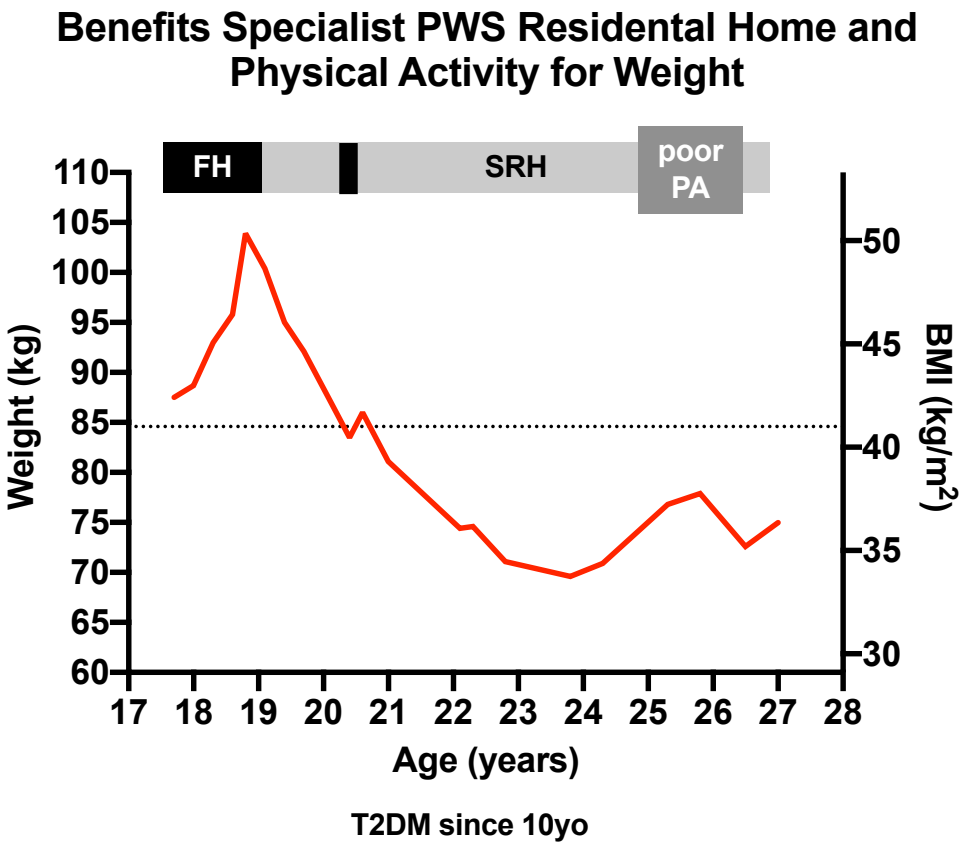


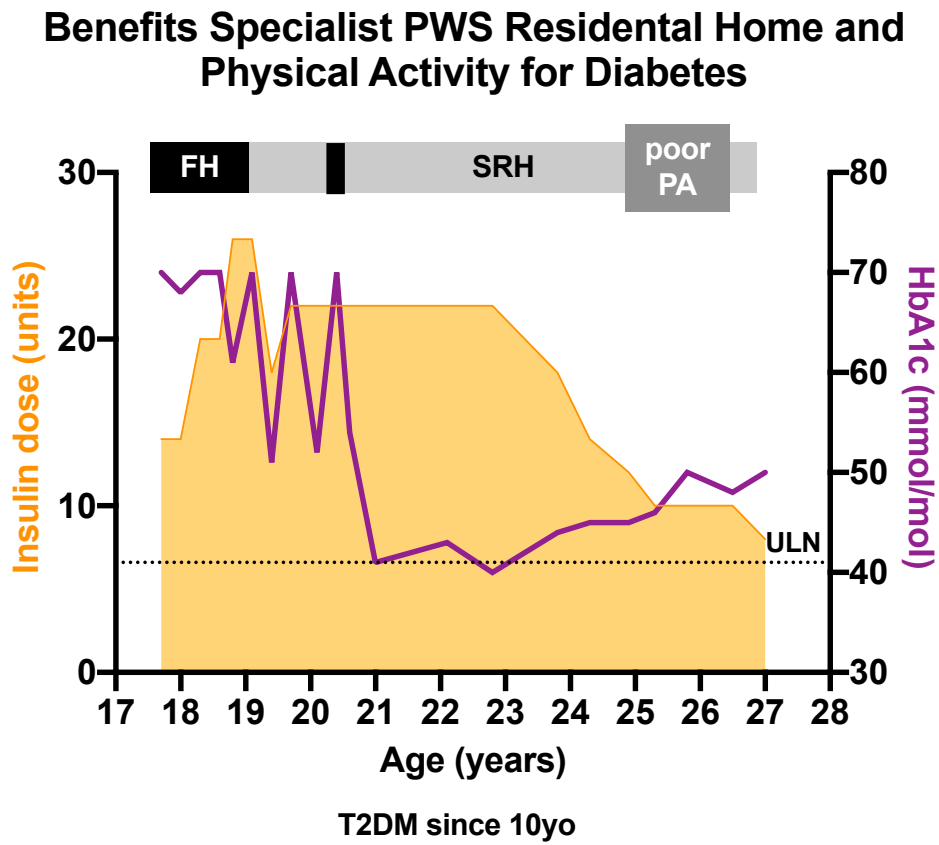

T2DM since 19yo

**Improved sugar control (HbA1c) and able to stop 4 out of 5 diabetes medicines including insulin only once in specialist PWS residential home**

**Code:**
**FH - family home**
**SRH - specialist PWS residential home**
**ULN - HbA1c upper limit of normal**
**T2DM - type 2 diabetes mellitus**

# Case Report #3




**Weight loss and improvement in sugar control (measured by HbA1c) only once in specialist PWS residential home.**

**Period of poor physical activity for non-medical reasons led to weight gain and worsening of sugar control.**

**Code:**
**FH - family home**
**SRH - specialist PWS residential home**
**PA - physical activity**
**ULN - HbA1c upper limit of normal**
**T2DM - type 2 diabetes mellitus**

# Phenotypes of Specific PWS Gene KO / Deletion Mice

Abnormal circadian rhythms
Reduced male fertility
Reduced food intake
Mild obesity
Reduced motor activity
Reduced orexin cell no.
Growth retardation
Leptin resistance POMC neurons

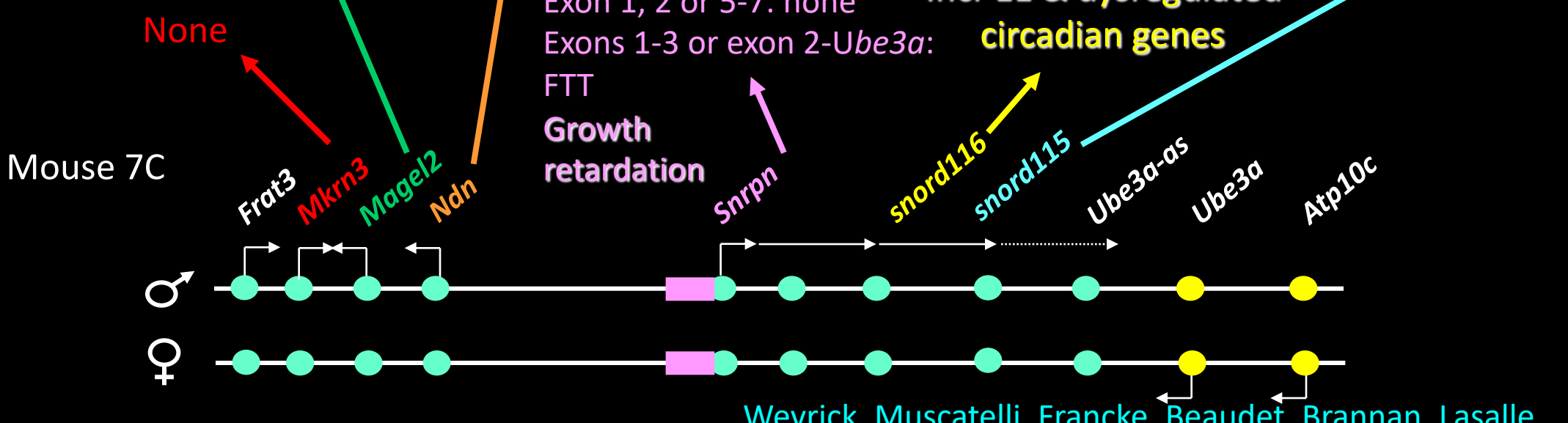
Abnormal central respiratory drive
Abnormal axonal growth brainstem serotonin, catecholamine, sympathetic neurons & retinal ganglion cells
Reduced GnRH neuron no. but fertile
Reduced oxytocin neuron number
Growth retardation
Increased skin scraping
Increased pain threshold
Abnormal sensory DRG

None
Abnormal 5HT-2CR mRNA processing
Abnormal RNA editing

Growth retardation
Hyperphagia
Incr EE & dysregulated circadian genes

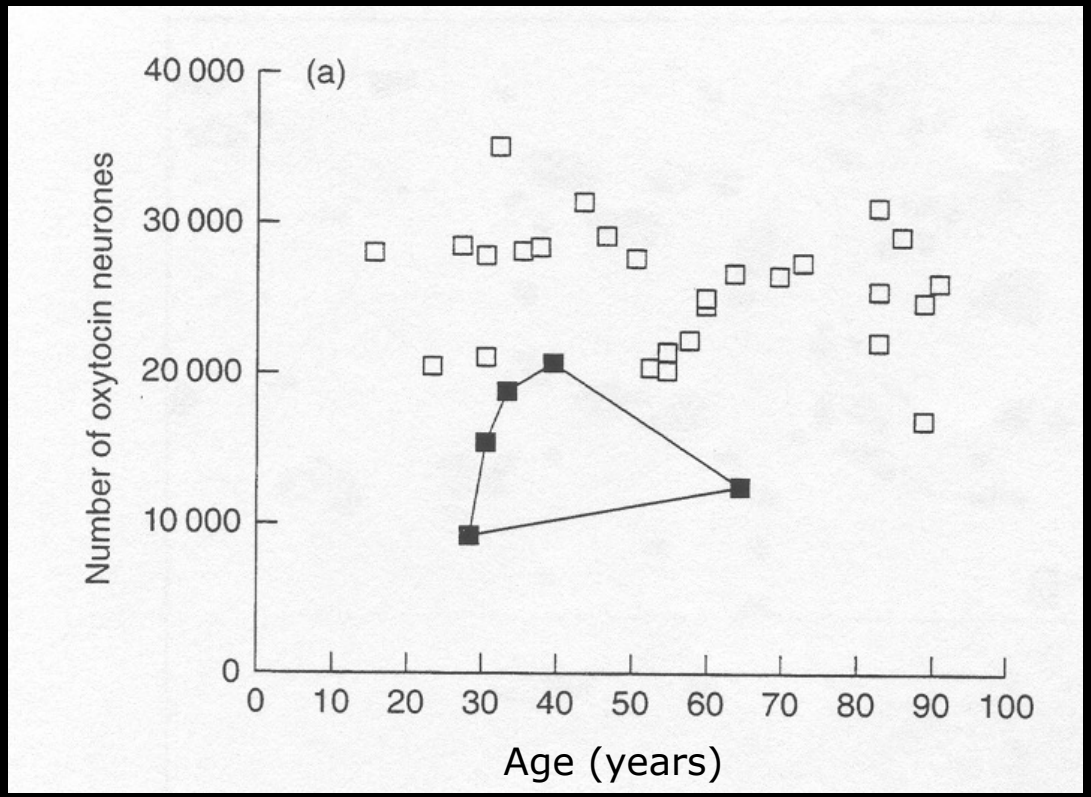
None

Exon 1, 2 or 5-7: none
Exons 1-3 or exon 2-U*be3a*: FTT
Growth retardation




Wevrick, Muscatelli, Francke, Beaudet, Brannan, Lasalle

# Reduced PVN Total and Oxytocin Cell Number in PWS




Human PWS hypothalamus

38% reduction in total PVN neurons

42% reduction in PVN oxytocin neurons

*Swaab et al. JCEM 80:573-579, 1995*

*Ndn* KO mouse

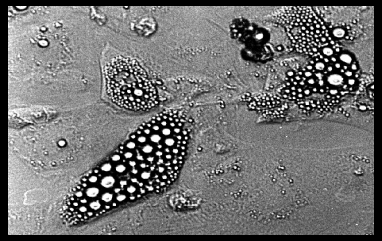
29% reduction in PVN oxytocin neurons

Muscatelli et al. *Human Mol Gen 9:3101-3110, 2000*

but….not obese

# Monogenic Causes of Human Obesity

Fat



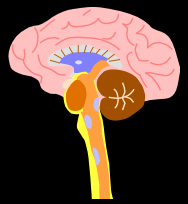
Leptin

NHLH2 transcription factor

Pro-hormone convertase-1 (PCSK1)

?Carboxypeptidase E (CpE) *

Hypothalamus



Leptin receptor

POMC ($\alpha$-MSH)

MC4 receptor

2nd order neurons

?Oxytocin

TrkB (BDNF receptor)

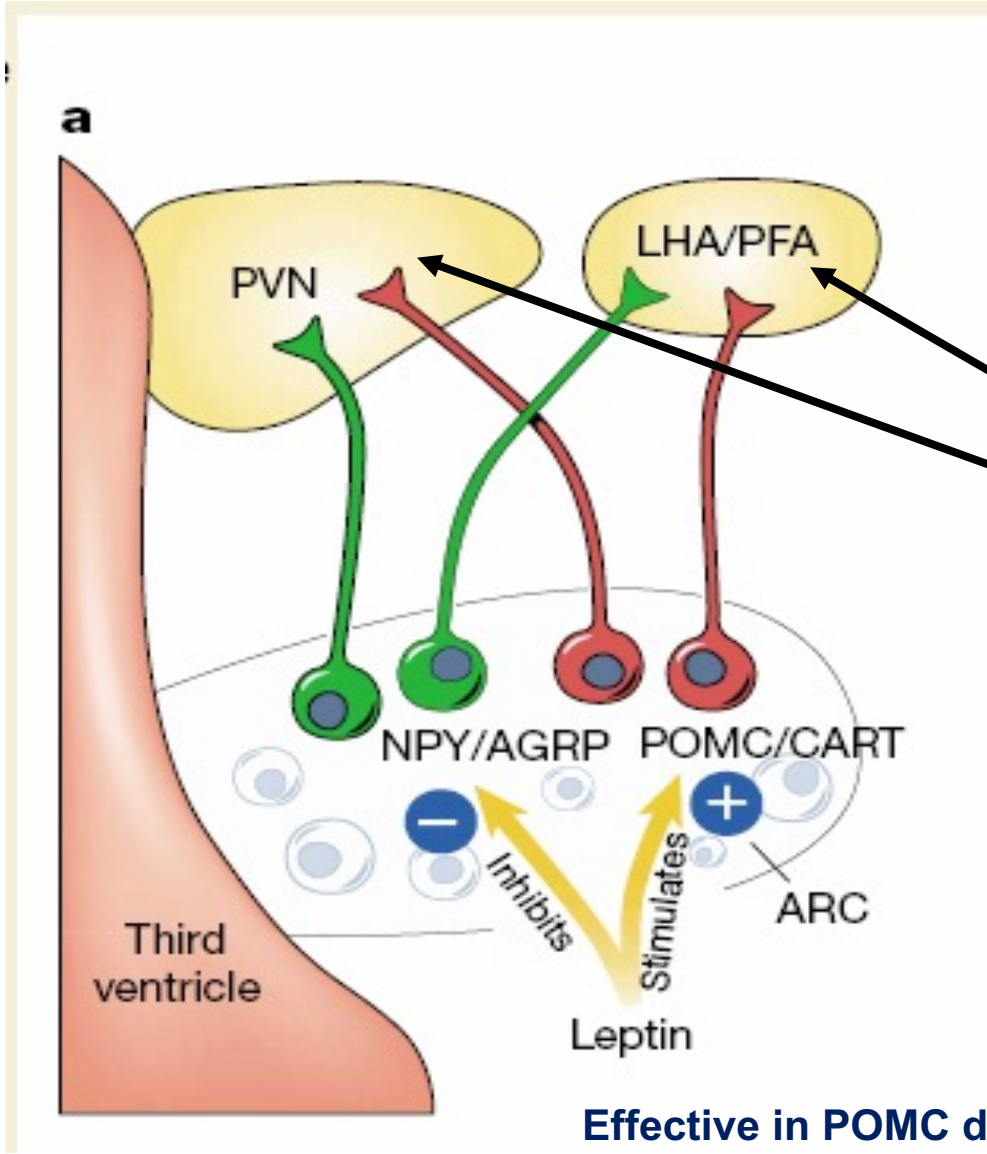
BDNF

* Sim-1 (PVN)

Reduce Appetite

*PWS-like phenotype

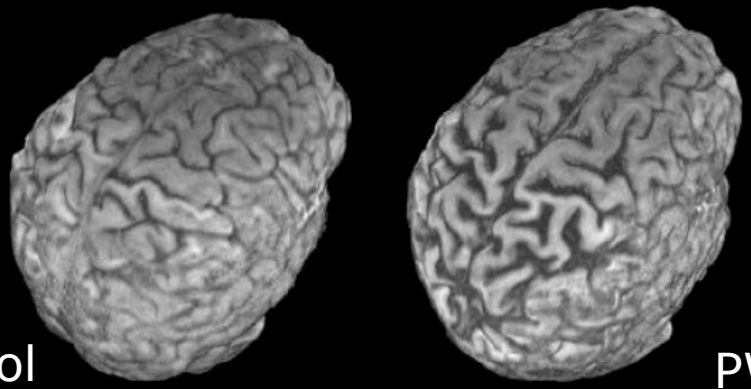
# Dual Hypothalamic Circuitry




**Setmelanotide**
**MC4R agonist**

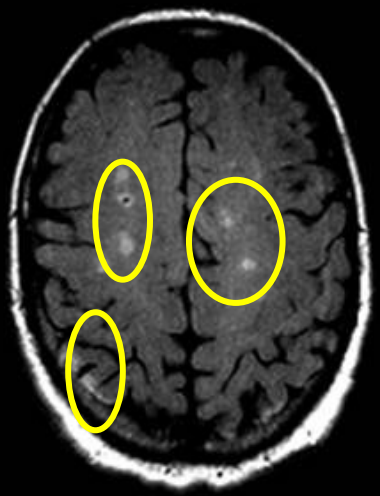
**Effective in POMC deficiency and LEPR mutations**
**Kuhnen et al. NEJM 2016**
**Clement et al. Nat Med 2018**

# Cortical Abnormalities in PWS

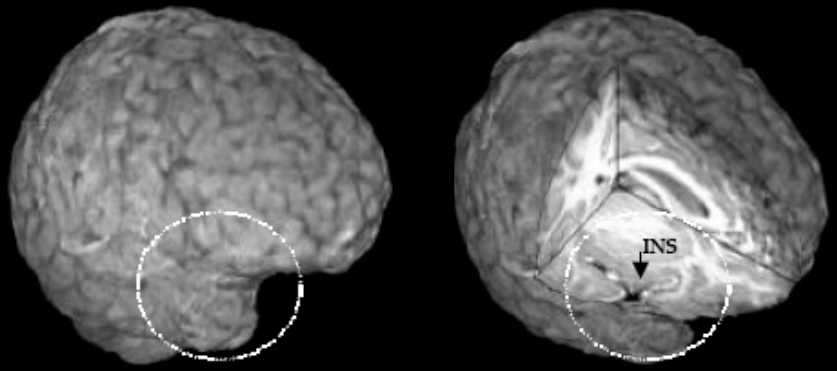


Control PWS

Decreased parieto-occipital grey matter
10 / 17



Incomplete insula cortex closure 13 / 17




White matter lesions
6 / 17 (especially OFC)

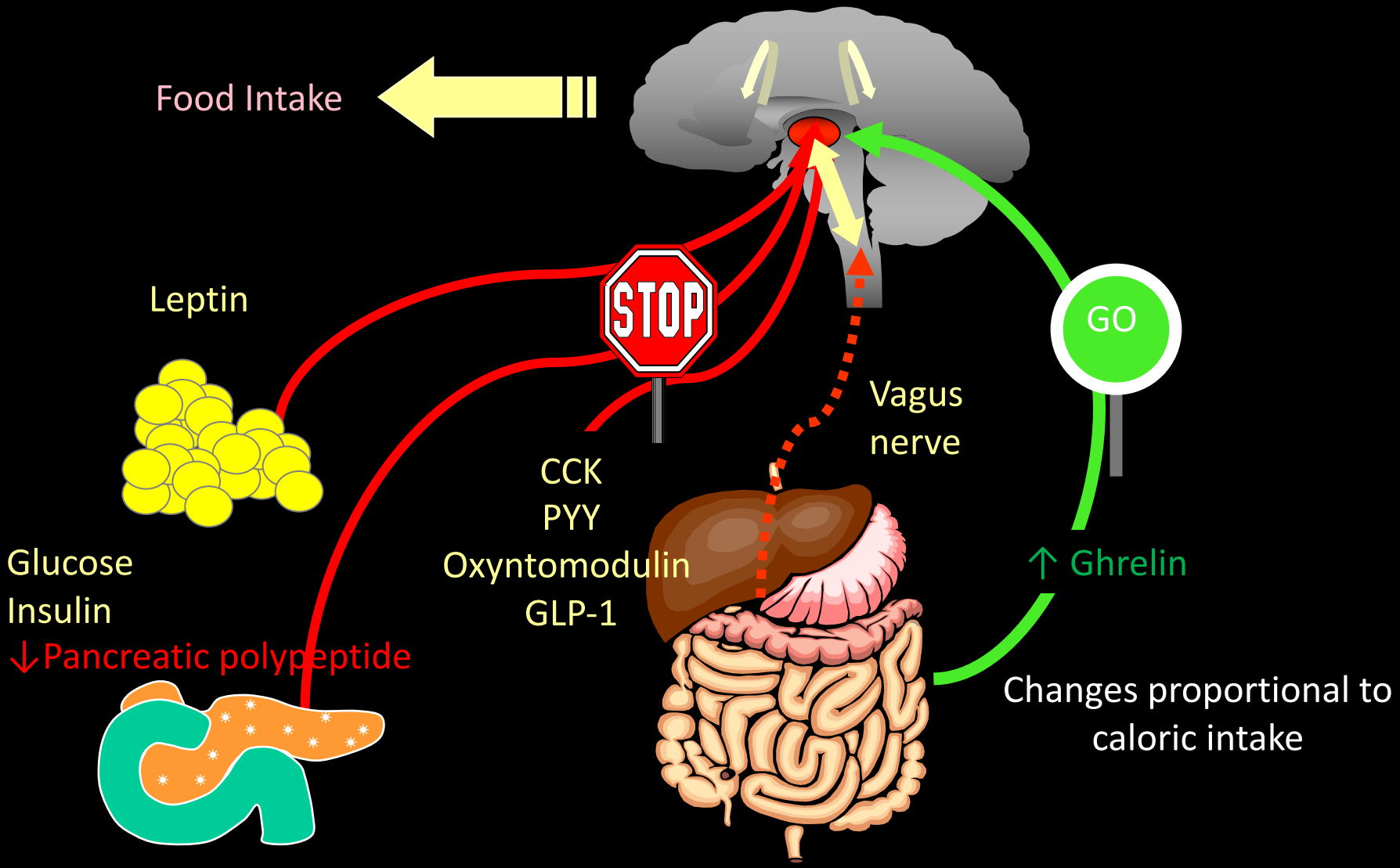
17 PWS subjects 11mo – 39y

Miller et al. *J Pediatr 149:192-8, 2006*
Miller et al. *Am J Med Genet A 143:476-8, 2007*

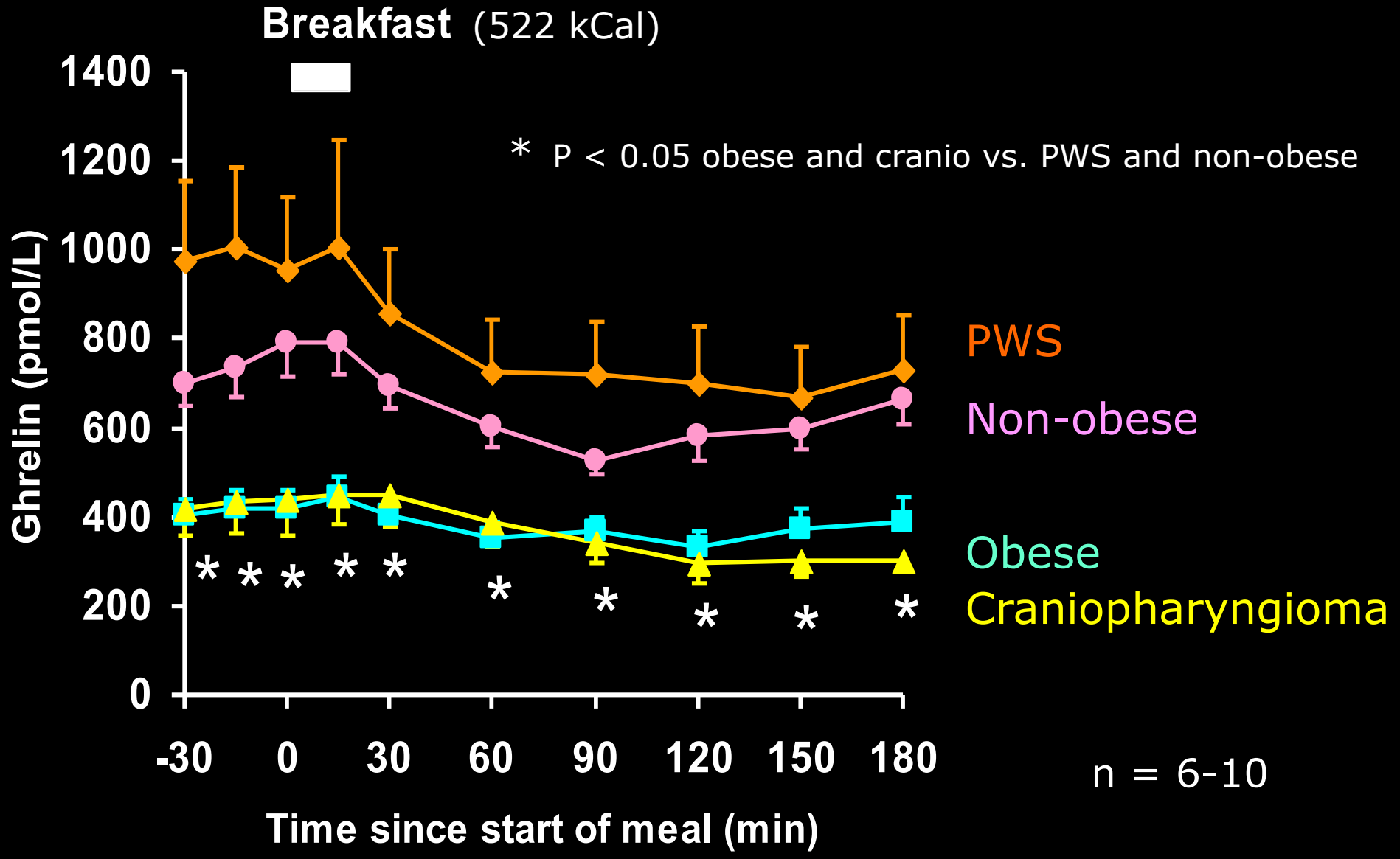
Neural structure and function in Prader-Willi Syndrome
Manning KE, Holland AJ. Diseases. 3:382-415, 2015

Increased brain age in adults with Prader-Willi syndrome
Azor AM er al. Neuroimage Clin. 21:101664, 2019

# Peripheral Signals Controlling Appetite

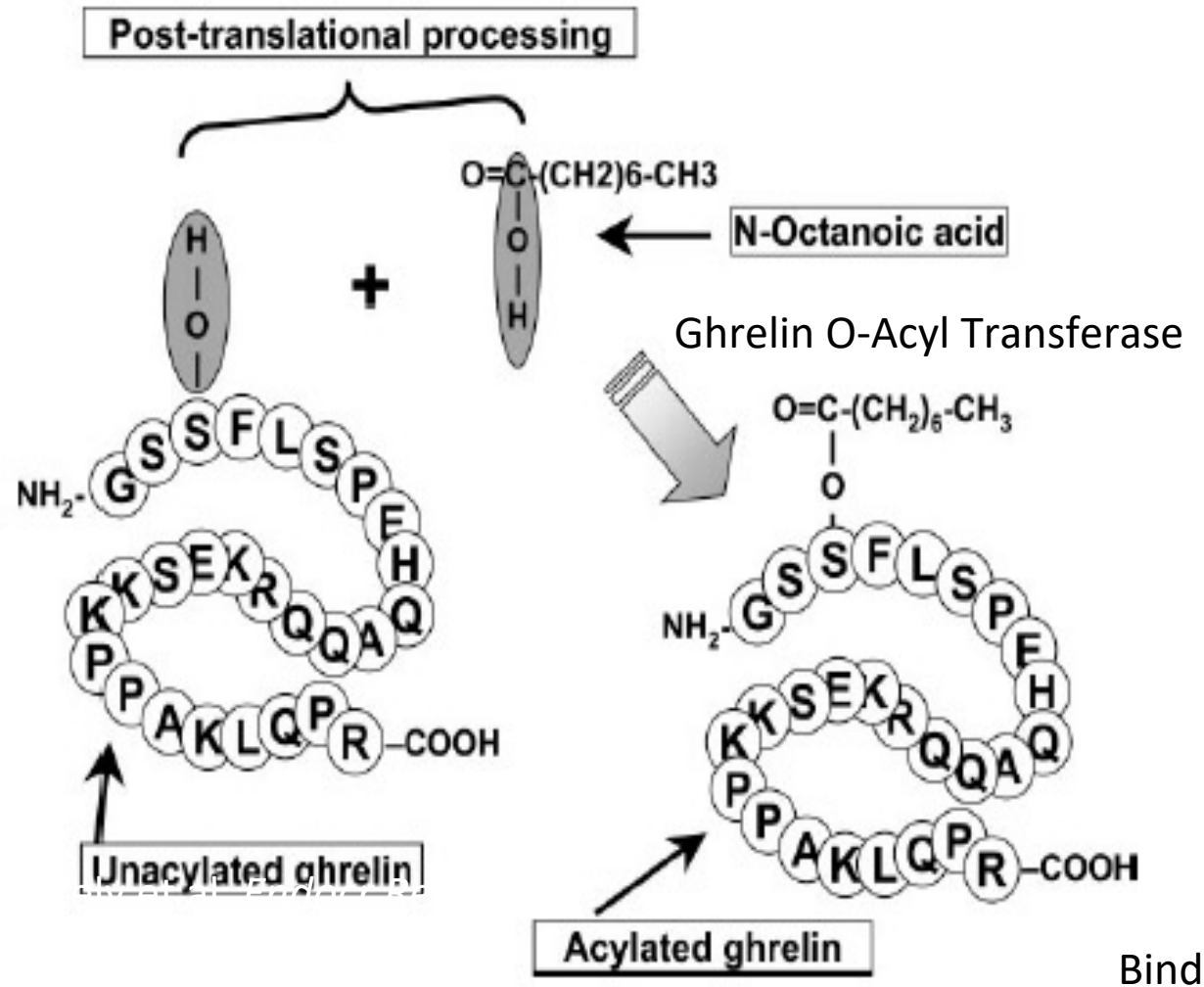


# Elevated Post-Prandial Ghrelin in PWS Adults




Goldstone et al. *JCEM 90: 2681-2690, 2005*

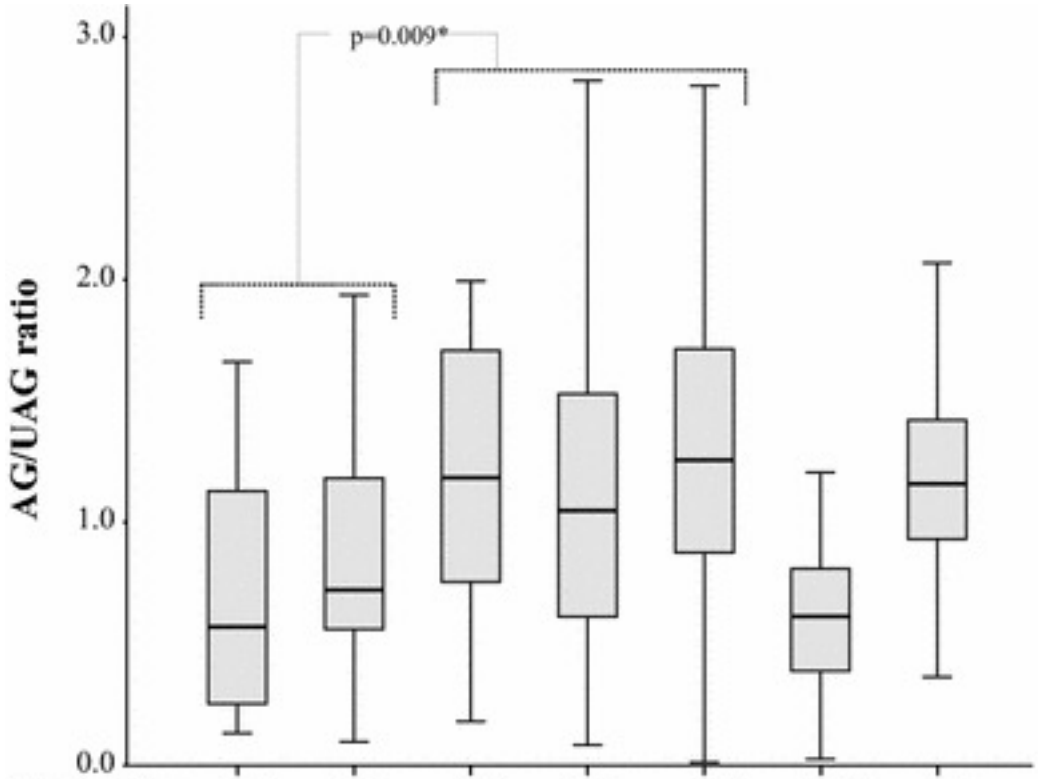
# Acyl vs. Desacyl Ghrelin




Binds to GHSR1a

van der Lely et al. *Endocr Rev 2004*

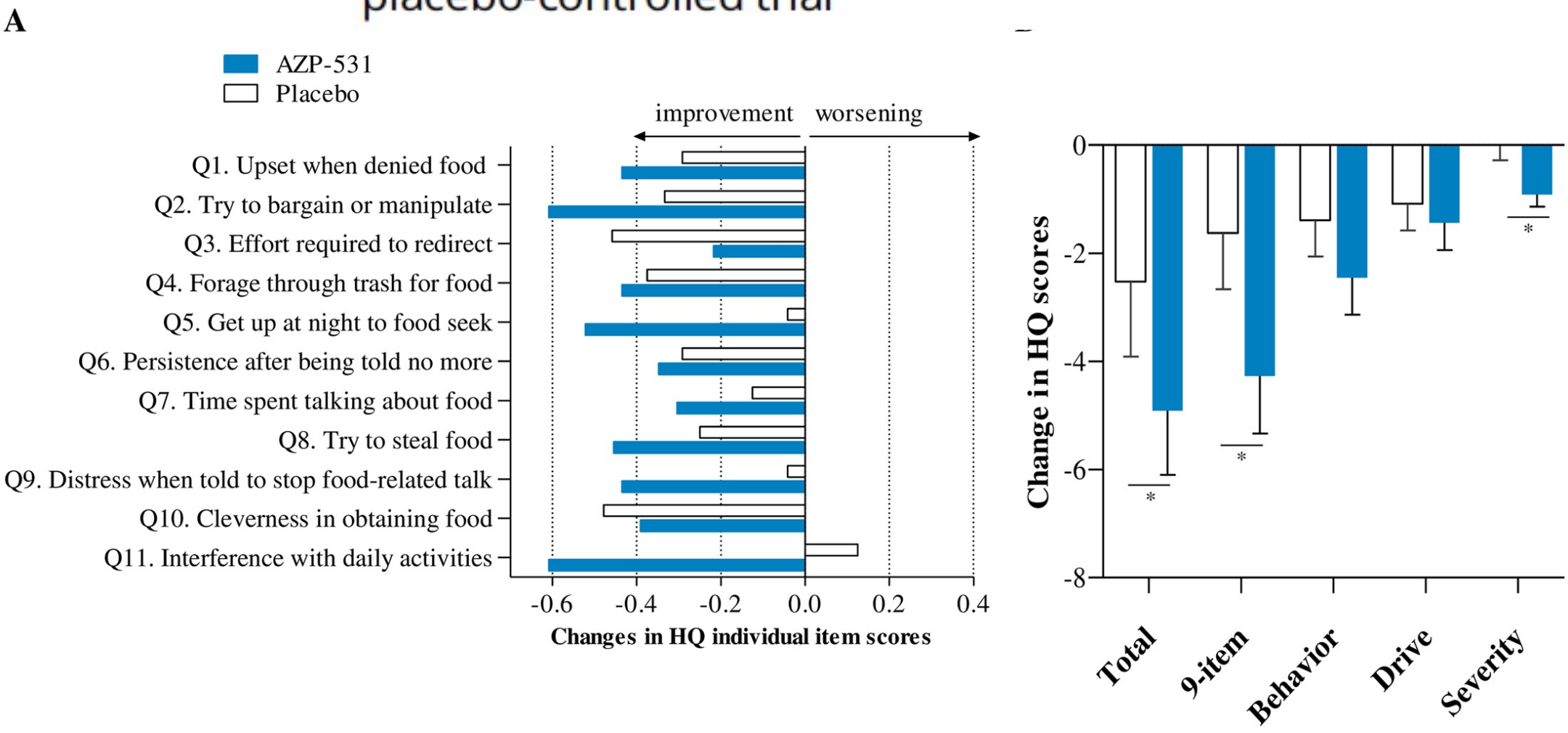
# Elevated ratio of acylated to unacylated ghrelin in children and young adults with Prader–Willi syndrome




| | PWS 1a | PWS 1b | PWS 2a | PWS 2b | PWS 3 | Healthy controls | Obese controls |
|---|---|---|---|---|---|---|---|
| N | 13 | 37 | 12 | 44 | 31 | 39 | 50 |
| Age (yrs)[¥] | 0.5 (0.2-4.1) | 8.9 (0.6-22.3) | 5.3 (1.5-9.3) | 11.2 (2.2-29.4) | 14.5 (4.7-26.1) | 7.3 (0.8-28.6) | 9.8 (4.3-16.9) |
| BMI SDS[§] | -2.0 | -0.6 | 0.9 | 1.6 | 2.7 | -0.2 | 2.8 |
| Deletion / mUPD^ | 7/6 | 14/18 | 4/6 | 27/14 | 17/11 | _ | _ |
| P-value of AG/UAG ratio vs healthy controls[a] | 0.837 | 0.225 | 0.243 | **0.002** | **0.005** | _ | **<0.001** |

Kuppens RJ et al. Endocrine 2015

# AZP-531, an unacylated ghrelin analog, improves food-related behavior in patients with Prader-Willi syndrome: A randomized placebo-controlled trial




Alllas S et al. PLOS ONE 2018

MILLENDO THERAPEUTICS

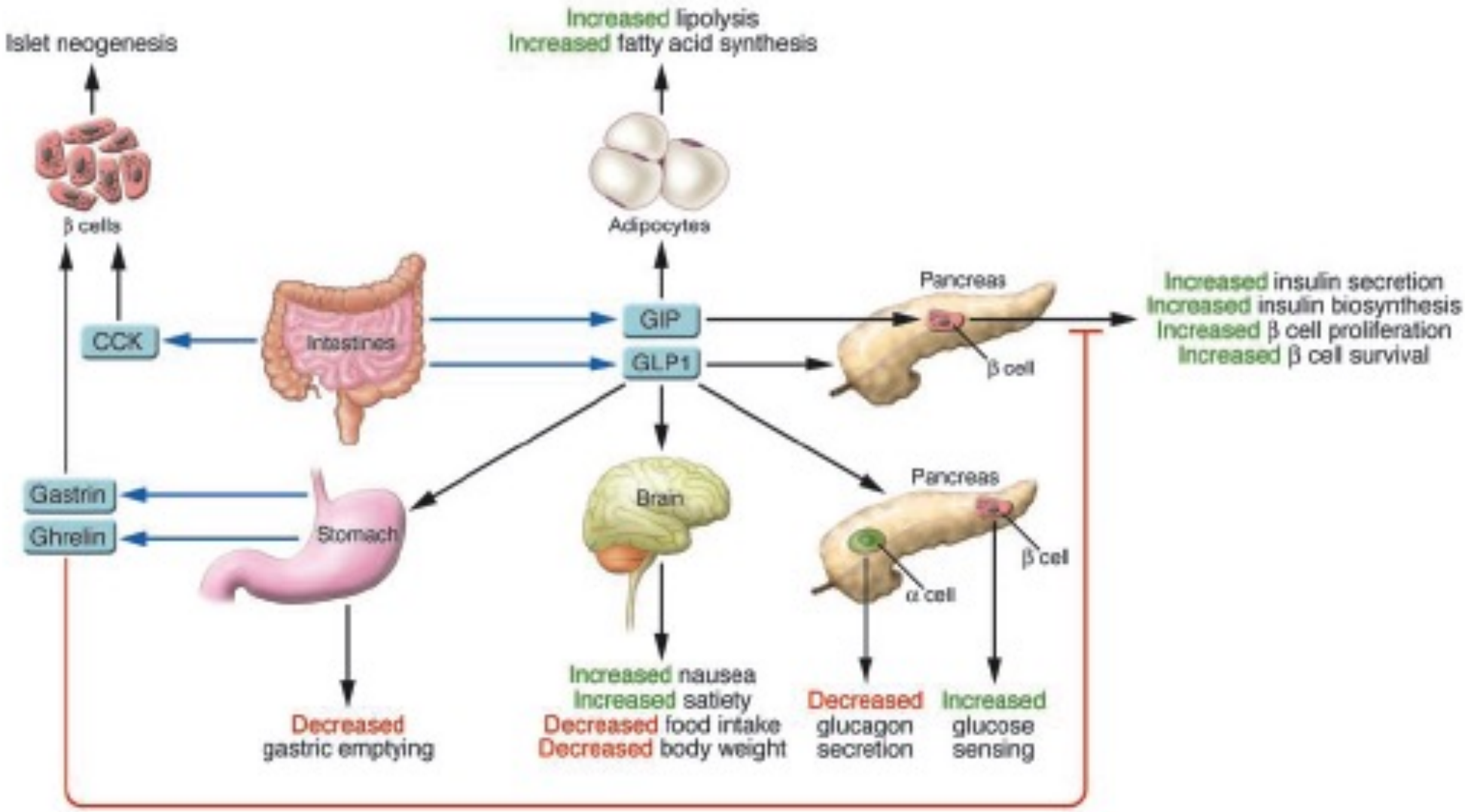
ZEPHYR

# Livoletide

## AZP01-CLI-003
## double-blind Phase 2b Trial

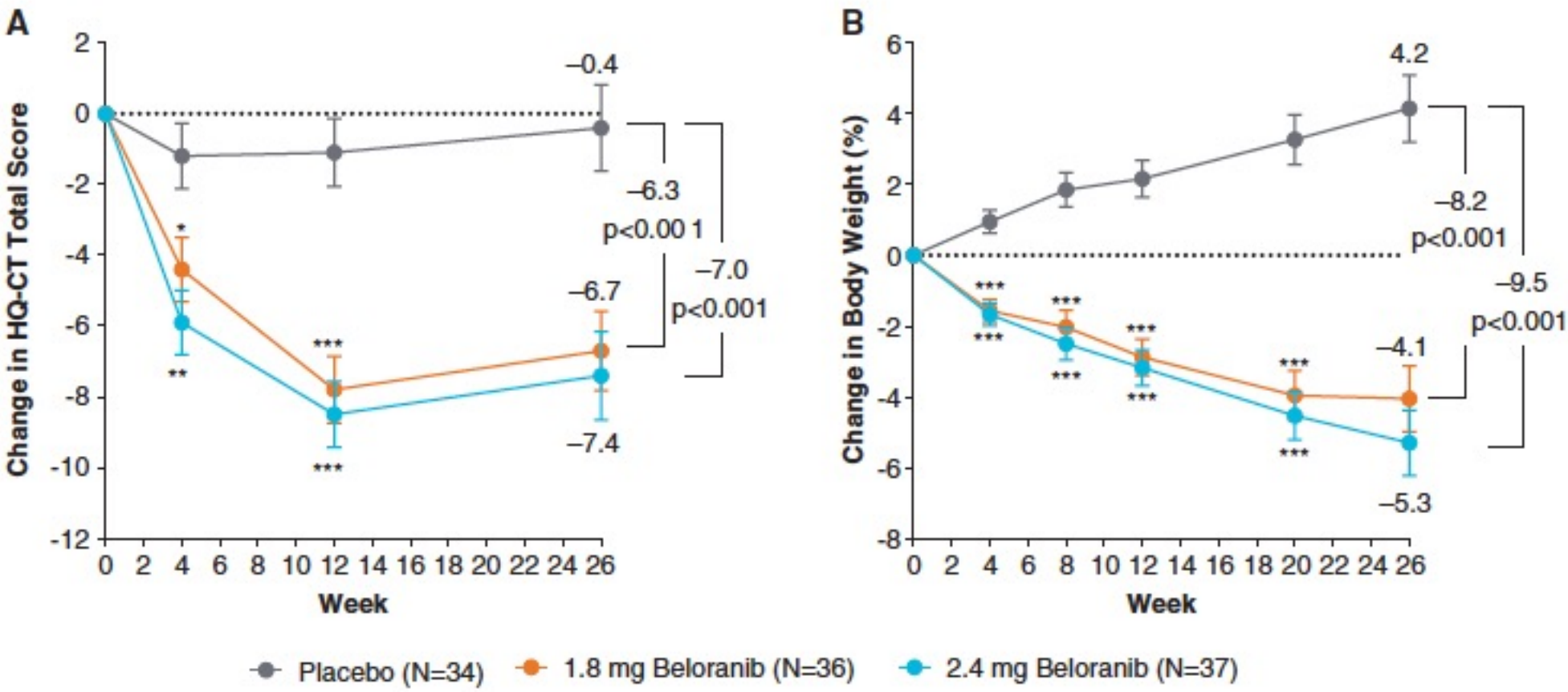
## Failure to meet primary outcomes for hyperphagia over 3 months Livoletide 60 or 120 µg/kg
## 8-65 yo, HQ-CT score ≥10/36

# GLP-1 Based Therapies




Drucker DJ et al. *JCI 2007*

# Effects of MetAP2 inhibition on hyperphagia and body weight in Prader–Willi syndrome: A randomized, double-blind, placebo-controlled trial




McCandless SE et al. Diabetes Obes Metab 2017

# Drug Trials for Hyperphagia in PWS

- **Beloranib** (Zafgen), *METAP2 enzyme inhibitor*, alters fat metabolism, 10% wt loss over 6 months, reduces hyperphagia scores. FDA clinical hold as PE/DVTs
- **Livoletide AZP-531** (Alize Pharma): *desacyl ghrelin analogue*
- **Setmelanotide RM-493** (Rhythm Pharmaceuticals): *MC4R agonist*
- **Rimonabant** CB1 antagonist: psychiatric side effects
- **GLWL-01 GOAT inhibitor**: no effect
- **Carbetocin** (Ferring Pharmaceuticals): *intranasal oxytocin*
- **Diazoxide**: potassium channel activator activates POMC, inhibits NPY neurons
- **Liraglutide** (NovoNordisk): *GLP-1 agonist*

**No data on newer anti-obesity drugs in PWS but most now withdrawn:**

- **Locaserin**: 5-HT2C receptor agonist
- **Contrave™**: Bupropion-Naltrexone
- **Qnexa™**: Phentermine-Topiramate

# DCCR Phase 2 Study in PWS

**Figure 3. Mean Change From Baseline to Visit 7 in Hyperphagia**

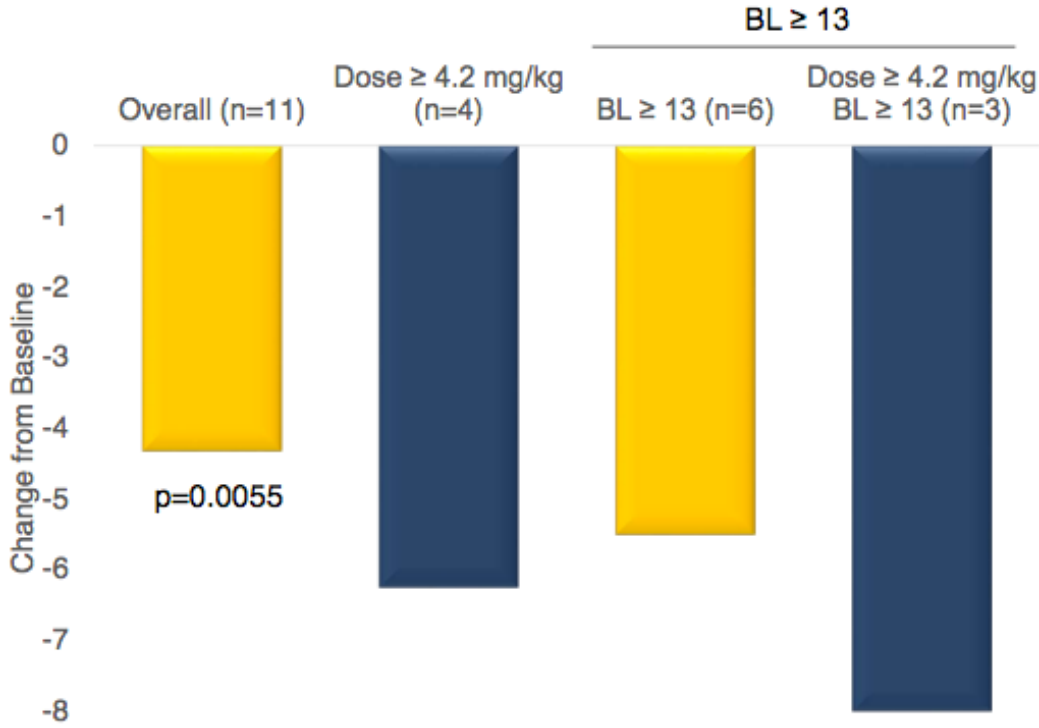
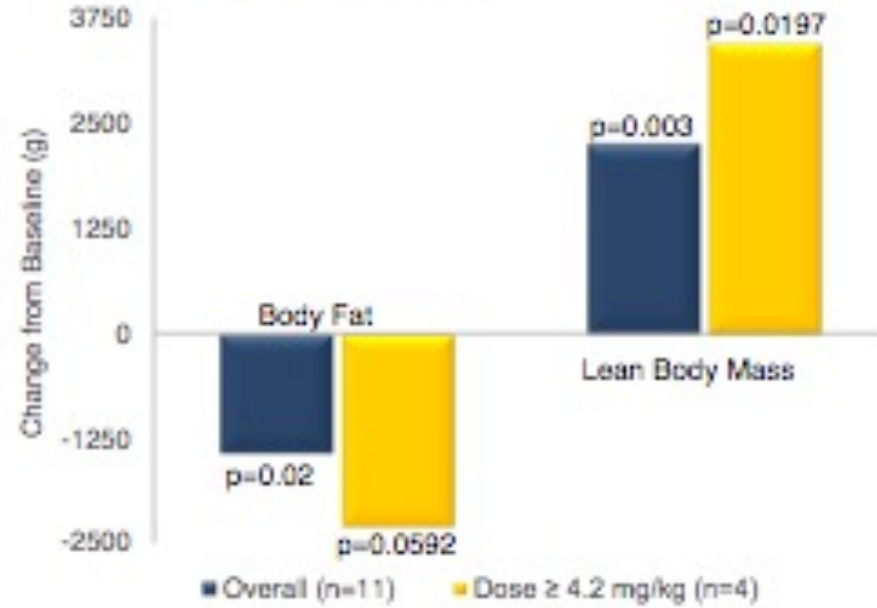


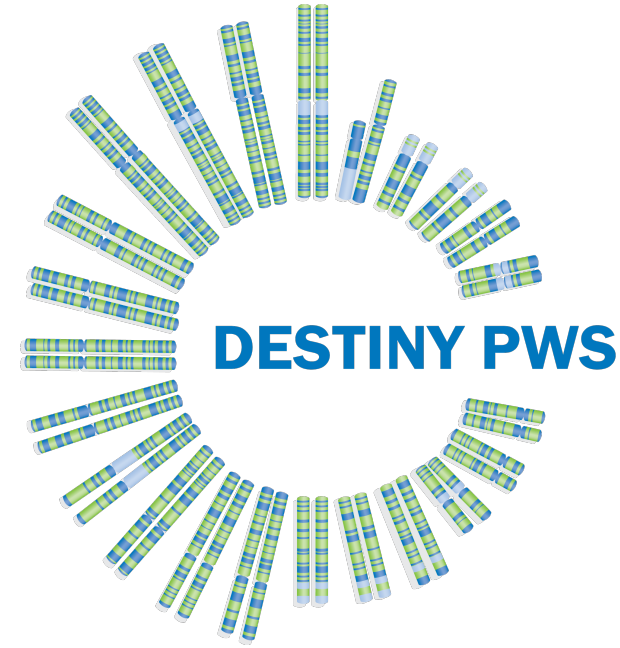

**Figure 5. Mean Changes from Baseline to Visit 7 in Body Composition by DEXA**




Kimonis V et al. Univ of California Irvine 2017

# Diazoxide (DCCR)

## c601: double-blind Ph3
## c602: open label extension

# Ongoing/Potential Drug Trials for Hyperphagia in PWS

- **PC1-target (Levo Therapeutics): correct underlying multiple defects**
- **Pitolisant (Harmony Biosciences): histamine H3-receptor antagonist**
- **Tesomet (Saniona): tesofensine (NA, DA, 5HT reuptake inhibitor) with metoprolol,**
- **Cannabidiol (Radius Healthcare): multiple mechanisms**
- **HM04 (Helsinn): ghrelin receptor antagonist**
- **?Newer GLP-1 analogue Semaglutide**

# Hormone Processing Defects and Obesity

letter

## Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene

Robert S. Jackson[1*], John W.M. Creemers[2*], Shinya Ohagi[3], Marie-Laure Raffin-Sanson[4], Louise Sanders[5], Carl T. Montague[5], John C. Hutton[6] & Stephen O'Rahilly[5]

**Human obesity has an inherited component, but in contrast to rodent obesity, precise genetic defects have yet to be defined[1]. A mutation of carboxypeptidase E (CPE), an enzyme active in the processing and sorting of prohormones, causes obesity in the *fat/fat* mouse[2,3]. We have previously described a woman with extreme childhood obesity (Fig. 1), abnormal glucose homeostasis, hypogonadotrophic hypogonadism, hypocortisolism and elevated plasma proinsulin and pro-opiomelanocortin (POMC) concentrations but a very low insulin level, suggestive of a defective prohormone processing by the endopeptidase, prohormone convertase 1 (PC1; ref. 4). We now report this proband to be a compound heterozygote for mutations in *PC1*. Gly→Arg[483] prevents processing of proPC1 and leads to its retention in the endoplasmic reticulum (ER). A→C[+4] of the intron-5 donor splice site causes skipping of exon 5 leading to loss of 26 residues, a frameshift and creation of a premature stop codon within the catalytic domain. PC1 acts proximally to CPE in the pathway of post-translational processing of prohormones and neuropeptides. In view of the similarity between the proband and the *fat/fat* mouse phenotype, we infer that molecular defects in prohormone conversion may represent a generic mechanism for obesity, common to humans and rodents.**

The 14 exons of the proband's *PC1* were characterized by PCR and single-strand conformation polymorphism (SSCP) analysis[5,6]. A variant was detected in exon 13 (Fig. 2*a*) and direct sequencing revealed it to be a heterozygous missense mutation, Gly→Arg[483] (GGG→AGG[483]) (Fig. 2*b*). This mutation, which removes a restriction site for *Nla*IV, was absent in 85 unrelated British Caucasian subjects (Fig. 2*c*).

The presence of this substitution in three of the proband's four children, all of whom were clinically unaffected, suggested the possibility of an undetected mutation in

**Fig. 1** Severe early-onset obesity. The proband aged 3 years, weighing 36 kg, with her father (now deceased). This photograph is reproduced with the written informed consent of the proband.

Jackson RS et al. Nat Genet 1997

Stijnen P et al. Endocr Rev 37:347-71, 2016

RESEARCH ARTICLE

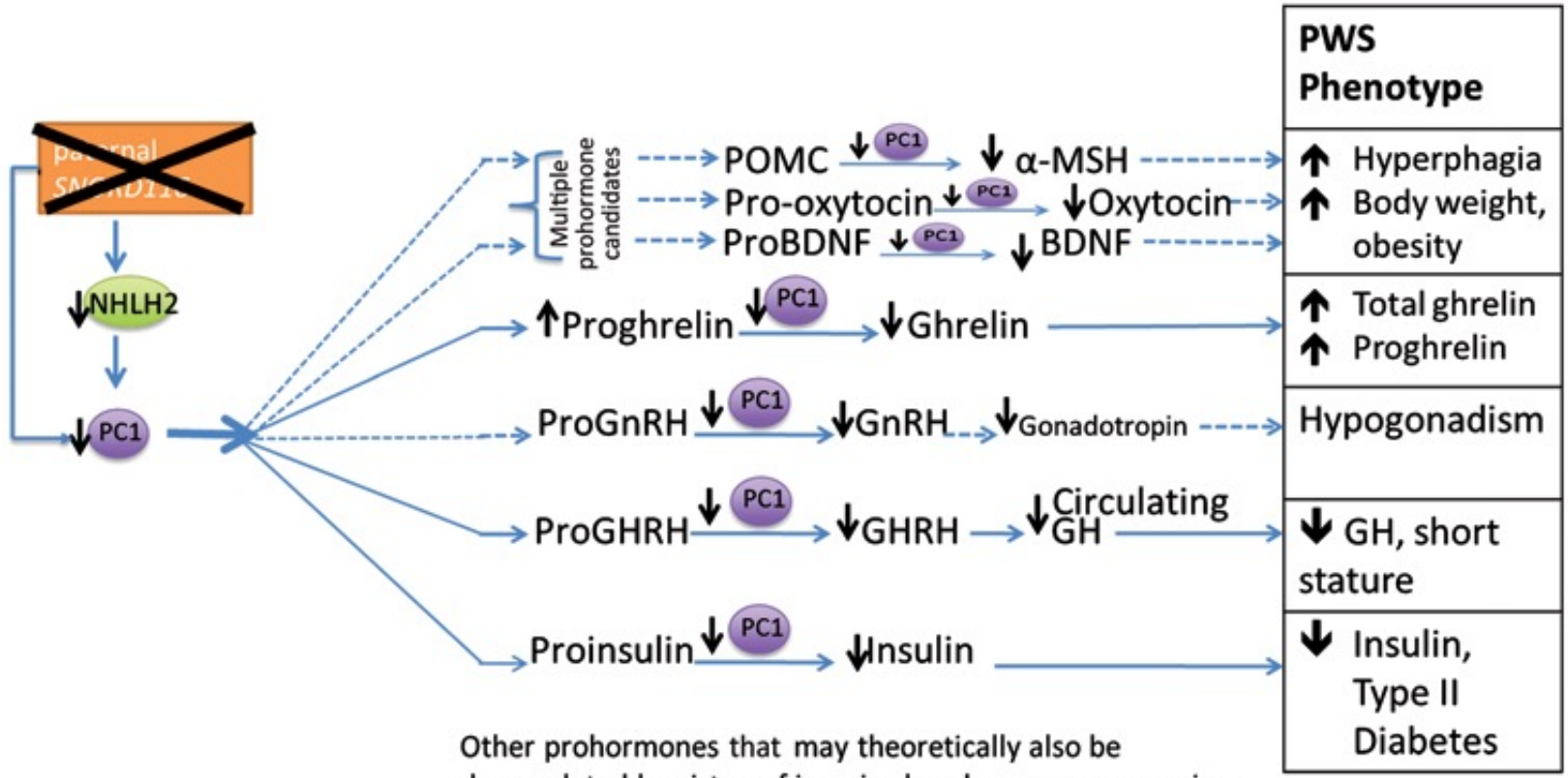
## Truncating Homozygous Mutation of Carboxypeptidase E (*CPE*) in a Morbidly Obese Female with Type 2 Diabetes Mellitus, Intellectual Disability and Hypogonadotrophic Hypogonadism

**Suzanne I. M. Alsters[1☯], Anthony P. Goldstone[2,3,4☯*], Jessica L. Buxton[1,5], Anna Zekavati[6], Alona Sosinsky[6], Andrianos M. Yiorkas[1], Susan Holder[7], Robert E. Klaber[8], Nicola Bridges[9], Mieke M. van Haelst[10], Carel W. le Roux[1,11], Andrew J. Walley[12], Robin G. Walters[13], Michael Mueller[6], Alexandra I. F. Blakemore[1*]**

Alsters SIM, Goldstone AP et al.

PloS ONE 10:e0131417, 2015

# PCSK1/NHLH2 Deficiency in PWS



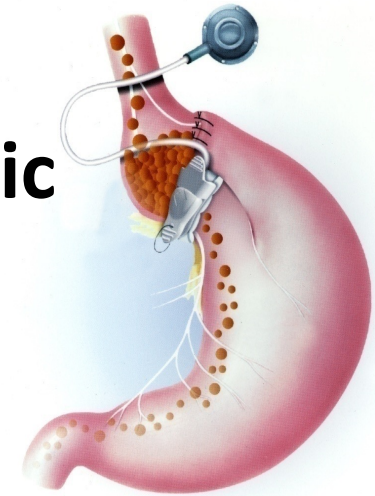

Other prohormones that may theoretically also be dysregulated by virtue of impaired prohormone processing:

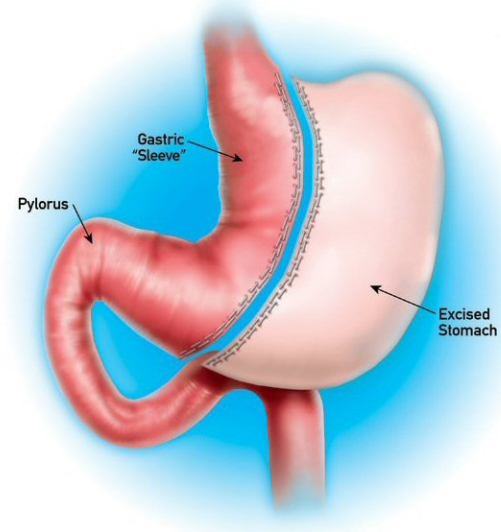
- proAgRP
- proNPY
- proCART
- proVasopressin
- proRenin
- proGlucagon
- proCRF
- proTRH

Burnett LC et al. JCI 2016

# Bariatric Surgical Procedures

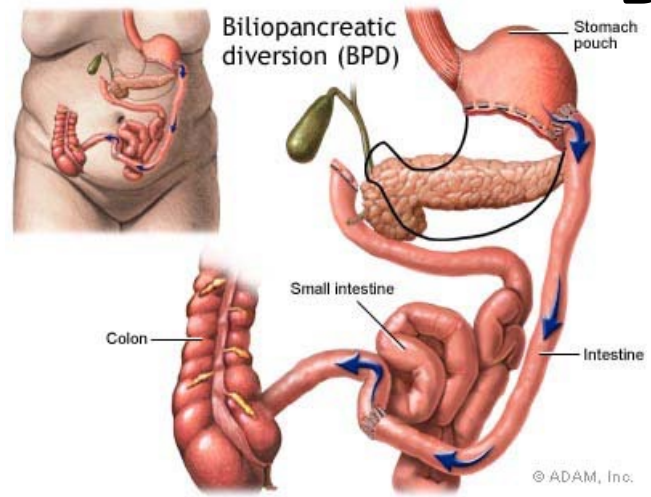
**Laparoscopic Gastring Banding**






**Vertical Sleeve Gastrectomy**

**Roux-en-Y Gastric Bypass**

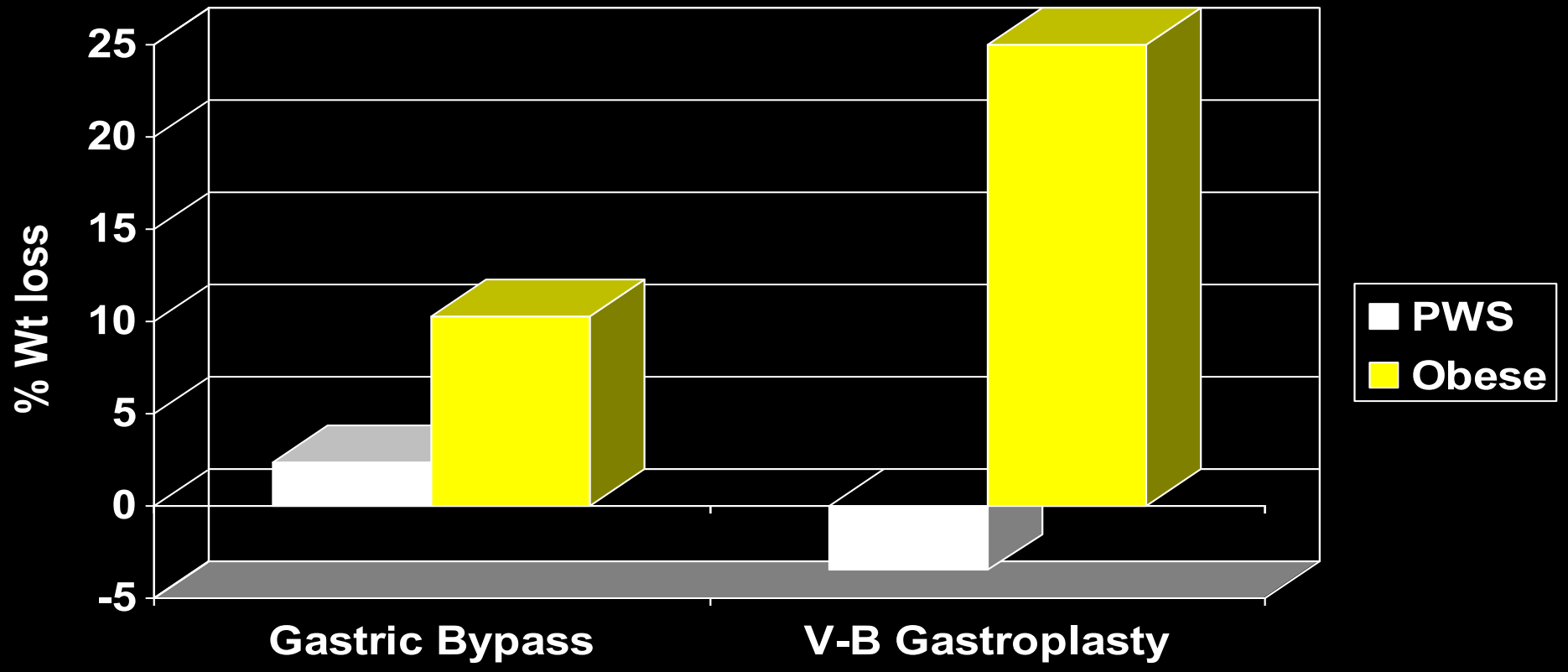



**Biliopancreatic Diversion**

# Bypass Procedures in PWS

| Yr | Author | Surgery | Success Rate | Complications |
|---|---|---|---|---|
| 1980 | Anderson | (10) Gastric Bypass<br>(1) Gastroplasty | | 1 wound infection<br>54% wt revise<br>1 dumping; 1 death from wt |
| 1983 | Touquet | Jejunoileal bypass | | wound infection; DVT/PE |
| 1991 | Laurent-Jacard | Biliopancreatic Diversion (BPD) | ?Wt regain 6 y | Diarrhoea<br>Vit D, B12, Folate, Fe Deficient |
| 2000 | Grugni | BPD | Wt loss then gain | Diarrhoea, anemia, osteopenia, low albumin |
| 2001 | Marinari | BPD | Wt loss<br>gain 20% 2y | 2 die unrelated cause; no nutrition info at 2y |
| 2005 | De Almeida | BPD | Wt loss initial<br>follow 12-28m | 2 pts; diarrhoea in both; anaemia, 1 Vit D def |
| 2010 | Marceau | BPD/DS | Wt loss w/ regain | all 3 ? revision w/ 1 death during revision 4 years postop |

# Weight Loss at 5 Years Post-Procedure




Scheimann AO et al. J Ped Gatro Nutr 46:80-83, 2008

# Vertical Sleeve Gastrectomy

LETTER TO THE EDITOR

## Laparoscopic Sleeve Gastrectomy in 108 Obese Children and Adolescents Ages 5 to 21 Years by Alqahtani AR, Antonisamy B, Alamri H, Elahmedi M, Zimmerman VA

*To the Editor:*

We read with great interest the recent article by Alqahtani et al[1] describing a single center's experience with laparoscopic sleeve gastrectomy between 2008 and 2011 performed on 108 children and adolescents between 5 and 21 years of age. Of note, the study included a subgroup of 13 children, including 9 with genetic obesity syndromes associated with hyperphagia (7 children with Prader-Willi syndrome and 2 children with Bardet-Biedl syndrome). Eight of 13 children (62%) in the subgroup were younger than 14 years, including a 5-year-old girl with Prader-Willi syndrome with a preoperative body mass index of 31.8 kg/m$^2$ and a history of obstructive sleep apnea and cardiac arrests. Outcome data were reported for only 1 of 13 children in the younger than 14 years subgroup, a decline in body mass index from 31.8 to 17.1 kg/m$^2$ reported at 12 months after sleeve gastrectomy for the 5-year-old girl with Prader-Willi syndrome. Additional outcome data for the other 8 children with genetic causes of hyperphagia and the genetic syndrome diagnostic criteria for these children were unavailable in the article.

Prader-Willi syndrome is a complex genetic disorder resulting from loss of the paternal copy of chromosome 15q11.2-13 and is considered one of the most common causes of severe obesity affecting an estimated 350,000 to 400,000 individuals globally.[2] Patients with Prader-Willi syndrome have an underlying defect in satiety, altered pain threshold, decreased ability to vomit, and increased risk for development of gastric dilation and necrosis.[3–5] Bardet-Biedl syndrome is a pleiotropic autosomal recessive disorder affecting ciliary function (prevalence rates ranging from 1 in 125,000 to 1 in 160,000 for individuals of European ancestry to 1 in 18,000 among consanguineous populations) accompanied by an increased risk for the development of severe obesity and diabetes mellitus.[6,7] Published data regarding outcomes of bariatric procedures in patients with genetic and hypothalamic conditions associated with hyperphagia such as Prader-Willi or Bardet-Biedl are quite limited and in many series fairly disappointing.

The results of a patient with Bardet-Biedl syndrome who underwent Roux-en-Y gastric bypass with sustained drop in body mass index 52.3 to 34.9 kg/m$^2$ at 42 months postoperatively with improvement in hypertension was published by Daskalakis et al[8] in 2009. Deaths have been reported among individuals with Prader-Willi syndrome after restrictive bariatric procedures including laparoscopic silicone gastric banding and BioEnterics intragastric balloon placement.[9,10] A long-term review of outcomes of bariatric surgery among individuals with Prader-Willi syndrome revealed suboptimal results in comparison with obese controls, advocating the use of a supervised hypocaloric diet with micronutrient supplementation, exercise, and restricted access to food, rather than the bariatric surgery procedures offered at that time, which did not include laparoscopic sleeve gastrectomy.[11]

We would request that the authors publish additional information regarding the diagnostic criteria of the individual cases, including genetic confirmation where available, and individual longitudinal outcomes for their children with hyperphagic disorders after sleeve gastrectomy, ideally with follow-up over several years. This would provide invaluable information for the clinical management of individuals with genetic syndromes associated with hyperphagia and morbid obesity, such as Prader-Willi and Bardet-Biedl syndromes, and to determine whether, indeed, sleeve gastrectomy is a procedure that should be considered in this unique patient population.

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ORIGINAL ARTICLE

## Laparoscopic Sleeve Gastrectomy in 108 Obese Children and Adolescents Aged 5 to 21 Years

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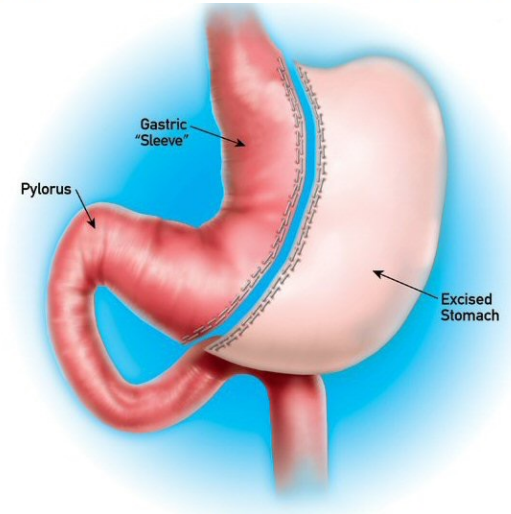
*Annals of Surgery* • Volume 256, Number 2, August 2012




**"Currently, following up 16 PWS patients who underwent LSG. Within 4-year follow up period, PWS patients have displayed a median excess BMI loss of 60.2% compared with 61.3% in non-syndromic children and adolescents with absence of significant complications."**

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