

## **ADDITIONAL INFORMATION ON THE MANUSCRIPT:**

### **Genotype-by-nutrient interactions assessed in a sample of European obese women: a case-only study**

Authors: Santos JL<sup>1,2</sup>, Boutin P<sup>4</sup>, Verdich C<sup>1</sup>, Holst C<sup>1</sup>, Larsen LH<sup>3</sup>, Toubro S<sup>2</sup>, Dina C<sup>4</sup>, Saris WHM<sup>5</sup>, Blaak E<sup>5</sup>, Hoffstedt J<sup>6,7</sup>, Taylor MA<sup>8</sup>, Polak J<sup>9</sup>, Clement K<sup>10</sup>, Langin D<sup>11</sup>, Astrup A<sup>2</sup>, Froguel P<sup>4</sup>, Pedersen O<sup>6</sup>,

† NUGENOB stands for 'Nutrient-Gene interactions in human obesity—implications for dietary guidelines' supported by the European Union (Contract QLK1-CT-2000-00618). See [www.nugenob.org](http://www.nugenob.org)

#### **Contributorship of the authors and the NUGENOB Consortium**

**Project partners:** 1: Institute of Preventive Medicine, Danish Epidemiology Science Centre, Copenhagen University Hospital, Copenhagen, Denmark; 2: Dept. of Human Nutrition, The Royal Veterinary and Agricultural University, Copenhagen, Denmark; 3: Steno Diabetes Centre, Gentofte, Denmark; 4: Department of Human Genetics, Institute of Biology, Institute Pasteur de Lille, France; 5: Dept. of Human Biology, Nutrition and Toxicology Research Centre NUTRIM, Maastricht University, Maastricht, The Netherlands; 6: The Lipid Laboratory, Dept. of Medicine, Karolinska Institute, Huddinge University Hospital, Sweden; 7: The Obesity Unit, Dept. of Medicine, Karolinska Institute, Huddinge University Hospital, Sweden; 8: School of Biomedical

**Project Steering Committee:** Thorkild IA Sørensen (chair)<sup>1</sup>, Arne Astrup<sup>2</sup>, Oluf Pedersen<sup>3</sup>, Philippe Froguel<sup>4</sup>, Wim HM Saris<sup>5</sup>, Peter Arner<sup>6</sup>, Stephan Rössner<sup>7</sup>, Ian Macdonald<sup>8</sup>, Vladimir Stich<sup>9</sup>, Bernard Guy-Grand, replaced 2005 by Jean-Michel Oppert<sup>10</sup>, Dominique Langin<sup>11</sup>, and J Alfredo Martinez<sup>12</sup>. Camilla Verdich<sup>1</sup>,

**Project Co-ordination:** Thorkild IA Sørensen (project co-ordinator)<sup>1</sup>, Camilla Verdich (assistant co-ordinator)<sup>1</sup>, Gabby Hul (co-ordinator of biobank procedures)<sup>5</sup>, Moira A Taylor (co-ordinator of dietary

statistical analysis)<sup>1</sup>, Arne Astrup (dietary intervention)<sup>2</sup>, Philippe Froguel (gene finding)<sup>4</sup>, Oluf Pedersen (DNA sampling, gene analysis and genotyping)<sup>3</sup>.

**Development of standard operational procedures:** Thorkild IA Sørensen (study population, recruitment)<sup>1</sup> Søren Toubro (in-exclusion criteria)<sup>2</sup>, Claus Holst (randomisation)<sup>1</sup>, Moira A Taylor (dietary assessment and intervention)<sup>8</sup>, Gabby Hul (blood sampling and storage)<sup>5</sup>, Søren M Echwald (DNA sampling)<sup>3</sup>, Camilla Verdich

**Clinical investigators group:** Arne Astrup<sup>2</sup>, Martin Petersen<sup>2</sup>, Søren Toubro<sup>2</sup>, Kirsten Bryde Resmussen<sup>2</sup> Wim HM Saris<sup>5</sup>, Ellen Blaak<sup>5</sup>, Gabby Hul<sup>5</sup>, Patrik Löfgren<sup>6</sup>, Ingalena Andersson<sup>7</sup>, Gun Åberg<sup>7</sup>, Ian Macdonald<sup>8</sup>, Moira A Taylor<sup>8</sup>, Sue Bridgewater<sup>8</sup>, Jonathan Webber<sup>8</sup>, Kishor Patel<sup>8</sup>, Vladimir Stich<sup>9</sup>, Blanka

**Dietitian group:** Gitte Wenneberg<sup>2</sup>, Tine B Christensen<sup>2</sup>, Ulla Pedersen<sup>2</sup>, Marja van der Hulst<sup>5</sup>, Brigit Rooyackers<sup>5</sup>, Ingalena Andersson<sup>7</sup>, Gun Åberg<sup>7</sup>, Sue Bridgewater<sup>8</sup>, Moira A Taylor (chair)<sup>8</sup>, Eva Chocenska<sup>9</sup>,

**Molecular genetics group:** Oluf Pedersen<sup>3</sup>, Søren Echwald<sup>3</sup>, Lesli H Larsen<sup>3</sup>, Philippe Froguel<sup>4</sup>, Philippe

**Database management:** Claus Holst<sup>1</sup>, Camilla Verdich<sup>1</sup>.

**Statistical analysis:** Claus Holst<sup>1</sup>, Liselotte Petersen<sup>1</sup>, Thorkild IA Sørensen<sup>1</sup>, Jose Luis Santos<sup>12</sup>.

**Manuscript drafting:** José Luis Santos<sup>12</sup>, J Alfredo Martinez<sup>12</sup> and Thorkild IA Sørensen<sup>1</sup>.

**Manuscript revision for important content:** All co-authors.

**Guarantor:** Thorkild IA Sørensen<sup>1</sup>

**Conflict of interest:** None declared.

## Odds ratios (95% confidence interval) and p-values for interaction between candidate genes and daily fibre intake in the female obese-only sample

Gene	Polymorphism	<sup>1</sup> Model 1			<sup>2</sup> Model 2			<sup>3</sup> Model 3		
		ORI Middle Third	ORI Lower Third	<sup>4,5</sup> P	ORI Middle Third	ORI Lower Third	<sup>4,5</sup> P	ORI Middle Third	ORI Lower Third	<sup>4,5</sup> P
<b>HYPOTHALAMIC REGULATION OF APPETITE</b>										
<i>SLC6A14</i>	+22510 C/G	0.7 (0.4 - 1.1)	1.0 (0.6 - 1.7)	0.18	0.6 (0.3 - 1.0)	1.0 (0.6 - 1.7)	0.06	0.6 (0.4 - 1.0)	1.0 (0.6 - 1.7)	0.06
<i>CART</i>	-3608 T/C	1.1 (0.7 - 1.8)	1.0 (0.6 - 1.7)	0.93	1.2 (0.7 - 2.1)	0.9 (0.5 - 1.7)	0.56	1.1 (0.6 - 1.9)	0.8 (0.5 - 1.5)	0.56
	-1702 C/T	0.8 (0.5 - 1.3)	0.9 (0.5 - 1.49)	0.76	1.0 (0.6 - 1.7)	1.1 (0.6 - 2.0)	0.90	1.0 (0.6 - 1.6)	1.1 (0.6 - 1.8)	0.95
	-175 A/G	1.1 (0.6 - 1.8)	1.0 (0.6 - 1.7)	0.97	1.1 (0.6 - 2.0)	0.8 (0.4 - 1.5)	0.52	1.1 (0.6 - 1.9)	0.8 (0.4 - 1.4)	0.53
	-1336 delA	1.3 (0.8 - 2.3)	1.4 (0.7 - 2.5)	0.51	1.4 (0.8 - 2.6)	1.5 (0.8 - 3.1)	0.42	1.3 (0.7 - 2.4)	1.4 (0.7 - 2.8)	0.56
<i>GHSR</i>	Leu149Leu	0.5 (0.2 - 1.3)	0.6 (0.2 - 1.7)	0.31	0.3 (0.1 - 1.1)	0.4 (0.1 - 1.4)	0.17	0.4 (0.1 - 1.3)	0.6 (0.2 - 2.0)	0.33
<i>GAD2</i>	+83897 T/A	1.0 (0.6 - 1.5)	1.1 (0.7 - 1.8)	0.82	0.9 (0.6 - 1.6)	1.1 (0.6 - 1.9)	0.86	1.0 (0.6 - 1.6)	1.2 (0.7 - 2.0)	0.79
	+61450 C/A	1.1 (0.7 - 1.7)	1.2 (0.7 - 1.8)	0.83	1.1 (0.7 - 1.7)	1.2 (0.7 - 2.0)	0.81	1.1 (0.7 - 1.7)	1.2 (0.7 - 1.9)	0.83
	-243 A/G	1.2 (0.7 - 1.9)	0.1 (0.6 - 1.8)	0.83	1.1 (0.7 - 1.8)	1.0 (0.6 - 1.8)	0.91	1.2 (0.7 - 1.9)	1.1 (0.6 - 1.9)	0.83
<i>GHRL</i>	Leu72Met	0.7 (0.4 - 1.4)	0.9 (0.4 - 1.8)	0.64	0.7 (0.3 - 1.6)	1.0 (0.4 - 2.3)	0.65	0.7 (0.4 - 1.5)	1.0 (0.5 - 2.2)	0.66
<i>MKKS</i>	Arg517Cys	1.5 (0.8 - 2.6)	1.5 (0.8 - 2.8)	0.30	1.7 (0.9 - 3.2)	1.8 (0.9 - 3.5)	0.17	1.6 (0.9 - 3.0)	1.7 (0.9 - 3.2)	0.20
<i>LEPROTL1</i>	-2625 C/T	0.8 (0.4 - 1.6)	0.5 (0.2 - 1.3)	0.41	0.8 (0.4 - 1.9)	0.6 (0.2 - 1.6)	0.61	0.8 (0.4 - 1.8)	0.6 (0.2 - 1.6)	0.60
<i>PCSK1</i>	T690S C/G	0.7 (0.4 - 1.1)	1.2 (0.8 - 1.8)	0.56	1.0 (0.6 - 1.6)	1.2 (0.8 - 2.0)	0.19	1.2 (0.7 - 1.9)	0.9 (0.5 - 1.5)	0.57
<b>EFFICIENCY OF ENERGY EXPENDITURE</b>										
<i>UCP2</i>	-866 G/A	1.4 (1.0 - 2.2)	1.4 (0.8 - 2.2)	0.26	1.4 (0.9 - 2.3)	1.3 (0.8 - 2.3)	0.34	1.5 (0.9 - 2.3)	1.4 (0.8 - 2.4)	0.25
<i>UCP3</i>	-55 C/T	1.4 (0.9 - 2.1)	1.1 (0.7 - 1.79)	0.29	1.4 (0.9 - 2.3)	1.0 (0.6 - 1.8)	0.25	1.3 (0.8 - 2.1)	1.0 (0.6 - 1.6)	0.29
<b>REGULATION OF ADIPOCYTE DIFFERENTIATION AND FUNCTION</b>										
<i>FOXC2</i>	-512 C/T	1.0 (0.6 - 1.9)	0.6 (0.3 - 1.1)	0.12	1.1 (0.5 - 2.2)	0.5 (0.3 - 1.1)	0.08	1.1 (0.6 - 2.1)	0.5 (0.3 - 1.1)	0.07
<i>PPARGC1A</i>	Gly482Ser	0.7 (0.3 - 1.4)	0.5 (0.2 - 1.0)	0.18	0.5 (0.2 - 1.2)	0.4 (0.2 - 0.9)	0.09	0.6 (0.3 - 1.3)	0.4 (0.2 - 1.0)	0.16
	+2962A/G	0.7 (0.4 - 1.1)	0.7 (0.4 - 1.2)	0.25	0.6 (0.3 - 1.0)	0.6 (0.3 - 1.2)	0.17	0.7 (0.4 - 1.2)	0.8 (0.4 - 1.4)	0.38
<i>PPARG2</i>	Pro12Ala	0.9 (0.5 - 1.4)	0.8 (0.5 - 1.4)	0.76	1.1 (0.6 - 1.8)	0.9 (0.5 - 1.8)	0.83	0.9 (0.5 - 1.5)	0.8 (0.4 - 1.4)	0.68

	1431C/T	0.9 (0.5 – 1.4)	0.9 (0.5 – 1.5)	0.83	1.1 (0.6 – 1.8)	1.0 (0.5 – 2.0)	0.98	0.9 (0.5 - 1.5)	0.9 (0.5 - 1.6)	0.88
	-820 C/T	0.8 (0.5 – 1.3)	0.7 (0.4 – 1.3)	0.54	1.0 (0.6 – 1.7)	0.9 (0.5 – 1.7)	0.87	0.9 (0.2 - 1.5)	0.7 (0.4 - 1.3)	0.59
<i>PPARG3</i>	-681 C/G	1.0 (0.6 – 1.5)	0.8 (0.5 – 1.2)	0.43	1.0 (0.6 – 1.6)	0.8 (0.5 – 1.4)	0.61	0.9 (0.6 - 1.5)	0.7 (0.4 - 1.2)	0.43
<i>SREBF1</i>	17 C/G	1.0 (0.6 – 1.5)	0.7 (0.5 – 1.2)	0.38	1.0 (0.6 – 1.6)	0.7 (0.4 – 1.3)	0.44	1.0 (0.6 - 1.6)	0.7 (0.4 - 1.2)	0.40
<i>WAC</i>	-829 A/G	0.8 (0.5 – 1.3)	0.9 (0.5 – 1.6)	0.59	0.9 (0.5 – 1.5)	0.8 (0.4 – 1.6)	0.85	1.0 (0.6 - 1.7)	0.9 (0.5 - 1.7)	0.96

## REGULATION OF LIPID AND GLUCOSE METABOLISM

<i>HSD11B1</i>	-2490 G/A	0.8 (0.4 – 1.6)	0.7 (0.4 – 1.5)	0.71	0.6 (0.3 – 1.3)	0.6 (0.3 – 1.4)	0.34	0.6 (0.3 - 1.3)	0.7 (0.3 - 1.5)	0.43
<i>LIPC</i>	Ans215Ser	1.0 (0.7 – 1.6)	1.0 (0.6 – 1.6)	0.96	1.3 (0.8 – 2.0)	1.3 (0.8 – 2.2)	0.51	1.2 (0.8 - 1.9)	1.2 (0.7 - 2.0)	0.72
	-514 C/T	0.6 (0.3 – 0.9)	0.5 (0.3 – 0.9)	0.01	0.5 (0.3 – 0.9)	0.4 (0.3 – 0.8)	0.01	0.5 (0.3 - 0.9)	0.5 (0.3 - 0.8)	0.01
<i>IGF2</i>	1926 C/G	1.1 (0.7 – 1.7)	0.8 (0.5 – 1.2)	0.31	1.0 (0.6 – 1.7)	0.8 (0.4 – 1.3)	0.44	1.0 (0.6 - 1.6)	0.7 (0.4 - 1.2)	0.35
	Apal A/G	1.0 (0.7 – 1.6)	0.7 (0.4 – 1.1)	0.18	1.0 (0.6 – 1.6)	0.6 (0.4 – 1.1)	0.15	1.0 (0.6 - 1.5)	0.6 (0.4 - 1.0)	0.12
	-6815 A/T	0.9 (0.6 – 1.4)	0.8 (0.5 – 1.2)	0.50	0.9 (0.5 – 1.4)	0.8 (0.4 – 1.3)	0.61	0.8 (0.5 - 1.4)	0.7 (0.4 - 1.3)	0.54
<i>KCNJ11</i>	Glu23Lys	1.2 (0.8 – 1.9)	1.0 (0.6 – 1.7)	0.64	1.2 (0.8 – 2.0)	1.2 (0.7 – 2.0)	0.67	1.3 (0.8 - 2.0)	1.2 (0.7 - 2.0)	0.63
<i>ENPP1</i>	IVS20 del T-11	1.0 (0.7 – 1.6)	1.3 (0.8 - 2.1)	0.46	1.0 (0.6 – 1.6)	1.2 (0.7 – 2.0)	0.79	1.1 (0.7 - 1.8)	1.4 (0.8 - 2.3)	0.51
	Lys121Gln	0.9 (0.5 – 1.4)	0.9 (0.5 – 1.5)	0.81	0.8 (0.5 – 1.4)	0.9 (0.5 – 1.6)	0.80	0.9 (0.5 - 1.4)	0.9 (0.5 - 1.6)	0.82
	1044 A/G	1.0 (0.7 – 1.6)	1.0 (0.6 – 1.7)	0.99	0.9 (0.6 – 1.5)	0.9 (0.5 – 1.6)	0.95	1.0 (0.6 - 1.6)	1.1 (0.6 - 1.8)	0.97

## PRODUCTION OF ADIPOCYTOKINES

<i>ADIPOQ</i>	-11377 C/G	1.0 (0.7 – 1.5)	0.9 (0.6 – 1.5)	0.97	1.2 (0.7 – 1.9)	1.1 (0.6 – 1.9)	0.83	1.1 (0.7 - 1.7)	1.0 (0.6 - 1.7)	0.94
	+45 T/G	0.9 (0.5 – 1.4)	0.7 (0.4 – 1.3)	0.55	0.6 (0.4 – 1.1)	0.6 (0.3 – 1.1)	0.14	0.7 (0.4 - 1.1)	0.6 (0.3 - 1.1)	0.19
	+276 T/G	0.6 (0.3 – 1.2)	1.0 (0.5 – 2.2)	0.21	0.4 (0.2 – 0.9)	0.6 (0.2 – 1.4)	0.07	0.5 (0.2 - 1.0)	0.7 (0.3 - 1.6)	0.13
	-11391 G/A	1.7 (0.9 – 3.1)	1.9 (1.0 – 3.8)	0.13	1.8 (0.9 – 3.7)	2.1 (0.9 – 4.7)	0.17	1.7 (0.8 - 3.4)	2.0 (0.9 - 4.2)	0.20
<i>CD36</i>	-178 A/C	0.9 0.5 – 1.69	0.9 (0.5 – 1.6)	0.94	0.8 (0.4 – 1.5)	0.9 (0.4 – 1.9)	0.77	0.7 (0.4 - 1.3)	0.8 (0.4 - 1.6)	0.60
<i>IL6</i>	-174 G/C	1.1 (0.7 – 1.7)	1.6 (1.0 – 2.7)	0.18	0.9 (0.6 - 1.5)	1.1 (0.6 – 2.0)	0.79	1.1 (0.6 - 1.7)	1.4 (0.8 - 2.4)	0.56
<i>TNF<math>\alpha</math></i>	-308 G/A	0.8 (0.5 – 1.3)	0.8 (0.5 – 1.3)	0.54	0.8 (0.5 – 1.3)	0.8 (0.5 – 1.5)	0.68	0.9 (0.5 - 1.4)	0.9 (0.5 - 1.6)	0.85
<i>SERPINE1</i>	-675 insG	1.5 (0.9 – 2.5)	1.1 (0.7 – 2.0)	0.29	1.4 (0.8 – 2.5)	1.2 (0.6 – 2.2)	0.48	1.3 (0.8 - 2.4)	1.0 (0.6 - 1.9)	0.54

1.- Model 1: odds ratios adjusted by binary variables indicating the centre of study.

2.- Model 2: odds ratios adjusted by age, centre of study, smoking status, physical activity score and energy intake.

3.- Model 3: odds ratios adjusted by age, centre of study, smoking status, physical activity score and fat-free mass.

4.- P-values correspond to the null hypothesis of no interaction considering the joint gene-nutrient effects for the two binary variables defined for the nutrient variable. The reference category is the wild-type homozygous genotype and the upper tertile of fibre intake.

5.- P-values are not corrected for multiple comparisons. Some statistical tests are not independent since there are genetic polymorphisms located in the same gene that may exhibit linkage disequilibrium.

## Odds ratios (95% confidence interval) and p-values for interaction between candidate genes and P:S ratio in the female obese-only sample

Gene	Polymorphism	<sup>1</sup> Model 1			<sup>2</sup> Model 2			<sup>3</sup> Model 3		
		ORi Middle Third	ORi Lower Third	<sup>4, 5</sup> P	ORi Middle Third	ORi Lower Third	<sup>4, 5</sup> P	ORi Middle Third	ORi Lower Third	<sup>4, 5</sup> P
<b>HYPOTHALAMIC REGULATION OF APPETITE</b>										
<i>SLC6A14</i>	+22510 C/G	0.8 (0.4 - 1.7)	1.0 (0.4 - 2.5)	0.73	0.8 (0.4 - 1.7)	0.9 (0.4 - 2.5)	0.88	1.1 (0.7 - 1.7)	0.8 (0.5 - 1.3)	0.50
<i>CART</i>	-3608 T/C	0.7 (0.4 - 1.3)	0.6 (0.3 - 1.0)	0.12	0.8 (0.4 - 1.4)	0.6 (0.4 - 1.1)	0.26	0.8 (0.5 - 1.4)	0.6 (0.4 - 1.1)	0.30
	-1702 C/T	1.0 (0.6 - 1.6)	1.4 (0.9 - 2.2)	0.32	0.9 (0.5 - 1.4)	1.3 (0.8 - 2.1)	0.31	0.9 (0.5 - 1.4)	1.3 (0.8 - 2.1)	0.33
	-175 A/G	0.7 (0.4 - 1.2)	0.6 (0.3 - 0.9)	0.10	0.8 (0.4 - 1.3)	0.6 (0.3 - 1.0)	0.14	0.8 (0.4 - 1.3)	0.6 (0.3 - 1.0)	0.15
	-1336 delA	0.7 (0.4 - 1.3)	1.1 (0.6 - 2.0)	0.29	0.6 (0.3 - 1.2)	1.0 (0.5 - 1.7)	0.34	0.7 (0.4 - 1.2)	1.0 (0.6 - 1.9)	0.34
<i>GHSR</i>	Leu149Leu	1.3 (0.4 - 3.8)	1.8 (0.6 - 5.2)	0.55	0.9 (0.2 - 3.0)	1.6 (0.5 - 4.9)	0.58	0.9 (0.3 - 3.1)	1.6 (0.5 - 5.2)	0.56
<i>GAD2</i>	+83897 T/A	0.9 (0.5 - 1.4)	1.1 (0.7 - 1.8)	0.57	0.8 (0.5 - 1.3)	1.3 (0.7 - 2.0)	0.20	0.8 (0.5 - 1.3)	1.2 (0.7 - 2.0)	0.20
	+61450 C/A	0.8 (0.5 - 1.2)	1.0 (0.6 - 1.5)	0.59	0.7 (0.5 - 1.1)	0.9 (0.6 - 1.4)	0.34	0.7 (0.5 - 1.1)	0.9 (0.6 - 1.5)	0.35
	-243 A/G	0.9 (0.5 - 1.4)	1.0 (0.6 - 1.6)	0.82	0.8 (0.5 - 1.3)	1.0 (0.6 - 1.7)	0.59	0.8 (0.5 - 1.3)	1.0 (0.6 - 1.7)	0.60
<i>GHRL</i>	Leu72Met	0.8 (0.4 - 1.6)	0.6 (0.3 - 1.3)	0.45	0.8 (0.4 - 1.6)	0.7 (0.3 - 1.5)	0.57	0.8 (0.4 - 1.6)	0.7 (0.3 - 1.5)	0.60
<i>MKKS</i>	Arg517Cys	1.1 (0.7 - 2.0)	1.1 (0.6 - 1.9)	0.90	1.2 (0.7 - 2.2)	1.3 (0.7 - 2.3)	0.68	1.2 (0.7 - 2.1)	1.3 (0.7 - 2.4)	0.68
<i>LEPROTL1</i>	-2625 C/T	1.0 (0.6 - 1.6)	1.2 (0.8 - 2.0)	0.64	1.0 (0.6 - 1.6)	1.3 (0.8 - 2.2)	0.50	1.2 (0.6 - 2.7)	1.1 (0.4 - 2.6)	0.87
<i>PCSK1</i>	T690S C/G	1.1 (0.7 - 1.7)	1.1 (0.7 - 1.8)	0.43	1.0 (0.6 - 1.6)	1.1 (0.7 - 1.7)	0.96	1.0 (0.6 - 1.6)	1.0 (0.6 - 1.7)	0.99
<b>EFFICIENCY OF ENERGY EXPENDITURE</b>										
<i>UCP2</i>	-866 G/A	1.0 (0.4 - 1.6)	0.9 (0.6 - 1.4)	0.77	1.2 (0.7 - 1.9)	1.0 (0.6 - 1.6)	0.71	1.2 (0.7 - 1.9)	1.0 (0.6 - 1.6)	0.71
<i>UCP3</i>	-55 C/T	1.2 (0.8 - 1.9)	1.2 (0.8 - 1.8)	0.62	1.3 (0.8 - 2.1)	1.4 (0.9 - 2.3)	0.35	1.3 (0.8 - 2.1)	1.4 (0.9 - 2.3)	0.33
<b>REGULATION OF ADIPOCYTE DIFFERENTIATION AND FUNCTION</b>										
<i>FOXC2</i>	-512 C/T	1.4 (0.7 - 2.5)	1.1 (0.6 - 2.0)	0.60	1.3 (0.7 - 2.5)	1.3 (0.7 - 2.4)	0.63	1.4 (0.7 - 2.6)	1.3 (0.7 - 2.4)	0.58
<i>PPARGC1A</i>	Gly482Ser	0.6 (0.3 - 1.3)	0.7 (0.3 - 1.5)	0.45	0.7 (0.3 - 1.5)	0.8 (0.4 - 1.9)	0.70	0.7 (0.3 - 1.5)	0.8 (0.4 - 1.9)	0.70
	+2962A/G	1.0 (0.6 - 1.7)	0.9 (0.6 - 1.5)	0.91	1.1 (0.7 - 1.9)	1.1 (0.6 - 1.9)	0.91	1.1 (0.6 - 1.8)	1.0 (0.6 - 1.8)	0.95
<i>PPARG2</i>	Pro12Ala	1.0 (0.6 - 1.7)	1.0 (0.6 - 1.8)	0.99	1.1 (0.6 - 1.9)	1.3 (0.7 - 2.2)	0.71	1.1 (0.6 - 1.9)	1.2 (0.7 - 2.2)	0.79

	1431C/T	1.4 (0.9 – 2.3)	1.0 (0.6 – 1.7)	0.25	1.5 (0.9 – 2.6)	1.2 (0.7 – 2.1)	0.32	1.5 (0.9 - 2.6)	1.1 (0.6 - 2.0)	0.28
	-820 C/T	0.9 (0.6 – 1.6)	1.1 (0.6 – 1.8)	0.91	1.0 (0.6 – 1.8)	1.3 (0.7 – 2.3)	0.63	1.0 (0.6 - 1.7)	1.2 (0.7 - 2.2)	0.72
<i>PPARG3</i>	-681 C/G	1.3 (0.8 – 2.0)	1.2 (0.8 – 1.9)	0.50	1.3 (0.8 – 2.1)	1.3 (0.8 – 2.2)	0.41	1.3 (0.8 - 2.1)	1.3 (0.8 - 2.1)	0.42
<i>SREBF1</i>	17 C/G	1.5 (0.9 – 2.2)	1.2 (0.8 – 1.9)	0.31	1.2 (0.8 – 1.9)	1.0 (0.6 – 1.7)	0.66	1.2 (0.8 - 2.0)	1.1 (0.7 - 1.7)	0.68
<i>WAC</i>	-829 A/G	1.5 (0.9 – 2.6)	1.0 (0.6 – 1.7)	0.19	1.8 (1.0 – 3.2)	1.0 (0.5 – 1.7)	0.08	1.8 (1.0 - 3.1)	1.0 (0.5 - 1.7)	0.09

## REGULATION OF LIPID AND GLUCOSE METABOLISM

<i>HSD11B1</i>	-2490 G/A	0.7 (0.4 – 1.4)	0.9 (0.5 – 1.8)	0.60	0.6 (0.3 – 1.3)	0.7 (0.3 – 1.4)	0.36	0.6 (0.3 - 1.3)	0.7 (0.3 - 1.4)	0.36
<i>LIPC</i>	Ans215Ser	1.2 (0.8 – 1.9)	0.9 (0.6 – 1.5)	0.47	1.0 (0.6 – 1.5)	0.9 (0.5 – 1.4)	0.86	1.0 (0.6 - 1.6)	0.9 (0.5 - 1.4)	0.86
	-514 C/T	1.1 (0.7 – 1.7)	1.2 (0.8 – 1.9)	0.74	1.1 (0.7 – 1.8)	1.4 (0.8 – 2.2)	0.43	1.1 (0.7 - 1.8)	1.3 (0.8 - 2.2)	0.50
<i>IGF2</i>	1926 C/G	1.2 (0.8 – 1.9)	0.9 (0.6 – 1.4)	0.39	1.2 (0.7 – 1.9)	0.9 (0.5 – 1.5)	0.58	1.2 (0.7 - 1.9)	0.9 (0.6 - 1.5)	0.60
	Apal A/G	1.1 (0.7 – 1.7)	0.9 (0.6 – 1.4)	0.53	1.1 (0.7 – 1.7)	0.9 (0.6 – 1.5)	0.71	1.1 (0.7 - 1.8)	0.9 (0.6 - 1.5)	0.75
	-6815 A/T	1.3 (0.8 – 1.9)	1.4 (0.9 – 2.2)	0.34	1.2 (0.7 – 1.8)	1.5 (0.9 – 2.4)	0.30	1.2 (0.7 - 1.9)	1.4 (0.9 - 2.4)	0.37
<i>KCNJ11</i>	Glu23Lys	1.0 (0.6 – 1.5)	0.8 (0.5 – 1.2)	0.50	0.8 (0.5 – 1.3)	0.7 (0.4 – 1.2)	0.46	0.8 (0.5 - 1.4)	0.7 (0.4 - 1.2)	0.40
<i>ENPP1</i>	IVS20 del T-11	1.0 (0.6 – 1.5)	0.7 (0.5 – 1.2)	0.39	1.0 (0.6 – 1.6)	0.7 (0.5 – 1.2)	0.37	1.0 (0.6 - 1.6)	0.7 (0.5 - 1.2)	0.41
	Lys121Gln	0.9 (0.5 – 1.4)	1.1 (0.7 – 1.9)	0.57	0.9 (0.6 – 1.6)	1.2 (0.7 – 2.1)	0.58	0.9 (0.6 - 1.6)	1.3 (0.7 - 2.1)	0.52
	1044 A/G	1.2 (0.8 – 1.8)	0.9 (0.6 – 1.4)	0.46	1.1 (0.7 – 1.8)	0.8 (0.5 – 1.3)	0.36	1.1 (0.7 - 1.7)	0.8 (0.5 - 1.3)	0.38

## PRODUCTION OF ADIPOCYTOKINES

<i>ADIPOQ</i>	-11377 C/G	1.0 (0.7 – 1.6)	1.0 (0.6 – 1.6)	0.99	1.3 (0.8 – 2.0)	1.2 (0.7 – 2.0)	0.56	1.3 (0.8 - 2.1)	1.2 (0.8 - 2.0)	0.52
	+45 T/G	0.8 (0.5 – 1.3)	0.9 (0.5 – 1.6)	0.68	0.8 (0.5 – 1.4)	1.0 (0.6 – 1.7)	0.78	0.8 (0.5 - 1.4)	1.0 (0.6 - 1.8)	0.74
	+276 T/G	0.8 (0.4 – 1.6)	0.8 (0.4 – 1.5)	0.73	0.9 (0.5 – 2.0)	0.9 (0.4 – 1.8)	0.93	1.0 (0.5 - 2.0)	0.9 (0.4 - 2.0)	0.99
	-11391 G/A	1.1 (0.6 – 2.0)	1.6 (0.9 – 3.0)	0.27	1.0 (0.5 – 2.0)	1.6 (0.8 – 3.2)	0.34	1.1 (0.5 - 2.1)	1.6 (0.8 - 3.3)	0.31
<i>CD36</i>	-178 A/C	1.3 (0.8 – 2.3)	1.3 (0.8 – 2.3)	0.48	1.2 (0.7 – 2.2)	1.2 (0.6 – 2.3)	0.76	1.2 (0.7 - 2.2)	1.2 (0.7 - 2.3)	0.75
<i>IL6</i>	-174 G/C	1.1 (0.7 – 1.8)	1.4 (0.9 – 2.3)	0.32	1.2 (0.7 – 2.0)	1.8 (1.1 – 3.1)	0.09	1.2 (0.7 - 1.9)	1.7 (1.0 - 2.9)	0.15
<i>TNF<math>\alpha</math></i>	-308 G/A	1.2 (0.7 – 1.9)	0.6 (0.4 – 1.0)	0.04	1.0 (0.6 – 1.7)	0.6 (0.3 – 1.0)	0.11	1.0 (0.6 - 1.7)	0.6 (0.4 - 1.1)	0.13
<i>SERPINE1</i>	-675 insG	0.8 (0.5 – 1.3)	1.0 (0.6 – 1.7)	0.54	0.7 (0.4 – 1.2)	1.1 (0.6 – 1.9)	0.33	0.7 (0.4 - 1.3)	1.1 (0.6 - 2.0)	0.35

1.- Model 1: odds ratios adjusted by binary variables indicating the centre of study.

2.- Model 2: odds ratios adjusted by age, centre of study, smoking status, physical activity score and energy intake.

3.- Model 3: odds ratios adjusted by age, centre of study, smoking status, physical activity score and fat-free mass.

4.- P-values correspond to the null hypothesis of no interaction considering the joint gene-nutrient effects for the two binary variables defined for the nutrient variable. The reference category is the wild-type homozygous genotype and the upper tertile of P:S ratio

5.- P-values are not corrected for multiple comparisons. Some statistical tests are not independent since there are genetic polymorphisms located in the same gene that may exhibit linkage disequilibrium.

## Odds ratios (95% confidence interval) and p-values for interaction between candidate genes and percentage of dietary fat in the female obese-only sample

Gene	Polymorphism	<sup>1</sup> Model 1			<sup>2</sup> Model 2			<sup>3</sup> Model 3		
		ORi Middle Third	ORi Lower Third	<sup>4,5</sup> P	ORi Middle Third	ORi Lower Third	<sup>4,5</sup> P	ORi Middle Third	ORi Lower Third	<sup>4,5</sup> P
<b>HYPOTHALAMIC REGULATION OF APPETITE</b>										
<i>SLC6A14</i>	+22510 C/G	0.9 (0.4 – 2.0)	2.5 (0.9 – 5.0)	0.09	0.9 (0.4 – 2.0)	2.5 (0.8 - 10.0)	0.10	0.7 (0.4 - 1.3)	0.6 (0.4 - 1.1)	0.28
<i>CART</i>	-3608 T/C	0.6 (0.4 – 1.1)	0.8 (0.5 – 1.5)	0.19	0.6 (0.4 – 1.1)	0.8 (0.4 – 1.5)	0.30	0.7 (0.4 - 1.2)	0.9 (0.5 - 1.7)	0.41
	-1702 C/T	1.4 (0.9 – 2.3)	1.1 (0.7 - 1.8)	0.29	1.2 (0.7 – 2.0)	0.8 (0.5 – 1.4)	0.30	1.2 (0.7 - 2.1)	0.9 (0.5 - 1.5)	0.32
	-175 A/G	0.7 (0.4 – 1.2)	0.9 (0.5 – 1.7)	0.39	0.7 (0.4 – 1.3)	1.0 (0.6 – 2.0)	0.42	0.8 (0.4 - 1.3)	1.1 (0.6 - 2.1)	0.37
	-1336 delA	0.9 (0.5 – 1.5)	1.1 (0.6 – 2.0)	0.76	1.0 (0.5 – 1.9)	1.4 (0.7 – 2.9)	0.42	0.9 (0.5 - 1.8)	1.4 (0.7 -2.8)	0.41
<i>GHSR</i>	Leu149Leu	0.7 (0.2 – 2.1)	0.9 (0.3 – 2.6)	0.82	1.0 (0.3 – 3.6)	1.3 (0.4 – 5.1)	0.87	0.8 (0.2 - 2.8)	1.0 (0.3 - 3.5)	0.93
<i>GAD2</i>	+83897 T/A	0.8 (0.5 – 1.3)	0.7 (0.4 – 1.2)	0.45	0.7 (0.4 – 1.1)	0.7 (0.4 – 1.2)	0.27	0.7 (0.4 - 1.1)	0.7 (0.4 - 1.2)	0.25
	+61450 C/A	0.9 (0.6 – 1.5)	0.8 (0.5 – 1.3)	0.56	0.8 (0.5 – 1.3)	0.7 (0.4 – 1.2)	0.46	0.8 (0.5 - 1.3)	0.7 (0.4 -1.2)	0.48
	-243 A/G	0.8 (0.5 – 1.3)	0.6 (0.4 – 1.1)	0.23	0.7 (0.4 – 1.2)	0.7 (0.4 – 1.3)	0.34	0.7 (0.4 - 1.2)	0.7 (0.4 - 1.2)	0.31
<i>GHRL</i>	Leu72Met	1.0 (0.5 – 2.0)	0.6 (0.3 – 1.3)	0.27	1.0 (0.5 – 2.1)	0.6 (0.2 – 1.4)	0.32	1.0 (0.5 - 2.0)	0.6 (0.2 - 1.3)	0.33
<i>MKKS</i>	Arg517Cys	0.7 (0.4 – 1.3)	0.6 (0.3 – 1.1)	0.27	0.7 (0.4 – 1.2)	0.5 (0.3 – 1.0)	0.13	0.7 (0.4 - 1.3)	0.5 (0.3 - 1.0)	0.15
<i>LEPROTL1</i>	-2625 C/T	1.3 (0.8 – 2.0)	1.3 (0.8 – 2.2)	0.49	1.4 (0.8 – 2.3)	1.5 (0.9 – 2.7)	0.28	1.1 (0.5 - 2.5)	0.4 (0.2 - 1.2)	0.10
<i>PCSK1</i>	T690S C/G	1.1 (0.7 – 1.7)	1.1 (0.7 – 1.8)	0.81	1.0 (0.6 – 1.6)	1.1 (0.7 – 1.7)	0.96	0.8 (0.5 - 1.4)	1.2 (0.7 - 2.0)	0.36
<b>EFFICIENCY OF ENERGY EXPENDITURE</b>										
<i>UCP2</i>	-866 G/A	0.8 (0.5 – 1.3)	1.0 (0.6 – 1.6)	0.58	0.9 (0.5 – 1.4)	1.1 (0.6 – 1.9)	0.71	0.9 (0.5 - 1.4)	1.0 (0.6 - 1.7)	0.79
<i>UCP3</i>	-55 C/T	1.2 (0.8 – 1.8)	0.7 (0.5 – 1.2)	0.15	1.3 (0.8 – 2.1)	0.8 (0.5 – 1.4)	0.16	1.3 (0.8 - 2.2)	0.9 (0.6 - 1.5)	0.22
<b>REGULATION OF ADIPOCYTE DIFFERENTIATION AND FUNCTION</b>										
<i>FOXC2</i>	-512 C/T	1.2 (0.6 – 2.1)	1.1 (0.6 – 2.2)	0.90	1.2 (0.6 – 2.4)	1.1 (0.5 – 2.4)	0.84	1.2 (0.6 - 2.4)	1.2 (0.6 - 2.4)	0.81
<i>PPARGC1A</i>	Gly482Ser	0.6 (0.3 – 1.3)	0.6 (0.3 – 1.2)	0.32	0.7 (0.3 – 1.6)	0.7 (0.3 – 1.7)	0.66	0.7 (0.3 - 1.6)	0.7 (0.3 - 1.6)	0.64
	+2962A/G	0.7 (0.4 – 1.1)	0.7 (0.4 – 1.2)	0.25	0.8 (0.5 – 1.4)	0.8 (0.4 – 1.5)	0.74	0.8 (0.5 - 1.4)	0.8 (0.4 - 1.4)	0.63
<i>PPARG2</i>	Pro12Ala	0.9 (0.5 – 1.5)	1.2 (0.7 – 2.1)	0.46	0.9 (0.5 – 1.5)	1.0 (0.5 – 1.8)	0.84	1.0 (0.6 - 1.8)	1.2 (0.7 - 2.2)	0.76

	1431C/T	1.2 (0.7 – 2.0)	1.7 (1.0 – 2.9)	0.17	1.2 (0.7 – 2.2)	1.4 (0.8 – 2.7)	0.54	1.4 (0.8 - 2.6)	1.7 (0.9 - 3.2)	0.22
	-820 C/T	0.9 (0.6 – 1.6)	1.4 (0.8 – 2.5)	0.24	1.0 (0.5 – 1.7)	1.2 (0.7 – 2.3)	0.65	1.1 (0.6 - 1.9)	1.5 (0.8 - 2.7)	0.40
<i>PPARG3</i>	-681 C/G	1.4 (0.9 – 2.1)	1.9 (1.2 – 3.1)	0.03	1.5 (0.2 – 2.5)	1.8 (1.0 – 3.0)	0.11	1.7 (1.0 - 2.7)	1.9 (1.1 - 3.3)	0.04
<i>SREBF1</i>	17 C/G	1.4 (0.9 – 2.2)	1.2 (0.8 – 1.9)	0.31	1.2 (0.8 – 1.9)	1.0 (0.6 – 1.7)	0.72	1.2 (0.7 - 1.9)	1.0 (0.6 - 1.7)	0.82
<i>WAC</i>	-829 A/G	1.2 (0.7 – 2.0)	1.2 (0.7 – 2.1)	0.78	1.0 (0.6 – 1.7)	1.2 (0.6 – 2.3)	0.77	0.9 (0.5 - 1.6)	1.1 (0.6 - 2.1)	0.84

## REGULATION OF LIPID AND GLUCOSE METABOLISM

<i>HSD11B1</i>	-2490 G/A	0.7 (0.4 – 1.4)	0.9 (0.5 – 1.8)	0.60	0.6 (0.3 – 1.3)	0.7 (0.3 – 1.4)	0.36	0.6 (0.3 - 1.2)	0.6 (0.3 - 1.3)	0.29
<i>LIPC</i>	Ans215Ser	0.9 (0.5 – 1.3)	0.8 (0.5 – 1.3)	0.68	0.7 (0.5 – 1.2)	0.7 (0.4 – 1.3)	0.43	0.8 (0.5 - 1.3)	0.8 (0.4 - 1.3)	0.52
	-514 C/T	0.8 (0.5 – 1.2)	0.9 (0.6 – 1.5)	0.48	0.7 (0.54 – 1.2)	0.9 (0.5 – 1.6)	0.48	0.8 (0.5 - 1.3)	1.0 (0.6 - 1.6)	0.64
<i>IGF2</i>	1926 C/G	1.1 (0.7 – 1.7)	0.7 (0.4 – 1.1)	0.12	1.3 (0.8 – 2.2)	0.8 (0.5 – 1.4)	0.11	1.3 (0.8 - 2.2)	0.8 (0.5 - 1.4)	0.11
	Apal A/G	1.2 (0.8 – 1.8)	0.8 (0.5 – 1.3)	0.22	1.3 (0.8 – 2.2)	0.9 (0.5 – 1.5)	0.23	1.3 (0.8 - 2.2)	0.9 (0.5 - 1.5)	0.23
	-6815 A/T	1.1 (0.7 – 1.7)	0.4 (0.5 – 1.4)	0.52	1.2 (0.7 – 2.0)	1.0 (0.6 – 1.7)	0.69	1.2 (0.7 - 2.0)	1.1 (0.6 - 1.8)	0.71
<i>KCNJ11</i>	Glu23Lys	0.8 (0.5 – 1.3)	0.9 (0.5 – 1.4)	0.76	1.0 (0.6 – 1.7)	1.2 (0.7 – 2.1)	0.72	1.0 (0.6 - 1.6)	1.2 (0.7 - 2.1)	0.73
<i>ENPP1</i>	IVS20 del T-11	0.7 (0.5 – 1.1)	0.6 (0.4 – 1.0)	0.11	0.7 (0.5 – 1.2)	0.6 (0.4 – 1.1)	0.21	0.7 (0.4 - 1.2)	0.5 (0.3 - 0.9)	0.08
	Lys121Gln	0.6 (0.3 – 0.9)	0.5 (0.3 – 0.8)	0.01	0.6 (0.4 – 1.0)	0.6 (0.3 – 1.0)	0.09	0.6 (0.4 - 1.0)	0.6 (0.3 - 1.0)	0.08
	1044 A/G	0.8 (0.5 – 1.3)	0.7 (0.4 – 1.1)	0.25	0.9 (0.6 – 1.6)	0.7 (0.4 – 1.2)	0.39	0.9 (0.5 - 1.5)	0.6 (0.4 - 1.1)	0.24

## PRODUCTION OF ADIPOCYTOKINES

<i>ADIPOQ</i>	-11377 C/G	1.5 (1.0 – 2.3)	0.9 (0.5 – 1.4)	0.03	1.4 (0.9 – 2.3)	0.7 (0.4 – 1.3)	0.02	1.5 (0.9 - 2.4)	0.8 (0.5 - 1.3)	0.04
	+45 T/G	0.9 (0.5 – 1.5)	1.4 (0.8 – 2.6)	0.16	0.9 (0.5 – 1.7)	1.5 (0.8 – 2.8)	0.20	0.9 (0.5 - 1.6)	1.4 (0.8 - 2.7)	0.24
	+276 T/G	1.3 (0.6 – 2.5)	0.9 (0.4 – 1.9)	0.66	1.8 (0.8 – 3.8)	1.2 (0.5 – 2.7)	0.35	1.5 (0.7 - 3.2)	1.0 (0.4 - 2.2)	0.50
	-11391 G/A	0.9 (0.5 – 1.8)	1.2 (0.6 – 2.3)	0.74	0.9 (0.4 – 2.0)	1.6 (0.7 – 3.5)	0.25	0.9 (0.4 - 2.0)	1.6 (0.7 - 3.4)	0.25
<i>CD36</i>	-178 A/C	1.0 (0.6 – 1.7)	1.0 (0.5 – 1.8)	0.99	0.8 (0.4 – 1.5)	0.7 (0.3 – 1.4)	0.58	0.9 (0.5 - 1.7)	0.8 (0.4 - 1.6)	0.85
<i>IL6</i>	-174 G/C	1.1 (0.7 – 1.7)	1.0 (0.6 – 1.6)	0.19	1.3 (0.8 – 2.2)	1.4 (0.8 – 2.4)	0.53	1.3 (0.7 - 2.1)	1.2 (0.7 - 2.0)	0.70
<i>TNF<math>\alpha</math></i>	-308 G/A	1.2 (0.7 – 2.0)	1.2 (0.7 – 2.0)	0.71	1.3 (0.8 – 2.2)	1.6 (0.9 – 3.0)	0.28	1.2 (0.7 - 2.1)	1.5 (0.8 - 2.7)	0.41
<i>SERPINE1</i>	-675 insG	0.6 (0.4 – 1.0)	0.9 (0.5 – 1.6)	0.12	0.6 (0.3 – 1.1)	0.9 (0.5 – 1.8)	0.17	0.6 (0.3 - 1.1)	0.9 (0.5 - 1.8)	0.13

1.- Model 1: odds ratios adjusted by binary variables indicating the centre of study.

2.- Model 2: odds ratios adjusted by age, centre of study, smoking status, physical activity score and energy intake.

3.- Model 3: odds ratios adjusted by age, centre of study, smoking status, physical activity score and fat-free mass.

4.- P-values correspond to the null hypothesis of no interaction considering the joint gene-nutrient effects for the two binary variables defined for the nutrient variable. The reference category is the wild-type homozygous genotype and the lower tertile of the percentage of calories derived from fat.

5.- P-values are not corrected for multiple comparisons. Some statistical tests are not independent since there are genetic polymorphisms located in the same gene that may exhibit linkage disequilibrium.