HAROKOPIO UNIVERSITY

Weight Loss and Genetic variation

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"If the brain is mostly made of fat, then gaining weight in college helps you get smarter!"

"See a doctor. Your cholesterol is twice your weight."


Dear Diet,
Things just aren't going to work between us.
It's not me, it's you.
You're tasteless, boring & I can't stop cheating on you.
yourecards
someecards.com

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Genetic Predisposition to Weight Loss and Regain With Lifestyle Intervention: Analyses From the Diabetes Prevention Program and the Look AHEAD Randomized Controlled Trials

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Table 1—Look AHEAD and DPP (weight-loss sample) participant characteristics

Characteristics	Look AHEAD			DPP		
	Total (*N* = 3,906)	Comparison (*N* = 1,892)	Lifestyle (*N* = 2,014)	Total (*N* = 1,824)	Comparison (*N* = 907)	Lifestyle (*N* = 917)
Women (%)	2,251 (57.6)	1,081 (57.1)	1,170 (58.1)	1,241 (68.0)	623 (68.7)	618 (67.4)
Successful weight losers (%)†	2,116 (54.2)	475 (25.1)	1,641 (81.5)	834 (45.7)	201 (22.2)	633 (69.0)
Age (years)	59 (6.8)	59.1 (6.8)	58.9 (6.8)	50.7 (10.9)	50.7 (10.4)	50.7 (11.4)
Ethnicity (%)						
African American	586 (15.0)	280 (14.8)	306 (15.2)	371 (20.3)	190 (21.0)	181 (19.7)
American Indian/Alaskan Native[a]	81 (2.1)	41 (2.2)	40 (2.0)	56 (3.1)	28 (3.1)	28 (3.1)
Asian/Pacific Islander	26 (0.7)	10 (0.5)	16 (0.8)	89 (4.9)	37 (4.1)	52 (5.7)
Non-Hispanic white	2,747 (70.3)	1,350 (71.4)	1,397 (69.4)	991 (54.3)	499 (55.0)	492 (53.7)
Hispanic/Latino	392 (10.0)	173 (9.1)	219 (10.9)	317 (17.4)	153 (16.9)	164 (17.9)
Other (multiple)	74 (1.9)	38 (2.0)	36 (1.8)	—	—	—
BMI (kg/m^2)	36.1 (5.9)	36.2 (5.8)	36 (6.1)	34.1 (6.7)	34.3 (6.7)	34.0 (6.7)
Weight (kg)						
Overall Sample						
Baseline	101.8 (19.2)	102.2 (18.7)	101.4 (19.6)	94.6 (20.2)	94.8 (19.9)	94.4 (20.5)
Year 1	96.7 (19.4)	101.4 (18.9)	92.4 (18.9)	90.8 (20.5)	94.3 (20.4)	87.3 (19.9)
Year 2	97.6 (19.4)	100.9 (18.8)	94.6 (19.4)	91.6 (20.6)	94.7 (20.3)	88.5 (20.5)
Year 3	98.3 (19.5)	100.8 (19.1)	96.0 (19.6)	92.8 (21.2)	95.1 (20.4)	90.5 (21.8)
Year 4	98.4 (19.6)	100.6 (19.2)	96.3 (19.7)	94.1 (21.3)	95.6 (18.4)	92.7 (23.6)
Women						
Baseline	96.0 (17.5)	96.4 (17.4)	95.6 (17.7)	92.9 (20.4)	93.1 (20.1)	92.7 (20.7)
Year 1	91.4 (17.9)	95.6 (17.6)	87.5 (17.3)	89.2 (20.7)	92.5 (20.9)	86.0 (20.1)
Year 2	92.3 (18.0)	95.1 (17.6)	89.7 (18.0)	90.1 (20.8)	93.0 (20.6)	87.0 (20.5)
Year 3	92.8 (17.9)	94.7 (17.4)	91.1 (18.1)	91.7 (21.5)	93.4 (20.5)	90.0 (22.2)
Year 4	92.7 (17.9)	94.5 (17.7)	91.1 (18.0)	94.7 (22.5)	95.9 (18.8)	93.5 (25.5)
Men						
Baseline	109.7 (18.6)	109.8 (17.7)	109.6 (19.3)	98.3 (19.3)	98.5 (18.9)	98.1 (19.8)
Year 1	104.0 (19.0)	109.0 (17.8)	99.2 (18.9)	94.1 (19.4)	98.2 (18.7)	90.2 (19.3)
Year 2	104.9 (18.8)	108.4 (17.6)	101.4 (19.4)	94.9 (19.8)	98.4 (19.0)	91.5 (20.1)
Year 3	105.8 (19.2)	108.9 (18.2)	102.8 (19.6)	95.0 (20.6)	98.5 (19.7)	91.7 (20.9)
Year 4	106.1 (19.1)	108.8 (18.1)	103.6 (19.7)	93.0 (18.8)	94.9 (17.9)	91.2 (19.5)

All variables summarized in mean (SD) format, unless indicated otherwise. [a]The number of American Indian participants included in this study is lower than in the parent Look AHEAD trial due to lack of institutional review board approval. †This is the weight-regain analysis subsample that achieved at least 3% weight loss at year 1 (see the separate demographics table for this subsample in Table 2).

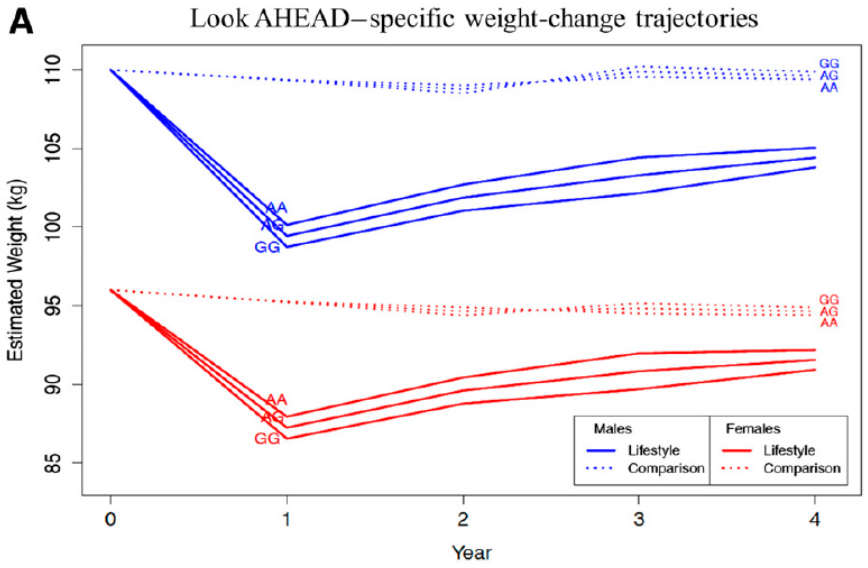
The associations of **91 established obesity-predisposing loci** with weight loss across 4 years and with weight regain across years 2–4 after a minimum of **3% weight loss** were tested.

Intensive lifestyle intervention (primarily fat gram, calorie, and physical activity goals) aimed **at ;7% weight loss.** The intensive lifestyle intervention included 16 individual sessions within the first 6 months with in-person or phone follow-up at least monthly thereafter.

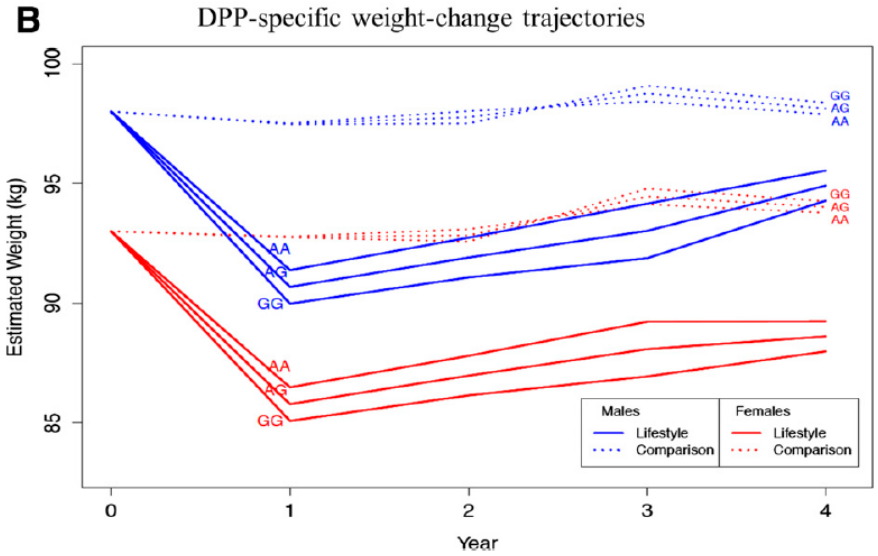
Table 2—Look AHEAD and DPP (weight-regain sample) participant characteristics

	Look AHEAD			DPP		
Characteristics	Total (*N* = 2,116)	Comparison (*N* = 475)	Lifestyle (*N* = 1,641)	Total (*N* = 834)	Comparison (*N* = 201)	Lifestyle (*N* = 633)
Women (%)	1,224 (58.0)	291 (61.3)	933 (56.9)	544 (65.2)	139 (69.2)	405 (64.0)
Age (years)	59.2 (6.8)	59.3 (6.7)	59.2 (6.9)	51.7 (11.0)	50.5 (9.6)	52.1 (11.4)
Ethnicity (%)						
African American	291 (13.8)	61 (12.8)	230 (14.0)	136 (16.3)	33 (16.4)	103 (16.3)
American Indian/Alaskan Native[a]	40 (1.9)	11 (2.3)	29 (1.8)	17 (2.0)	2 (1.0)	15 (2.4)
Asian/Pacific Islander	14 (0.7)	1 (0.2)	13 (0.8)	45 (5.4)	5 (2.5)	40 (6.3)
Non-Hispanic white	1,518 (72.0)	350 (74.0)	1,168 (71.0)	486 (58.3)	129 (64.2)	357 (56.4)
Hispanic/Latino	220 (10.4)	43 (9.1)	177 (10.8)	150 (18.0)	32 (15.9)	118 (18.6)
Other (multiple)	33 (1.6)	9 (1.9)	24 (1.5)	—	—	—
BMI (kg/m^2)	36.1 (6.1)	36.9 (6.0)	35.9 (6.1)	33.7 (6.4)	34.5 (6.7)	33.4 (6.3)
Weight (kg)						
Overall						
Baseline	102.0 (19.8)	103.8 (20.1)	101.4 (20.0)	93.7 (19.9)	95.5 (20.2)	93.1 (19.8)
Year 1	91.8 (18.5)	96.7 (18.8)	90.4 (18.2)	84.9 (18.5)	88.8 (19.4)	83.6 (18.0)
Women						
Baseline	95.9 (17.8)	97.6 (18.4)	95.3 (17.6)	91.4 (20.0)	93.2 (19.4)	90.8 (20.2)
Year 1	86.6 (16.8)	91.0 (17.2)	85.2 (16.4)	82.8 (18.6)	86.5 (19.1)	81.5 (18.3)
Men						
Baseline	110.3 (19.0)	113.4 (18.9)	109.5 (20.0)	97.9 (19.0)	100.7 (21.0)	97.2 (18.4)
Year 1	98.9 (18.4)	105.8 (17.6)	97.1 (18.2)	88.9 (17.5)	94.0 (19.4)	87.5 (16.7)
Weight regain (kg)†						
Overall						
Year 2	2.4 (5.2)	0.6 (6.4)	2.9 (4.6)	2.0 (4.2)	2.7 (4.9)	1.7 (4.0)
Year 3	3.7 (7.2)	1 (8.1)	4.5 (6.7)	3.3 (5.8)	4.2 (6.4)	3.0 (5.6)
Year 4	4.2 (8.0)	1.4 (8.5)	5.1 (7.7)	4.3 (7.7)	4.6 (9.2)	4.2 (7.2)
Women						
Year 2	2.1 (5.3)	0.2 (6.7)	2.7 (4.6)	2.1 (4.4)	2.9 (5.0)	1.8 (4.2)
Year 3	3.4 (7.1)	0.4 (8.9)	4.4 (6.1)	3.5 (6.2)	4.2 (6.9)	3.3 (6.0)
Year 4	3.8 (8.1)	0.7 (9.2)	4.8 (7.5)	4.9 (8.4)	4.4 (10.0)	5.1 (7.7)
Men						
Year 2	2.7 (5.0)	1.3 (6.0)	3.0 (4.7)	1.7 (3.8)	2.2 (4.7)	1.6 (3.6)
Year 3	4.1 (7.4)	2.0 (6.7)	4.7 (7.4)	2.8 (4.9)	4.2 (5.3)	2.4 (4.8)
Year 4	4.9 (7.8)	2.4 (7.2)	5.5 (7.8)	3.3 (6.1)	5.2 (5.9)	2.9 (6.2)

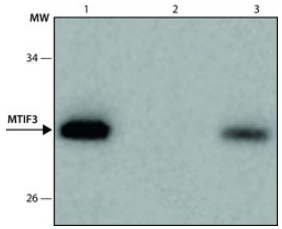
All variables summarized in mean (SD) format, unless indicated otherwise. [a]The number of American Indian participants included in this study is lower than the parent Look AHEAD trial due to lack of institutional review board approval. †Weight regain calculated as Y_j weight – Y_1 weight (kg) for j = 2, 3, 4.



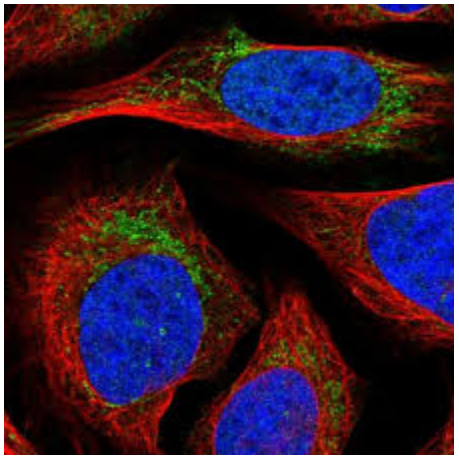
The intronic rs1885988 variant (at **MTIF3** modified weight-loss response to lifestyle intervention. The effect within the combined interventions reached statistical significance in **year 3**. Each copy of the minor G allele was associated with a mean **-1.14** kg lower weight in the lifestyle arm versus a mean **0.33** kg higher weight in the comparison



Hence, the mean differences in year-3 weight change between the lifestyle intervention and comparison arms were estimated at **-1.48** kg between AA homozygotes and AG heterozygotes, and **-2.96** kg between AA and GG homozygotes.



MTIF3 encodes a 29-kDa nuclear-encoded protein that promotes the formation of the initiation complex on the mitochondrial **55S ribosome**. The mitochondrial ribosome is responsible for the synthesis of 13 of the inner mitochondrial membrane proteins and its regulation is essential for ATP synthesis, energy balance, and modulation of reactive oxygen species production in the mitochondria by the electron transport chain

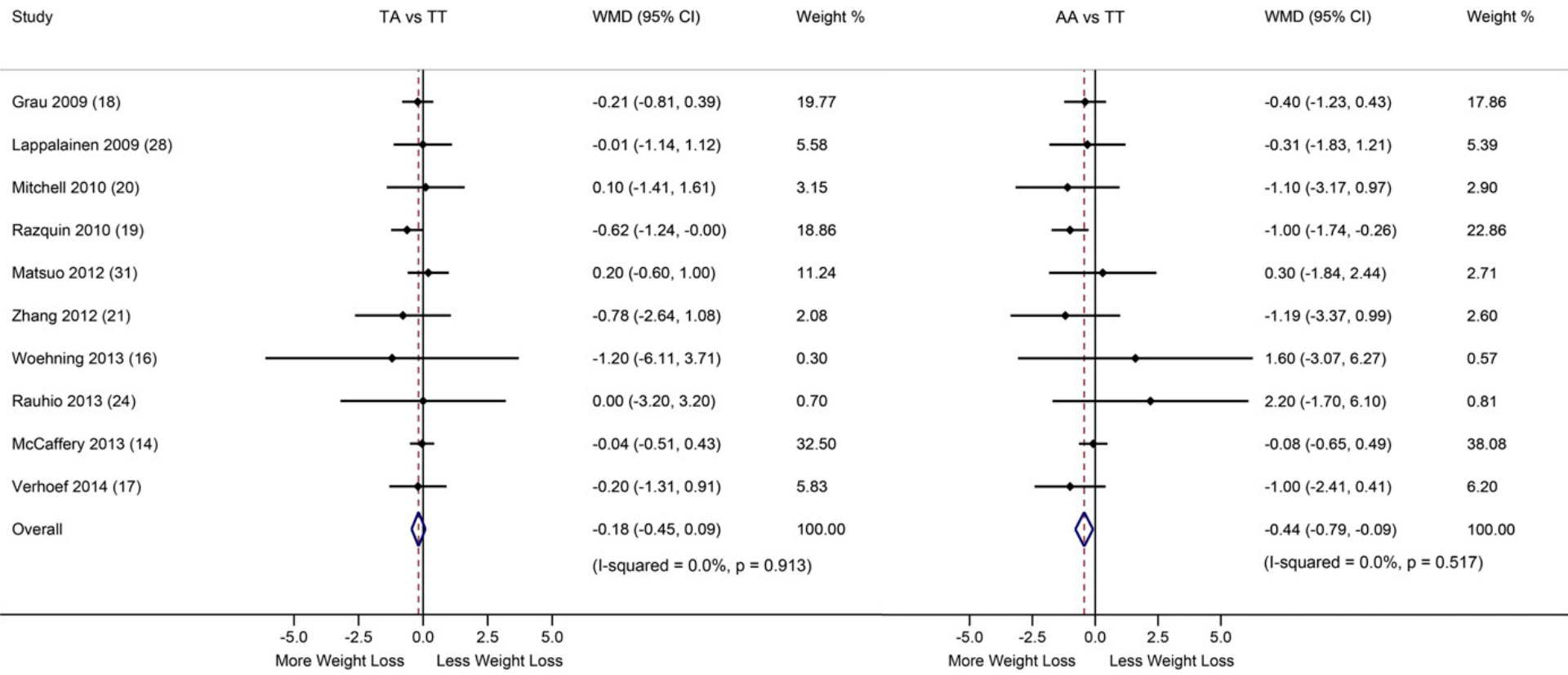


Here, the minor G allele was associated with lifestyle elicited weight loss in both trials and with weight regain in the DPP but not Look AHEAD. The minor G allele has previously been associated with higher BMI

In conclusion, they assessed the effects on weight change of 91 established BMI-associated loci in two large RCTs of intensive lifestyle modification.

FTO genotype and weight loss in diet and lifestyle interventions: a systematic review and meta-analysis[1,2]

*Lingwei Xiang,[3] Hongyu Wu,[4] An Pan,[5] Bhakti Patel,[3] Guangda Xiang,[6] Lu Qi,[4,7] Robert C Kaplan,[3] Frank Hu,[4,7] Judith Wylie-Rosett,[3] and Qibin Qi[3]**

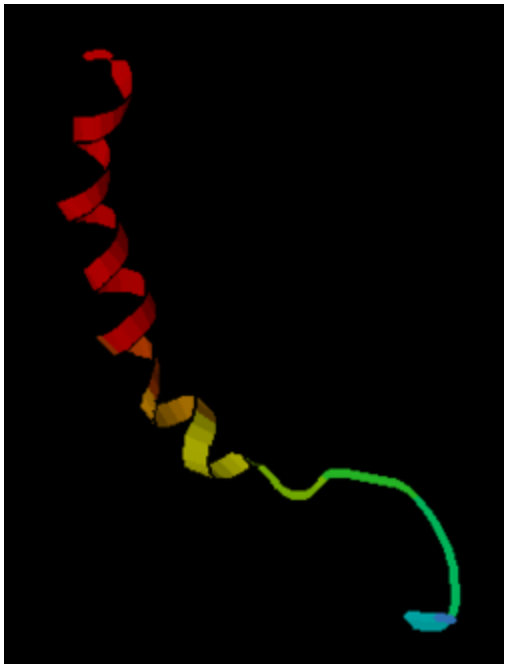


Am J Clin Nutr 2016;103:1162–70.

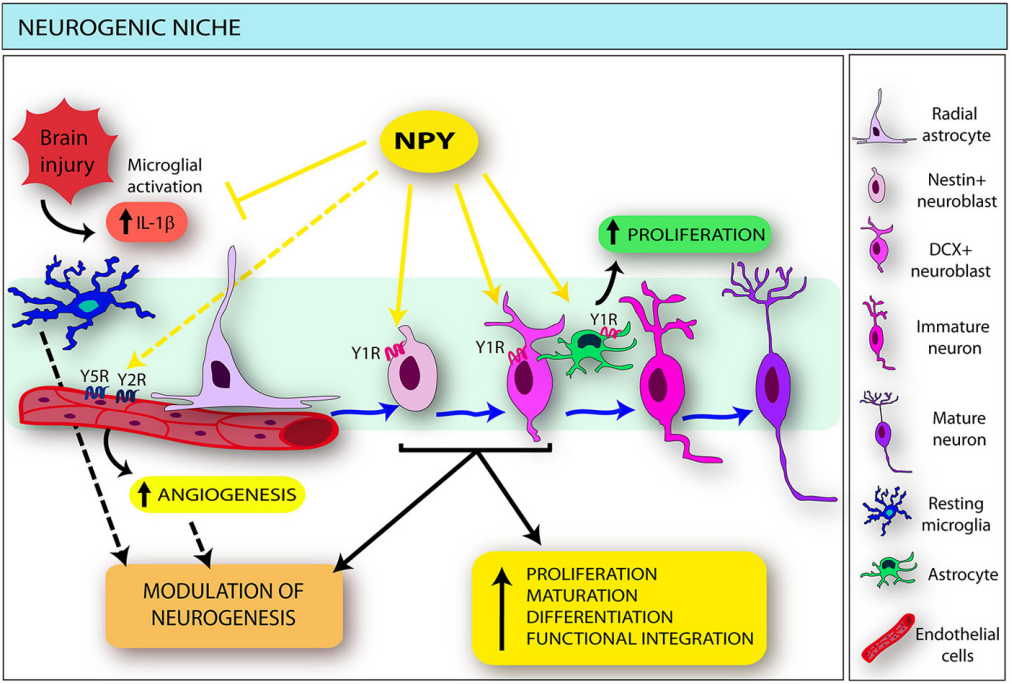
Neuropeptide Y genotype, central obesity, and abdominal fat distribution: the POUNDS LOST trial[1,2]

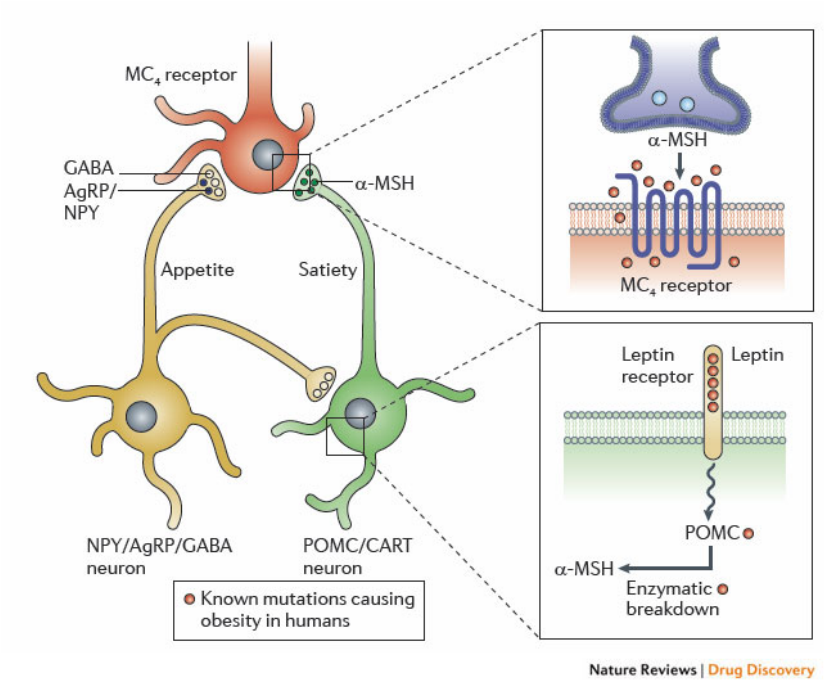
Xiaochen Lin,[3,6,13] Qibin Qi,[4,7,14] Yan Zheng,[4] Tao Huang,[4] Mark Lathrop,[8,9] Diana Zelenika,[10] George A Bray,[11] Frank M Sacks,[4] Liming Liang,[3,5,15] and Lu Qi[4,12,15]**

- **Neuropeptide Y** (**NPY**) is a 36-amino acid neuropeptide that acts as a neurotransmitter in the brain and in the autonomic nervous system of humans.
- In the autonomic system it is produced mainly by neurons of the sympathetic nervous system and serves as a strong vasoconstrictor and also causes **growth of fat tissue**.
- In the brain, it is produced in various locations including the hypothalamus, and is thought to have several functions, including: **increasing food intake** and storage of energy as fat, **reducing anxiety and stress**, **reducing pain perception**, affecting the circadian rhythm, **reducing voluntary alcohol intake**, **lowering blood pressure**, and controlling epileptic seizures.
- A functional polymorphism in the **promoter region of NPY,** rs16147(C-399T), was found to show allele-specific effects on NPY gene expression and NPY peptide concentrations



Am J Clin Nutr 2015;102:514–9.





NPY regulates the white adipose tissue (WAT) metabolism via the nerve endings housed in WAT; adipokines, secreted by WAT, then exert as a sensory input and inform the brain of body fat levels

In this study, they aimed to investigate whether the **rs16147 genotypes** modulated the effects of **weight loss diets** varying in macronutrients on changes of **waist circumference** and **abdominal fat distribution** in a **2-y diet** intervention study, the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial.

The POUNDS LOST trial

- is a 2-y randomized clinical trial to compare the effects on body weight of energy-reduced diets with different

  dietary intakes of macronutrients
- In total, 811 overweight adults were randomly assigned to one of the 4 diets with targeted percentages of energy derived from fat, protein, and carbohydrates

20%	20%	40%	40%
65%	55%	45%	35%
15%	25%	15%	25%

The energy deficit was **750 kcal** from baseline, and **low glycemic index** food was used for the diets.

TABLE 1
Baseline characteristics of the study participants[1]

	NPY rs16147 genotype			
	CC (n = 203)	CT (n = 341)	TT (n = 179)	P value
Age, y	52.5 ± 8.7[2]	50.6 ± 9.5	49.9 ± 9.3	0.02
Sex, n (%)				0.66
Female	126 (28.6)	211 (47.8)	104 (23.6)	
Male	77 (27.3)	130 (46.1)	75 (26.6)	
Ethnicity, n (%)				0.01
Caucasian	146 (25.4)	274 (47.6)	155 (27.0)	
African American	44 (39.3)	53 (47.3)	15 (13.4)	
Hispanic	10 (40.0)	11 (44.0)	4 (16.0)	
Others	3 (27.3)	3 (27.3)	5 (45.4)	
Diet groups (% energy from fat/protein/carbohydrate), n (%)				0.85
Group 1 (20/25/55)	48 (27.3)	88 (50.0)	40 (22.7)	
Group 2 (20/15/65)	51 (28.0)	79 (43.4)	52 (28.6)	
Group 3 (40/25/35)	52 (28.7)	84 (46.4)	45 (24.9)	
Group 4 (40/15/45)	52 (28.3)	90 (48.9)	42 (22.8)	
Dietary fat (% energy from fat/other), n (%)				0.84
Low fat (20)	99 (27.6)	167 (46.7)	92 (25.7)	
High fat (40)	104 (28.5)	174 (47.7)	87 (23.8)	
BMI, kg/m^2	32.8 ± 4.1	32.7 ± 3.7	32.4 ± 5.0	0.58
Waist circumference, cm	104.0 ± 13.4	103.7 ± 12.7	103.0 ± 13.2	0.49
TAT mass, kg	16.1 ± 4.6	16.8 ± 3.8	17.0 ± 4.0	0.70
VAT mass, kg	5.4 ± 2.7	5.5 ± 2.5	5.9 ± 2.4	0.75
SAT mass, kg	16.1 ± 4.8	17.3 ± 4.0	16.7 ± 3.9	0.50

There was no statistically significant difference in baseline BMI, WC, and abdominal adiposity distribution across the genotypes, after adjusting for age, sex, and ethnicity

TABLE 2

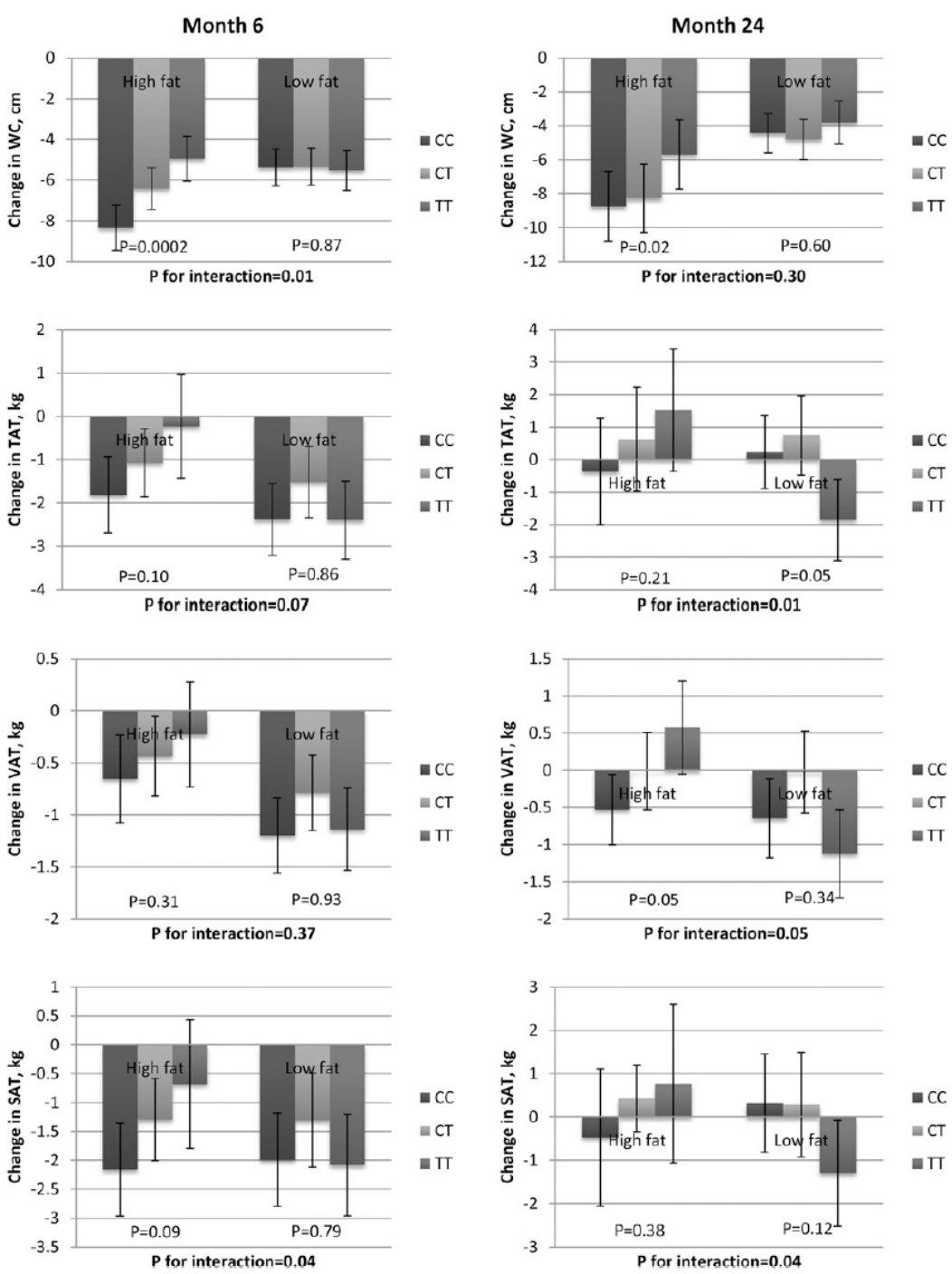
Analyses of the effect of the *NPY* rs16147 genotype on changes in waist circumference and abdominal fat distribution from baseline to 6 and 24 mo[1]

	Month 6				Month 24			
	n	β	SE	*P* value	*n*	β	SE	*P* value
WC, cm	643	0.70	0.32	0.03	548	0.70	0.43	0.11
TAT, kg	112	0.37	0.29	0.20	84	0.03	0.45	0.95
VAT, kg	132	0.14	0.13	0.27	102	0.05	0.18	0.77
SAT, kg	112	0.36	0.28	0.21	84	0.04	0.61	0.93

[1]Estimates and standard errors for the subgroup analyses were reported after adjusting for age, sex, ethnicity, diet intervention, baseline value for respective variable, and baseline BMI. β represents change in outcomes for the increase in each T allele of *NPY* rs16147. SAT, subcutaneous adipose tissue; TAT, total abdominal adipose tissue; VAT, visceral adipose tissue; WC, waist circumference.

The C allele of rs16147 was associated with a statistically significantly greater reduction in WC in all the participants at 6 months

Am J Clin Nutr 2015;102:514–9.



They found a statistically significant interaction between the NPY genotype and dietary fat on WC: the genotype effects were stronger in the high-fat diet group than in the low-fat diet group at 6 mo (P-interaction = 0.01). Within the high-fat group, the T allele was statistically significantly associated with smaller loss in WC.

At 24 mo, T allele carriers in the high-fat group were prone to regain abdominal fat.

Am J Clin Nutr 2015;102:514–9.

In conclusion, we found that the *NPY* rs16147 genotypes affected the reduction of central adiposity and the deposition of abdominal fat in response to weight loss diets in overweight or obese participants. Dietary fat intake statistically significantly modified the genetic effects such that individuals carrying the C allele of the *NPY* rs16147 SNP might benefit more by taking a high-fat weight loss diet.

Am J Clin Nutr 2015;102:514–9.

Polymorphism in the *CLOCK* gene may influence the effect of fat intake reduction on weight loss

Viviana Loria-Kohen Ph.D. [a,*], Isabel Espinosa-Salinas Ph.D. student [a], Helena Marcos-Pasero Ph.D. student [a], Thais Lourenço-Nogueira Ph.D. [b], Jesús Herranz B.Sc. [a], Susana Molina Ph.D. [a], Guillermo Reglero Ph.D. [a,c], Ana Ramirez de Molina Ph.D. [a]

The aim of this study was to assess the effect of a weight loss treatment on obesity-associated variables with respect to the **CLOCK and FTO** genotypes.

Nutrition xxx (2015) 1–8

Weight loss program

20% less energy than the baseline daily energy intake (determined using a 3-d food and drink record provided by each participant at the beginning of the intervention).

The diets were designed to have 50% to 53% carbohydrates, 21% to 23% proteins, and 24% to 29% fat.

The weight loss program was followed for 12 wk, with dietary counseling

Table 1
Parameters evaluated before and after intervention in the total group

Parameters	Before treatment	After treatment	*P* value
N = 179			
Women, n (%)	140 (77)		
Age (y)	42.48 (0.80)*		
Anthropometrics values			
Weight (kg)	83.3 (1.05)	79.23 (1.1)	<0.0001
BMI (kg/m^2)	30.58 (0.27)	29.05 (0.27)	<0.0001
TFM (%)	41.59 (0.5)	39.14 (0.5)	<0.0001
TFM (kg)	34.7 (0.63)	31.02 (0.57)	<0.0001
TMM (%)	25.66 (0.28)	26.72 (0.3)	<0.0001
WC (cm)	99.77 (0.82)	95.87 (0.82)	<0.0001
Blood pressure values			
SBP (mm Hg)	127.95 (0.95)	123.36 (1.02)	<0.0001
DBP (mm Hg)	79.96 (0.62)	75.87 (0.67)	<0.0001
Biochemical values			
Glucose (mg/dL)	84.35 (1.07)	80.51 (0.94)	<0.0001
Insulin (μUI/mL)	10.08 (0.55)	8.75 (0.45)	<0.001
APO-A1 (mg/dL)	153.82 (2.26)	150.45 (2.26)	0.0287
APO-B (mg/dL)	110.24 (2.06)	104.63 (1.98)	<0.0001
TC (mg/dL)	208.91 (2.63)	199.72 (2.76)	<0.0001
HDL-C (mg/dL)	51.25 (1.04)	49.53 (0.95)	0.0103
LDL-C (mg/dL)	131.47 (2.37)	130.56 (2.6)	0.3702
TG (mg/dL)	113.85 (3.76)	95.75 (3.09)	<0.0001
HOMA	2.04 (0.13)	1.71 (0.1)	<0.001
Dietetic parameters			
Total energy (kJ)	1948.03 (37.73)	1605.67 (32.17)	<0.0001
Proteins (%)	17.67 (0.25)	19.16 (0.29)	<0.0001
Carbohydrates (%)	36.85 (0.49)	41.82 (0.61)	<0.0001
Fats (%)	40.97 (0.45)	36.41 (0.52)	<0.0001
Physical activity (METs)	1805.48 (140.23)	1823.04 (162.17)	0.8591

The changes in reported dietary intake (total energy, fat, protein, and carbohydrate) at the end of the study ($P < 0.05$) confirmed that the participants had adhered to the regimen imposed. No significant changes were seen in terms of the amount of physical activity undertaken.

Table 2
Genotypic and allelic distributions of polymorphisms

Gene symbol	SNP	Major allele homozygote*	Heterozygote*	Minor allele homozygote*	Allele 1*	Allele2*	HWE† *P* value
CLOCK	*rs*3749474	46.79	39.74	13.46	0.333	0.667	0.2373
	*rs*1801260	39.38	41.88	18.75	0.396	0.604	0.1443
	*rs*4580704	37.89	43.48	18.63	0.403	0.597	0.2684
FTO	*rs*8050136	31.68	52.17	16.15	0.422	0.578	0.4486
	*rs*9939609	32.3	52.17	15.53	0.416	0.584	0.4162

Table 3
Variables monitored before and after intervention, with respect to genotype (*CLOCK* gene)

CLOCK	*rs*3749474					*rs*4580704				
	CC		TT + CT		*P* value*	CC		GG + CG		*P* value*
N = 159	Before	After	Before	After		Before	After	Before	After	
Anthropometrics values										
Weight (kg)	82.38 (1.55)†	78.6 (1.6)	83.88 (1.63)	79.33 (1.59)	1.00	85.62 (1.99)	81.3 (1.99)	81.61 (1.29)	77.54 (1.29)	1.00
BMI (kg/m^2)	30.61 (0.4)	29.1 (0.4)	30.7 (0.42)	29.04 (0.38)	1.00	30.63 (0.46)	29.09 (0.44)	30.62 (0.37)	29.03 (0.36)	1.00
TFM (%)	41.15 (0.72)	38.71 (0.71)	42.79 (0.72)	40.17 (0.73)	1.00	41.27 (0.85)	38.75 (0.86)	42.44 (0.62)	39.84 (0.61)	1.00
TFM (kg)	33.67 (0.81)	30.28 (0.79)	35.91 (1.03)	31.85 (0.88)	1.00	35.38 (1.18)	31.4 (1.01)	34.48 (0.78)	30.86 (0.71)	1.00
TMM (%)	25.99 (0.43)	26.92 (0.44)	24.94 (0.39)	26.15 (0.42)	1.00	25.93 (0.48)	27.06 (0.51)	25.14 (0.35)	26.23 (0.36)	1.00
WC (cm)	99.79 (1.17)	95.94 (1.16)	100.01 (1.29)	95.6 (1.22)	1.00	100.38 (1.59)	96.47 (1.47)	99.59 (0.98)	95.36 (1)	0.62
Blood pressure										
SBP (mm Hg)	128.44 (1.41)	123.49 (1.41)	127.2 (1.43)	123.08 (1.54)	1.00	126.57 (1.4)	122.03 (1.73)	128.55 (1.36)	124.22 (1.33)	1.00
DBP (mm Hg)	80.68 (0.95)	75.8 (0.91)	79.64 (0.9)	75.62 (0.98)	1.00	78.67 (0.95)	74.55 (1.05)	81.03 (0.86)	76.65 (0.87)	1.00
Biochemical values										
Glucose (mg/dL)	86.88 (2.15)	81.33 (1.73)	84.14 (1.18)	79.84 (1.02)	1.00	84.43 (1.27)	79.55 (1.08)	85.88 (1.7)	81.34 (1.39)	1.00
Insulin (μUI/mL)	10.74 (0.7)	8.54 (0.5)	10.17 (1.06)	8.8 (0.76)	1.00	10.5 (0.97)	8.93(0.73)	10.38 (0.81)	8.67 (0.59)	1.00
APO A-1 (mg/dL)	153.11 (3.13)	152.39 (3.28)	156.9 (3.87)	149.05 (3.35)	0.26	156.15 (5.18)	152.28 (4.23)	154.33 (2.43)	149.82 (2.65)	1.00
APO B (mg/dl)	109.55 (2.91)	104.81 (2.69)	111.2 (3.32)	105.27 (3.02)	1.00	108.01 (3.81)	104.93 (3)	111.44 (2.61)	105.07 (2.64)	0.76
TC (mg/dL)	209.88 (3.44)	201.59 (3.31)	210.22 (4.49)	198.63 (4.51)	1.00	206.57 (4.7)	198.78 (4.28)	211.07 (3.51)	200.75 (3.62)	1.00
HDL-C (mg/dL)	50.82 (1.6)	50.27 (1.29)	52.8 (1.63)	49.16 (1.47)	0.28	52.6 (2.29)	50.32 (1.91)	51.42 (1.17)	49.23 (1.02)	1.00
LDL-C (mg/dL)	132.9 (3.19)	131.83 (3.45)	132.62 (3.91)	129.84 (4.03)	1.00	128.51 (4.24)	128.06 (3.89)	134.48 (3.07)	132.53 (3.49)	1.00
TG (mg/dL)	115.36 (5.87)	98.14 (4.32)	114.01 (5.8)	92.73(4.75)	1.00	117.25 (6.21)	94.56 (5.02)	112.44 (5.22)	95.9 (4.04)	1.00
HOMA	2.26 (0.19)	1.7 (0.13)	2.02 (0.24)	1.68 (0.16)	1.00	2.09 (0.2)	1.74 (0.16)	2.16 (0.21)	1.7 (0.13)	1.00
Dietetic parameters										
Total energy (KJ)	1906.53 (45.07)	1612.31 (47.87)	2047.17 (61.58)	1588.45 (43.83)	0.29	2103 (71.7)	1616.46 (49.1)	1908.88 (43.87)	1577.63 (41.53)	0.51
Proteins (%)	17.69 (0.35)	19.37 (0.49)	17.49 (0.36)	19.03 (0.35)	1.00	17.62 (0.41)	19.36 (0.38)	17.5 (0.31)	19.07 (0.42)	1.00
Carbohydrates (%)	36.17 (0.67)	41.63(1.02)	37.14 (0.77)	41.92 (0.76)	1.00	37.51 (0.98)	42.21 (0.82)	36.5 (0.58)	41.47 (0.85)	1.00
Fats (%)	41.69 (0.63)	36.62 (0.79)	40.63 (0.7)	36.22 (0.74)	1.00	40.47 (0.86)	35.84 (0.83)	41.37 (0.54)	36.83 (0.68)	1.00
Physical activity (METs)	1786.37 (198.55)	1831.38 (196.94)	1884.22 (235.12)	1872.19 (273.45)	1.00	1793.57 (284.49)	1586.88 (166.66)	1901.22 (176.09)	1993.26 (247.5)	1.00

Table 4
Variables monitored before and after the intervention, with respect to genotype (gene CLOCK continuation)

Gene CLOCK	*rs1801260*				
	CC		GG + CG		*P* value*
N = 159	Before	After	Before	After	
Anthropometrics values					
Weight (kg)	82.34 (1.46)†	77.57 (1.34)	83.99 (1.72)	80.38 (1.82)	1.00
BMI (kg/m^2)	30.75 (0.41)	29 (0.36)	30.46 (0.41)	29.07 (0.44)	1.00
TFM (%)	42.97 (0.69)	40.33 (0.68)	40.67 (0.71)	38.26 (0.71)	0.49
TFM (kg)	35.43 (0.97)	31.28 (0.8)	33.93 (0.85)	30.62 (0.85)	1.00
TMM (%)	24.98 (0.39)	26.05 (0.4)	26.07 (0.42)	27.17 (0.42)	0.31
WC (cm)	99.37 (1.14)	94.85 (1.05)	100.32 (1.3)	96.63 (1.31)	1.00
Blood pressure					
SBP (mm Hg)	128.83 (1.49)	124.42 (1.39)	126.46 (1.28)	122.13 (1.63)	1.00
DBP (mm Hg)	81.5 (0.89)	77.35 (0.87)	78.31 (0.92)	74.09 (1.02)	1.00
Biochemical values					
Glucose (mg/dL)	83.2 (1.19)	79.29 (0.97)	87.93(2.13)	82.28 (1.75)	0.54
Insulin (μUI/mL)	10.43 (0.93)	8.82 (0.66)	10.42 (0.75)	8.72 (0.62)	1.00
APO A-1 (mg/dL)	153.18 (2.66)	147.91 (3.01)	157.3 (4.5)	154.26 (3.54)	1.00
APO B (mg/dL)	109.14 (2.89)	104.29 (2.83)	111.06 (3.31)	105.19 (2.74)	1.00
TC (mg/dL)	206.86 (3.86)	197.95 (3.96)	212.11 (4.14)	201.89 (3.84)	1.00
HDL-C (mg/dL)	51.03 (1.28)	48.95 (1.19)	52.92 (2)	50.51 (1.57)	1.00
LDL-C (mg/dL)	130.77 (3.53)	130.56 (3.81)	133.52 (3.5)	130.56 (3.54)	1.00
TG (mg/dL)	113.28 (5.63)	95.67 (4.52)	114.9 (5.7)	94.15 (4.29)	1.00
HOMA	2.09 (0.22)	1.69 (0.14)	2.2 (0.19)	1.75 (0.15)	1.00
Dietetic parameters					
Total energy (kJ)	1951.01 (51.03)	1581.75 (39.03)	2019.07 (61.31)	1605.72 (51.91)	1.00
Proteins (%)	17.31 (0.34)	18.59 (0.39)	17.83 (0.35)	19.83 (0.44)	1.00
Carbohydrates (%)	37.27 (0.72)	41.69 (0.75)	36.46 (0.74)	41.78 (1)	1.00
Fats (%)	40.85 (0.64)	36.26 (0.74)	41.16 (0.7)	36.72 (0.77)	1.00
Physical activity (METs)	1752.7 (192.79)	1785.53 (268.8)	2012.14 (249.13)	1918.16 (181.56)	1.00

Table 5
Variables monitored before and after intervention, with respect to genotype (*FTO* gene)

FTO	rs8050136					rs9939609				
	CC		AA + AC		*P* value*	TT		AA + at		*P* value*
N = 159	Before	After	Before	After		Before	After	Before	After	
Anthropometrics values										
Weight (kg)	83.08 (1.91)†	79.46 (1.91)	83.15 (1.37)	78.72 (1.36)	1.00	83.49 (1.89)	80.17 (1.9)	82.96 (1.37)	78.36 (1.36)	1.00
BMI (kg/m^2)	30.42 (0.52)	29.04 (0.49)	30.72 (0.35)	29.06 (0.34)	1.00	30.54 (0.52)	29.27 (0.49)	30.67 (0.35)	28.94 (0.34)	0.97
TFM (%)	41.42 (0.85)	39.46 (0.84)	42.26 (0.62)	39.41 (0.62)	0.53	41 (0.86)	39.17 (0.85)	42.47 (0.62)	39.56 (0.62)	0.11
TFM (kg)	34.36 (1.06)	31.27 (0.98)	35.04 (0.83)	30.96 (0.73)	1.00	34.15 (1.05)	31.29 (0.96)	35.15 (0.84)	30.95 (0.73)	0.30
TMM (%)	25.7 (0.46)	26.49 (0.47)	25.32 (0.36)	26.56 (0.37)	0.80	26.02 (0.49)	26.76 (0.5)	25.17 (0.35)	26.43 (0.36)	0.40
WC (cm)	99.27 (1.5)	95.6 (1.52)	100.18 (1.04)	95.85 (1)	1.00	99.61 (1.49)	96.23 (1.52)	100.02 (1.05)	95.55 (0.99)	1.00
Blood pressure										
SBP (mm Hg)	127.18 (1.73)	122.72 (1.69)	128.08 (1.23)	123.7 (1.34)	1.00	128.04 (1.69)	123.94 (1.75)	127.67 (1.24)	123.09 (1.32)	1.00
DBP (mm Hg)	79.55 (1.07)	74.12 (1.18)	80.4 (0.81)	76.7 (0.81)	0.52	79.79 (1.05)	74.47 (1.19)	80.29 (0.82)	76.54 (0.81)	0.68
Biochemical values										
Glucose (mg/dL)	84.06 (1.37)	79.96 (1.2)	85.92 (1.58)	81.01 (1.3)	1.00	83.77 (1.37)	79.94 (1.18)	86.07 (1.58)	81.03 (1.31)	1.00
Insulin (μUI/mL)	10.39 (1.34)	9.36 (0.94)	10.45 (0.66)	8.48 (0.5)	1.00	10.45 (1.25)	9.56 (0.93)	10.42 (0.68)	8.34 (0.49)	0.76
APOA1 (mg/dL)	158.73 (5.16)	152.97 (4.81)	153.3 (2.7)	149.74 (2.52)	1.00	157.5 (5.12)	152.97 (4.71)	153.83 (2.71)	149.71 (2.55)	1.00
APOB (mg/dL)	109.61 (3.91)	105.57 (3.46)	110.39 (2.61)	104.76 (2.44)	1.00	110.33 (3.82)	106.47 (3.24)	110.05 (2.64)	104.33 (2.5)	1.00
TC (mg/dL)	211.1 (5.06)	200.21 (4.84)	208.56 (3.39)	199.91 (3.38)	1.00	211.2 (4.94)	201.03 (4.51)	208.49 (3.43)	199.52 (3.48)	1.00
HDL-C (mg/dL)	53.07 (2.14)	50.81 (1.95)	51.31 (1.33)	49.12 (1.08)	1.00	52.38 (2.14)	50.66 (1.91)	51.62 (1.33)	49.17 (1.09)	1.00
LDL-C (mg/dL)	131.76 (4.44)	129.95 (4.28)	132.43 (3.03)	131.23 (3.29)	1.00	131.92 (4.33)	130.99 (4)	132.36 (3.07)	130.76 (3.37)	1.00
TG (mg/dL)	116.31 (7.29)	97.13 (5.51)	113.31 (4.8)	94.61 (3.84)	1.00	116.87 (7.09)	98.38 (5.39)	113.02 (4.86)	94 (3.87)	1.00
HOMA	2.14 (0.32)	1.81 (0.2)	2.13 (0.16)	1.67 (0.12)	1.00	2.14 (0.3)	1.86 (0.2)	2.13 (0.17)	1.64 (0.12)	1.00
Dietetic parameters										
Total energy (kJ)	1872.73 (67.34)	1575.8 (52.15)	2033.29 (47.31)	1600.44 (39.75)	0.48	1883.25 (67)	1582.15 (51.77)	2029.74 (47.57)	1597.81 (40.04)	0.52
Proteins (%)	18.16 (0.45)	18.83 (0.49)	17.26 (0.29)	19.34 (0.37)	0.23	18.1 (0.44)	18.68 (0.48)	17.28 (0.29)	19.43 (0.37)	0.13
Carbohydrates (%)	37.6 (0.93)	42.55 (1.1)	36.55 (0.62)	41.39 (0.73)	1.00	37.62 (0.91)	42.36 (1.07)	36.54 (0.62)	41.45 (0.74)	1.00
Fats (%)	39.15 (0.7)	36.33 (1.07)	41.9 (0.59)	36.5 (0.6)	0.30	39.26 (0.7)	36.51 (1.04)	41.87 (0.59)	36.42 (0.6)	0.25
Physical activity (METs)	1439.15 (175.5)	1793.19 (257.53)	2055.76 (206.61)	1859.72 (213.07)	0.72	1427.66 (172.62)	1803.56 (251.04)	2066.89 (208.19)	1855.36 (215.54)	0.57

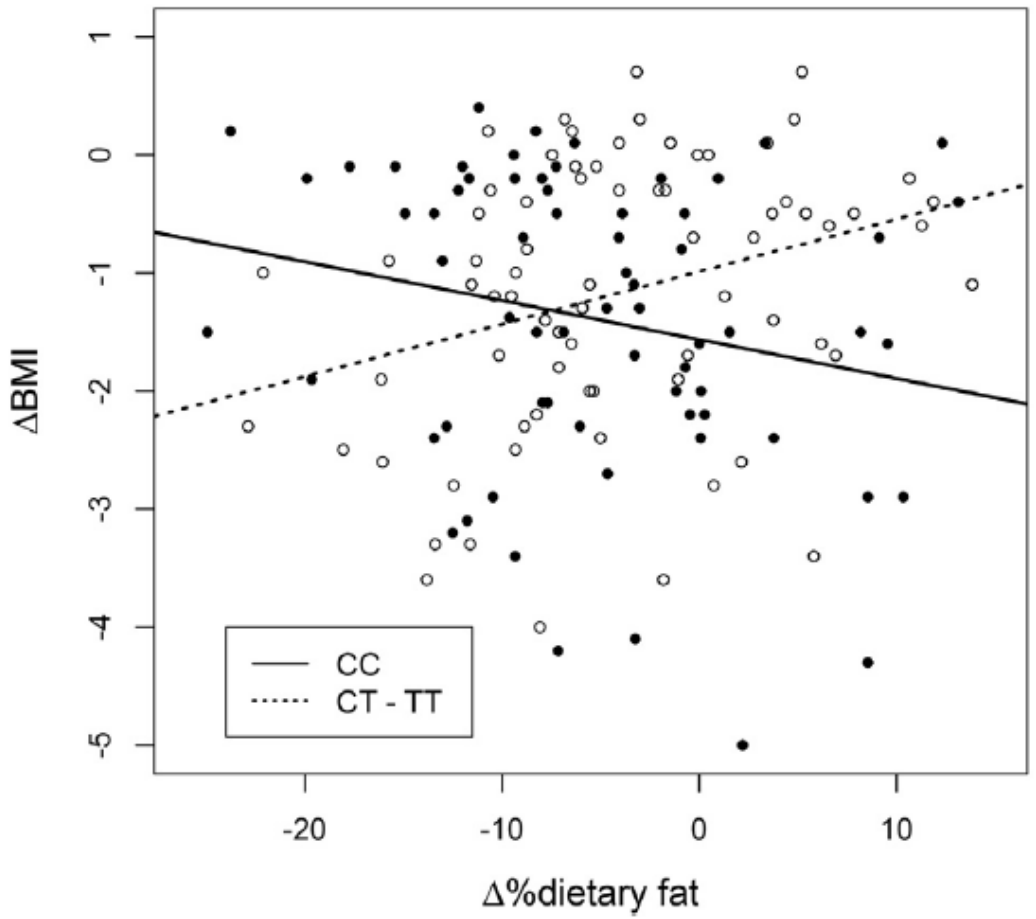


Fig. 1. Influence of the interaction genotype × diet on change in BMI. Participants carrying *CLOCK rs*3749474 (TT + CT) showed a positive association between the change in the percentage intake of dietary fat and the change in BMI (effect size: $\beta = 0.044$; 95% confidence interval [CI], 0.0119–0.0769; $P = 0.008$). Participants homozygous for the wild-type allele (CC) showed a negative, although nonsignificant, association (effect size: $\beta = -0.032$; 95% CI, –0.0694 to 0.036; $P = 0.077$). BMI, body mass index.

Conclusions

- Possession of CLOCK rs3749474 may influence the effect of reducing the percentage **intake of dietary fat** on obesity associated variables. Participants carrying this SNP (TT þ CT; 53% of the studied population) may benefit more fully from dietary fat restriction as a weight loss treatment.
- Neither the interaction genotype change in the percentage intake of carbohydrate nor the genotype change in the percentage intake of energy had any effect on the obesity-associated variables measured.
- This effect was not observed in FTO gene polymorphisms studied

An integrated transcriptomic and epigenomic analysis identifies *CD44* gene as a potential biomarker for weight loss within an energy-restricted program

Mirian Samblas[1] · Maria Luisa Mansego[1,2] · Maria Angeles Zulet[1,2,3] · Fermín I. Milagro[1,2] · J. Alfredo Martinez[1,2,3]

In this context, the present study aimed to evaluate white blood cell transcriptome and methylome before an energy-restricted diet, and to identify novel genes that are able to distinguish individual's responses by using the integrative analysis of mRNA expression and DNA methylation arrays.

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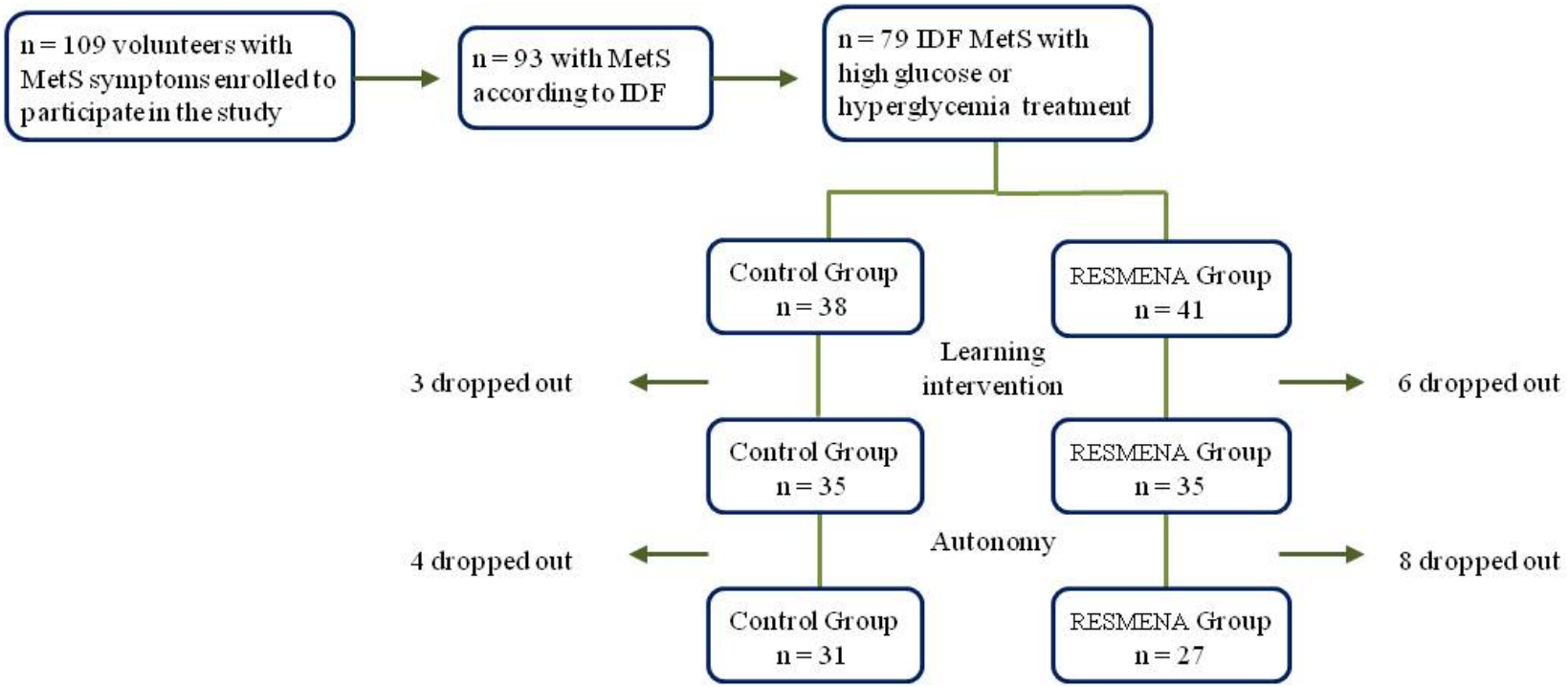
The RESMENA study ("REducción del Síndrome Metabólico en Navarra") is a Spanish, randomized controlled and longitudinal trial (NCT01087086) over a 6-month period that aimed to improve the parameters related with the MetS



Int. J. Mol. Sci. **2013**, *14*

Table 4. Comparison of control and RESMENA dietary records at the endpoint.

	Control	RESMENA	*p*
Energy (kcal/day)	1513 ± 54	1569 ± 77	0.542
Meal Frequency (meals/day)	4.3 ± 0.2	5.8 ± 0.2	<0.001
Proteins (% TCV/day)	16.9 ± 0.4	20.4 ± 0.9	0.001
Lipids (% TCV/day)	40.8 ± 1.5	37.7 ± 1.0	0.108
CHO (% TCV/day)	37.1 ± 1.5	36.9 ± 1.1	0.940
Fiber (% TCHO/day)	11.4 ± 0.8	12.0 ± 0.6	0.573
GL (U/day)	73.4 ± 5.9	70.0 ± 5.5	0.682
EPA+DHA (g/day)	0.30 ± 0.08	0.39 ± 0.17	0.617
TAC (mmol/day)	6.1 ± 0.6	8.5 ± 0.9	0.031
Fruits (kcal/day)	117 ± 21	185 ± 27	0.049

The volunteers were randomly ascribed to one of the two following groups: **the control diet** was based on the American Heart Association (AHA) criteria and the **RESMENA diet** was characterized by a higher meal frequency and a different macronutrient distribution (40% carbohydrates, 30% lipids and 30% proteins). The prescribed diets had the same energy restriction (− 30% of the studied requirements).

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Subjects were classified in two groups depending on their weight loss at the end of the treatment: low responders (LR) when the weight loss was < 8% of the initial weight, and high responders (HR) when the volunteers lost > 8% of initial weight.

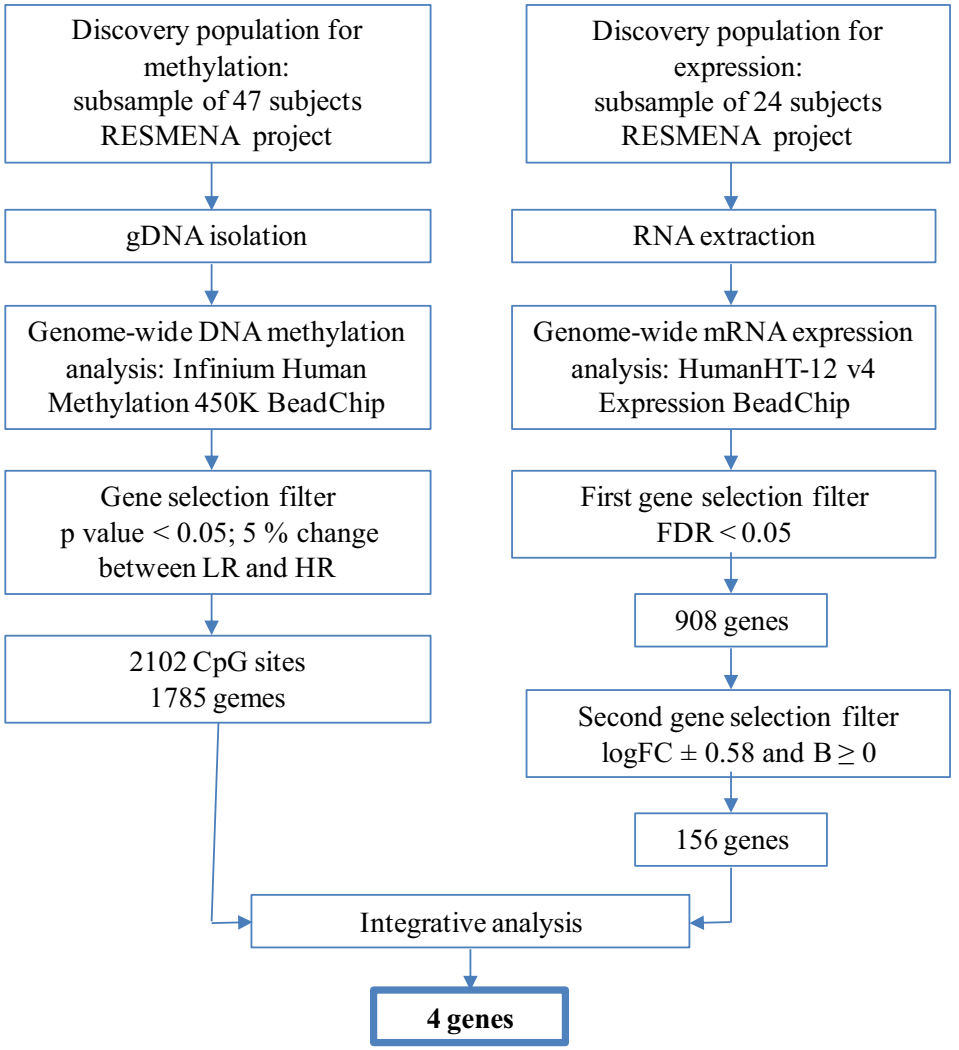


Fig. 1 Schematic diagram of the study design and integrative analysis of methylation and expression arrays

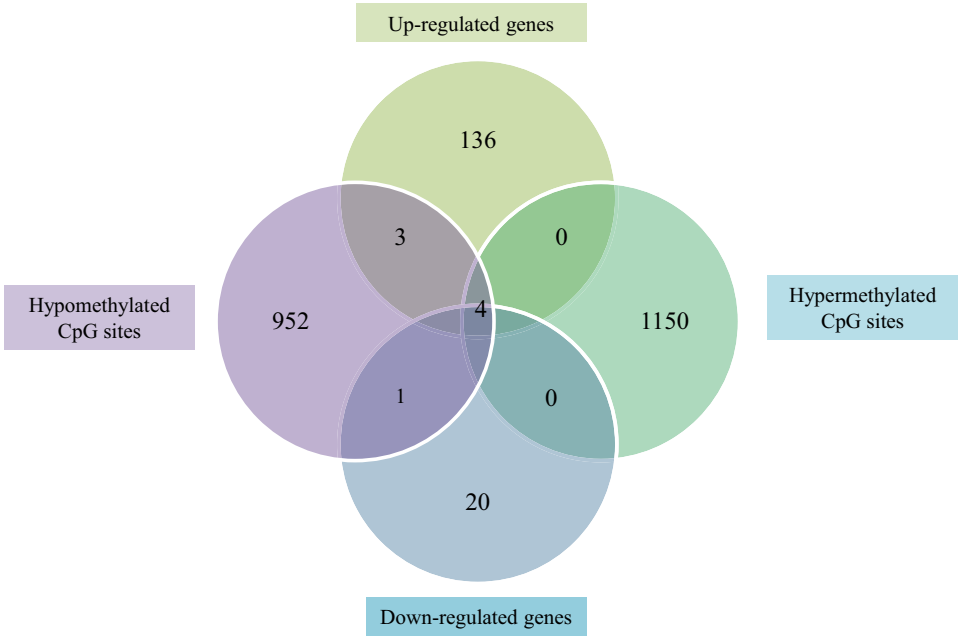


Table 2 Significant differentially expressed and methylated loci between LR and HR

Gene name	Probe set	logFC[a]	*p* value[b]	FDR[c]	LR vs HR
CD44	cg08688659	0.105	0.008	0.999	LR < HR
	ILMN_1803429	0.640	< 0.001	0.028	LR > HR
FBXW5	cg14357259	0.078	0.047	0.999	LR > HR
	ILMN_1701375	− 0.740	< 0.001	0.029	LR < HR
ITPR1	cg18689402	0.159	0.042	0.999	LR < HR
	ILMN_1789505	0.912	< 0.001	0.022	LR > HR
MTSS1	cg03102442	0.055	0.009	0.999	LR < HR
	ILMN_2073289	0.702	< 0.001	0.022	LR > HR

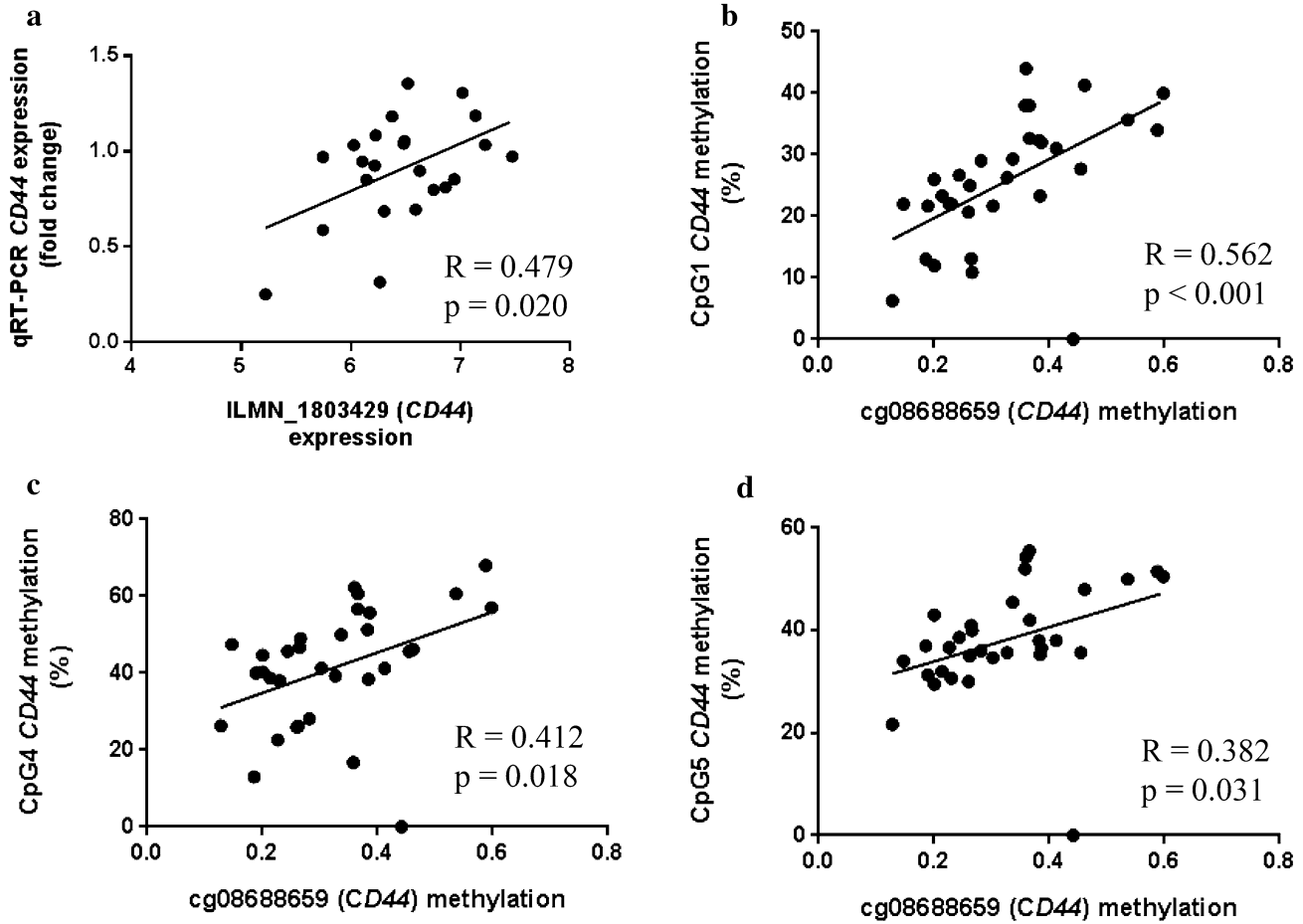


Fig. 3 Positive association between *CD44* expression levels by qRT-PCR and ILMN_1803429 (*CD44*) expression by microarray ($n = 24$) (**a**), and between DNA methylation data of several *CD44* CpG sites located in *CD44* measured by MassARRAY® EpiTYPER™ [CpG1 (**b**) CpG4 (**c**) and CpG5 (**d**)] with the CpG site (cg08688659, corresponding to CpG5) from the methylation array ($n = 32$) (**b**–**d**). Data were analysed by Pearson's test, $p < 0.05$

https://doi.org/10.1007/s00394-018-1750-x

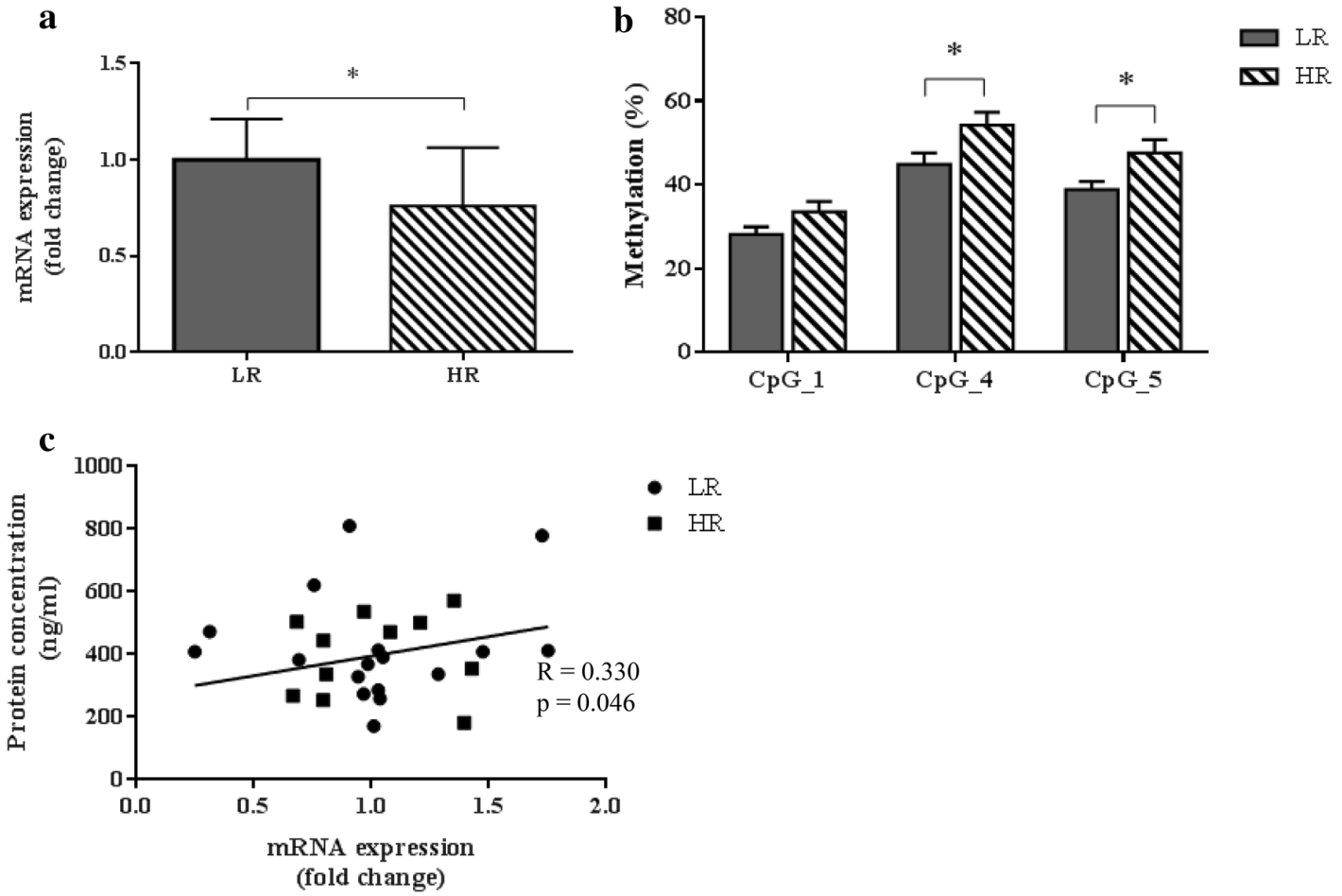
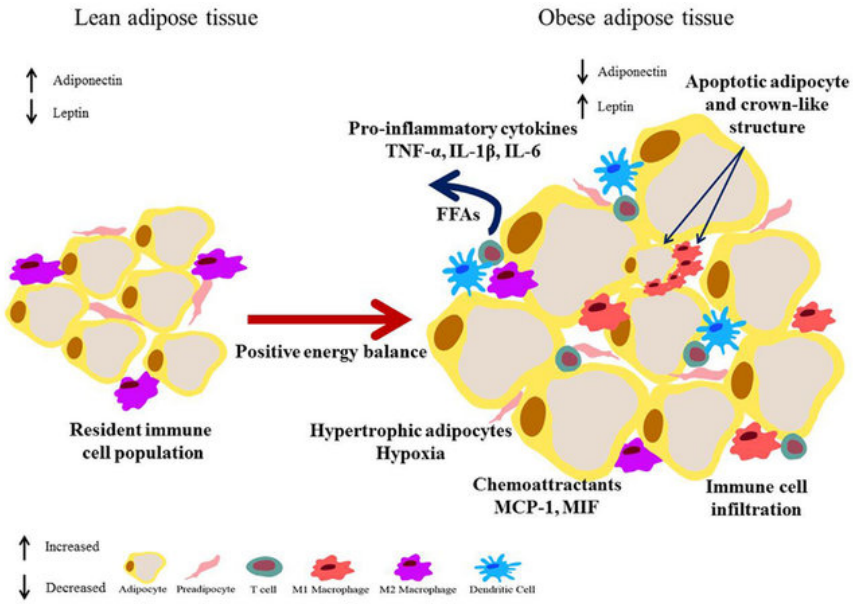


Fig. 4 Differences of *CD44* mRNA expression levels between LR and HR subjects (**a**). Differences of DNA methylation levels of three CpG sites located in *CD44* between LR and HR (**b**). The *CD44* mRNA expression was found to be correlated with protein expression (**c**). Results are expressed as means ± SD (LR, $n = 31$; HR, $n = 16$). Unpaired t Student's test was used to compare LR with HR. *$p < 0.05$. Linear relationship between protein and mRNA expression was tested using Pearson's correlation coefficient (R), $p < 0.05$, one-tailed test



The expression of *CD44* has been related to adipose tissue macrophage accumulation and liver steatosis in morbid obesity, with a dramatic expression decrease as a result of massive weight loss.

In addition, *CD44* is implicated in the development of adipose tissue inflammation and insulin resistance, having been suggested as a biomarker for insulin resistance and a possible therapeutic target for T2D.

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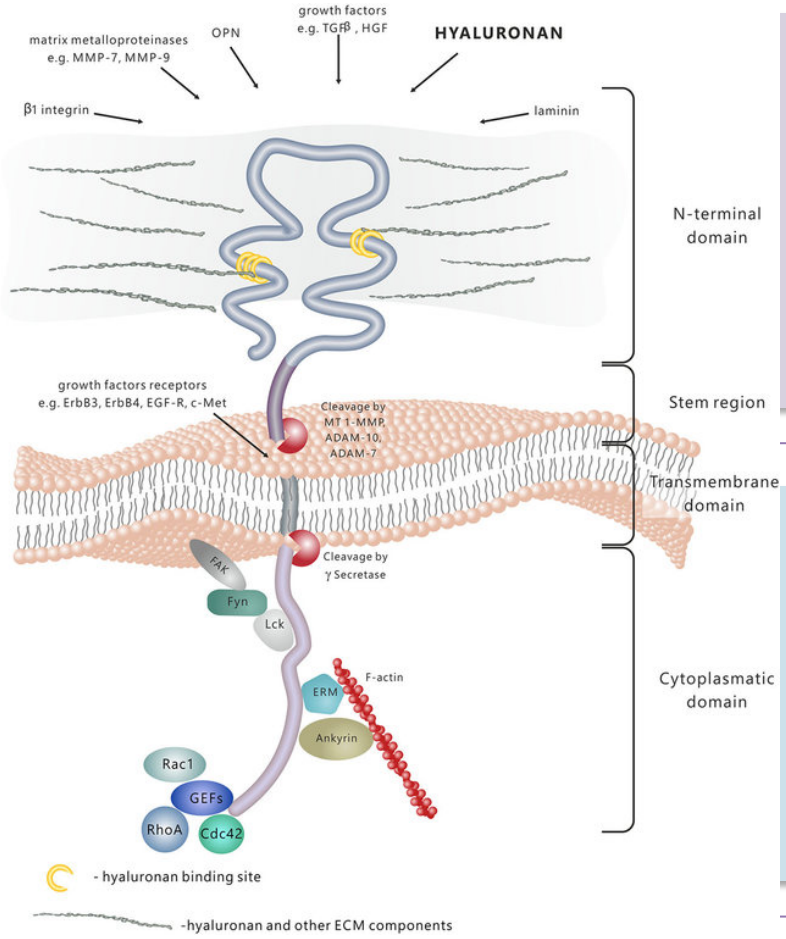
Why WBC for DNA methylation

Recent studies have demonstrated that DNA methylation changes in **blood** reflect DNA methylation changes in **pancreatic islets**, and that DNA methylation levels in leukocytes mirror **sub- cutaneous adipose tissue** methylation pattern, which support the use of circulating cells to study epigenetic alterations in primary tissue

Conclusions



CD44 is an important gene involved in the amplification of the inflammatory process in obese subjects, and the higher expression of the gene before an energy-restricted diet may impair the effectiveness of weight-loss dietary interventions.

DNA methylation has been suggested as a powerful tool for diagnosis and prognosis.

nutrients

MDPI

Article

Interaction between an *ADCY3* Genetic Variant and Two Weight-Lowering Diets Affecting Body Fatness and Body Composition Outcomes Depending on Macronutrient Distribution: A Randomized Trial

Leticia Goni [1,2], Jose Ignacio Riezu-Boj [1,2,3], Fermín I. Milagro [1,2,3,4], Fernando J. Corrales [5,6], Lourdes Ortiz [7], Marta Cuervo [1,2,3,4,*] and J. Alfredo Martínez [1,2,3,4,8]

ADCY3 encodes an **adenylate cyclase** with a wide tissue distribution showing high levels in subcutaneous and visceral adipose tissue, intermediate levels in brain, and rather low levels in pancreas and skeletal muscle in Genotype-Tissue Expression (GTEx) project data. ADCY3 catalyzes the **synthesis of cyclic AMP (cAMP)** from ATP. cAMP is an essential second messenger in intracellular signaling downstream of key metabolic mediators such as **glucagon-like peptide 1, ghrelin and α-melanocyte-stimulating hormone**, and cAMP signaling has been linked to **control of adipose tissue development and function**, as well as insulin secretion in beta cells

nature genetics

BRIEF COMMUNICATION

https://doi.org/10.1038/s41588-017-0022-7

Loss-of-function variants in *ADCY3* increase risk of obesity and type 2 diabetes

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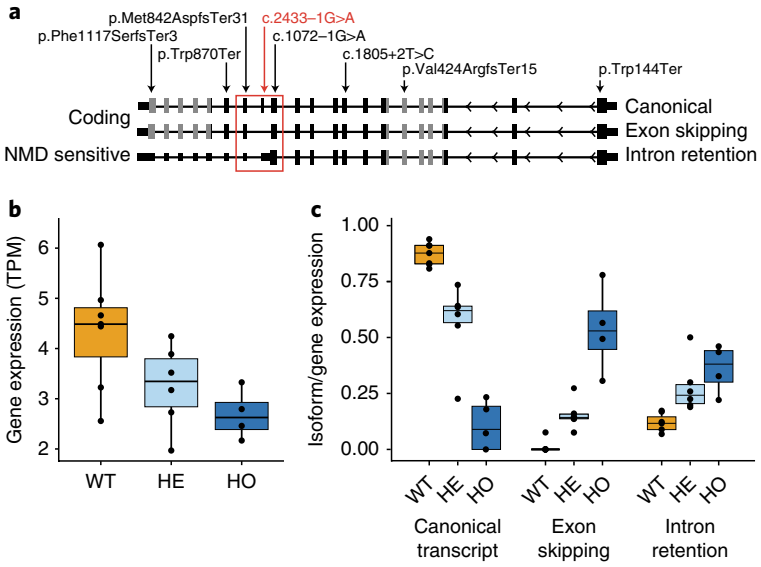


Fig. 1 | *ADCY3* isoforms, observed loss-of-function variants and functional consequences based on RNA sequencing of leukocytes from 17 Greenlandic individuals. a, Schematic illustration of *ADCY3* displaying the three relevant transcript isoforms with their predicted functional

We predicted the isoform with intron retention to be sensitive to nonsense-mediated decay owing to the introduction of a premature stop codon12 (Fig. 1a). This predicted degradation naturally would lead to further reduction of ADCY3 protein levels.

Notably, we found that the overall RNA expression level of ADCY3 was severely decreased in homozygous carriers of the variant (AA), while heterozygous carriers (GA) showed an intermediate expression level (Fig. 1b).

We quantified these alternative splicing events by comparing expression of the three predicted ADCY3 isoforms Both analyses demonstrated that homozygous AA carriers had a severely affected splicing pattern and mainly used intron retention or exon skipping (Fig. 1c)

Table 1 | Association of *ADCY3* c.2433-1G>A with obesity and type 2 diabetes-related traits in Greenlandic cohorts

		Recessive model				Additive model			
Trait	***N***	β_{SD}	SE_{SD}	β	***P***	β_{SD}	SE_{SD}	β	***P***
Type 2 diabetes (cases/ controls)	301/ 2,585			0.50	$\mathbf{7.8 \times 10^{-5}}$			0.081	**0.0014**
BMI (kg/m²)	4,001	1.2	0.36	7.3	**0.00094**	0.18	0.075	1.00	**0.017**
Fat percentage	2,701	1.1	0.35	8.1	**0.0024**	0.18	0.078	1.56	**0.024**
Fasting plasma glucose (mM)	3,622	0.77	0.34	0.76	**0.022**	0.12	0.072	0.11	0.088
2-h plasma glucose (mM)	3,387	0.73	0.35	2.3	**0.035**	0.13	0.073	0.45	0.090

By genotyping this site in two Greenlandic cohorts showed that the variant has an overall minor allele frequency (MAF) of **2.3% in the Greenlandic study** population and a frequency of **3.1% in the Inuit-ancestry** part of the population. Notably, the seven homozygous carriers had **BMI that was 7.3 kg/m2 higher**

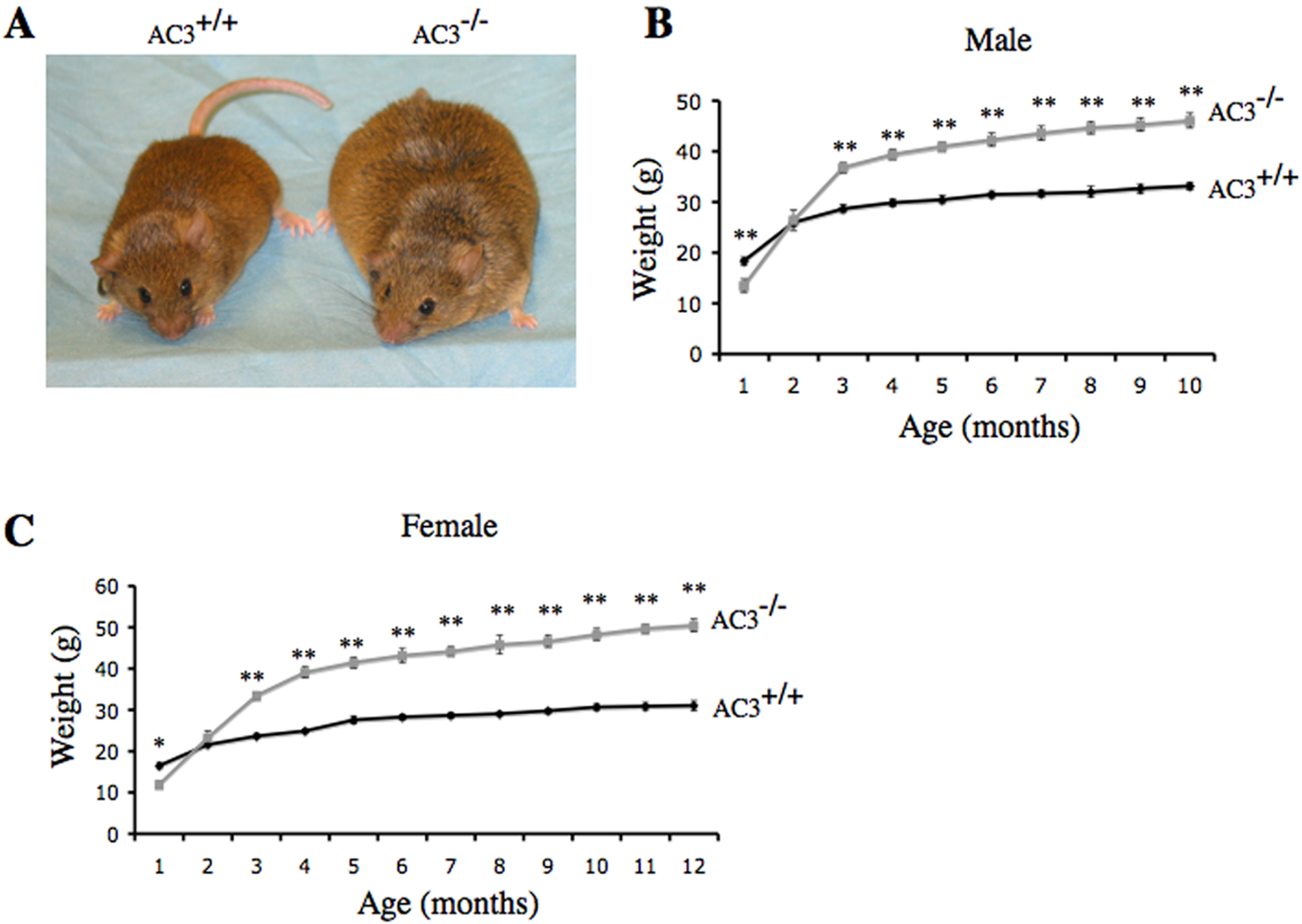
The association with **type 2 diabetes** remained significant after adjustment for BMI, suggesting that it is not simply mediated by increased BMI.

Finally, we also observed nominally significant effects of the variant on **dyslipidemia and insulin resistance**

Adcy3 gain of function protects against diet- induced obesity and Adcy3-knockout mice show

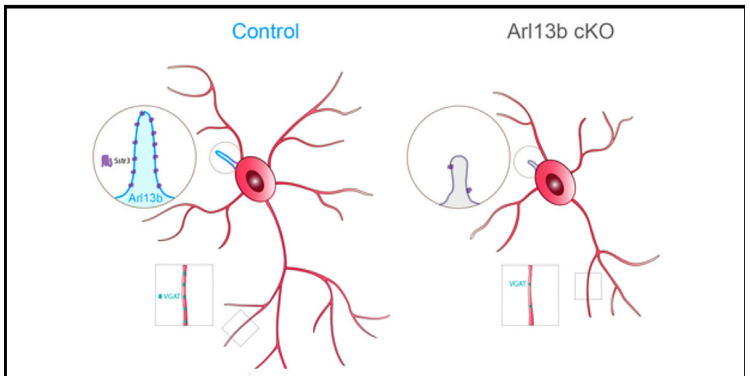
increased fat mass, hyperphagia, depression-like phenotypes and leptin resistance.

Possibly, leptin resistance occurs through disrupted cAMP signaling in primary cilia in hypothalamus, affecting the down- stream signaling and morphology of neurons


A
AC3+/+
AC3-/-
B
Male
Weight (g)
Age (months)
AC3-/-
AC3+/+
C
Female
Weight (g)
Age (months)
AC3-/-
AC3+/+

Developmental Cell

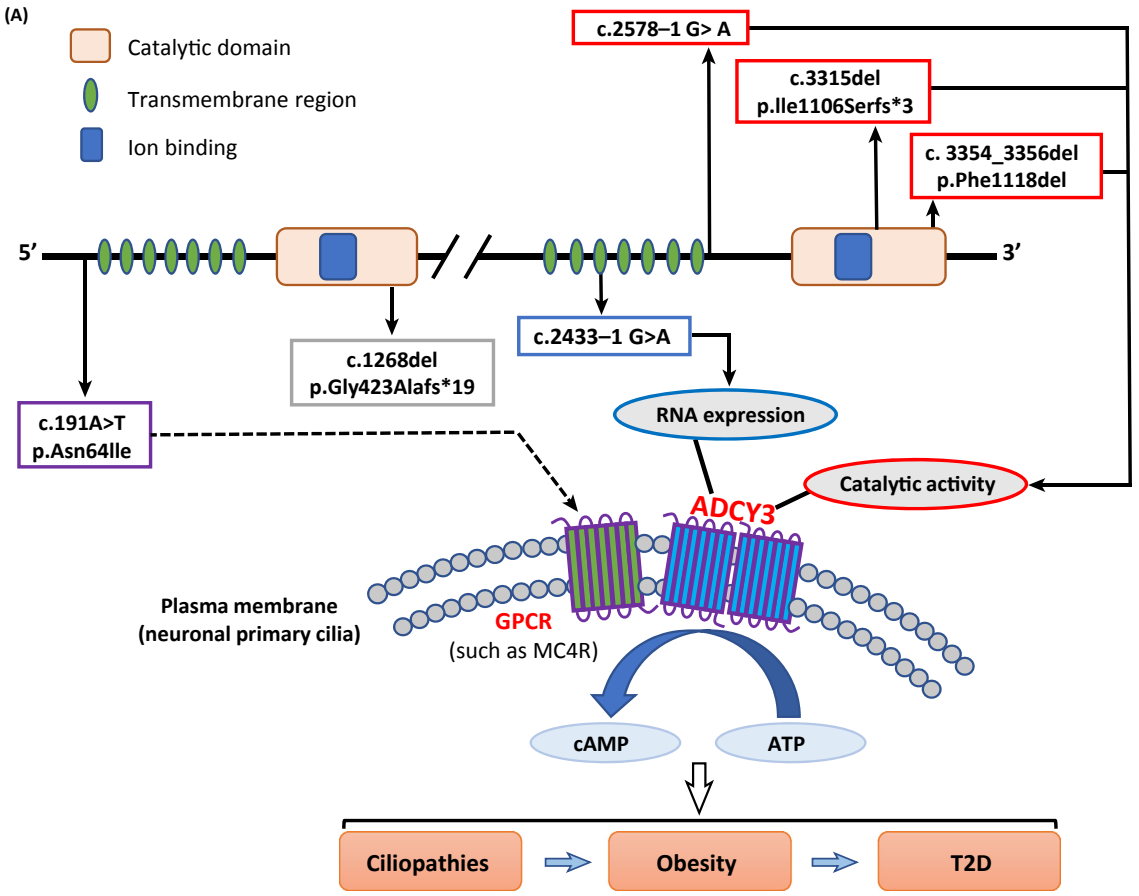
Primary Cilia Signaling Shapes the Development of Interneuronal Connectivity



New ADCY3 Variants Dance in Obesity Etiology

Yan Tian,[1,3] Boqiang Peng,[2,3] and Xianghui Fu[1,*,@]

CellPress REVIEWS



Weight Loss Protocol

Low-fat diet: 60% of total energy from carbohydrates, 18% from protein, and 22% from fat

Moderately-high-protein diet: 40% of total energy from carbohydrates, 30% from protein, and 30% from fat.

Prescribed diets provided a 30% restriction of the total energy expenditure estimated for each subject. No initial prescribed diets had less than **1200 kcal/day**.

Body composition and distribution (fat mass, lean mass, trunk fat, android fat, gynoid fat, and visceral fat) was analyzed by dual energy x-ray absorptiometry **(DEXA) scan**

16 weeks the intervention trial

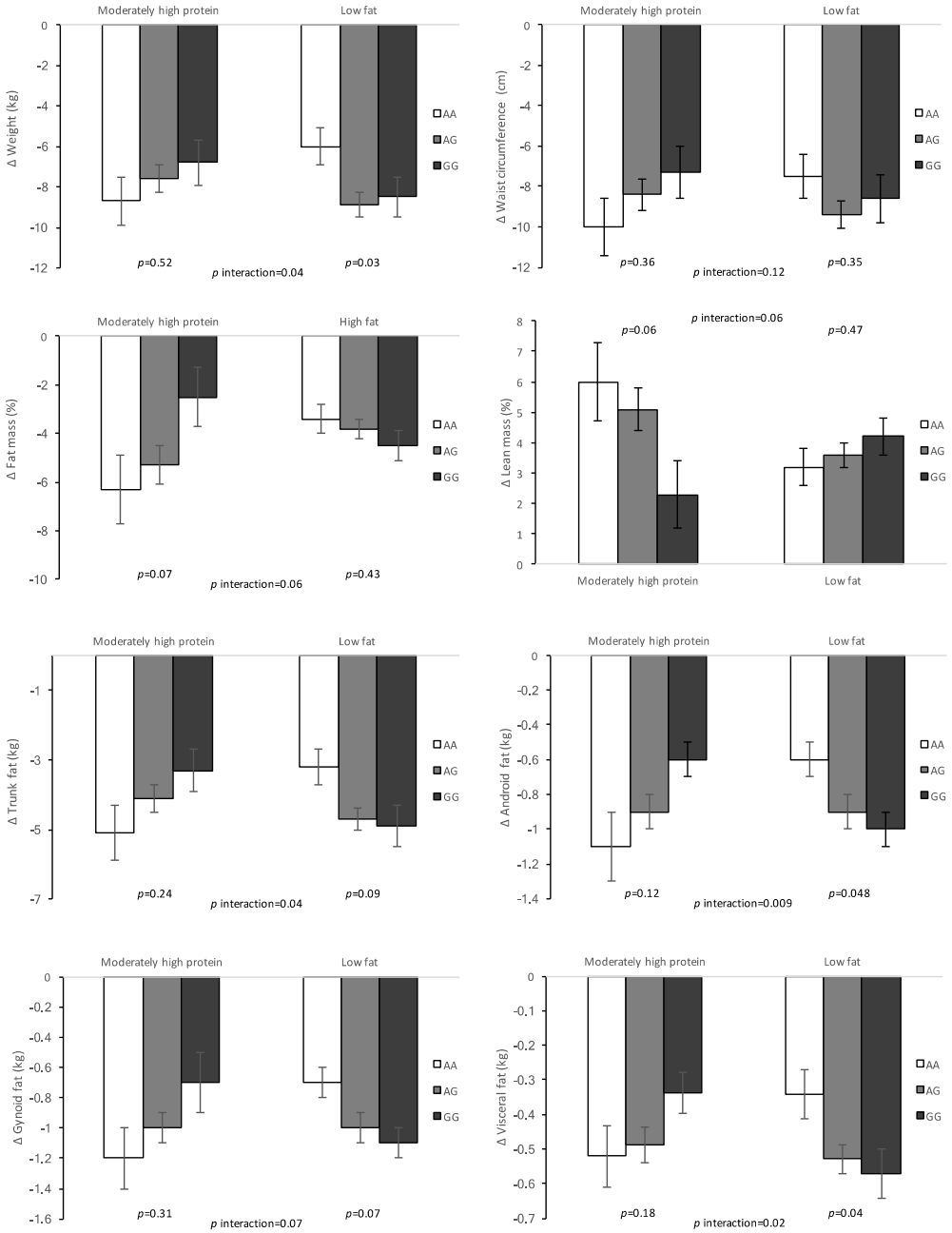


Figure 1. Effect of the *ADCY3* rs10182181 genetic variant on changes in body fatness and composition in response to moderately-high-protein/low-fat diet after 16 weeks of diet intervention (co-dominant model).

Conclusion

The current study reported for the first time a significant gene–diet interaction between *ADCY3* rs10182181 genetic variant and dietary macronutrient composition of low calorie diets on changes in anthropometric and body composition measurements.

Among individuals with the rs10182181 minor G-allele consuming the low-fat diet showed greater effect on changes in trunk fat, android fat and gynoid fat, compared with the moderately-high-protein diet over the 16-week dietary intervention.

ARTICLE

https://doi.org/10.1038/s41467-019-08492-8 OPEN

Genome-wide gene-based analyses of weight loss interventions identify a potential role for *NKX6.3* in metabolism

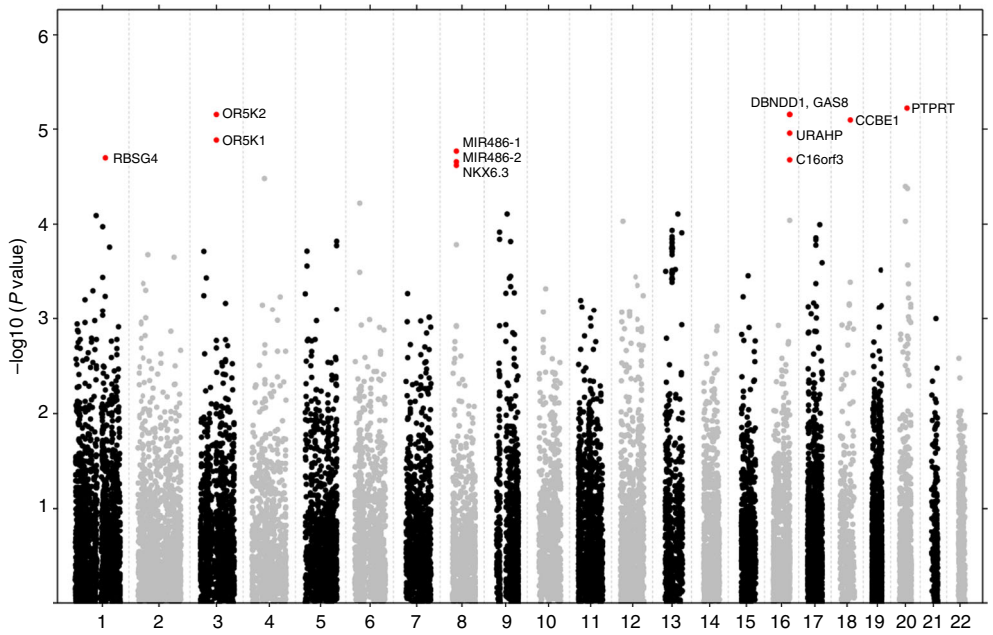
Armand Valsesia[1], Qiao-Ping Wang[2,3], Nele Gheldof[1], Jérôme Carayol[1], Hélène Ruffieux[1,4], Teleri Clark[2], Victoria Shenton[2], Lisa J. Oyston[2], Gregory Lefebvre[1], Sylviane Metairon[1], Christian Chabert[1], Ondine Walter[1], Polina Mironova[1], Paulina Lau[5], Patrick Descombes[1], Nathalie Viguerie[6], Dominique Langin[6,7], Mary-Ellen Harper[8], Arne Astrup[9], Wim H. Saris[10], Robert Dent[4], Greg G. Neely[2] & Jörg Hager[1]

Table 1 Descriptive statistics for the two studies used in the analysis

	OPTIFAST900 ($n = 1166$)	DIOGENES ($n = 789$)	*p*-value
Number of males (%)	237 (26.58%)	310 (33.95%)	-
Age at baseline (years)	46.50 ± 0.32	41.37 ± 0.23	$p < 0.001$
BMI at baseline (kg/m^2)	43.17 ± 0.23	34.53 ± 0.19	$p < 0.001$
Weight at baseline (kg)	121.66 ± 0.76	99.74 ± 0.67	$p < 0.001$
Weight after 5-week LCD (kg)	110.31 ± 0.68	92.20 ± 0.61	$p < 0.001$
Change in weight during LCD (kg)	−11.35 ± 0.11	−7.55 ± 0.11	$p < 0.001$
Change in weight during LCD (%)	−9.28 ± 0.06	−7.51 ± 0.09	$p < 0.001$
Fasting glucose levels (mmol/L) at baseline	5.71 ± 0.05	5.12 ± 0.03	$p < 0.001$
HOMA-IR at baseline	4.16 ± 0.14	3.15 ± 0.10	$p < 0.001$

The *p*-value was obtained from a two-sided *t*-test and assesses differences between the two cohorts
LCD: low caloric diet, HOMA-IR: homeostasis model assessment of insulin resistance

5 weeks the intervention trial



To better extract association signals, they used a **gene-based approach** that enables to integrate individual SNP association signals into a locus-wise signal

Fig. 1 Manhattan plot: Gene-based association results for the discovery cohort (Optifast900), Highlighted genes (in red) correspond to loci with genome-wide significant association signals (FDR < 5%). Source data are provided as a Source Data file

Table 2 Top hits from the gene-based GWA

Gene	Chr	Start	Stop	OPTIFAST900 ($n = 1166$)	DIOGENES ($n = 789$)	Meta-analysis
MIR486-2	8	41497961	41538025	**1.7e-05 (0.043)**	**0.000618 (0.004)**	**1e-06 (1.2e-05)**
MIR486	8	41497958	41538026	**2.2e-05 (0.043)**	**0.000661 (0.004)**	**2e-06 (1.2e-05)**
NKX6-3	8	41483828	41524878	**2.4e-05 (0.043)**	**0.00185 (0.0074)**	**2.6e-05 (0.0001)**
RBSG4	1	167124598	167185042	**2e-05 (0.043)**	**0.011 (0.033)**	**3.8e-05 (0.00011)**
DBNDD1	16	90051272	90106539	**7e-06 (0.035)**	0.0305 (0.073)	**0.0116 (0.02)**
PTPRT	20	40681391	41838557	**6e-06 (0.035)**	0.1728 (0.28)	**0.0062 (0.012)**
GAS8	16	90066036	90131379	**7e-06 (0.035)**	0.1958 (0.28)	0.06909 (0.1)
CCBE1	18	57078170	57384644	**8e-06 (0.035)**	0.2008 (0.28)	0.000346 (0.00083)
C16orf3	16	90075315	90116309	**2.1e-05 (0.043)**	0.2118 (0.28)	0.1049 (0.14)
URAHP	16	90086168	90134191	**1.1e-05 (0.04)**	0.2747 (0.33)	0.1339 (0.16)
OR5K2	3	98196524	98237475	**7e-06 (0.035)**	0.5784 (0.63)	0.1578 (0.17)
OR5K1	3	98168420	98209372	**1.3e-05 (0.04)**	0.8541 (0.85)	0.3117 (0.31)

This table present gene-based association *p*-values for the two cohorts and their meta-analysis. False-discovery rate (FDR) adjusted *p*-value is indicated within parenthesis. For the discovery cohort (Optifast900), the FDR is a genome-wide FDR. For the replication cohort (DIOGENES) and the meta-analysis results, the FDR is adjusted for a two-stage analysis. FDRs less than 5% are shown in bold. Source data are provided as a Source Data file

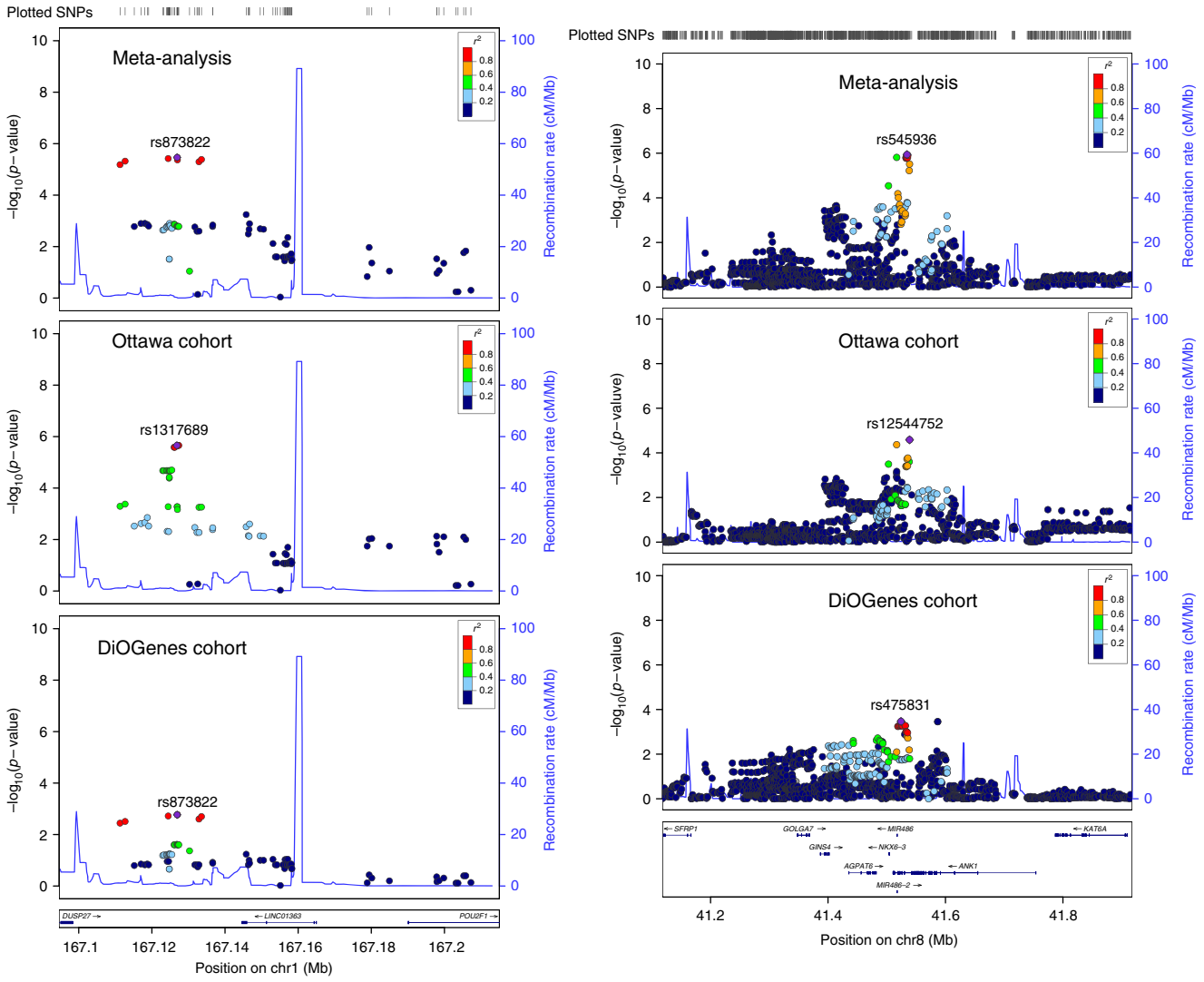


Fig. 2 LocusZoom plots for the RBSG4 (LINC01363) and the MIR486/NKX6.3 loci. Left (right) panel corresponds to RBSG4 (MIR486/NKX6.3/ANK1). Panels from top to bottom correspond to results from the meta-analysis, the Optifast900 cohort and the DiOGenes cohort. Source data are provided as a Source Data file

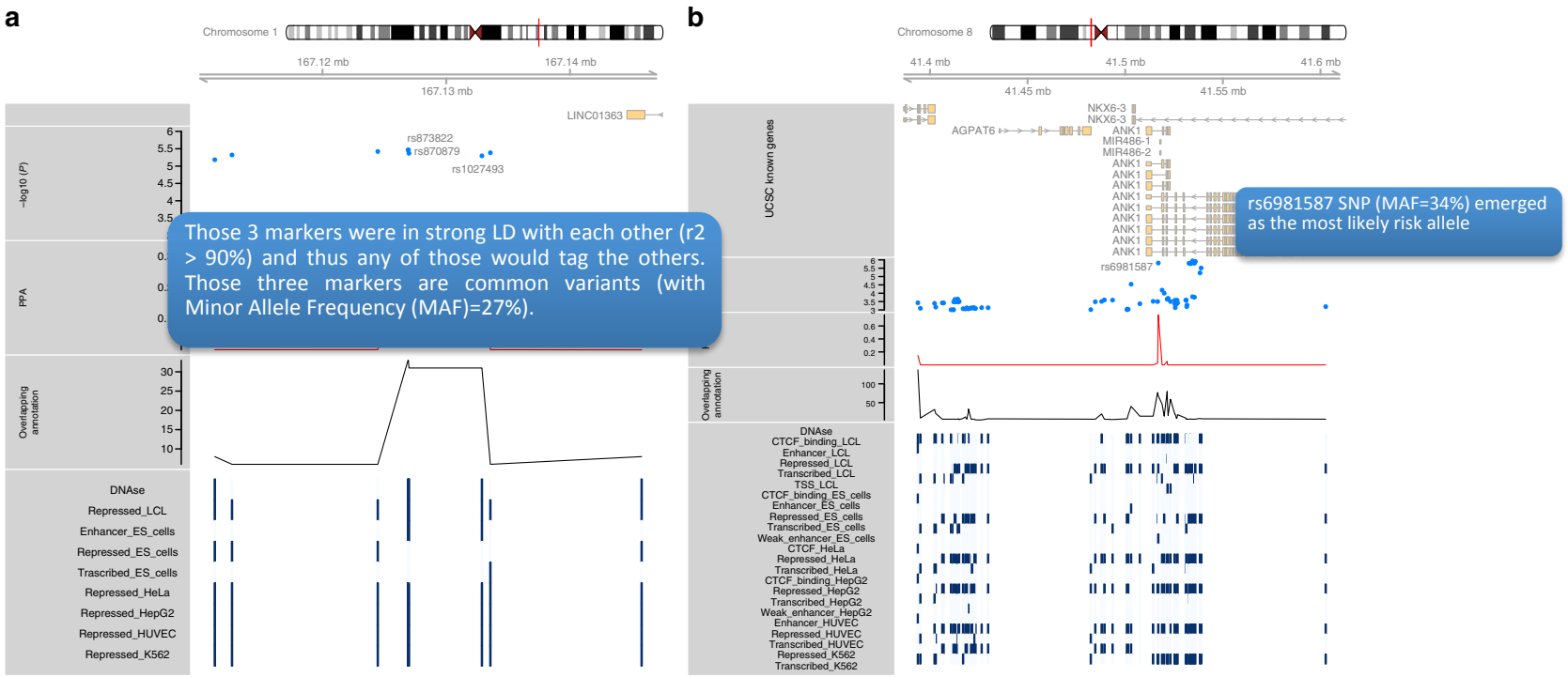


Fig. 3 *Bayesian risk variant inference for SNPs within the RBSG4 and the MIR486/NKX6.3 loci.* Panel (**a**) corresponds to RBSG4 (LINC01363) and panel (**b**) to MIR486/NKX6.3. Tracks from top to bottom display: (1) gene track, (2) −log10 association *p*-values from the meta-analysis, (3) posterior probability of disease association (PPA), (4) the number of overlapping epigenomic annotation at a given marker, (5) the detail of the epigenomic marks that overlap a given variant. The risk inference analyses are limited to variants with p-values smaller than 10^{-3}; all other variants are not displayed. Due to a large number of DNase annotation tracks (>100 for specific variants), these tracks have been reduced to a single one (referred as "DNase"). Source data are provided as a Source Data file

Figure 3 summarizes the results of the Bayesian modeling and presents the overlap between variants and epigenomic annotations.

Table 3 Prioritized SNPs from Bayesian risk variant inference

SNP	Chr	Position	Effect allele	Effect allele frequency	Optifast900	Meta-analysis
rs873822	1	167126910	C	66%	0.13 ± 0.04 ($p = 0.00053$)	0.14 ± 0.03 ($p = 3.43e-6$)
rs870879	1	167126987	G	66%	0.13 ± 0.04 ($p = 0.00068$)	0.13 ± 0.03 ($p = 4.27e-6$)
rs1027493	1	167132882	C	67%	0.13 ± 0.04 ($p = 0.00056$)	0.13 ± 0.03 ($p = 5.06e-6$)
rs6981587	8	41516915	C	77%	−0.19 ± 0.05 ($p = 0.000043$)	−0.17 ± 0.03 ($p = 1.54e-6$)

This table present single-SNP association *p*-values for the two cohorts and their meta-analysis for the top risk variant SNPs. Beta coefficients, with their standard error and *p*-value are provided, as estimated by the linear mixed effect model. Positive betas indicate that the effect allele associates with greater weight loss. Source data are provided as a Source Data file

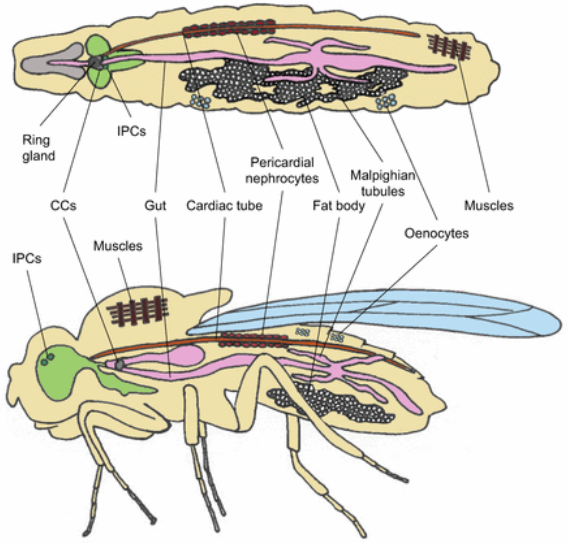
For the four SNPs in the two genomic loci, consistent effect sizes were observed between the two cohorts, as well as similar allele frequencies (Table 3).

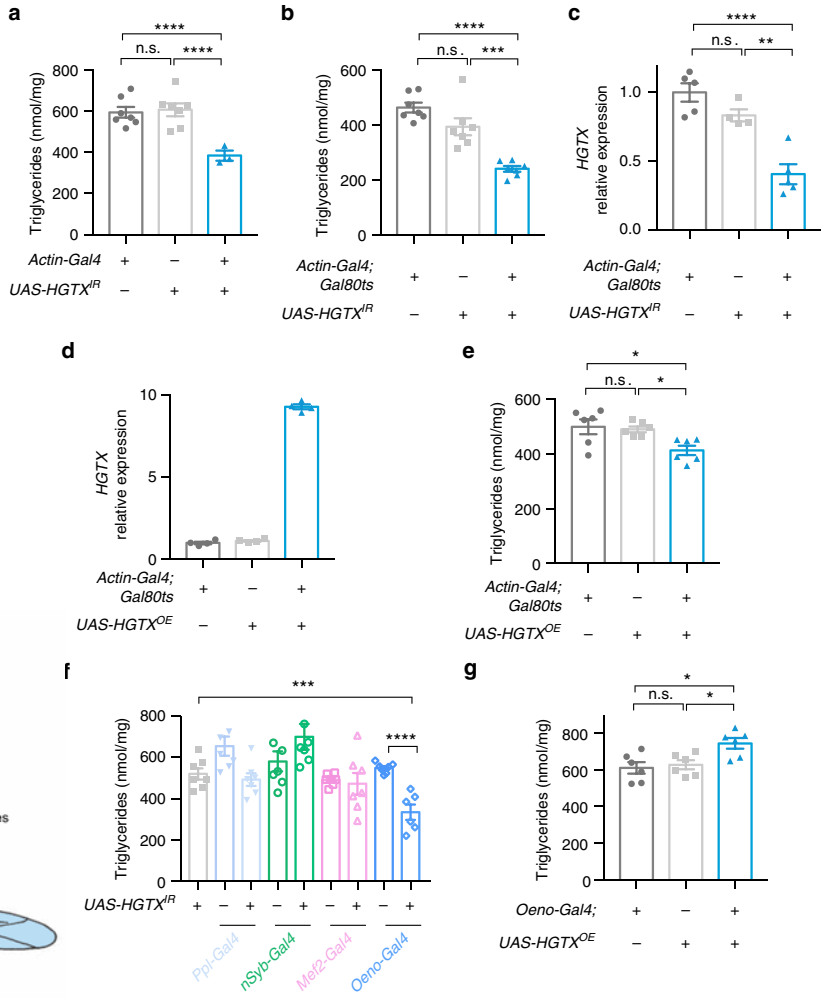
These analyses are useful to identify the most likely regulatory variants. However, they do not enable to infer which gene(s) may be impacted.

Indeed, within the MIR486/NKX6.3 locus (Fig. 3b), there are two other genes (ANK1 and AGPAT6) that are in the vicinity of the top regulatory variant and that would also deserve functional follow-up.

Because RBSG4 and MIR486 are not conserved in the fly, they focused their analysis on Ank/ANK1, HGTX/NKX6-3 and CG3209/AGPAT6 and each gene was targeted using whole body RNAi knockdown (Actin-Gal4).

From the viable HGTX knockdown flies (Actin-Gal4 > UAS-HGTX RNAi), they observed a significant reduction in triglyceride (TAG) level compared to controls (Fig. 4a).





To confirm inducible RNAi knockdown efficiency, they used qPCR and observed approximate 60% reduction in HGTX mRNA levels (Fig. 4c).

HGTX over-expression led to a mild reduction in TAG (Fig. 4e).

To find the specific tissue in which HGTX acts, they carried out tissue specific HGTX RNAi targeting expression in the fat body (Ppl-Gal4), muscle (Mef2-Gal4), brain (nSyb-Gal4) or oenocytes (Oeno-Gal4).

s triglyceride (TAG) in *Drosophila*. **a** Whole-body *HGTX* RNAi decreased TAG level in adult flies, $n = 4$–8 groups, 10 flies each. e of whole-body *HGTX* RNAi flies, $n = 7$ groups, 5 flies each. **c** *HGTX* mRNA was significantly reduced in adult inducible RNAi ach. **d** *HGTX* mRNA overexpression detected by qPCR, $n = 4$ groups, 5 flies each. **e** TAG levels in adult inducible whole-body ı = 6 groups, 5 flies each. **f** TAG levels in tissue-specific *HGTX* RNAi flies, $n = 6$–7 groups, 5 flies each. **g** TAG levels in -expression flies, $n = 6$ groups, 5 flies each. Data are represented as means ± SEM. One-way ANOVA with Bonferroni's ı < 0.05, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$, NS, not significant. Source data are provided as a Source Data file

Conclusions

Oenocytes are hepatocyte-like cells and are important to regulate the fly lipid metabolism. Specifically, these cells regulate whole- body TAG level and have a bidirectional metabolic role. Under starvation conditions, oenocytes accumulate lipid droplets; when food is abundant, they regulate growth, development and feeding behavior. This two-way coupling between body fat and oenocytes is analogous to the liver—adipose axis in mammals.

In conclusion, they performed a weight loss GWA using data from a large clinical practice (the Canadian Optifast900 meal replacement program).

Two loci (RBSG4 and MIR486/NKX6.3) were successfully replicated with data from a controlled trial (DiOGenes).

Several independent studies provided evidence for a biological link between the NKX6-3/MIR486 locus and metabolic disorders including T2D and obesity.