Universidad de Navarra | CENTRO DE INVESTIGACIÓN EN NUTRICIÓN

Real Academia Nacional de Farmacia

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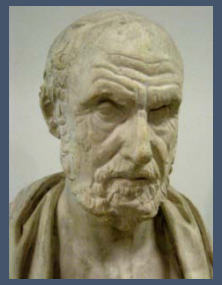
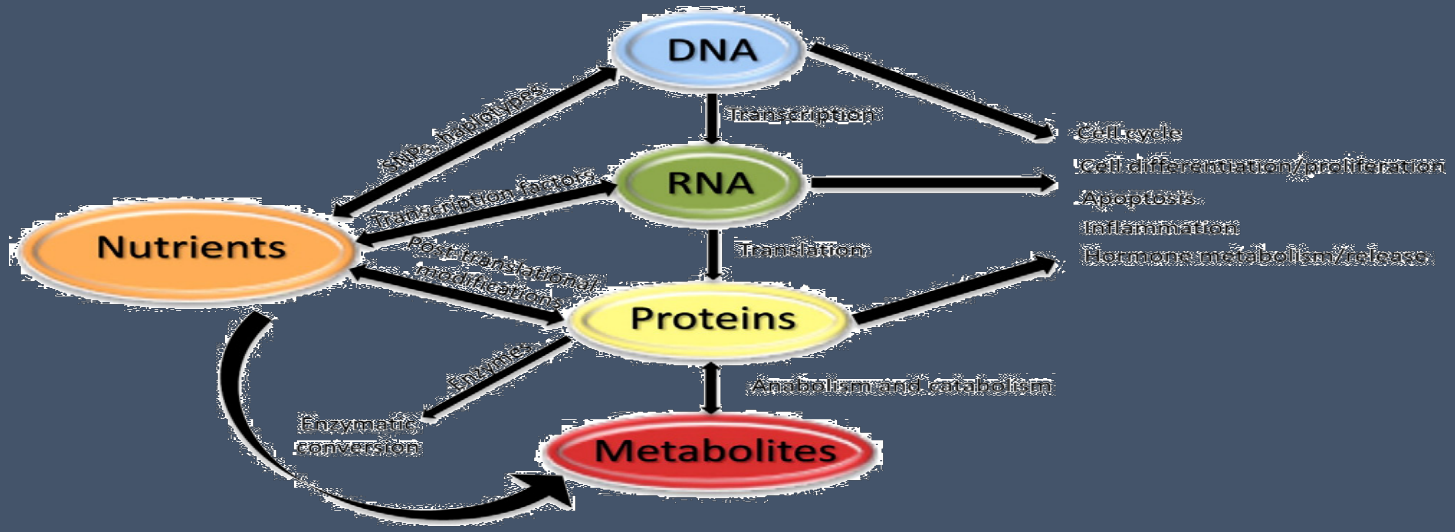
Centro de Investigación en Nutrición
Universidad de Navarra

Medicina Personalizada y Nutrición



Biblia: Noé, Libro de Daniel,…
Hipócrates (Cos, 460 a. C.“…TU alimento es la base de TU salud”
Galeno (Roma 130-200 dC) “Actitudes personales y respuesta única al alimento”
C. Bernard. (s XIX) “No hay enfermedad, sino pacientes”
Mendel: (s XIX) Transmisión de rasgos individualizados entre generaciones
Garrod (ppios s XX) La respuesta nutricional depende del metabolismo personal
Williams (1956): Variación individual en las respuestas hormonales al alimento
Ley et al (2000s): Impacto de microbiota intestinal sobre nutrición de precisión
Nutrición de Precisión 4.0. Emergen las ciencias ómicas



NUTRICIÓN PERSONALIZADA BASADA EN EL GENOTIPO

La carga genética puede determinar requerimientos nutricionales únicos y respuestas a distintos alimentos y nutrientes

Basado en:

- La secuenciación del genoma humano,

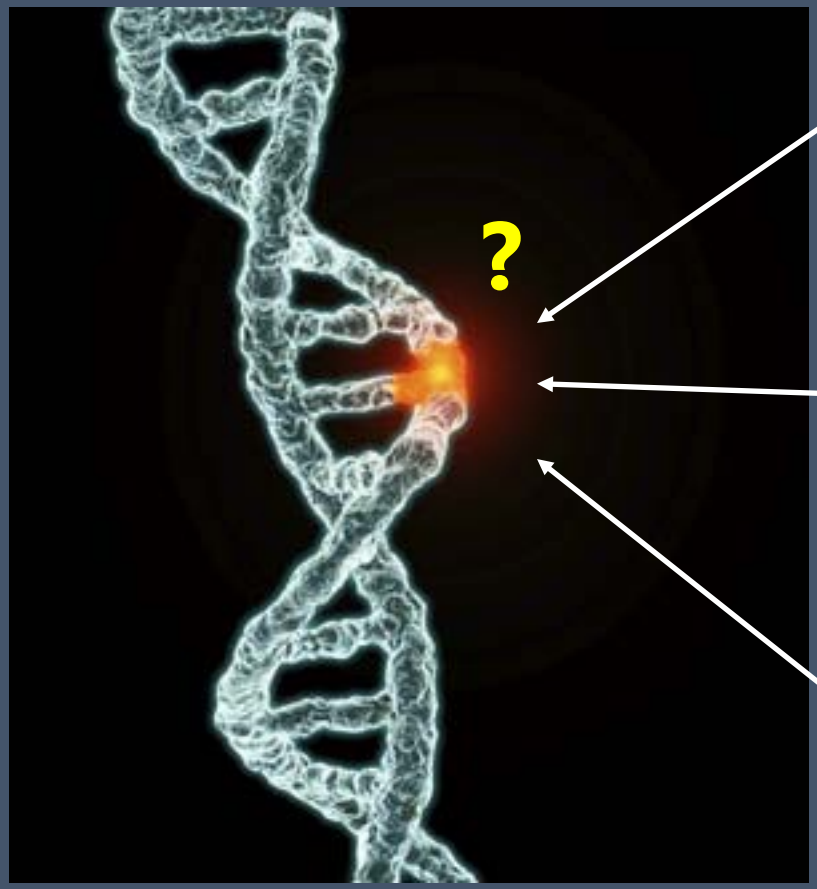
- Análisis subsiguientes de la variación genética humana,

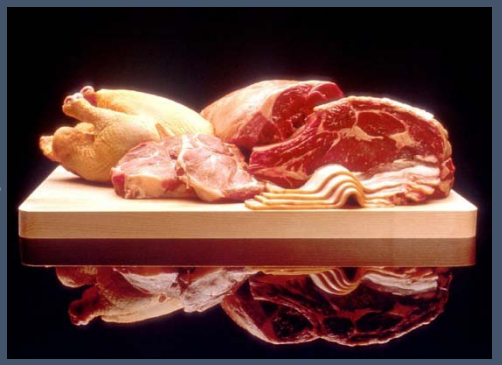
-Estudios que asocian variantes genéticas con marcadores de enfermedad

-Impacto de la nutrición/nutrientes sobre la expresión génica.

-Conocimiento de aproximaciones ómicas y microbiota intestinal.

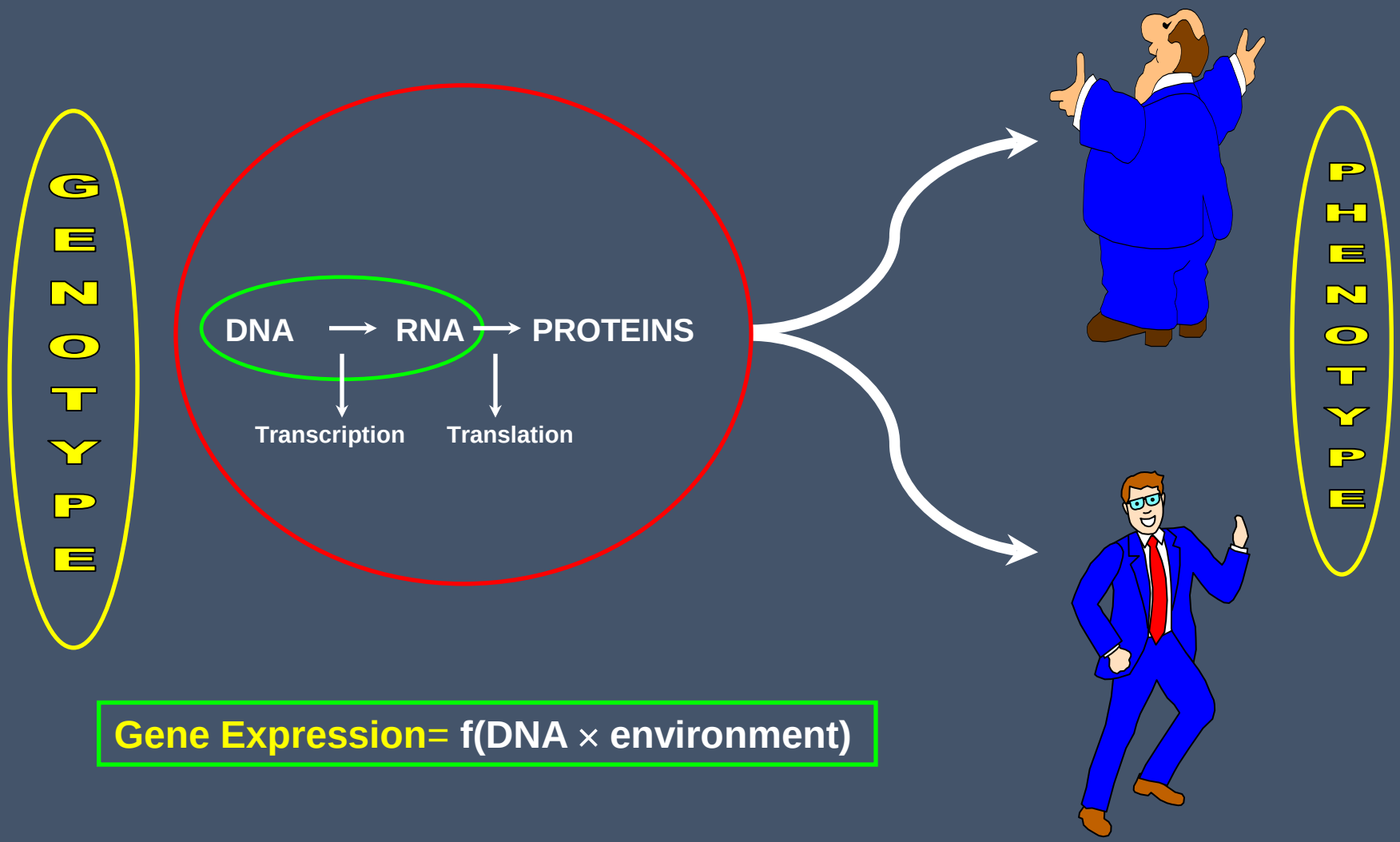
NUTRIGENETICA: Nutrición Personalizada basada en el genotipo





NUTRIGENOMICA es el estudio de las relaciones moleculares entre la **nutrición** y la respuesta **genética**, con el objetivo de extrapolar cómo esos cambios sutiles pueden afectar **la Salud Humana**.

GENOTIPO x NUTRICIÓN → METABOTIPO

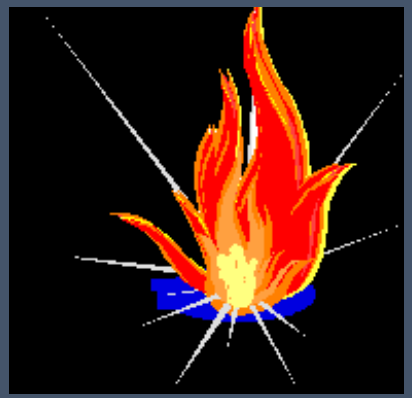


Gene Expression= f(DNA × environment)

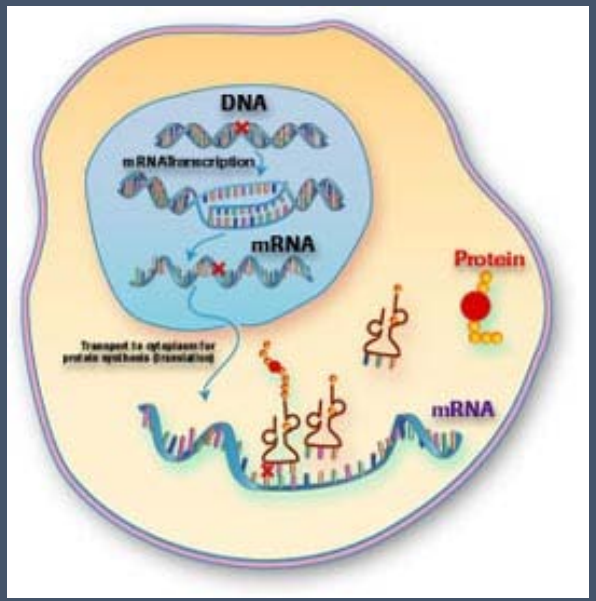
FUNCIONES DE LOS NUTRIENTES

Nutrientes

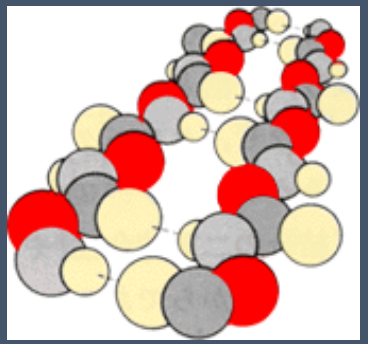
Energía



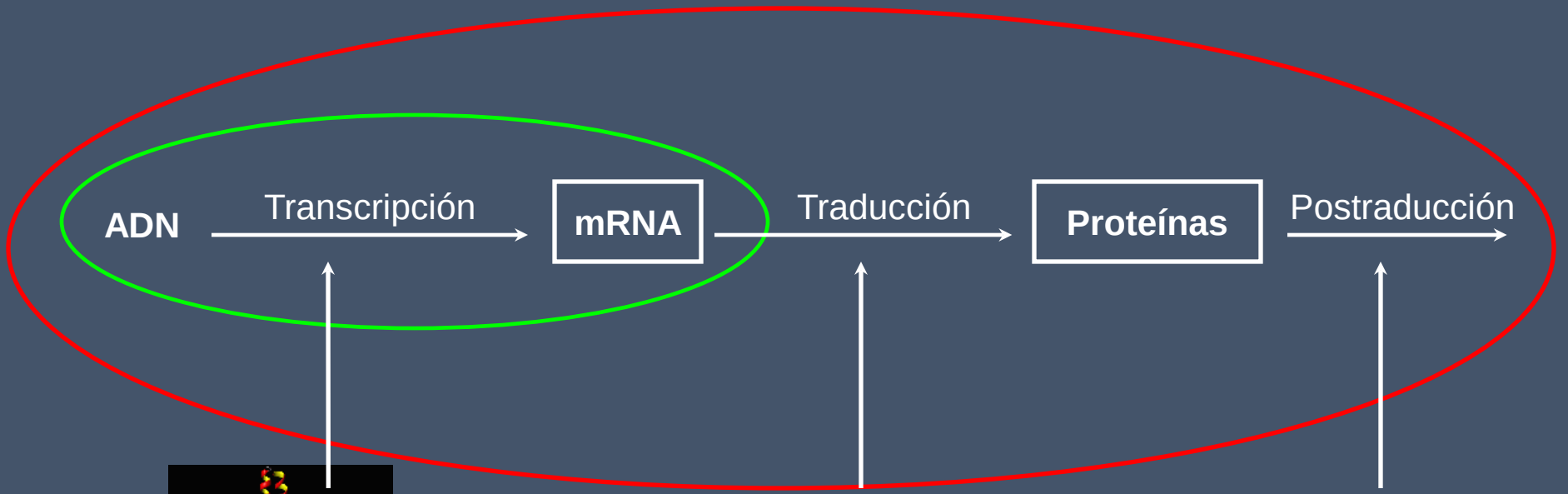
Elementos Reguladores

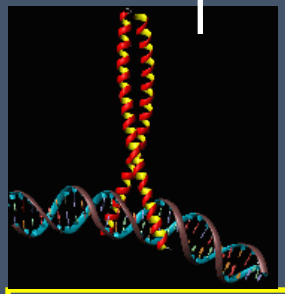


Componentes estructurales



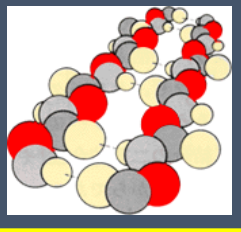
EXPRESIÓN GÉNICA: CONTROL NUTRICIONAL





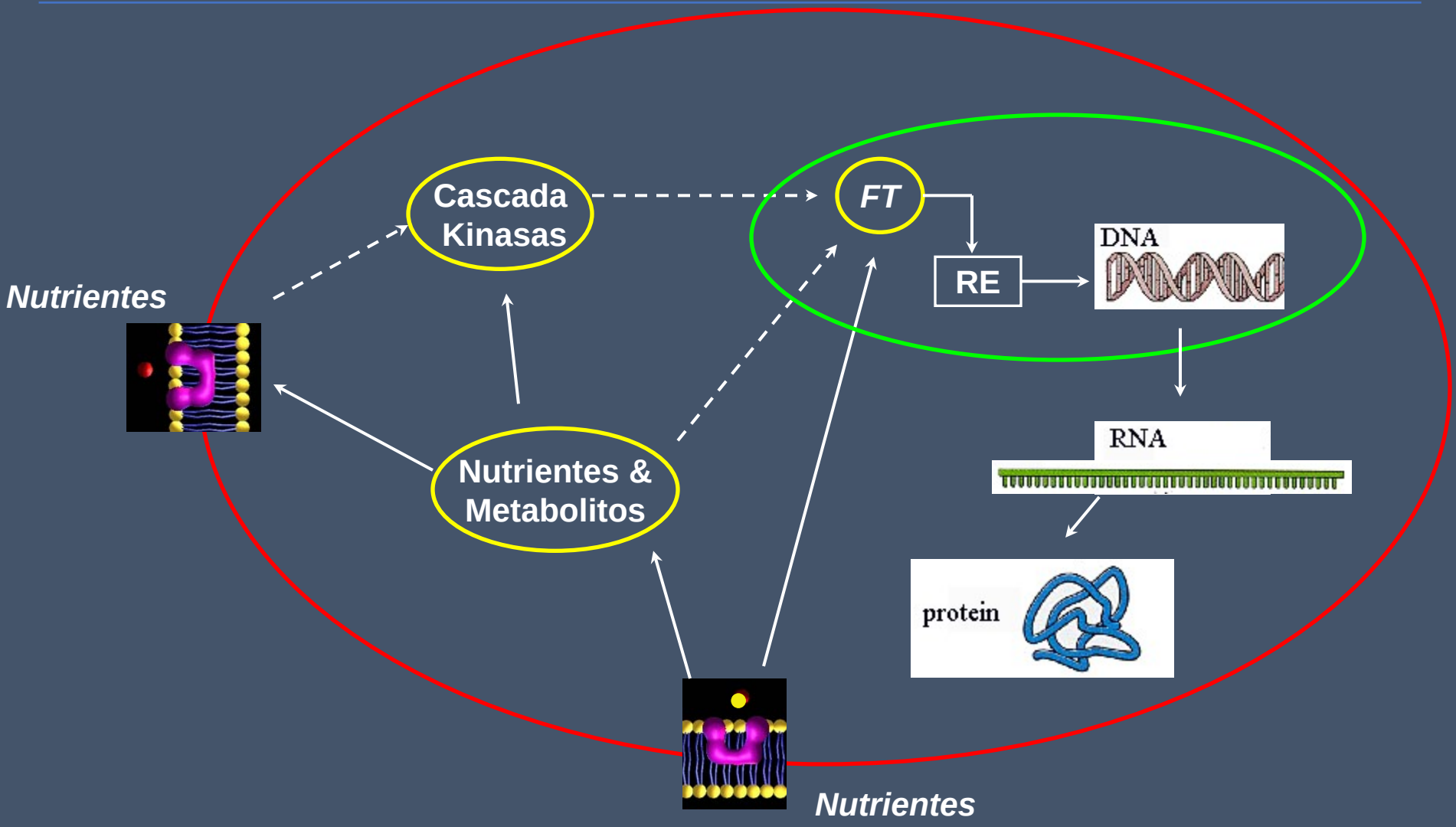
Ácidos grasos
Retinoles
Vitamina D
Glucosa
Energía

Amino ácidos
Hierro
Selenio



Minerales
Vitaminas

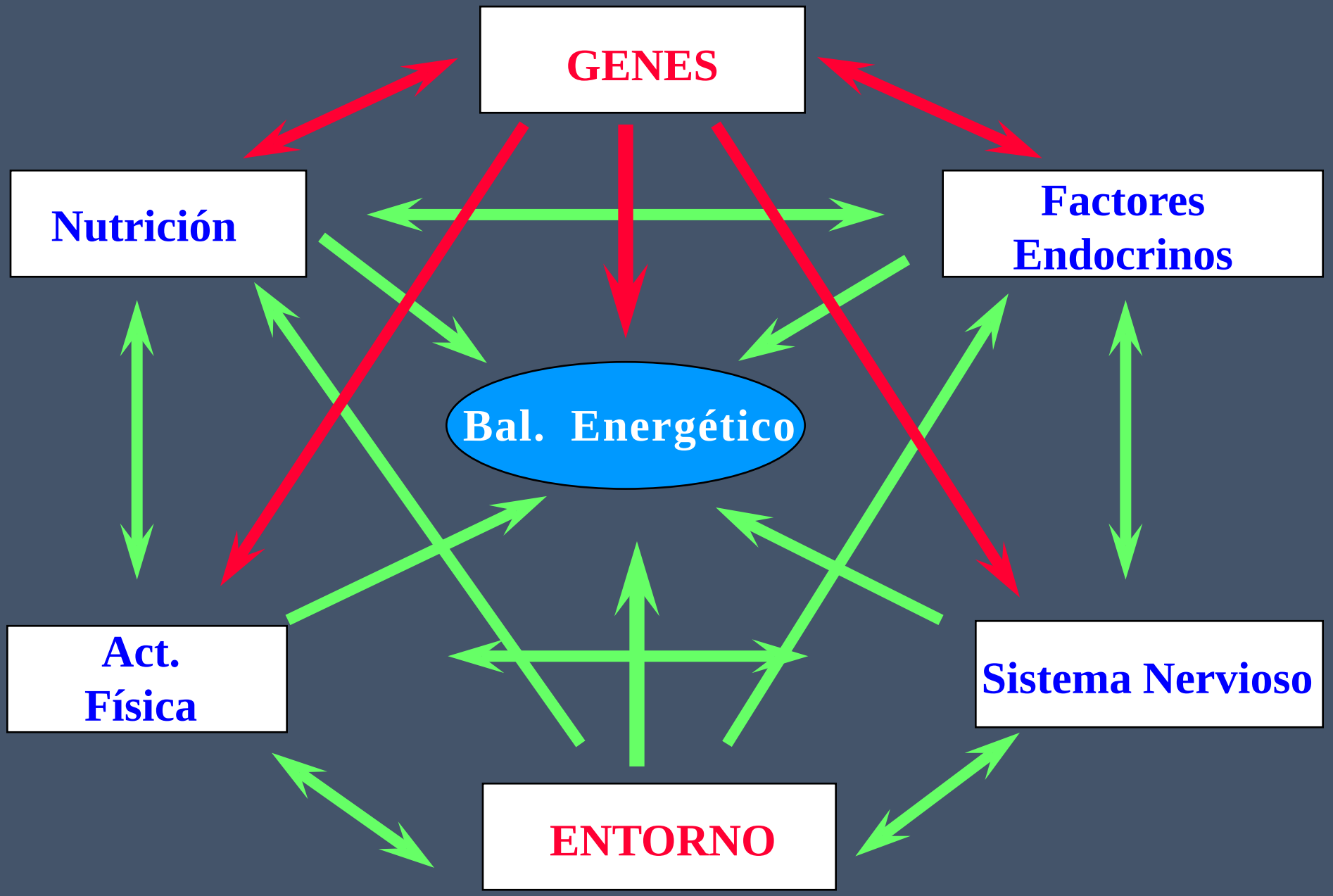
CONTROL EXPRESIÓN GÉNICA: MECANISMOS



Mecanismos : - Receptores (membrana/nucleo)

- Metabolismo intermedio
- Factores de Transcripción (*FT*): afinidad y concentraciones

OBESIDAD: FACTORES ETIOLÓGICOS



PERSONALIZACION: INVESTIGACION GENETICA

- **Genotipo:** genes/alelos responsables de los rasgos
- **Fenotipo**: manifestaciones externas de una característica observable

Síndromes Mendelianos

- Autosómico dominante
- Autosómico recesivo
- X-ligados

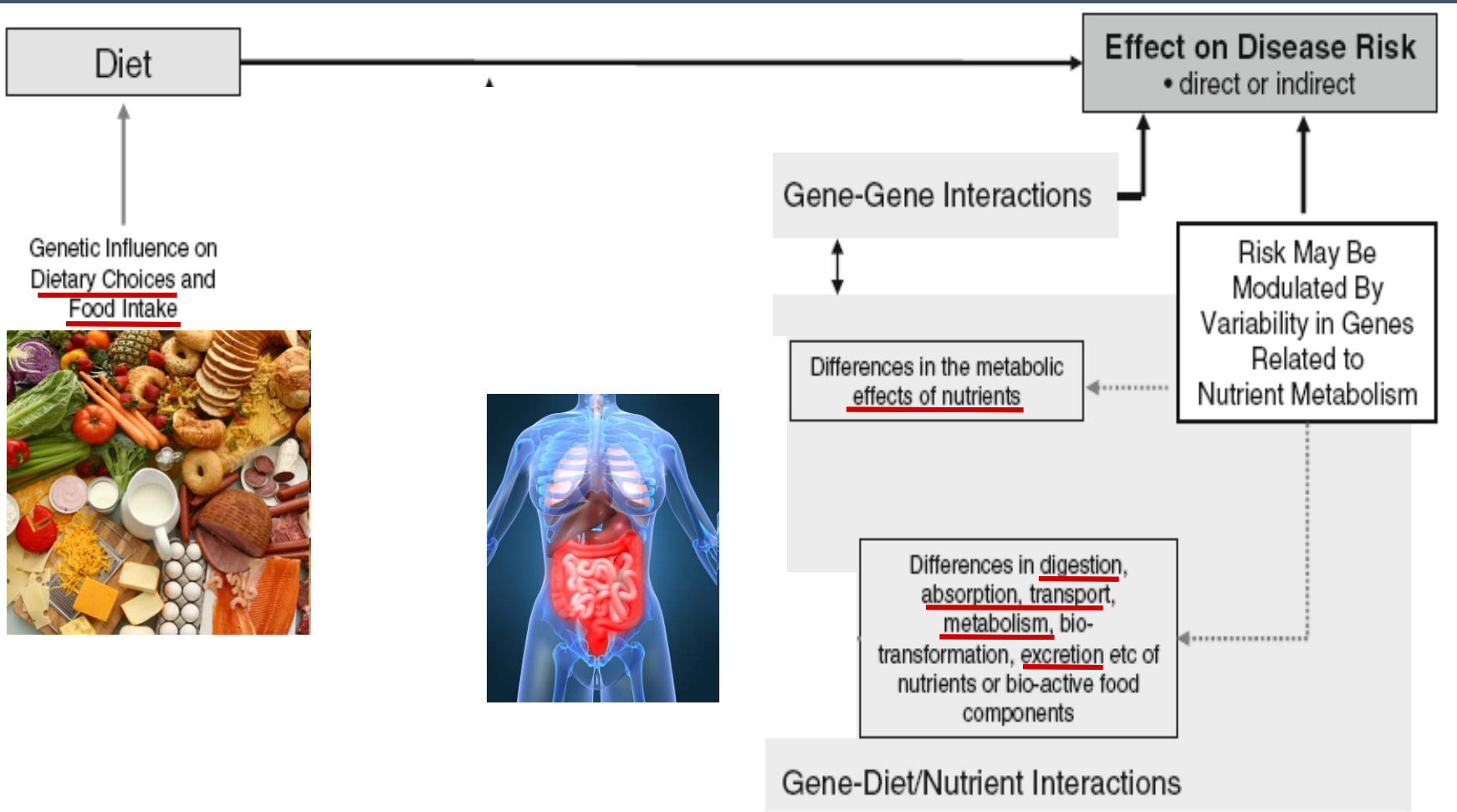
Modelos Animales

- Animales genéticamente obesos
- Animales Transgénicos
- Q Trait Loci (QTL)

Estudios de Asociación y Ligamiento

- Genes Candidatos y GWAS
- Segregación familiar

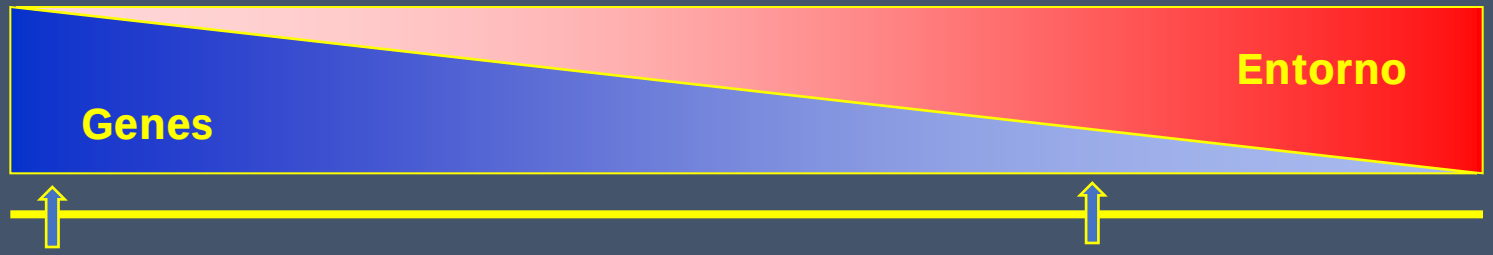
Personalización: Interacciones Nutricionales y Genéticas



Posibles interacciones de la dieta con la variabilidad genética afectan al riesgo de enfermedad.

Jenab MZ et al. Hum Genet (2009) 125: 507–525

Genética del Metabolismo Humano: Interacciones Gen X Entorno



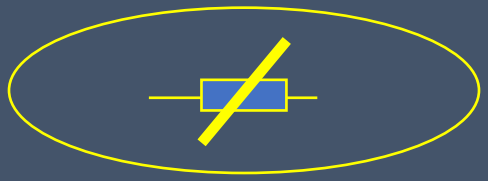
Monogénicas

- Casos Raros
- Síndromes

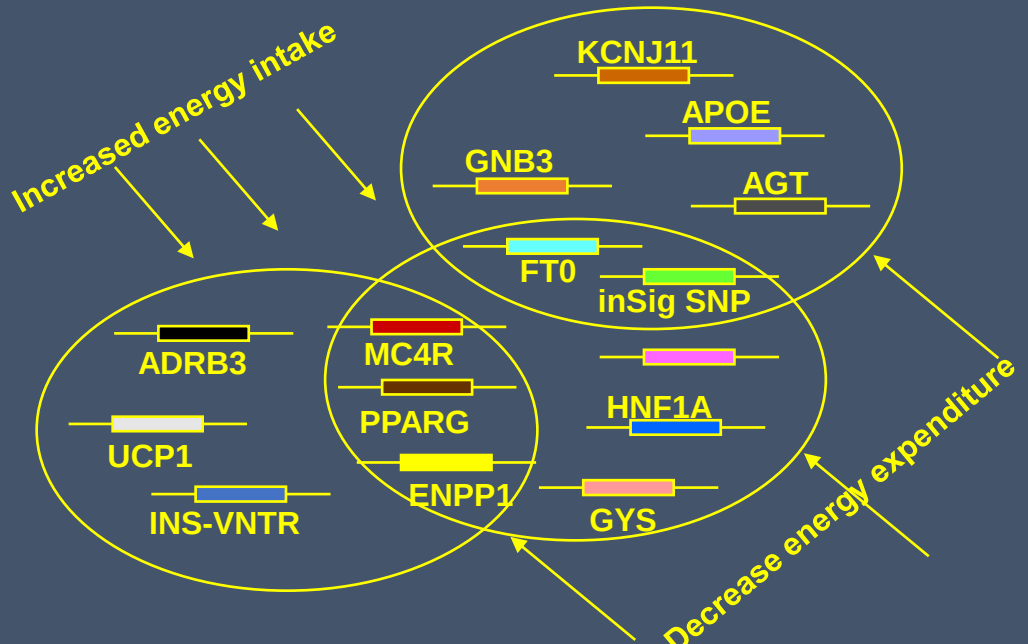
Poligénicas

Combinación individual en interacción con factores ambientales

1 gen 1 enfermedad



LEP, LEPR, POMC,PCSK1
SIM,,



PREDISPOSICIÓN (% RIESGO) → HAPLOTIPO X ENTORNO

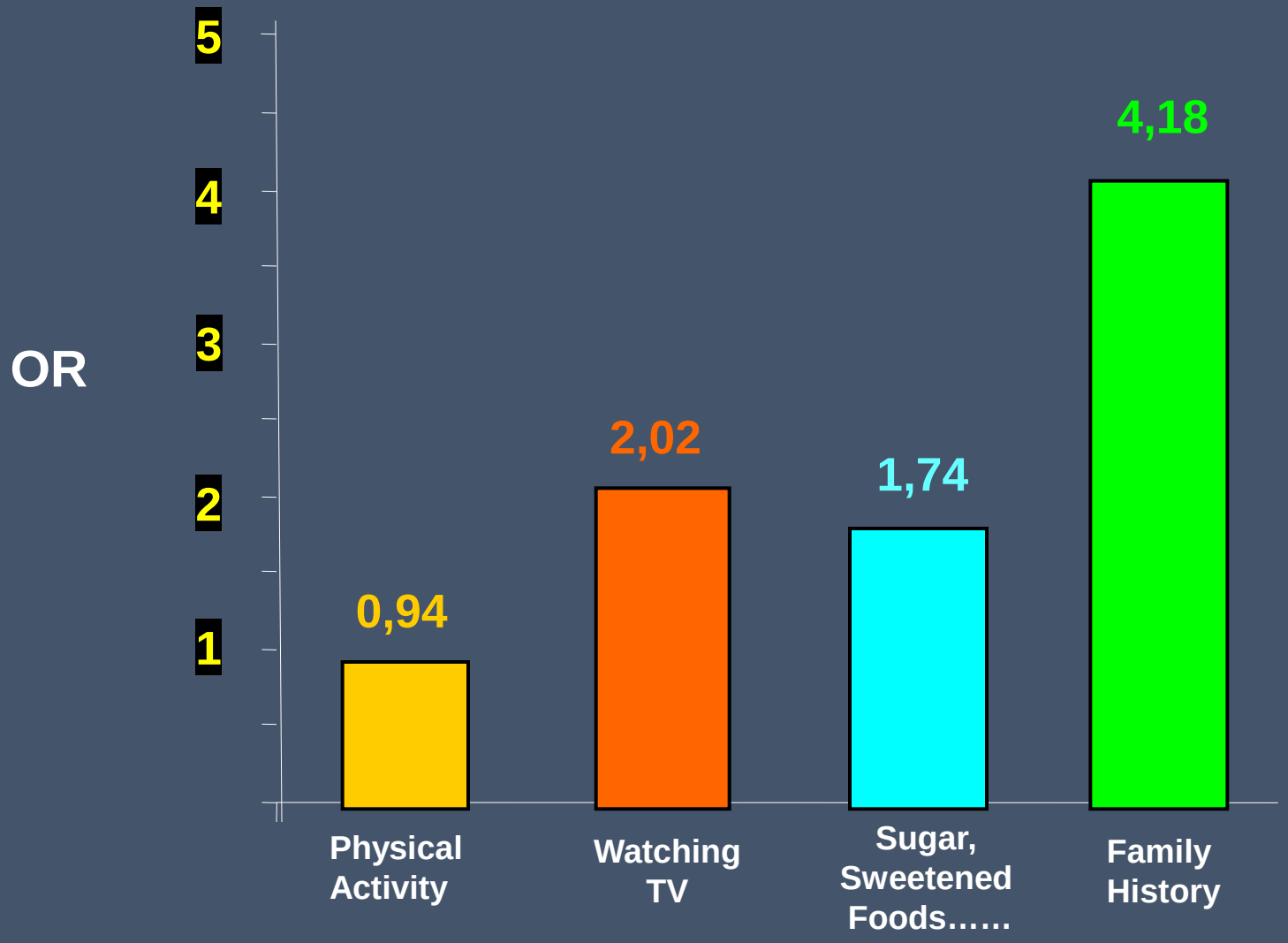
ENFERMEDADES MONOGÉNICAS	ENFERMEDADES POLIGÉNICAS
Celiaquía Intolerancia Lactosa Hipercolesterolemia familiar Fenilcetonuria Galactosemia	Obesidad Diabetes Tipo 2 Hiperlipidemias Enfermedad Cardiovascular Hipertension Osteoporosis Enf. Neurodegenerativas Cáncer

Estilo de vida, alcohol, tabaquismo, ejercicio, hábitos dietéticos, sueño…

- **Factores Exógenos** :

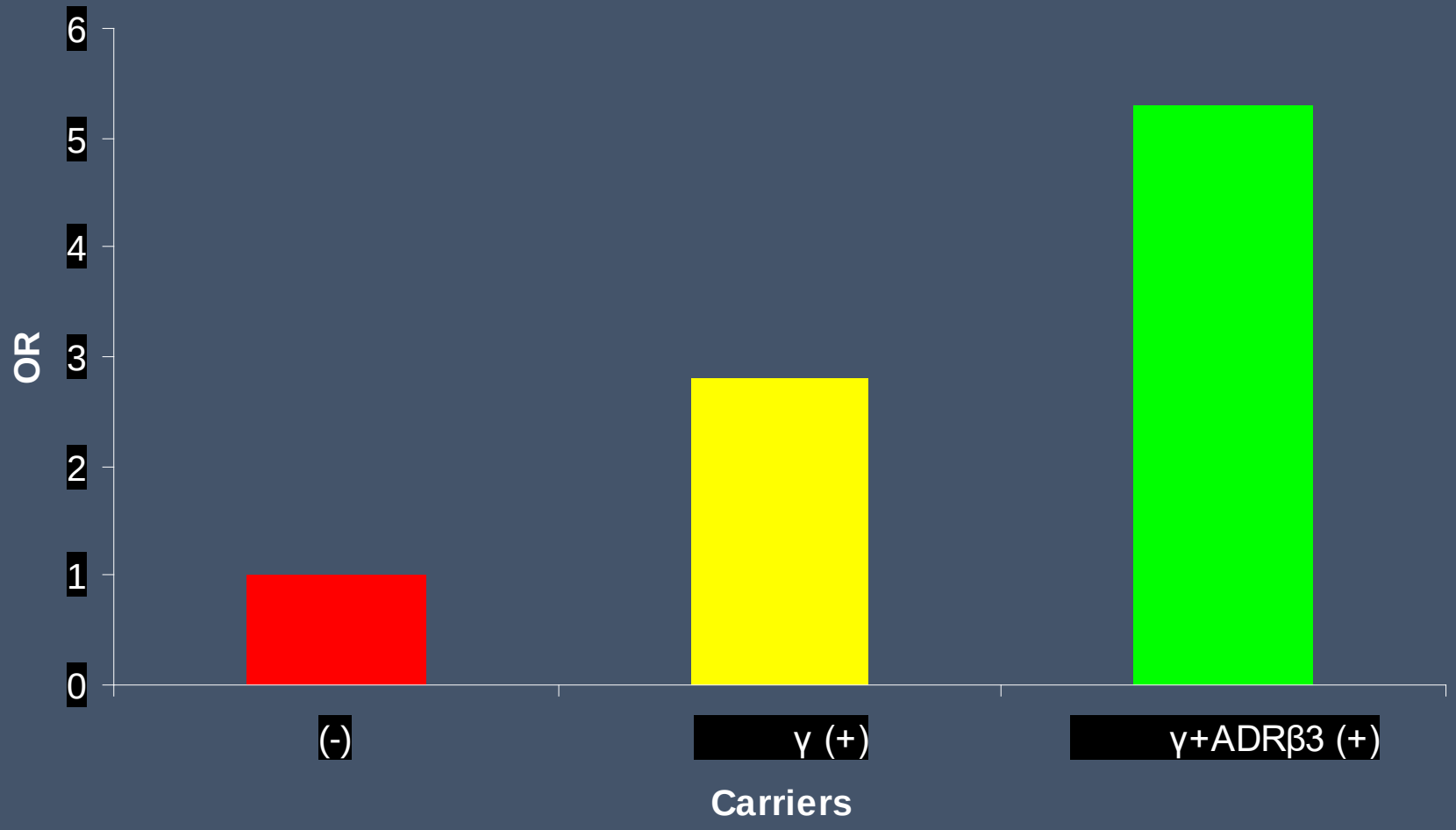
Toxinas. Contaminantes, microorganismos, alergenos

FACTORES PREDICTORES: OBESIDAD INFANTIL



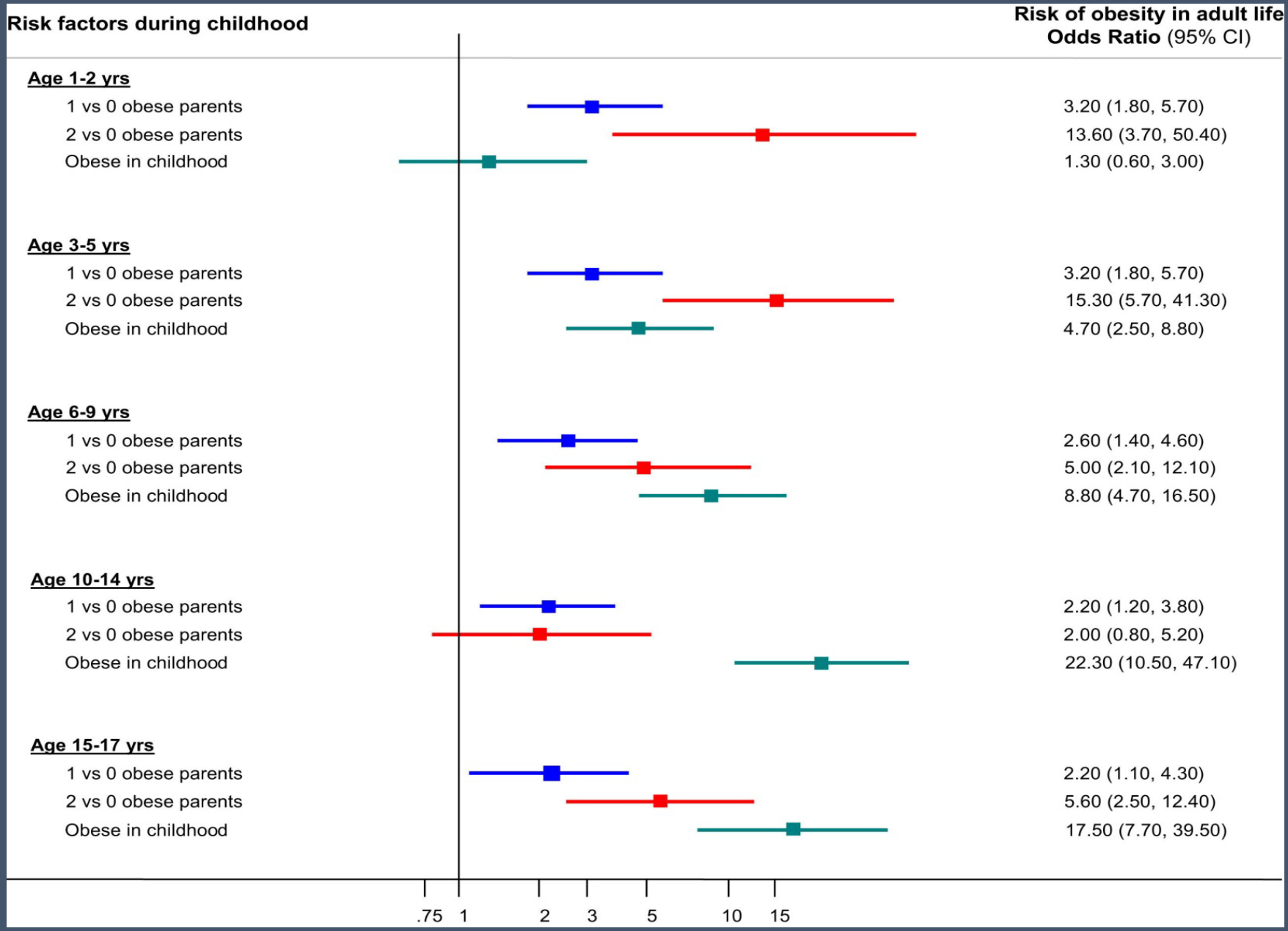
Ochoa, *et al. 2006*

INTERACCIONES PPARγ2 x ADRβ3



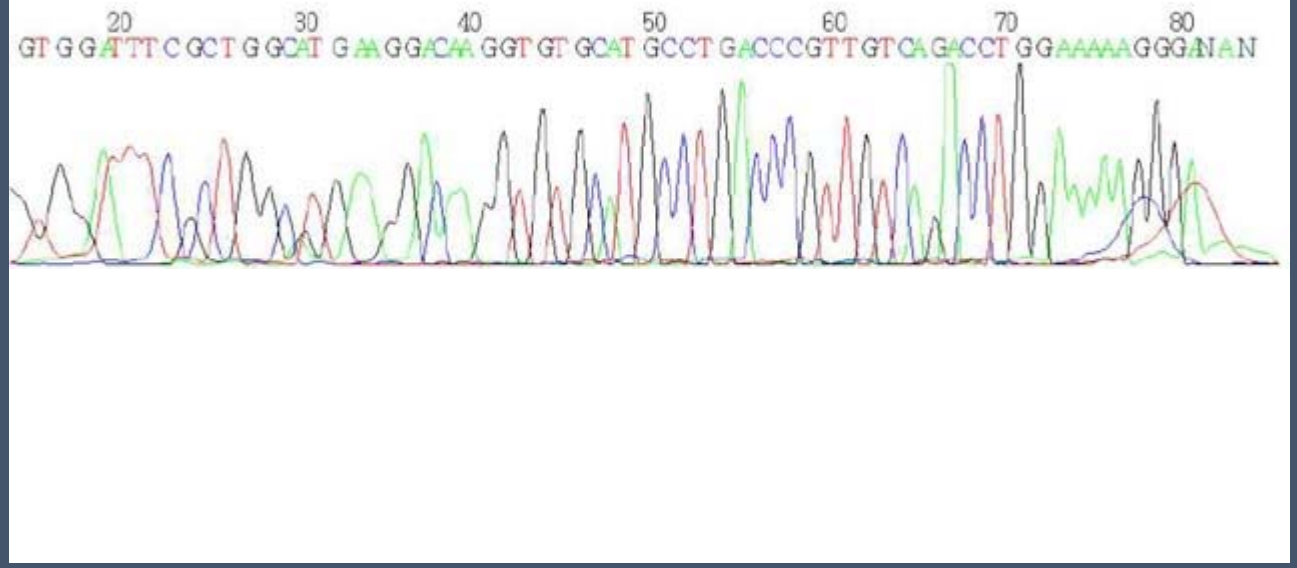
Ochoa, *et al.* 2004

SOBREPESO INFANTIL Y RIESGO DE OBESIDAD EN EL ADULTO



Loos. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2012;26: 211–226


ATCTCTTGGCTCCAGCATCGATGAAGAACGCA
TCATTTAGAGGAAGTAAAAGTCGTAACAAGGT
GAACTGTCAAAACTTTTAACAACGGATCTCTT
TGTTGCTTCGGCGGCGCCCGCAAGGGTGCCCG
GGCCTGCCGTGGCAGATCCCCAACGCCGGGCC
Adquisición de datos
ÓMICAS & GWAS
CGGATCTCTTGGCTCCAGCATCGATGAAGAAC
GATGAAGAACGCAGCGAAACGCGATATGTAAT


20
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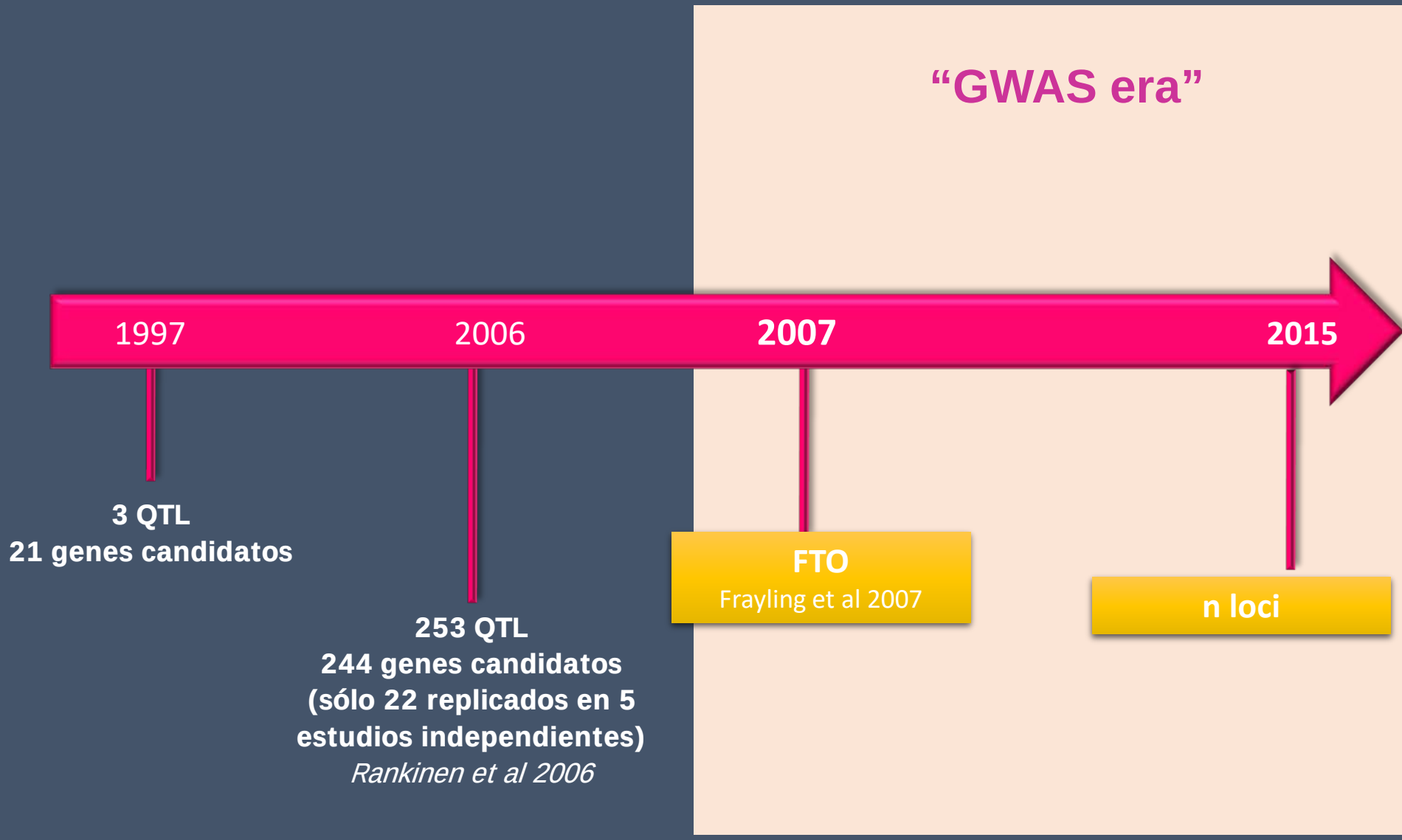
80

Hitos en adquisición de datos genéticos en Obesidad



APROXIMACIONES ESTRATÉGICAS EN ADQUISICIÓN DE DATOS GENÉTICOS

ESTUDIOS DE GENES CANDIDATOS

Casos clínicos (genes alterados asociados con enfermeda vs “Sanos" no alteración)

Cribado gen conocido

SNPs asociados a enfermedad

Estudios celulares/moleculares
Fisiología

GWAS
Genome-Wide Association Studies

Miles de personas

Cribado amplio de genoma

Identificación genética

Bioquímica
Genética
Genómica comparativa

Estudios celulares/moleculares
Fisiología

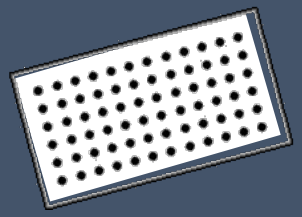
HERRAMIENTAS: Microchip scanning

Construir el Chip

PCR Masiva

PCR PURIFICACIÓN y PREPARACIÓN

IMPRESIÓN ROBÓTICA



Recogida Muestra

Aislamiento ARN

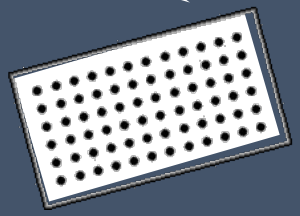
delgados

obesos

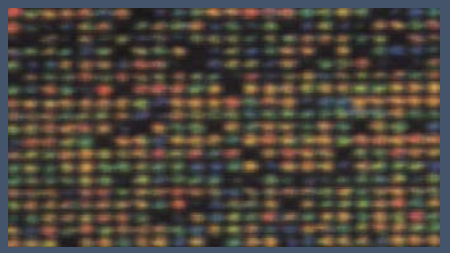
Transcripción Inversa

Etiquetar con tinte Flúor

Hibridación Competitiva



Detección con laser confocal



Análisis de datos computerizados

Moreno *et al.* 2010

HERRAMIENTAS: Microchip Scanning

Macronutrient Metabolism

Fold	*Code*	*Name*
~49.2	D45862	**Leptin, ob**
15.7□	J02773	**Low molecular weight FABP**
7.3	J00713	**Carboxypeptidase-a- 5**
~6.7□	U64451	**Short-branched chain acyl-CoA DH precursor**
~4.9□	AF063302	**Carnitine palmitoyltransferase I beta**
~4.6□	AF034577	**Pyruvate dehydrogenase kinase isoenzyme 4**
4.1	M95591	**Squalene synthetase**
3.3	S69874	**Fatty acid-binding protein (FABP)**
3.2	K03249	**Enoyl-CoA-hydratase-3-hydroxyacyl-CoA DH**
3	AB002558	**Glycerol 3-phosphate dehydrogenase**
2.9	AB005743	**Fatty acid transporter**
2.8	L07114	**Apolipoprotein B**
2.5	U20643	**Aldolase A**
2.5	M26594	**Malic enzyme**
2.4	M60322	**Aldose reductase**
2.2	S56481	**Beta 3-adrenergic receptor**
2.2	S81497	**Lysosomal acid lipase**
2.2	J02585	**Liver stearyl-CoA desaturase**
2.2	X15580	**6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase**
2.2	L12016	**Tricarboxylate transport protein**
2.2	U32314	**Pyruvate carboxylase**
2.2	D10354	**Alanine aminotransferase**
2.2	L25331	**Lysyl hydroxylase**
2.1	D43623	**Carnitine palmitoyltransferase I like protein**
2	D10655	**Dihydrolipoamide acetyltransferase**
2	AF035943	**Uncoupling protein-3**

Transcription factor

3.7□	AB015724	**Nuclear receptor binding factor-1**
2.8□	X12752	**DNA binding protein C/EBP**
2.5	S77528	**C/EBP-related transcription factor**
2.1	AB011365	**PPAR-gamma protein**
2	AF022081	**Small nuclear RING finger protein**
2	X13167	**NF-1 like DNA-binding protein**

Hormone receptor and signal transduction

~10.7□	M96159	**Adenylyl cyclase type V**
4	S79241	**Oxytocin receptor**
3.6□	U93880	**Insulin receptor substrate-3 (IRS-3)**
3	K03045	**Retinol-binding protein (RBP)**
2.9	D38036	**Truncated TSH receptor**
2.9	Z83757	**Growth hormone receptor**
2	X92069	**P2X5 receptor (ATP-gated ion channels)**
2.8	E12286	**GM2 activator protein**
2.7	X17053	**Immediate-early serum-responsive JE**
2.6	S74351	**Protein tyrosine phosphatase**
2.6□	X06107	**Insulin-like growth factor I**
2.5	M64300	**Signal-related kinase (ERK2)**
2.4	D85183	**SHPS-1 (protein tyrosine phosphatase)**
2.4	L13619	**Insulin-induced growth-respons protein**
2.4□	L35767	**Very low density lipoprotein receptor,**
2.3	S49003	**Short isoform growth hormone receptor**
2.3	D85435	**Protein kinase C delta-bindig protein**
2.2	D89655	**Scavenger receptor class B**
2.2	U21101	**Cyclic GMP stimulated phosphodiesterase**
2.2□	J03819	**Thyroid (T3) hormone receptor**
2	AF022952	**Vascular endothelial growth factor B**
2	S50461	**Signal-transducing G protein alpha 12 subunit**
2	L25633	**Neuroendocrine-specific protein**
2	M12492	**Type II cAMP-dependent PK regulatory subunit**

Cellular cytoskeleton

~4.9□	K00512	**Myelin basic protein**
~4.0□	AF004811	**Moesin**
3.5	X60351	**Alpha B-crystallin**
3.1	AF041373	**Clathrin assembly protein short form**
2.7	U50717	**Synaptic density protein PSD-93**
2.5	M83196	**Microtubule-associated protein 1A**

□corresponds to a transcript absent in the control group (basal line).

Macronutrient Metabolism

Fold	*Code*	*Name*
-22.5	AF001898	**Aldehyde dehydrogenase (ALDH)**
-22.1□	AB009999	**CDP-diacylglycerol synthase**
~-20.0□	AB017260	**High-affinity carnitine transporter**
-19.0□	D37920	**Squalene epoxidase**
-9.1	L25387	**Phosphofructokinase C**
~-6.4□	AB010428	**Acyl-CoA hydrolase**
-6.0	S68135	**GLUT1**
-3.8	M18467	**Aspartate aminotransferase**
-2.9	AF080468	**Glycogen storage disease type 1b protein**
-2.8	S49760	**Diacylglycerol kinase**
-2.6	X04979	**Apolipoprotein E**
-2.4	M93297	**Ornithine aminotransferase**
-2.2	L07736	**Carnitine palmitoyl-transferase I**

Redox and stress proteins

-7.8-34.1□	S82820	**Glutathione S-transferase Yc2 subunit**
-4.8-6.2	X62660	**Glutathione S-transferase subunit 8**
-4.2	M11794	**Metallothionein-2 and metallothionein-1**
-2.6-3.2	X02904	**Glutathione S-transferase P subunit**

Transcription factor

-25.2	U78102	**Krox20 ó EGR-2(early growth response protein 2)**
-5.2	X94246	**Pax-8 protein**
-2.7	M91802	**Homeobox protein (Hox 1.11)**

Hormone and signal transduction

-117.5	S49491	**Proenkephalin**
~-92.3□	J04488	**Prostaglandin D synthetase**
~-47.3	D63772	**Neuronal high affinity glutamate transporter**
~-8.6□	M12450	**Vitamin D binding protein**
-4.1	U57715	**FGF receptor activating protein FRAG1**
-2.8	U48596	**MAP kinase kinase kinase 1 (MEKK1)**
-2.3	L06096	**Inositol trisphosphate receptor subtype 3 (IP3R-3)**
-2.3	U53184	**Estrogen-responsive uterine**
-2.3	X59132	**Secretin receptor**
-2.2	D64045	**Phosphatidylinositol 3-kinase p85 alpha subunit**
-2.1	AF014009	**Acidic calcium-independent phospholipase A2**
-2	M91599	**Fibroblast growth factor receptor subtype 4**

Cellular cytoskeleton

~-21.4□	X81448	**Keratin 18**
~-12.2□	M93638	**Keratin 5**
~-6.6□	AF013247	**Beta-A4 crystallin**
~-3.8□	M59936	**Connexin-31**
-3.2	X67788	**Ezrin p81**
-2.3	X81449	**Keratin 19**

□corresponds to a transcript absent in the obese group (basal line).

From obesity genetics to the future of personalized obesity therapy

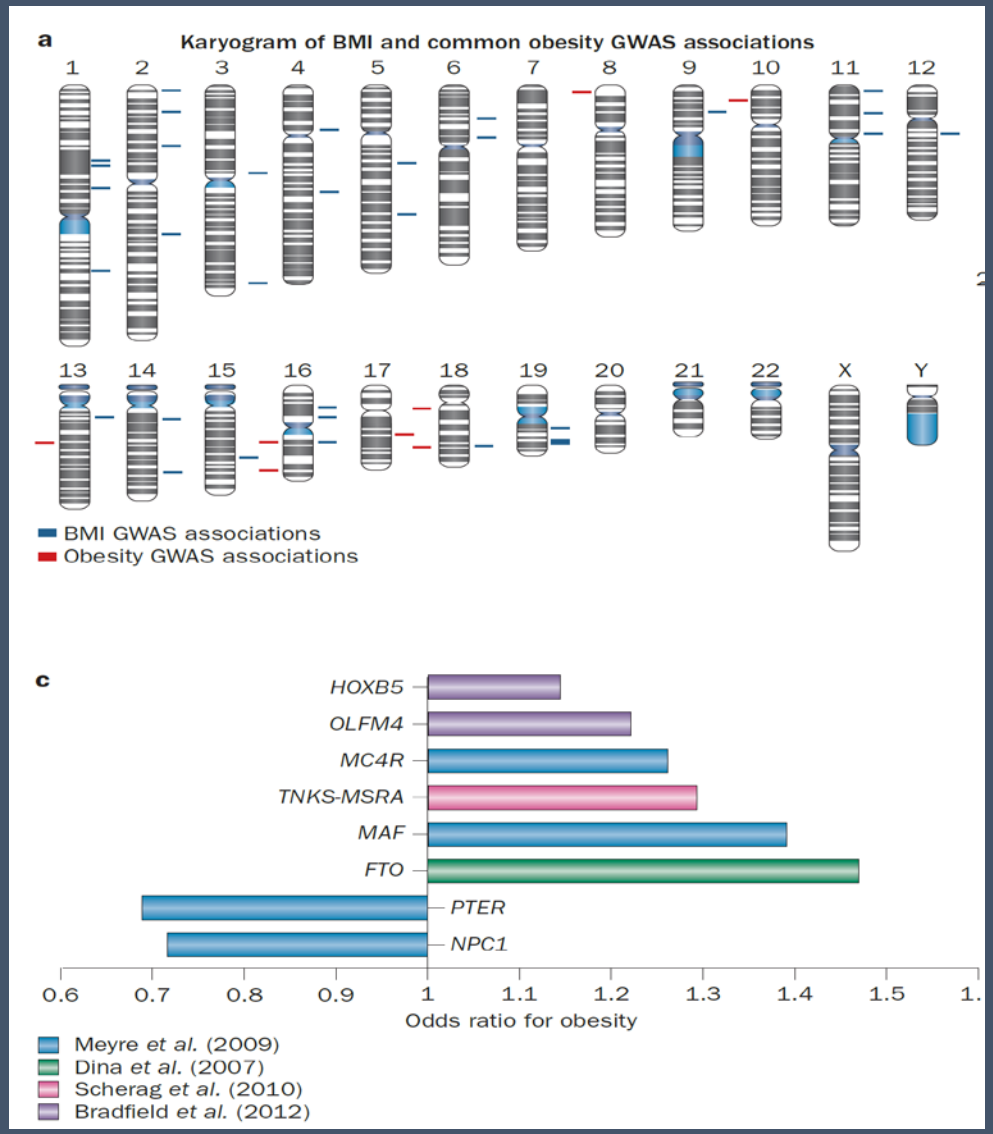
Julia S. El-Sayed Moustafa and Philippe Froguel

Abstract | Obesity is a disorder characterized by an excess accumulation of body fat resulting from a mismatch between energy intake and expenditure. Incidence of obesity has increased dramatically in the past few years, almost certainly fuelled by a shift in dietary habits owing to the widespread availability of low-cost, hypercaloric foods. However, clear differences exist in obesity susceptibility among individuals exposed to the same obesogenic environment, implicating genetic risk factors. Numerous genes have been shown to be involved in the development of monofactorial forms of obesity. In genome-wide association studies, a large number of common variants have been associated with adiposity levels, each accounting for only a small proportion of the predicted heritability. Although the small effect sizes of obesity variants identified in genome-wide association studies currently preclude their utility in clinical settings, screening for a number of monogenic obesity variants is now possible. Such regular screening will provide more informed prognoses and help in the identification of at-risk individuals who could benefit from early intervention, in evaluation of the outcomes of current obesity treatments, and in personalization of the clinical management of obesity. This Review summarizes current advances in obesity genetics and discusses the future of research in this field and the potential relevance to personalized obesity therapy.

El-Sayed Moustafa, J. S. & Froguel, P. *Nat. Rev. Endocrinol.* **9**, 402–413 (2013); published online 26 March 2013; corrected online 5 November 2013; doi:10.1038/nrendo.2013.57

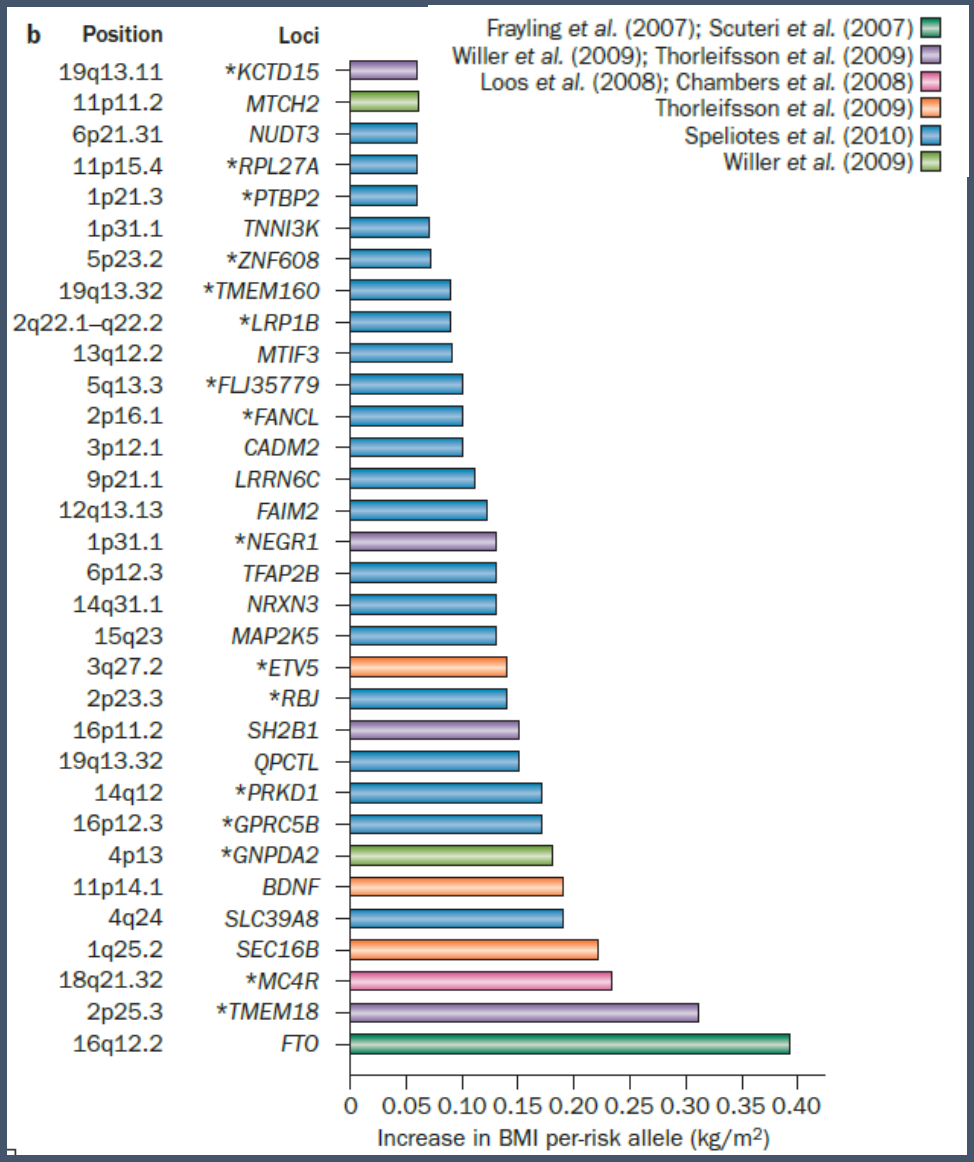
Loci asociados al IMC y la obesidad, y probabilidades informadas

- Asociación de IMC (barras azules)
- Asociación con la Obesidad (barras rojas)



Nature Reviews (2013)

TAMAÑO DEL EFECTO PARA VARIANTES GENÉTICAS ASOCIADAS AL IMC



*gene closest to the reported association

El-Sayed M et al. Nat Rev Endocrinol, 2013

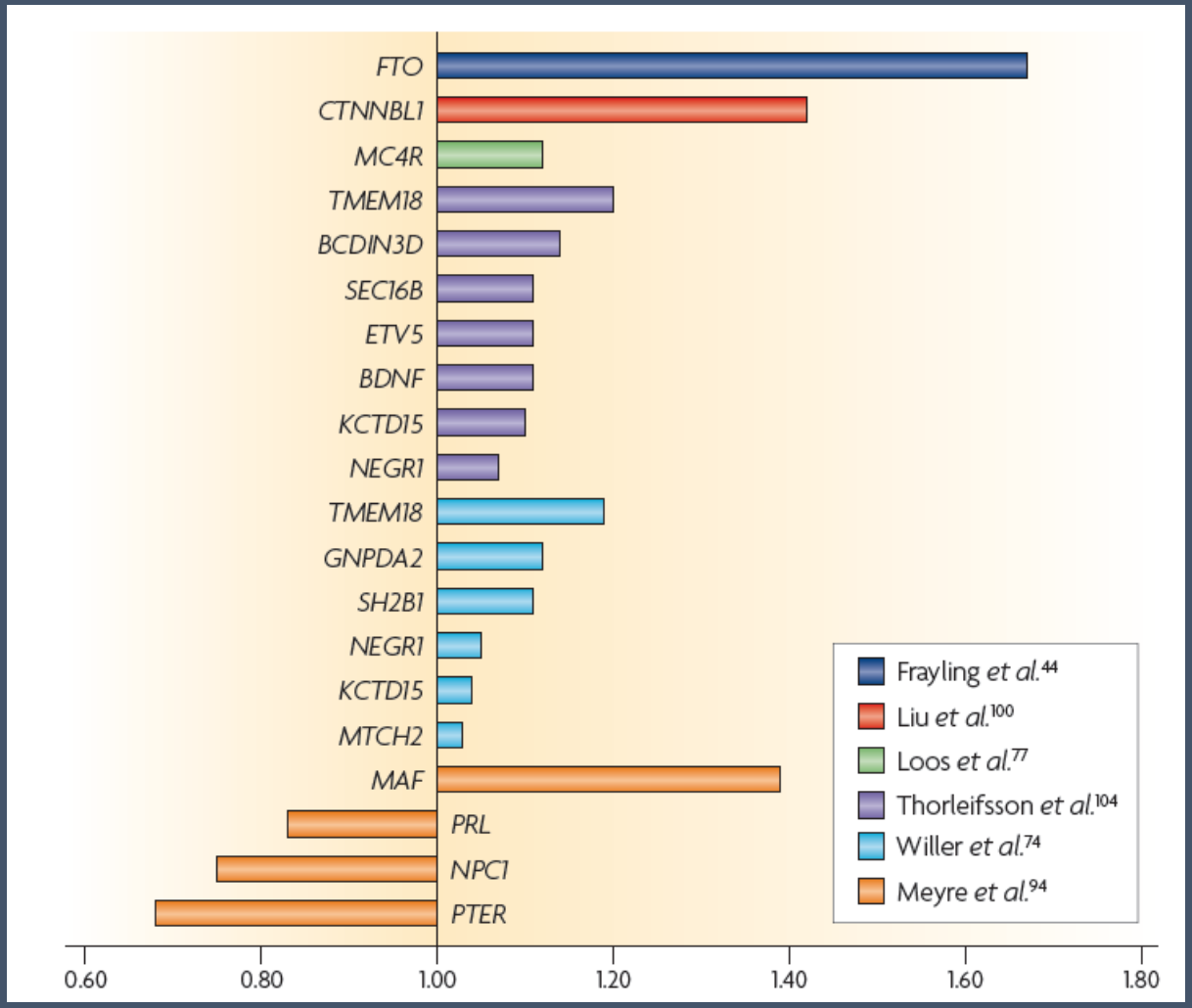
REVIEWS

The genetic contribution to non-syndromic human obesity

Andrew J. Walley, Julian E. Asher* and Philippe Froguel*‡*

Abstract | The last few years have seen major advances in common non-syndromic obesity research, much of it the result of genetic studies. This Review outlines the competing hypotheses about the mechanisms underlying the genetic and physiological basis of obesity, and then examines the recent explosion of genetic association studies that have yielded insights into obesity, both at the candidate gene level and the genome-wide level. With obesity genetics now entering the post-genome-wide association scan era, the obvious question is how to improve the results obtained so far using single nucleotide polymorphism markers and how to move successfully into the other areas of genomic variation that may be associated with common obesity.

GENES ASOCIADOS a la OBESIDAD HUMANA (GWAS)



Walley et al Nat Rev Genet. 2009;10:31-42

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Review

Genome-wide association studies of obesity and metabolic syndrome

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ABSTRACT

Until just a few years ago, the genetic determinants of obesity and metabolic syndrome were largely unknown, with the exception of a few forms of monogenic extreme obesity. Since genome-wide association studies (GWAS) became available, large advances have been made. The first single nucleotide polymorphism robustly associated with increased body mass index (BMI) was in 2007 mapped to a gene with for the time unknown function. This gene, now known as fat mass and obesity associated (*FTO*) has been repeatedly replicated in several ethnicities and is affecting obesity by regulating appetite. Since the first report from a GWAS of obesity, an increasing number of markers have been shown to be associated with BMI, other measures of obesity or fat distribution and metabolic syndrome. This systematic review of obesity GWAS will summarize genome-wide significant findings for obesity and metabolic syndrome and briefly give a few suggestions of what is to be expected in the next few years.

Variaciones genéticas habituales asociadas con categorías extremas de obesidad, se solapan al menos parcialmente con las del IMC en general

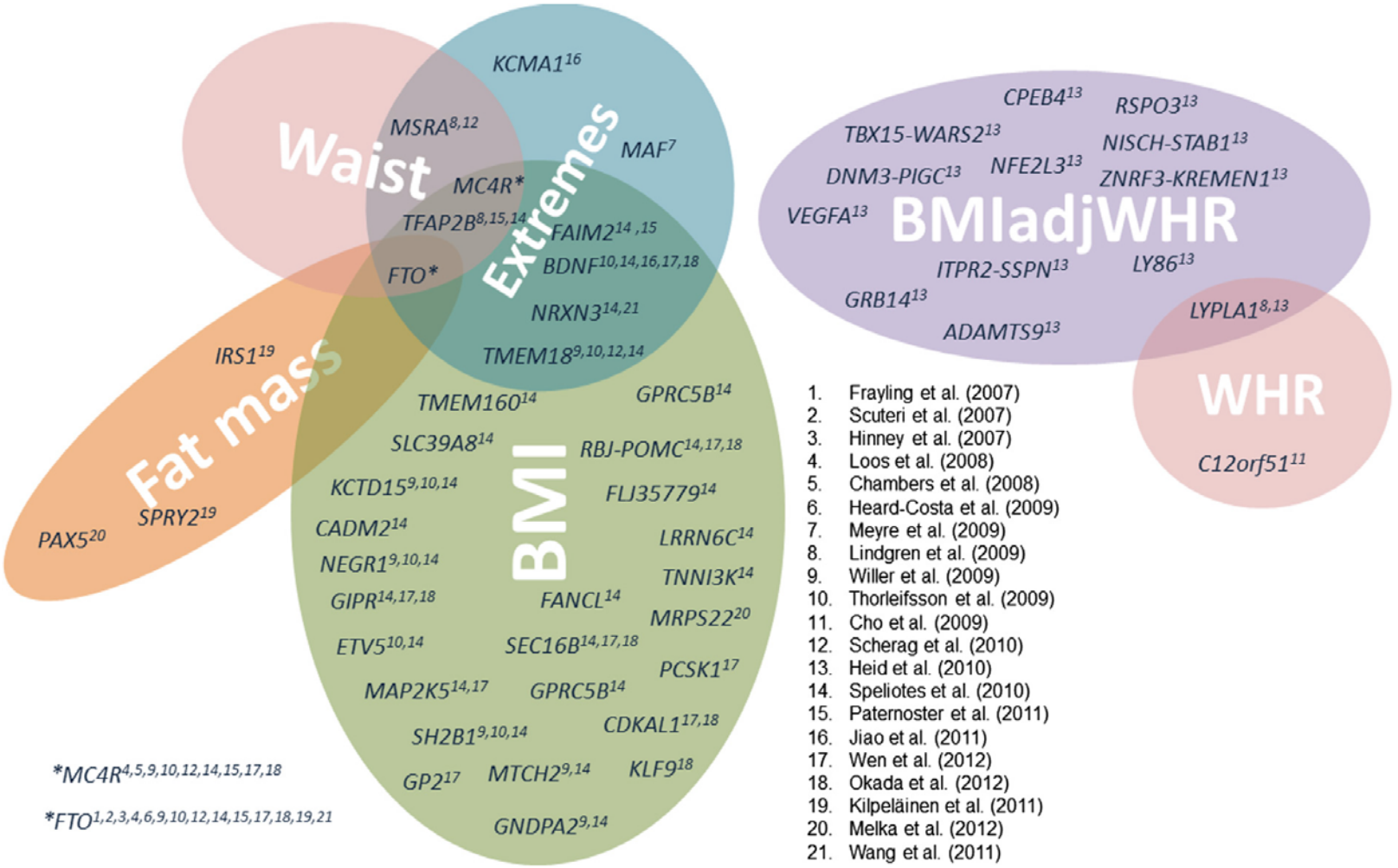

Fig. 2. Summary of loci found by genome-wide association studies to be associated with body mass index (BMI), waist circumference (waist), waist–hip ratio (WHR), extreme obesity phenotypes (extremes) or BMI-adjusted WHR (BMIadjWHR) with $p < 5 \times 10^{-8}$.

NUTRITION REVIEWS

Lead Article

Single-nucleotide polymorphisms and DNA methylation markers associated with central obesity and regulation of body weight

Leticia Goni, Fermín I Milagro, Marta Cuervo, and J Alfredo Martínez

Visceral fat is strongly associated with the development of specific obesity-related metabolic alterations. Genetic and epigenetic mechanisms seem to be involved in the development of obesity and visceral adiposity. The aims of this review are to identify the single-nucleotide polymorphisms related to central obesity and to summarize the main findings on DNA methylation and obesity. A search of the MEDLINE database was conducted to identify genome-wide association studies, meta-analyses of genome-wide association studies, and gene-diet interaction studies related to central obesity, and, in addition, studies that analyzed DNA methylation in relation to body weight regulation. A total of 8 genome-wide association studies and 9 meta-analyses of genome-wide association studies reported numerous single-nucleotide polymorphisms to be associated with central obesity. Ten studies analyzed gene-diet interactions and central obesity, while 2 epigenome-wide association studies analyzed DNA methylation patterns and obesity. Nine studies investigated the relationship between DNA methylation and weight loss, excess body weight, or adiposity outcomes. Given the development of new sequencing and omics technologies, significantly more knowledge on genomics and epigenomics of obesity and body fat distribution will emerge in the near future.

Meta-análisis de estudios GWAS

Table 2 **Single-nucleotide polymorphisms reported to be associated with central-obesity-related traits (waist circumference, waist-hip ratio, and visceral adipose tissue) in meta-analyses of genome-wide association studies reaching significance levels of $P < 10^{-8}$.**

Gene	SNP	Population	Sex	Trait	Discovery meta-analysis		Follow-up studies		Combined meta-analysis		Reference
					No. of subjects	*P* value	No. of subjects	*P* value	No. of subjects	*P* value	
FTO	rs9939609	Whites, Asians, African Americans, Hispanics	F and M	WC	159,848	5.4×10^{-43}	–	–	–	–	Kilpeläinen et al. (2011)[31]
RSPO3	rs9491696	European ancestry	F and M	WHR adj BMI	77,164	2.10×10^{-14}	113,582	3.27×10^{-28}	190,746	1.84×10^{-40}	Heid et al. (2010)[32]
LYPLAL1/SLC30A10	rs2820443	European, European-American descent	F	WHR adj BMI	73,137	3.69×10^{-18}	74,657	9.51×10^{-37}	147,794	4.62×10^{-37}	Randall et al. (2013)[33]
VEGFA	rs1358980	European, European-American descent	F	WHR adj BMI	73,137	1.11×10^{-13}	74,657	1.38×10^{-19}	147,794	2.41×10^{-31}	Randall et al. (2013)[33]
GRB14/COBLL1	rs6717858	European, European-American descent	F	WHR adj BMI	73,137	2.78×10^{-15}	74,657	3.64×10^{-16}	147,794	1.99×10^{-29}	Randall et al. (2013)[33]
VEGFA	rs6905288	European ancestry	F and M	WHR adj BMI	77,129	4.72×10^{-10}	95,430	1.18×10^{-16}	172,559	5.88×10^{-25}	Heid et al. (2010)[32]
TBX15-WARS2	rs984222	European ancestry	F and M	WHR adj BMI	77,167	3.81×10^{-14}	109,623	1.56×10^{-12}	186,790	8.69×10^{-25}	Heid et al. (2010)[32]
NFE2L3	rs1055144	European ancestry	F and M	WHR adj BMI	77,145	1.49×10^{-8}	113,636	3.26×10^{-18}	190,781	9.97×10^{-25}	Heid et al. (2010)[32]
GRB14	rs10195252	European ancestry	F and M	WHR adj BMI	77,119	3.23×10^{-10}	102,449	3.18×10^{-16}	179,568	2.09×10^{-24}	Heid et al. (2010)[32]
ADAMTS9	rs2371767	European, European-American descent	F	WHR adj BMI	73,137	1.63×10^{-8}	74,657	8.55×10^{-17}	147,794	7.07×10^{-23}	Randall et al. (2013)[33]
LYPLAL1	rs4846567	European ancestry	F and M	WHR adj BMI	77,167	2.37×10^{-12}	91,820	3.15×10^{-10}	168,987	6.89×10^{-21}	Heid et al. (2010)[32]
DNM3-PIGC	rs1011731	European ancestry	F and M	WHR adj BMI	77,094	1.72×10^{-10}	92,018	7.47×10^{-9}	169,112	9.51×10^{-18}	Heid et al. (2010)[32]
ITPR2-SSPN	rs718314	European ancestry	F and M	WHR adj BMI	77,167	2.41×10^{-8}	107,503	1.49×10^{-10}	184,670	1.14×10^{-17}	Heid et al. (2010)[32]
LY86	rs1294421	European ancestry	F and M	WHR adj BMI	77,154	6.31×10^{-9}	102,189	2.69×10^{-10}	179,343	1.75×10^{-17}	Heid et al. (2010)[32]
HOXC13	rs1443512	European ancestry	F and M	WHR adj BMI	77,165	3.33×10^{-8}	112,353	2.92×10^{-10}	189,518	6.38×10^{-17}	Heid et al. (2010)[32]
CETP	rs173539	European ancestry	F and M	HDLc-WC	22,161	1.0×10^{-16}	–	–	–	–	Kraja et al. (2011)[34]
ZNF259	rs2075290	European ancestry	F and M	WC-TG	22,161	1.1×10^{-16}	–	–	–	–	Kraja et al. (2011)[34]
APOA5	rs2266788	European ancestry	F and M	WC-TG	22,161	2.2×10^{-16}	–	–	–	–	Kraja et al. (2011)[34]
BUD13	rs10790162	European ancestry	F and M	WC-TG	22,161	6.6. × 10–16	–	–	–	–	Kraja et al. (2011)[34]
PPARG	rs4684854	European, European-American descent	F	WHR adj BMI	73,137	2.36×10^{-8}	74,657	1.48×10^{-7}	147,794	4.17×10^{-14}	Randall et al. (2013)[33]
ADAMTS9	rs6795735	European ancestry	F and M	WHR adj BMI	77,162	2.47×10^{-7}	84,480	6.75×10^{-8}	161,642	9.79×10^{-14}	Heid et al. (2010)[32]
GCKR	rs780093	European ancestry	F and M	WC-TG	22,161	1.9×10^{-12}	–	–	–	–	Kraja et al. (2011)[34]
ZNRF3-KREMEN1	rs4823006	European ancestry	F and M	WHR adj BMI	77,086	2.41×10^{-5}	93,911	2.41×10^{-5}	170,997	1.10×10^{-11}	Heid et al. (2010)[32]
TFAP2B	rs987237	European ancestry	F and M	WC	38,635	1.10×10^{-4}	12,369–43,016	2.57×20^{-1}–2.22×10^{-5}	118,691	1.87×10^{-11}	Lindgren et al. (2009)[35]
MAP3K1	rs11743303	European, European-American descent	F	WHR adj BMI	73,137	2.27×10^{-6}	74,657	7.15×10^{-7}	147,794	2.69×10^{-11}	Randall et al. (2013)[33]
LPL	rs301	European ancestry	F and M	HDLc-WC	22,161	3.2×10^{-11}	–	–	–	–	Kraja et al. (2011)[34]
LY86	rs1294421	European ancestry	F and M	WHR	9,803	1.62×10^{-9}	6,703	6.85×10^{-3}	16,506	2.19×10^{-10}	Berndt et al. (2013)[36]
NISCH-STAB1	rs6784615	European ancestry	F and M	WHR adj BMI	76,859	3.18×10^{-7}	109,028	1.56×10^{4}	185,887	3.84×10^{-10}	Heid et al. (2010)[32]
RSPO3	rs7745274	European ancestry	F and M	WHR	10,077	3.91×10^{-6}	6,250	5.33×10^{-5}	16,327	8.80×10^{-10}	Berndt et al. (2013)[36]
CCDC121	rs3749147	European ancestry	F and M	WC-TG	22,161	1.4×10^{-9}	–	–	–	–	Kraja et al. (2011)[34]
CPEB4	rs6861681	European ancestry	F and M	WHR adj BMI	77,164	1.40×10^{-6}	85,722	2.13×10^{-4}	162,886	1.91×10^{-9}	Heid et al. (2010)[32]
C2orf16	rs1919128	European ancestry	F and M	WC-TG	22,161	2.0×10^{-9}	–	–	–	–	Kraja et al. (2011)[34]
HSD17B4	rs10478424	European, European-American descent	F	WHR adj BMI	73,137	1.02×10^{-5}	74,657	3.81×10^{-5}	147,794	3.45×10^{-9}	Randall et al. (2013)[33]
ZNF512	rs13022873	European ancestry	F and M	WC-TG	22,161	5.0×10^{-9}	–	–	–	–	Kraja et al. (2011)[34]
LYPLAL1	rs2820464	European ancestry	F and M	WHR	9,458	4.54×10^{-10}	6,177	1.16×10^{-1}	15,635	7.35×10^{-9}	Berndt et al. (2013)[36]
MSRA	rs545854	European ancestry	F and M	WC	36,865	1.32 × 10–5	3,406–31,481	4.63×10^{-1}–5.31×10^{-4}	80,210	8.89×10^{-9}	Lindgren et al. (2009)[35]
THNSL2	rs1659258	Caucasians, African Americans	F	VAT (CT)	10,557	1.58×10^{-8}	3,158	1.6×10^{-8}	–	–	Fox et al. (2012)[37]
LHX2	rs2075064	African ancestry	F and M	WC adj BMI	23,564	5.5×10^{-8}	10,027	3.2×10^{-2}	33,591	2.2×10^{-8}	Liu et al. (2013)[38]
RREB1	rs6931262	African ancestry	F and M	WHR adj BMI	19,744	5.3×10^{-8}	7,606	4.5×10^{-2}	27,350	2.5×10^{-8}	Liu et al. (2013)[38]
LYPLAL1	rs2605100	European ancestry	F	WHR	21,397	1.30×10^{-8}	6,021–20,213	8.17×10^{-2}–9.06×10^{-2}	47,633	2.55×10^{-8}	Lindgren et al. (2009)[35]
COBLL1	rs13389219	European ancestry	F and M	WHR	9,880	2.68×10^{-6}	6,772	3.09×10^{-3}	16,652	3.24×10^{-8}	Berndt et al. (2013)[36]
LOC100129150	rs9987289	European ancestry	F and M	HDLc-WC	22,161	3.7×10^{-8}	–	–	–	–	Kraja et al. (2011)[34]
NRXN3	rs10146997	Caucasian descent	F and M	WC	31,373	6.4×10^{-7}	38,641	0.009	70,014	5.3×10^{-8}	Heard-Costa et al. (2009)[39]
LIPC	rs10468017	European ancestry	F and M	HDLc-WC	22,161	5.5×10^{-8}	–	–	–	–	Kraja et al. (2011)[34]

Abbreviations: adj, adjusted for; BMI, body mass index; CT, computed tomography; F, female; HDLc, high-density lipoprotein cholesterol; M, male; SNP, single-nucleotide polymorphism; TG, triglycerides; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-hip ratio; –, no available data.
Data were sorted first by combined meta-analysis *P* values, then by follow-up study *P* values, and lastly by discovery meta-analysis *P* values.

Nutrition Reviews (2015)

International Journal of Obesity (2012) **36,** 479 - 484

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PEDIATRIC REVIEW

Genetic influences in childhood obesity: recent progress and recommendations for experimental designs

JR Fernandez[1,2], YC Klimentidis[2], A Dulin-Keita[1] and K Casazza[1]

The increasing prevalence of pediatric obesity around the world has become an area of scientific interest because of public health concern. Although since early stages of the lifespan body weight might be heavily influenced by an individual's behavior, epidemiological research highlights the involvement of genetic influences contributing to variation in fat accumulation and thus body composition. Results from genome-wide association studies and candidate gene approaches have identified specific regions across the human genome influencing obesity-related phenotypes. Reviewing the scientific literature provides support to the belief that at the conceptual level scientists understand that genes and environments do not act independently, but rather synergistically, and that such interaction might be the responsible factor for differences within and among populations. However, there is still limited understanding of genetic and environmental factors influencing fat accumulation and deposition among different populations, which highlights the need for innovative experimental designs, improved body composition measures and appropriate statistical methodology.

International Journal of Obesity (2012) **36,** 479–484; doi:10.1038/ijo.2011.236; published online 13 December 2011

Keywords: childhood obesity; genes; admixture; statistics; body composition

GENES ASOCIADOS A LA OBESIDAD

32 genes from GWAs

127 genes from candidate studies

Table 1. List of loci associated with BMI from GWAS[25]

Chromosome	Position (bp)	SNP	Nearest gene
1	72585028	rs2815752	*NEGR1*
1	74764232	rs1514175	*TNNI3K*
1	96717385	rs1555543	*PTBP2*
1	176156103	rs543874	*SEC16B*
2	612827	rs2867125	*TMEM18*
2	25011512	rs713586	*RBJ*
2	59156381	rs887912	*FANCL*
2	142676401	rs2890652	*LRP1B*
3	85966840	rs13078807	*CADM2*
3	187317193	rs9816226	*ETV5*
4	44877284	rs10938397	*GNPDA2*
4	103407732	rs13107325	*SLC39A8*
5	75050998	rs2112347	*FLJ35779*
5	124360002	rs4836133	*ZNF608*
6	34410847	rs206936	*NUDT3*
6	50911009	rs987237	*TFAP2B*
9	28404339	rs10968576	*LRRN6C*
11	8561169	rs4929949	*RPL27A*
11	27682562	rs10767664	*BDNF*
11	47607569	rs3817334	*MTCH2*
12	48533735	rs7138803	*FAIM2*
13	26918180	rs4771122	*MTIF3*
14	29584863	rs11847697	*PRKD1*
14	79006717	rs10150332	*NRXN3*
15	65873892	rs2241423	*MAP2K5*
16	19841101	rs12444979	*GPRC5B*
16	28793160	rs7359397	*SH2B1*
16	52361075	rs1558902	*FTO*
18	55990749	rs571312	*MC4R*
19	39001372	rs29941	*KCTD15*
19	50894012	rs2287019	*QPCTL*
19	52260843	rs3810291	*TMEM160*

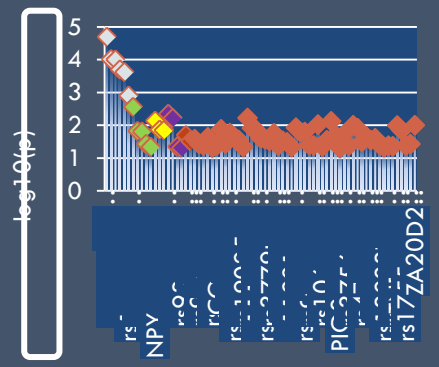


Table 2. Genes associated with obesity from candidate gene studies, based on Rankinen *et al.*[18] and Walley *et al.*[77]

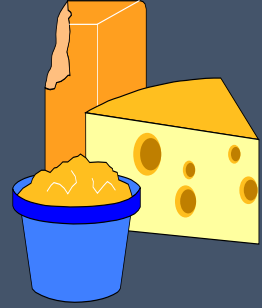
Chromosome	Candidate gene studies
1	*LEPR*[a]
1	*LMNA*
2	*KLF7*
3	*ADIPOQ*
3	*PPARG*
3	*GHSR*
4	*UCP1*
4	*TBC1D1*
4	*NPY2R*[a]
5	*ADRB2*
5	*NR3C1*
5	*PCSK1*[a]
6	*ENPP1*[a]
6	*CNR1*[a]
7	*LEP*
7	*NAMPT*[a]
8	*ADRB3*[a]
8	*MTMR9*
11	*INS*
11	*UCP2*
11	*UCP3*
12	*GNB3*
12	*IL6*
12	*TNF*
12	*VDR*
14	*DLK1*
15	*PLIN*
16	*SOCS1*
17	*ACE*
17	*SOCS3*
18	*MC4R*[a]
19	*LDLR*
19	*LIPE*
X	*HTR2C*

[a]indicates association in children.

Discrepancias entre GWAS y datos de genes candidatos

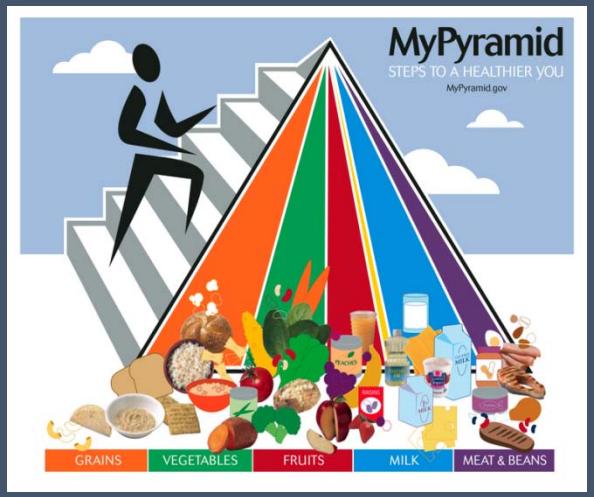
Fernández *et al*. *International Journal of Obesity* (2012) 36, 479—484.

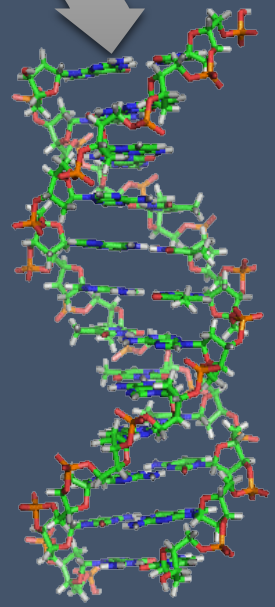
Nutrigenómica y Nutrigenética



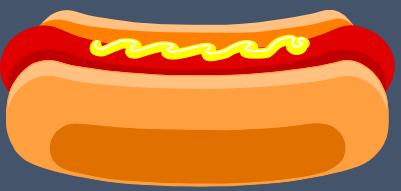
Efectos de la dieta en la expresión génica

NUTRIGENÓMICA



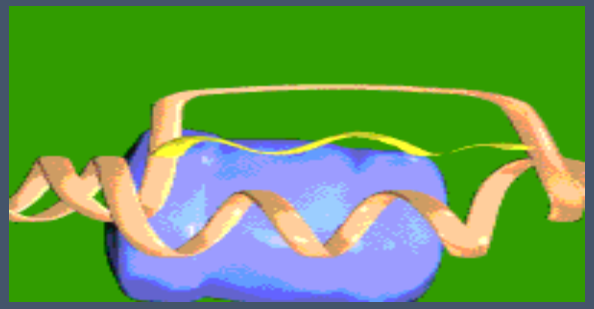


NUTRIGENÉTICA



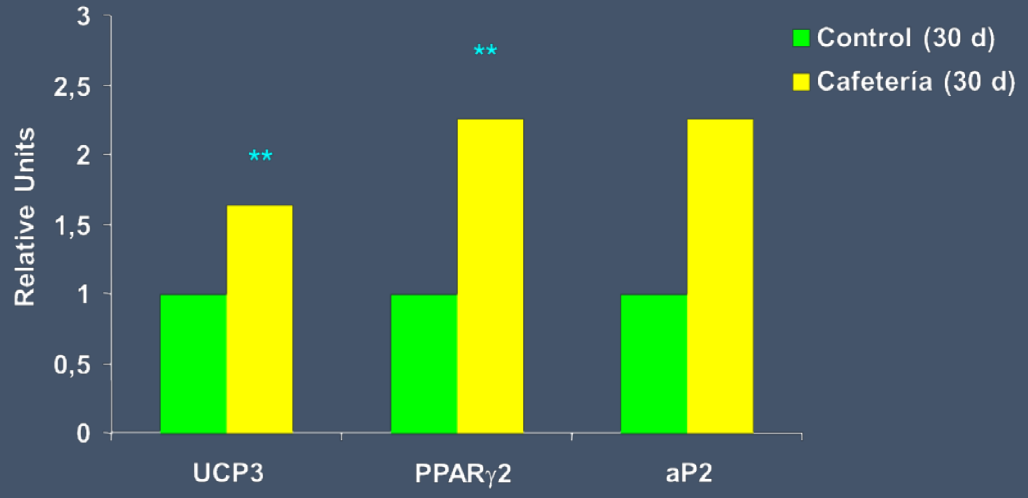
El genotipo influye la respuesta asociada con la nutrición y el metabolismo personalizados

INTERACCIONES NUTRIGENÓMICAS



Nutrición → **Expresión GÉNICA** → **Fenotipo**

EXPRESIÓN GÉNICA DEPENDIENTE DE LA DIETA



Margareto, *et al.* 2001

EXPRESIÓN GÉNICA DEPENDIENTE DE LA DIETA

Viguerie, *et al.* 2010

INTERACCIONES GENOTIPO - NUTRICION

Genotipo

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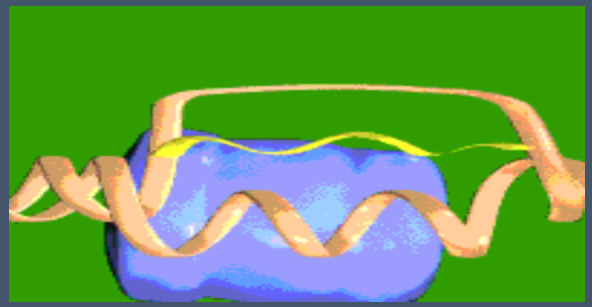
Nutrición

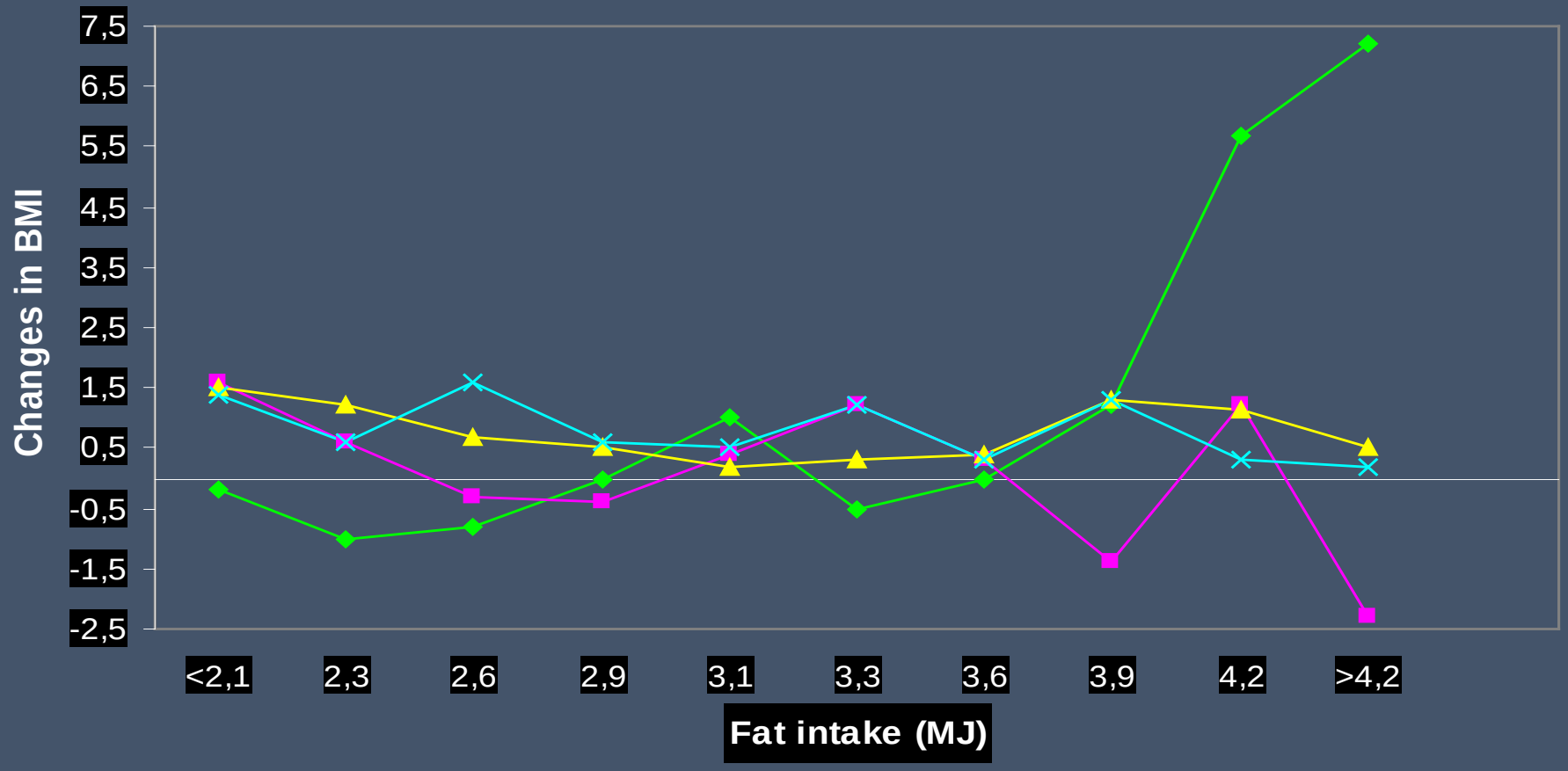
Expresión génica

Fenotipo

Estado Nutricional

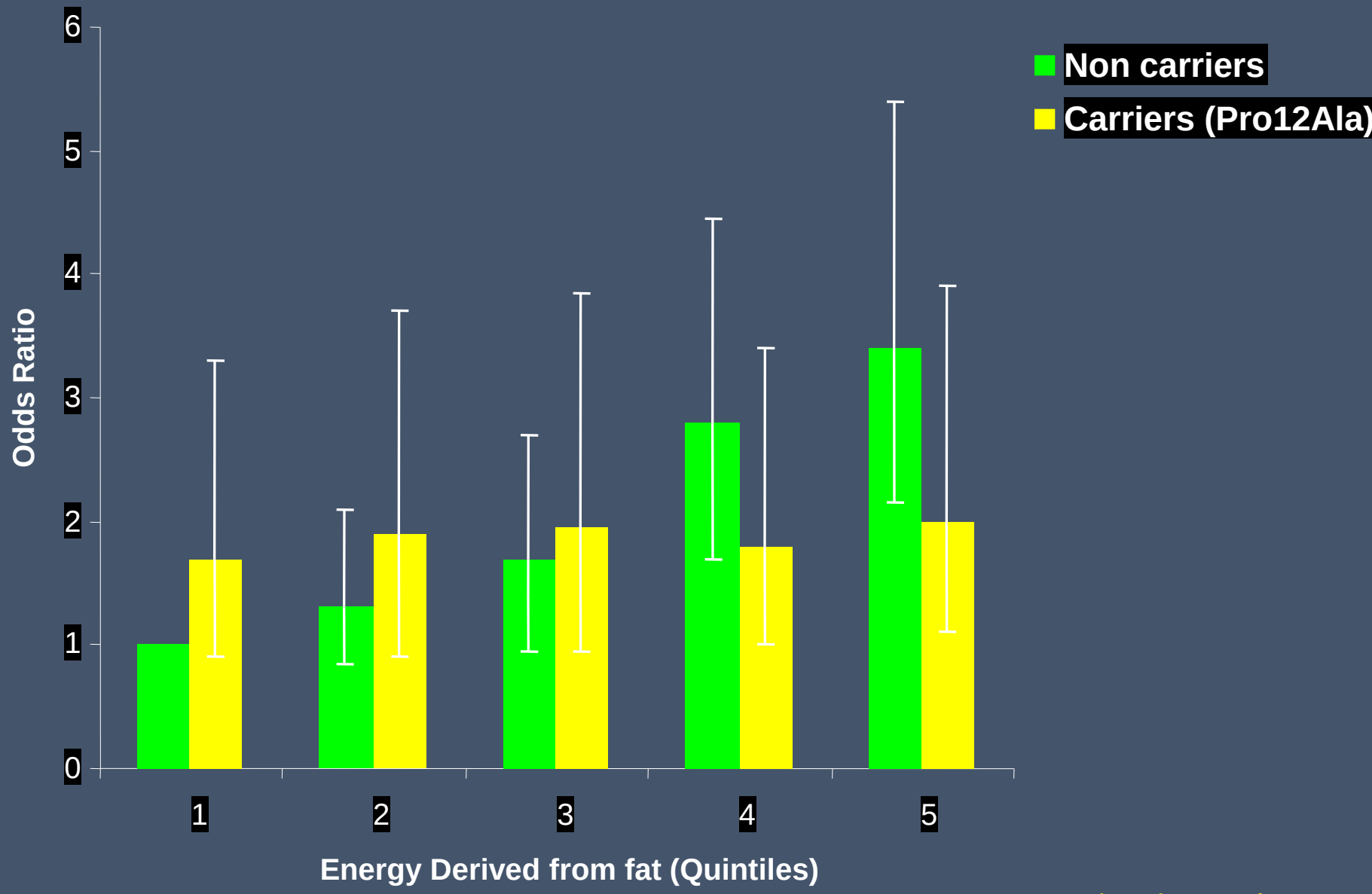


INTERACCIONES IMC, INGESTA DE GRASA Y GENOTIPO



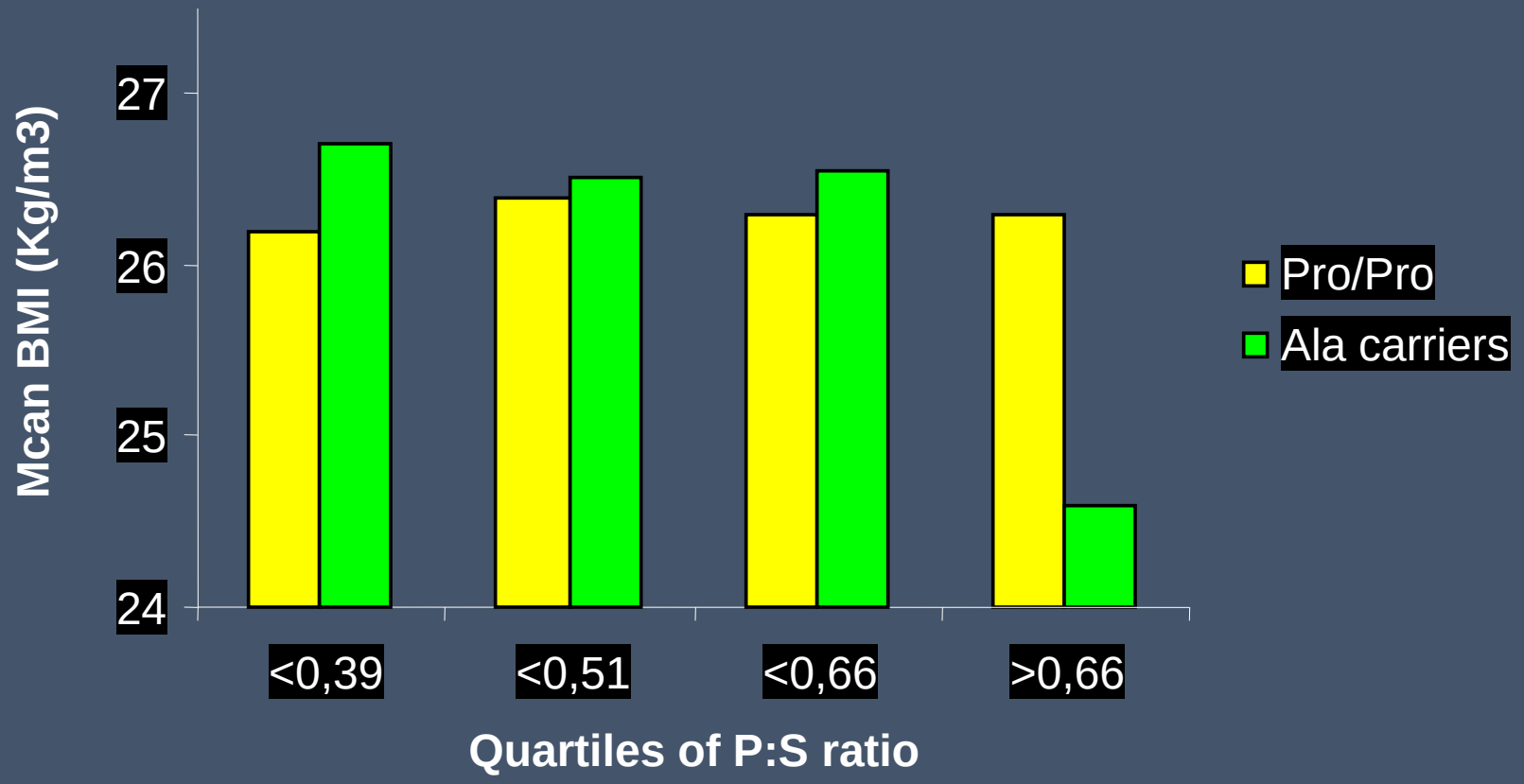
SORENSEN, *et al.* 1997

INTERACCIONES GENOTIPO X NUTRIENTE (GRASA)



Memisoglu, *et al.* 2003

INTERACCIONES GENOTIPO - NUTRICION



Luan, *et al.* 2001

La distribución de ácidos grasos dietéticos modifica el riesgo de obesidad asociado al polimorfismo rs9939609 del gen FTO en un estudio de caso-control en niños españoles

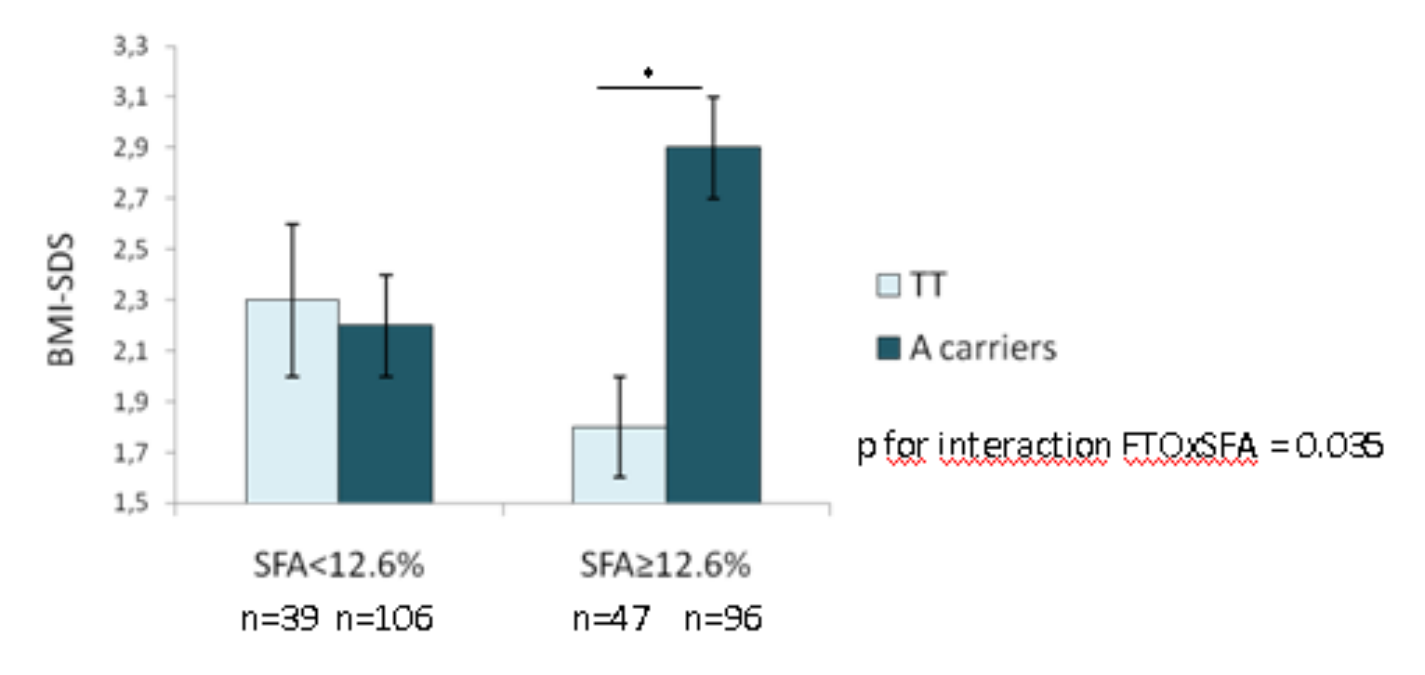
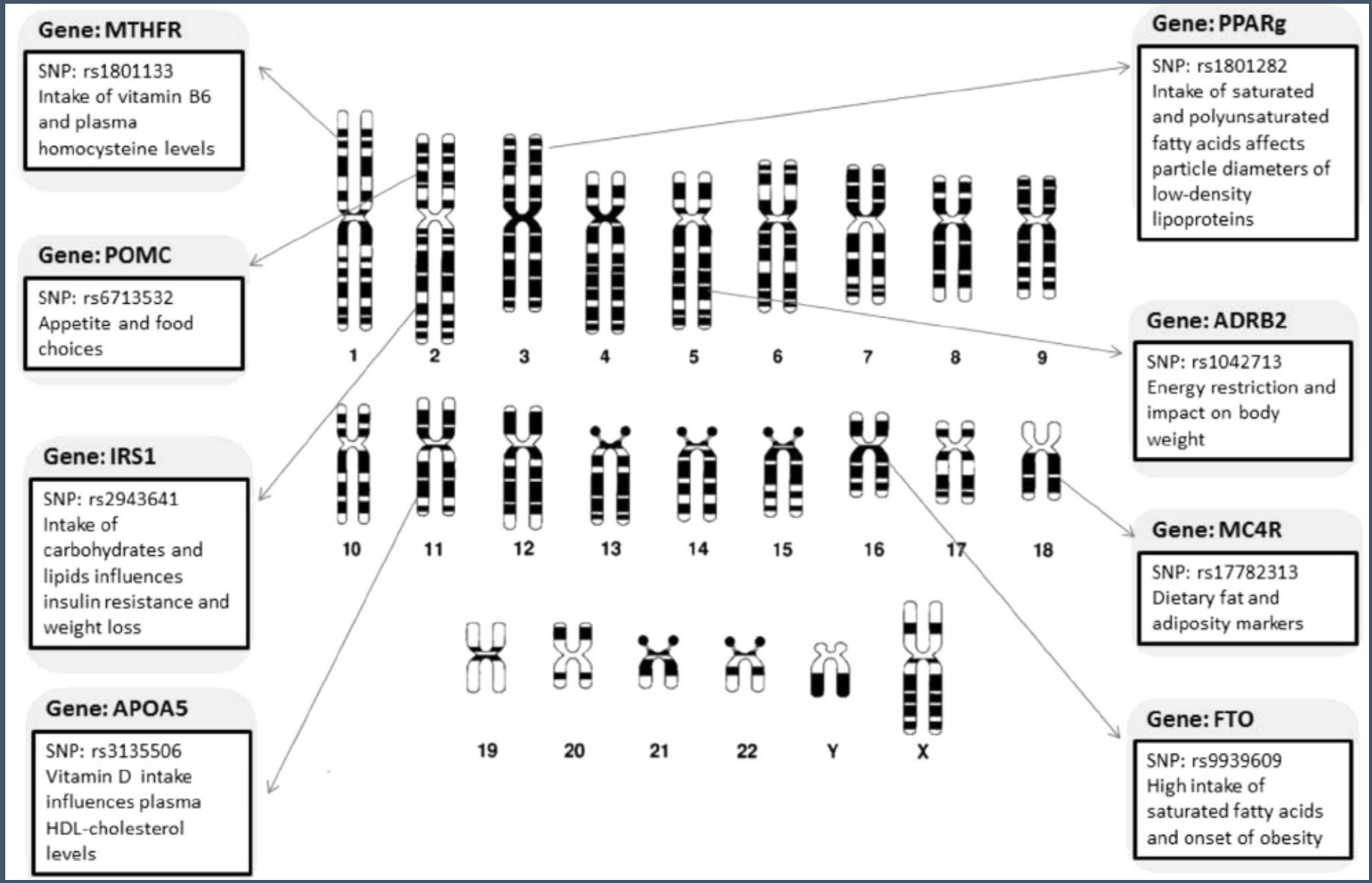


Fig. 2. BMI-standard deviation score (SDS) of children and adolescents according to SFA consumption (percentage of total energy, dichotomised by the median) and the presence of the fat mass and obesity associated (FTO) rs9939609 polymorphism in a dominant model. Values are means, with their standard errors represented by vertical bars.

Br J Nutr, 2012; 107 **(4):** 533-8

INTERACCIONES GEN - NUTRIENTE



San-Cristóbal R et al. J Acad Nut. Diet, 2013

INTERPRETACIÓN!

Leading Edge
Review

Cell

The Hunger Genes: Pathways to Obesity

Agatha A. van der Klaauw[1] and I. Sadaf Farooqi[1,*]
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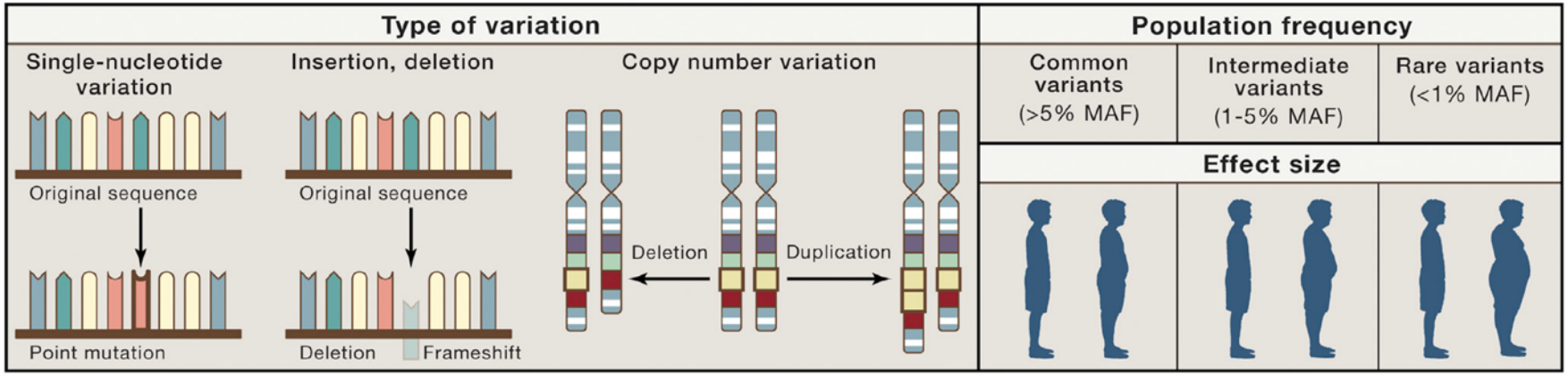


Figure 4. Types of Genetic Variation Contributing to Body Weight Regulation

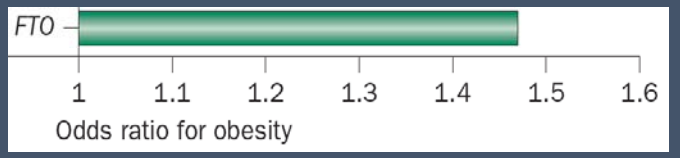
Genetic effects on body weight are mediated by different types of variants, their frequency in the population, and the effect of the variant on the phenotype. Variants include single-nucleotide variations in which only one nucleotide is changed, copy number variations in which a stretch of DNA is repeated or deleted (often containing many genes), or small insertions and deletions of a few base pairs. Common variants are found at a minor allele frequency (MAF) of more than 5% in a population, whereas intermediate (1%–5%) and rare variants (< 1%) are found at lower frequencies. Generally, the effect size of common obesity-associated variants on body weight is modest. Several rare variants have been associated with severe obesity.

KARYOGRAM DEPICTING LOCI THAT HAVE BEEN ASSOCIATED WITH BODY WEIGHT LOSS IN RESPONSE TO A NUTRITIONAL INTERVENTION

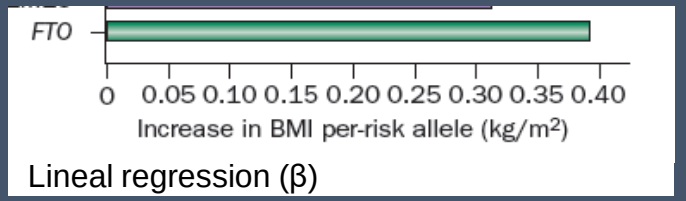
CONTRIBUCIÓN GENÉTICA A LA REGULACIÓN DEL PESO

1. Risk alleles — rs9939609 (FTO): TT TA AA

2. Obesity risk



3. Allele contribution to body weight



Lineal regression (β)

4. Genetic predisposition score (GPS)

$GPS = (SNP_1 + SNP_2 + \ldots SNP_n)$

Goni L. et al., 2015

$GPS = (SNP_1 + SNP_2 + \ldots SNP_n) / \Sigma SNP$

Peterson RE. et al., 2011

$Weighted\ GPS = (\beta_1 x SNP_1 + \beta_2 x SNP_2 + \ldots \beta_n x SNP_n)$

Renström F. et al., 2011

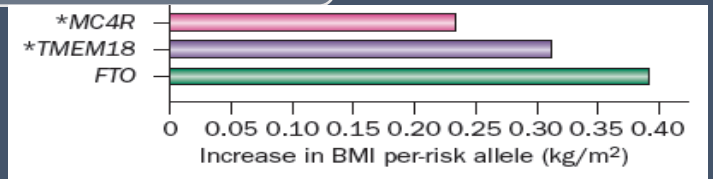
$Weighted\ GPS = (\beta_1 x OR_1 + \beta_2 x OR_2 + \ldots \beta_n x OR_n)$

Cheung CYY et al., 2010

$Weighted\ GPS = (\beta_1 x SNP_1 + \beta_2 x SNP_2 + \ldots \beta_n x SNP_n) \times (\Sigma SNP / \Sigma \beta s)$

Qi Q. et al., 2014

5. Propensity score matching ?



TESTS GENÉTICOS

SNP	polimorfismo
01	APOA5 (rs662799) g.4430 T>C
02	APOB (rs5742904) c.10580 G>A
03	APOA1 (rs670) g.4926 G>A
04	ESR1 (rs2234693) c.453-387 T>C
05	FTO (rs9939609) c.46-23525 T>A
06	GC (rs2282679) c.*26-796 A>C
07	GCKR (rs1260326) c.1337 C>T
08	GNB3 (rs5443) c. 825 C>T
09	MTNR1B (rs10830963) c.223+5596 C>G
10	MC4R (rs17782313) g.5785109 T>C
11	LPL (rs328) c.1421 C>G
12	LIPG (rs4939883) g.47167214 C>T
13	CETP (rs1800777) c.1403 G>A
14	LIPC (rs1800588) g.4501 C>T
15	NOS3 (rs1799983) c.894 G>T
16	PLIN4 (rs894160) c.772-799 G>A
17	PPARA (rs1800206) c.484 C>G
18	PPARG (rs1801282) c.34 C>G
19	CELSR2 (rs12740374) c.*919 G>T
20	MTHFR (rs1801133) c.665 C>T
21*	LCT/MCM6 (rs4988235) c.1917+326 T>C
23	APOE (rs429358) c.388 T>C
24	APOE (rs7412) c.526 C>T

Gen

SNP

SNP (Alternative nomenclature)

GRS basado en contabilizar los alelos de riesgo

TESTS GENÉTICOS

Gen	SNP	Genotipo	Score/SNP	Score/patolog	(minor-minor)	(major-minor)	(major-major)	Major allele	Minor allele
OBESIDAD									
FTO	**rs9939609**	**AA**	**0,6**	4,1	0,6	0,3	0	T	A
		Prevalencia	*15*		*15*	*60*	*25*		
MC4R	**rs17782313**	**CC**	**2,5**		2,5	2	0	T	C
		Prevalencia	*3*		*3*	*47*	*50*		
MTHFR	**rs1801133**	**CC**	**0**		0,2	0	0	C	T
		Prevalencia	*50*		*10*	*40*	*50*		
DIABETES									
FTO	**rs9939609**	**AA**	**2**	3,7	2	0,6	0	T	A
		Prevalencia	*15*		*15*	*60*	*25*		
PPARA	**rs1800206**	**CC**	**0**		0,3	0,2	0	C	G
		Prevalencia	*95*		*1*	*4*	*95*		
PPARG	**rs1801282**	**CG**	**0,3**		0,3	0,2	0	C	G
		Prevalencia	*15*		*5*	*15*	*80*		
MTNR1B	**rs10830963**	**CC**	**0**		0,3	0,1	0	C	G
		Prevalencia	*52*		*4*	*44*	*52*		
GNB3	**rs5443**	**TT**	**0,4**		0,4	0,2	0	C	T
		Prevalencia	*10*		*10*	*55*	*35*		
HIPERTENSIÓN									
MTHFR	**rs1801133**	**CC**	**0**	1,4	0,2	0,1	0	C	T
		Prevalencia	*50*		*10*	*40*	*50*		
NOS3	**rs1799983**	**CT**	**0**		0,2	0	0	C	T
		Prevalencia	*34*		*7*	*34*	*59*		
GNB3	**rs5443**	**TT**	**0,4**		0,4	0,1	0	C	T
		Prevalencia	*10*		*10*	*55*	*35*		
INTOLERANCIA A LA LACTOSA									
LCT	**rs4988235**	**TT**	**-4**	-5	4	0	-4	T	C
		Prevalencia	*55*		*10*	*35*	*55*		

(C;C) 4x lactose intolerance **(C;T) 0x lactose intolerance** **(T;T) -4x lactose tolerance**

TESTS GENÉTICOS
INTERACCIONES GEN-DIETA

Gen	SNP	Major allele	Minor allele	INTERACCIONES	
APOA1	rs670	G	A	Si GG (3)	Si su dieta es
APOA1	rs670	G	A	Si AA (1)	Una dieta ric
LIPC	rs1800588	C	T	Si TT (1)	Una dieta ric
MTHFR	rs1801133	C	T	Si TT (1)	Si la ingesta
NOS3	rs1799983	C	T	Si TT (1)	Los ácidos gr
PLIN	rs894160	G	A	Si AA (1)	Una dieta ric
PPARA	rs1800206	C	G	Si GG (1)	Si su dieta es
PPARG	rs1801282	C	G	Si GG (1)	Si su dieta es

Si su dieta es **rica en grasas** o si su ingesta de **grasas monoinsaturadas**, como el aceite de oliva, es muy elevada, usted tiene mayor predisposición que la mayoría de la población para desarrollar **diabetes tipo 2, obesidad e hipertensión**.
Le recomendamos una **dieta algo más baja en grasas** para prevenir estas posibles consecuencias.

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RESEARCH PAPER

A genetic risk tool for obesity predisposition assessment and personalized nutrition implementation based on macronutrient intake

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Abstract There is little evidence about genetic risk score (GRS)–diet interactions in order to provide personalized nutrition based on the genotype. The aim of the study was to assess the value of a GRS on obesity prediction and to further evaluate the interactions between the GRS and dietary intake on obesity. A total of 711 seekers of a Nutrigenetic Service were examined for anthropometric and body composition measurements and also for dietary habits and physical activity. Oral epithelial cells were collected for the identification of 16 SNPs (related with obesity or lipid metabolism) using DNA zip-coded beads. Genotypes were coded as 0, 1 or 2 according to the number of risk alleles, and the GRS was calculated by adding risk alleles with such a criterion. After being adjusted for gender, age, physical activity and energy intake, the GRS demonstrated that individuals carrying >7 risk alleles had in average 0.93 kg/m^2 of BMI, 1.69 % of body fat mass, 1.94 cm of waist circumference and 0.01 waist-to-height ratio more than the individuals with ≤7 risk alleles. Significant interactions for GRS and the consumption of energy, total protein, animal protein, vegetable protein, total fat, saturated fatty acids, polyunsaturated fatty acids, total carbohydrates, complex carbohydrates and fiber intake on adiposity traits were found after adjusted for confounders variables. The GRS confirmed that the high genetic risk group showed greater values of adiposity than the low risk group and demonstrated that macronutrient intake modifies the GRS association with adiposity traits.

Keywords Genetic risk score · Obesity · Adiposity · Gene–macronutrient interaction

Introduction

The prevalence of obesity is rising steadily not only in high-income countries but also in low-income countries. Indeed, it has been estimated that 1.12 billion adults will be obese by 2030 (Kelly et al. 2008). Consequently, the prevalence of obesity-associated metabolic diseases, such as type 2 diabetes, cardiovascular disease or certain can-

POLIMORFISMOS INCLUÍDOS EN EL GENETIC PROPENSITY SCORE

Table 2 Genotype, minor allele frequency (MAF) and Hardy–Weinberg equilibrium calculations of the 16 SNPs included in the GRS

Gene	SNP	Major/ minor allele[a]	Major allele homozygote (%)	Heterozygote (%)	Minor allele homozygote (%)	MAF	HWE *p* value
FTO	rs9939609	T/A	218 (30.6)	351 (49.4)	142 (20.0)	0.45	0.973
MC4R	rs17782313	T/C	442 (62.2)	237 (33.3)	32 (4.5)	0.21	0.974
MTHFR	rs1801133	C/T	257 (36.2)	340 (47.8)	114 (16.0)	0.40	0.930
PPARA	rs1800206	C/G	591 (83.1)	116 (16.3)	3 (0.5)	0.09	0.507
PPARG	rs1801282	C/G	594 (82.5)	110 (15.5)	7 (1.0)	0.09	0.453
APOA5	rs662799	T/C	620 (87.2)	88 (12.4)	3 (0.4)	0.07	0.948
APOE	rs429358	T/C	574 (80.7)	129 (18.1)	8 (1.1)	0.10	0.804
APOE	rs7412	C/T	624 (87.8)	84 (11.8)	3 (0.4)	0.06	0.923
LIPC	rs1800588	C/T	406 (57.1)	250 (36.3)	47 (6.6)	0.24	0.489
PLIN1	rs894160	G/A	378 (53.2)	282 (39.7)	51 (7.2)	0.27	0.872
NOS3	rs1799983	G/T	286 (40.2)	326 (45.8)	99 (13.9)	0.37	0.692
GCKR	rs1260326	C/T	208 (29.2)	367 (50.9)	141 (19.8)	0.45	0.465
LPL	rs328	C/G	510 (71.7)	189 (26.6)	12 (1.7)	0.15	0.244
CELSR2	rs12740374	G/T	440 (61.9)	241 (33.9)	30 (4.2)	0.21	0.676
CETP	rs1800777	G/A	681 (95.8)	28 (3.9)	2 (0.3)	0.02	0.005
LIPG	rs4939883	C/T	508 (71.4)	179 (25.2)	24 (3.4)	0.16	0.100

SNP single nucleotide polymorphism, *MAF* minor allele frequency, *HWE p value* hardy–weinberg equilibrium *p* value

[a] According to Hap-Map CEU for European population

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ASOCIACION ENTRE EL "GENETIC PROPENSITY SCORE" Y VARIABLES ANTROPOMÉTRICAS

	Linear regression coefficients				Logistic regression coefficients			
	Model 1		Model 2		Model 1		Model 2	
	B (95 % CI)	*p* value	B (95 % CI)	*p* value	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
BMI (kg/m^2)								
≤7 risk alleles	0 (ref.)		0 (ref.)		1 (ref.)		1 (ref.)	
>7 risk alleles	1.02 (0.17–1.87)	0.019	0.93 (0.17–1.68)	0.016	1.41 (1.04–1.93)	0.031	1.42 (1.02–1.99)	0.038
Percentage of BFM								
≤7 risk alleles	0 (ref.)		0 (ref.)		1 (ref.)		1 (ref.)	
>7 risk alleles	1.81 (0.59–3.03)	0.004	1.69 (0.58–2.80)	0.003	1.72 (1.22–2.42)	0.002	1.72 (1.19–2.48)	0.004
Waist circumference (cm)								
≤7 risk alleles	0 (ref.)		0 (ref.)		1 (ref.)		1 (ref.)	
>7 risk alleles	2.14 (0.08–4.21)	0.042	1.94 (0.12–3.75)	0.036	1.54 (1.04–2.29)	0.032	1.57 (1.02–2.40)	0.039
Waist-to-hip ratio								
≤7 risk alleles	0 (ref.)		0 (ref.)		1 (ref.)		1 (ref.)	
>7 risk alleles	0.00 (−0.01–0.002)	0.445	0.00 (−0.01–0.01)	0.480	1.15 (0.82–1.61)	0.401	1.14 (0.81–1.61)	0.454
Waist-to-height ratio								
≤7 risk alleles	0 (ref.)		0 (ref.)		1 (ref.)		1 (ref.)	
>7 risk alleles	0.01 (0.00–0.03)	0.036	0.01 (0.00–0.02)	0.029	1.39 (0.95–2.02)	0.089	1.41 (0.94–2.10)	0.096

Model 1: Adjusted for gender and age

Model 2: Adjusted for gender, age, physical activity and energy intake

BMI body mass index, *BMF* body fat mass, *95 % CI* 95 % confidence interval, *OR* odds ratio

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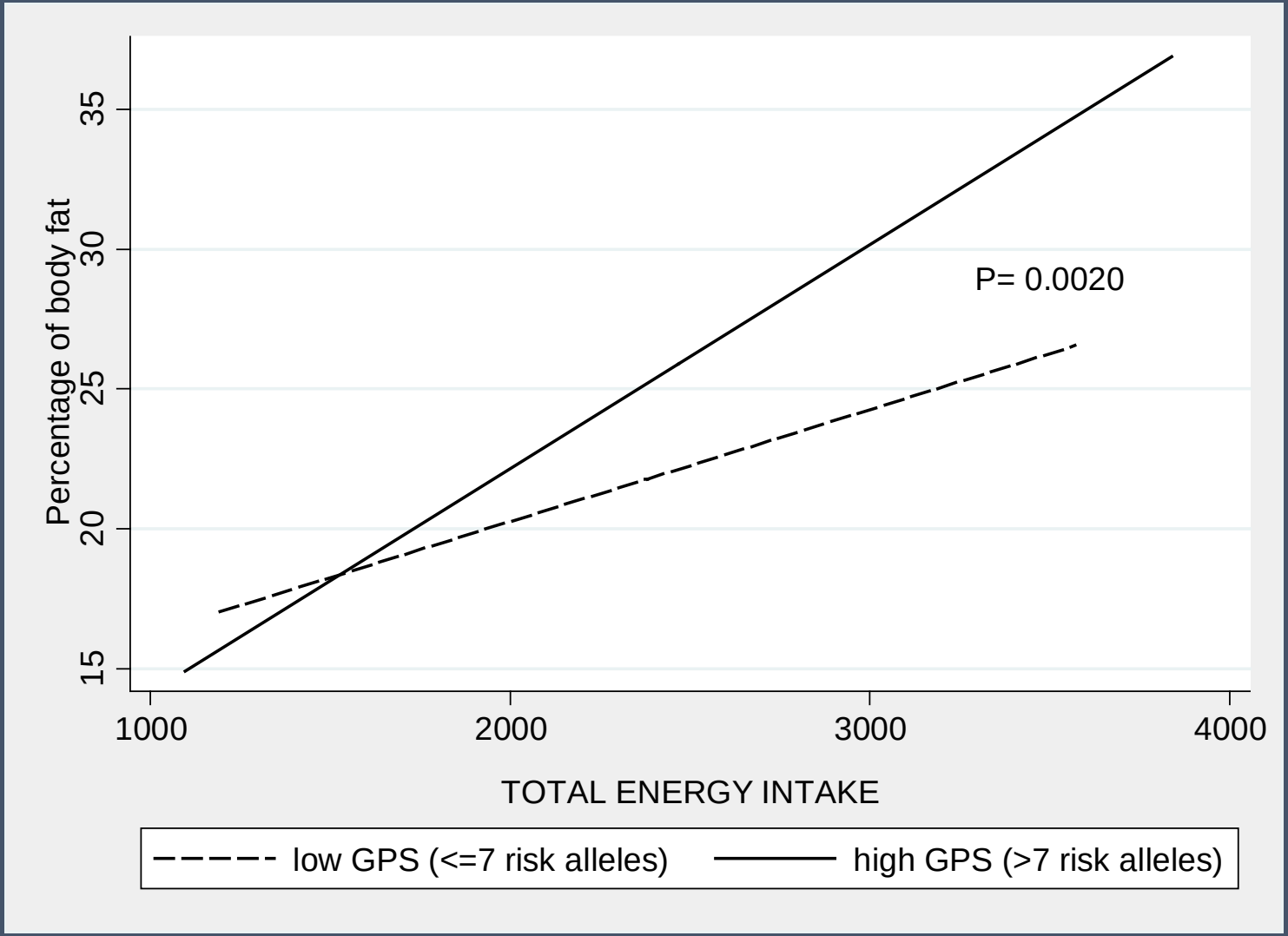
INTERACCIÓN ENTRE EL "GENETIC PROPENSITY SCORE" Y LA INGESTA DE ENERGÍA



Adjusted for age, gender and physical activity

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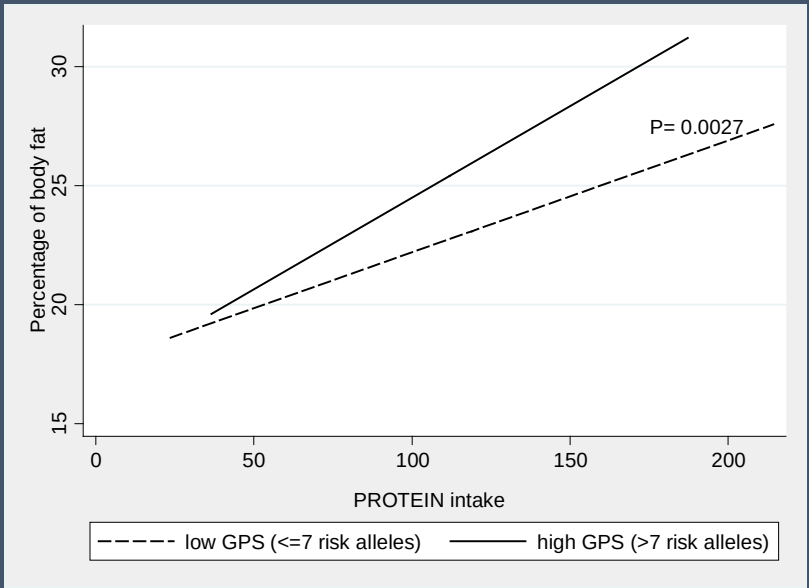
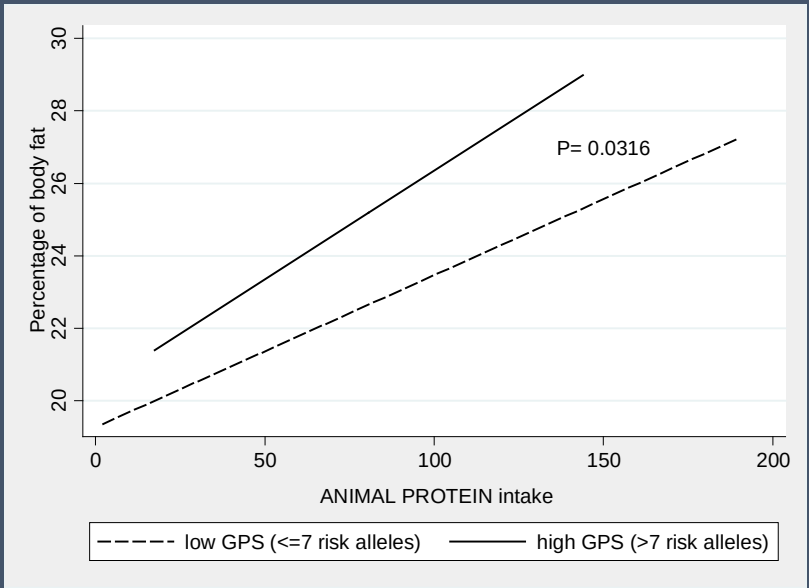
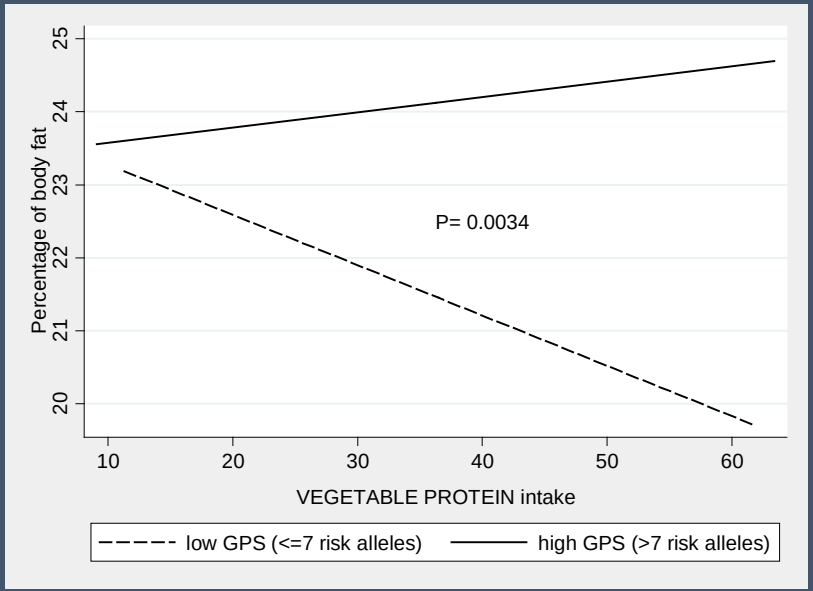
INTERACCIÓN ENTRE EL "GENETIC PROPENSITY SCORE" Y LA INGESTA DE PROTEÍNA







Adjusted for age, gender , physical activity and energy intake

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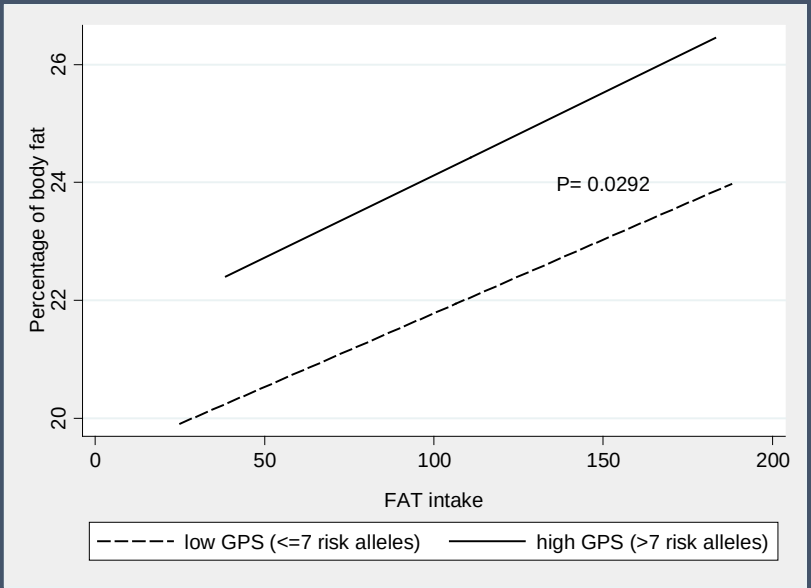
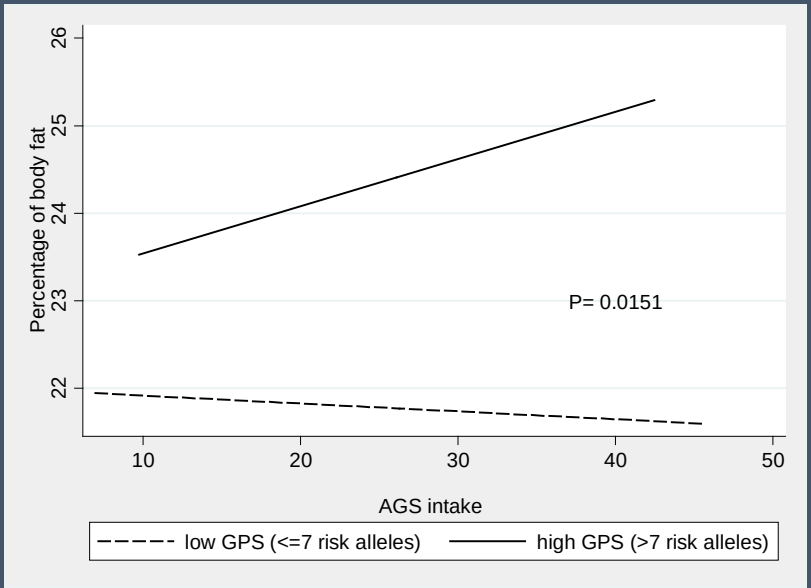
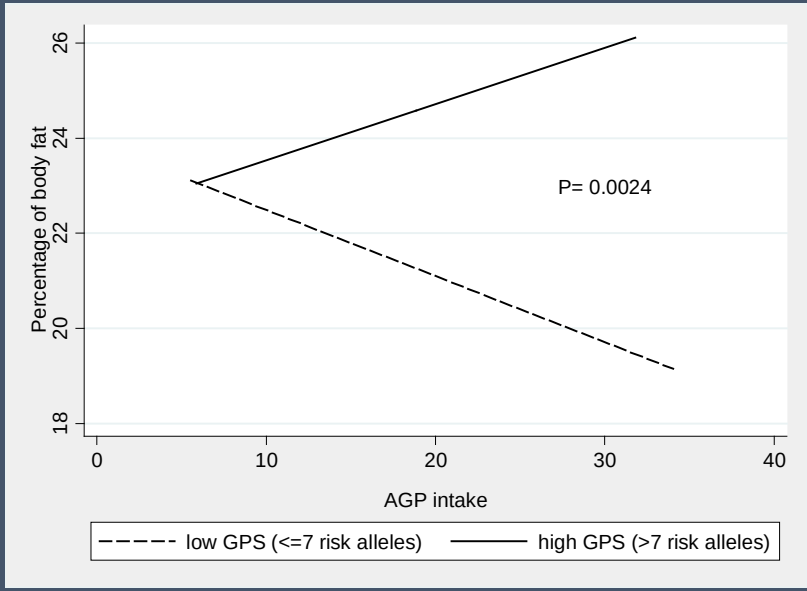
INTERACCIÓN ENTRE EL "GENETIC PROPENSITY SCORE" Y LA INGESTA DE GRASA DIETÉTICA







Adjusted for age, gender , physical activity and energy intake

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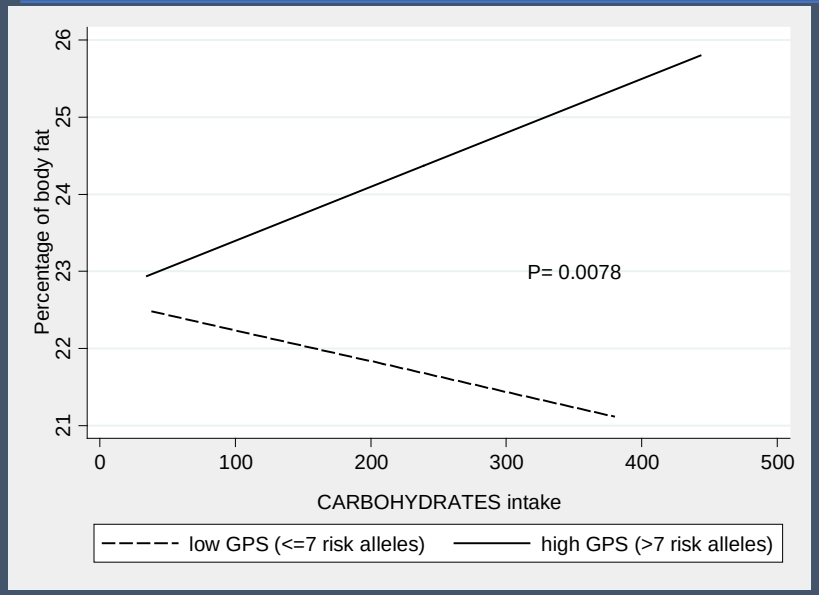
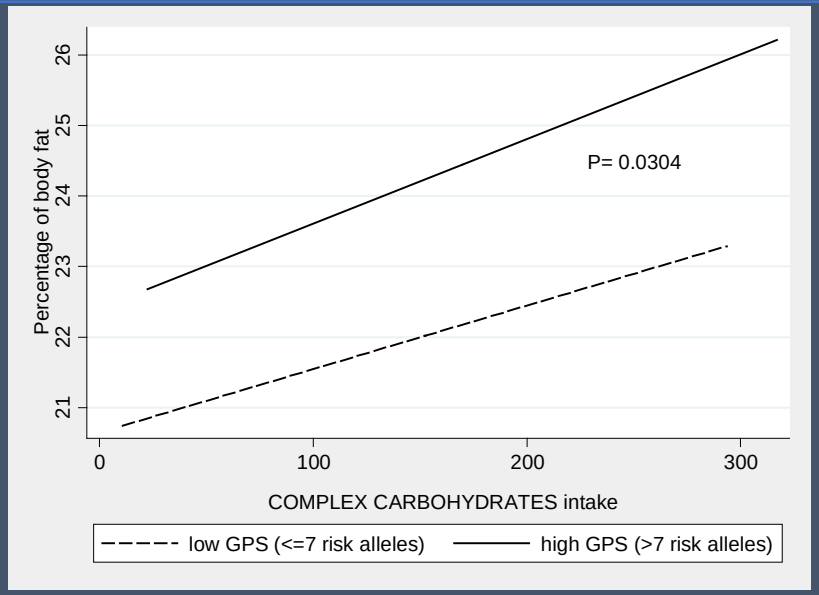
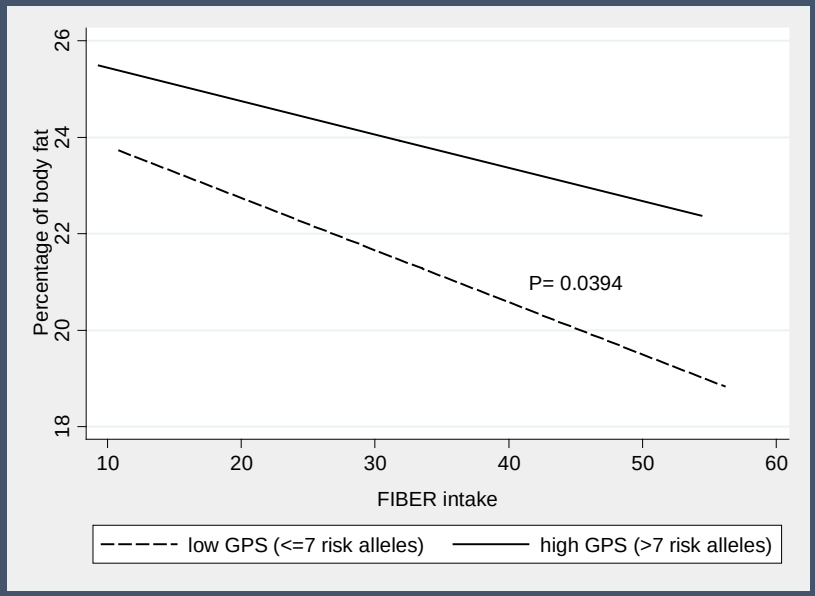
INTERACCIÓN ENTRE EL "GENETIC PROPENSITY SCORE" Y LA INGESTA DE CARBOHIDRATOS Y FIBRA







Adjusted for age, gender , physical activity and energy intake

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INTERACCIONES GEN-NUTRIENTE QUE DETERMINAN FENOTIPOS RELACIONADOS CON EL PESO

Authors and reference	Phenotype	Studied population	Description of the gene-diet interaction
Smith *et al.*[60]	Waist and hip circumference, BMI	Caribbean-origin Hispanics (N.=920, aged 45-74 y) living in the Boston area	The PLIN 11482G > A (rs894160) polymorphism interacted with complex carbohydrate intake in determining obesity-related measures. When complex carbohydrate intake was low (<144 g/d), waist circumference was larger in PLIN 11482G > A carriers. Conversely, when complex carbohydrate intake was high waist and hip circumferences were less in PLIN 11482G > A carriers.
Richardson *et al.*[61]	Waist circumference and BMI	Two populations of European ancestry (Framingham and GOLDN participants)	PLIN4 (rs8887) interacted with dietary PUFA in determining anthropometric traits and this acts in part through creation of a microRNA-522 regulatory site. The association data indicate for rs8887 minor allele carriers that elevated intake of PUFA n-3 resulted in decreasing anthropometrics compared to non-carriers
Zillikens *et al.*[62]	BMI	4575 elderly men and women in the population-based Rotterdam Study	SIRT1 genetic variants interacted with intakes of fat, vitamin E, calcium, and milk on BMI. The most relevant was the interaction between vitamin E intake and rs146756. This SNP was associated with BMI in the lowest tertile, but no association was observed in the higher tertiles.
Junyent *et al.*[63]	Waist circumference and BMI	936 participants in the GOLDN Study.	The ADAM17_i33708A>G polymorphism interacted with n-6 PUFA intake in determining obesity. When n-6 PUFA intake was the association of the A allele with higher BMI disappeared.
Sonestedt *et al.*[64]	BMI	4839 participants in the population-based Malmö Diet and Cancer Study	FTO (rs9939609) polymorphism interacted with fat and carbohydrate intake in determining BMI. High-fat and low-carbohydrate diets accentuated the susceptibility to obesity in carriers of the risk-allele.
Luan *et al.*[65]	BMI	592 non-diabetic participants in the Isle of Ely Study	The Pro12Ala polymorphism in the PPARG gene interacted with the PUFA:SFA ratio on BMI. When this ratio was low, the BMI in Ala carriers was greater than that in Pro homozygotes, but when the ratio was high, the opposite was seen
Memisoglu *et al.*[66]	BMI	2141 participants in the Nurses' Health Study	The Pro12Ala polymorphism in the PPARG gene interacted with total fat intake on BMI. Among Pro/Pro individuals, those in the highest quintile of total fat intake, had significantly higher BMI compared with those in the lowest quintile, whereas among 12Ala-carriers there was no significant trend.
Lamri *et al.*[67]	BMI	4679 participants in the French general population, the D.E.S.I.R. cohort	The Pro12Ala polymorphism in the PPARG gene interacted with total fat intake on BMI. AlaAla individuals had a higher BMI than Pro carriers among high fat consumers.
Phillips *et al.*[68]	BMI, waist circumference	1754 participants in the LIPGENE-SU.VI.MAX Study	The FTO (rs9939609) polymorphism interacted with SFA intake in determining BMI and waist circumference. High SFA intake accentuated the associations in carriers of the risk-allele (A).
Robitaille *et al.*[69]	Waist circumference	632 men from Canada	The PPARalpha-L162V polymorphism interacted with total fat or saturated fat intake in determining waist circumference. Fat intake was directly related to waist circumference only in L162L homozygotes
Miyaki *et al.*[70]	Obesity	295 healthy Japanese men	The Trp64Arg polymorphism in the ADRB3 gene interacted with total energy intake in determining obesity risk. The Arg64-allele was associated with greater obesity risk only in the highest energy intake quartile

Corella D et al. Minerva Endocrinol, 2015

INTERACCIONES GEN-NUTRIENTE RELATIVA A RASGOS DE OBESIDAD CENTRAL

Reference	Gene	SNP	Population	Sex	No. of subjects	Energy or nutrient	Results
Robitaille et al. (2003)[43]	*PPARG*	rs1801282	French Canadian	F and M	720	TF and SFA	The higher the TF intake, the greater the WC in P12/P12 homozygotes
Robitaille et al. (2007)[44]	*CPT1A*	rs17610395	French Canadian	F and M	351	TF	The higher the TF intake, the greater the WC in A275/A275 homozygotes
Robitaille et al. (2007)[44]	*CPT1B*	rs470017	French Canadian	F and M	351	TF	The higher the TF intake, the greater the WC in E531/K531 heterozygotes
Song et al. (2007)[45]	*IL6R*	rs8192284	Japanese	M	285	Energy	The higher the energy intake, the greater the WC in T allele carriers (TT and TG)
Smith et al. (2008)[46]	*PLIN*	rs894160	Puerto Rican	F and M	920	Complex CH	The lower the complex CH intake, the greater the WC in A allele carriers
Smith et al. (2008)[46]	*PLIN*	rs894160	Puerto Rican	F and M	921	Complex CH	The higher the complex CH intake, the lower the WC in A allele carriers
Phillips et al. (2009)[47]	*STAT3*	rs8069645, rs744166, rs1053005, rs2293152, rs2306580	French	F and M	1,754	SFA	The higher the SFA intake, the greater the WC in subjects carrying >2 risk alleles
Phillips et al. (2010)[48]	*IL6, LTA, TNF-alpha*	rs1800797, rs1800629, rs915654	French	F and M	1,754	SFA/PUFA plasma concentrations	The lower the SFA/PUFA plasma concentrations, the greater the WC in risk genotype carriers
Phillips et al. (2010)[49]	*ACC2*	rs4766587	French	F and M	464	PUFA	The higher the PUFA intake, the greater the WC in AA homozygotes
Dedoussis et al. (2011)[50]	*PPARG*	rs1801282	Greek (young)	F	1,332	MUFA	The higher the MUFA intake, the lower the WC in P12/P12 homozygotes
Mattei et al. (2011)[51]	*APOA1*	rs670	Puerto Rican	F and M	821	TF	The lower the TF intake, the lower the WC in common allele homozygotes
Phillips et al. (2012)[52]	*FTO*	rs9939609	French	F and M	1,754	SFA	The higher the SFA intake, the greater the WC in A allele carriers

Abbreviations: CH, carbohydrates; F, female; M, male; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; SFA/PUFA, saturated fatty acids to polyunsaturated fatty acids ratio; SNP, single-nucleotide polymorphism; TF, total fat; WC, waist circumference.

Goni L et al. Nutrition Reviews, 2014

APROXIMACIONES PERSONALIZADAS CONTRA LA OBESIDAD

Terapia nutricional y dietética

Tratamientos con fármacos

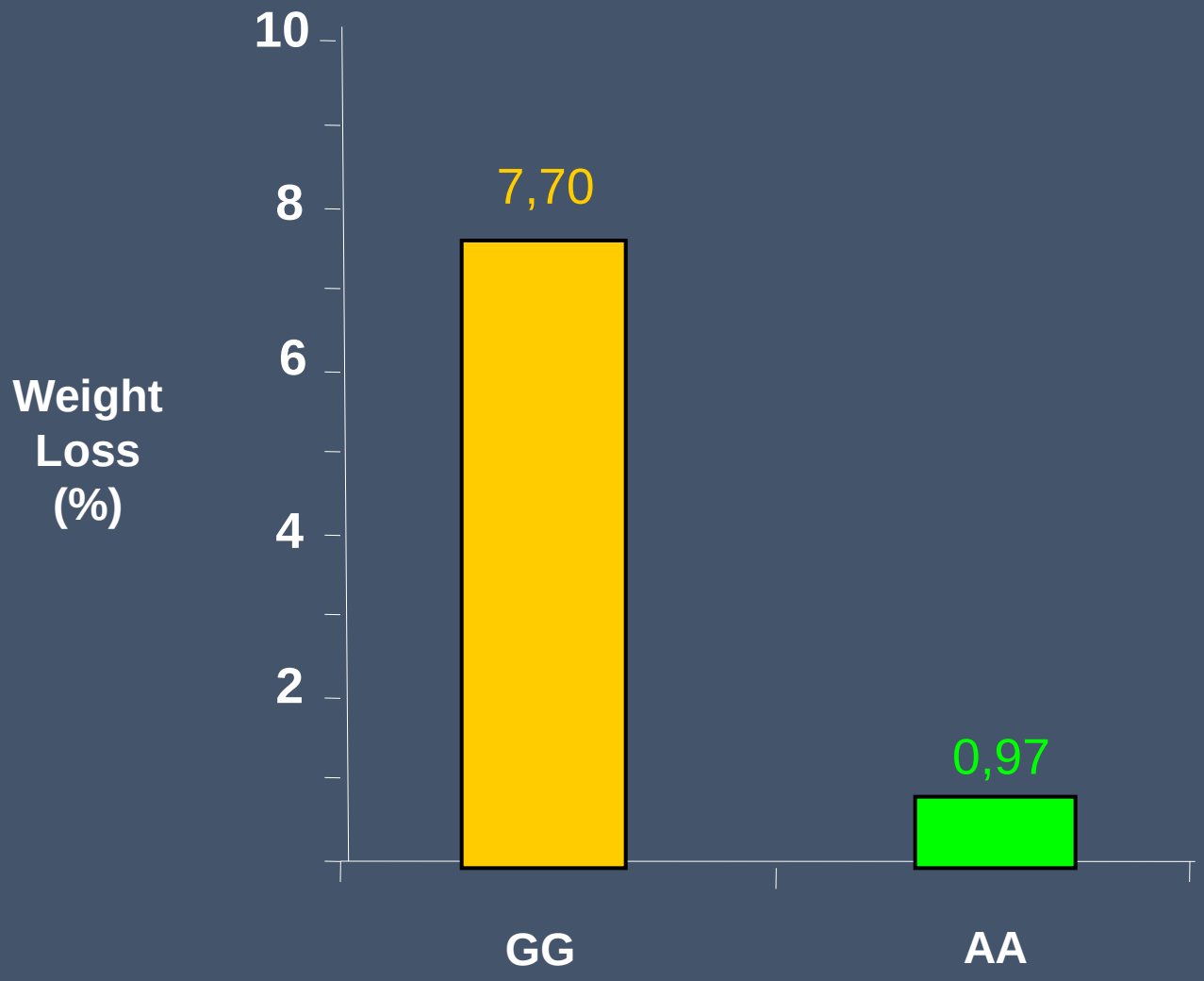
Programas Actividad Física

Cirugía Bariátrica

Otras: Nutrición……

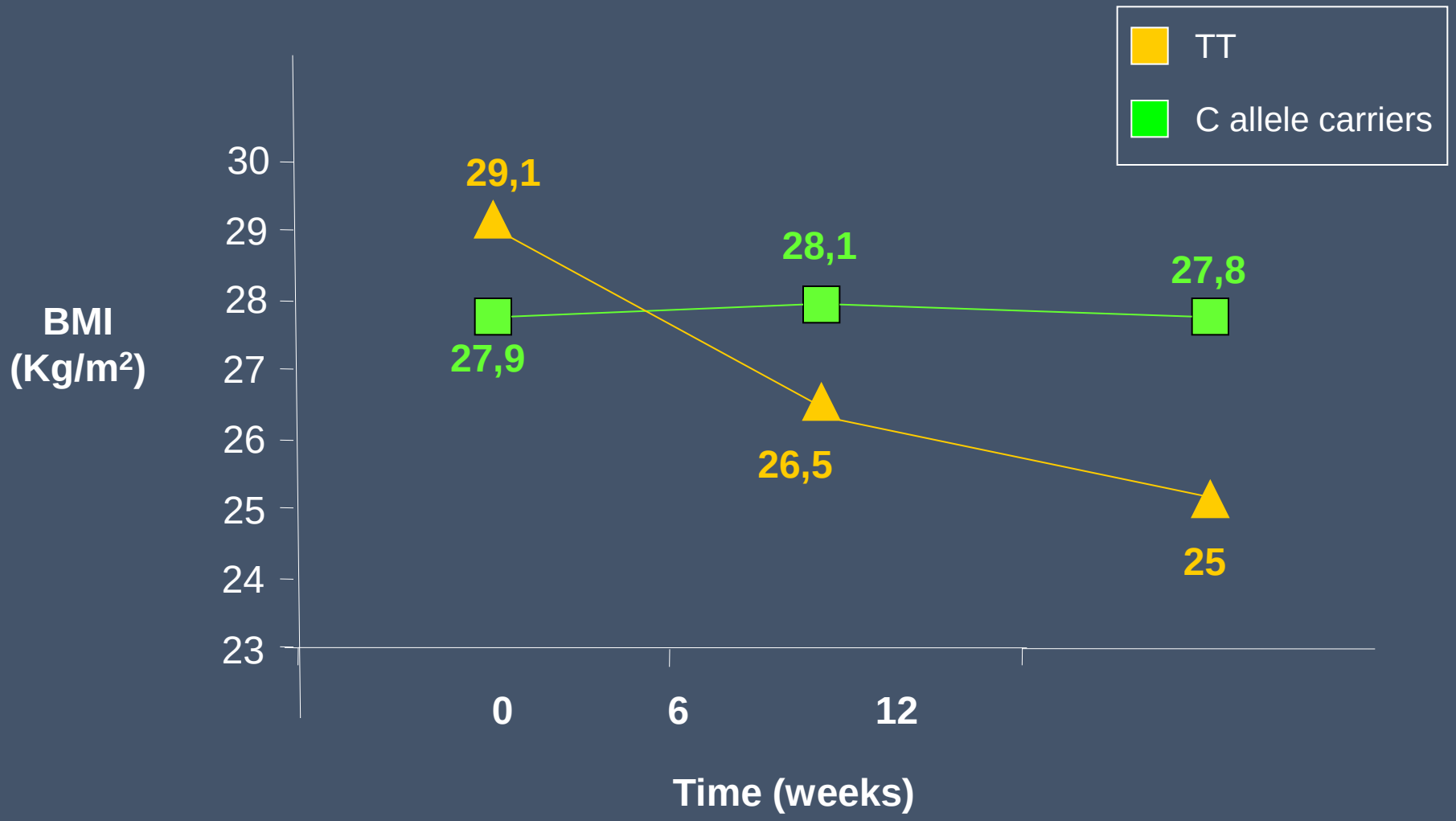
.....Personalizada

GEN DE LA PERILIPINA Y PÉRDIDA DE PESO



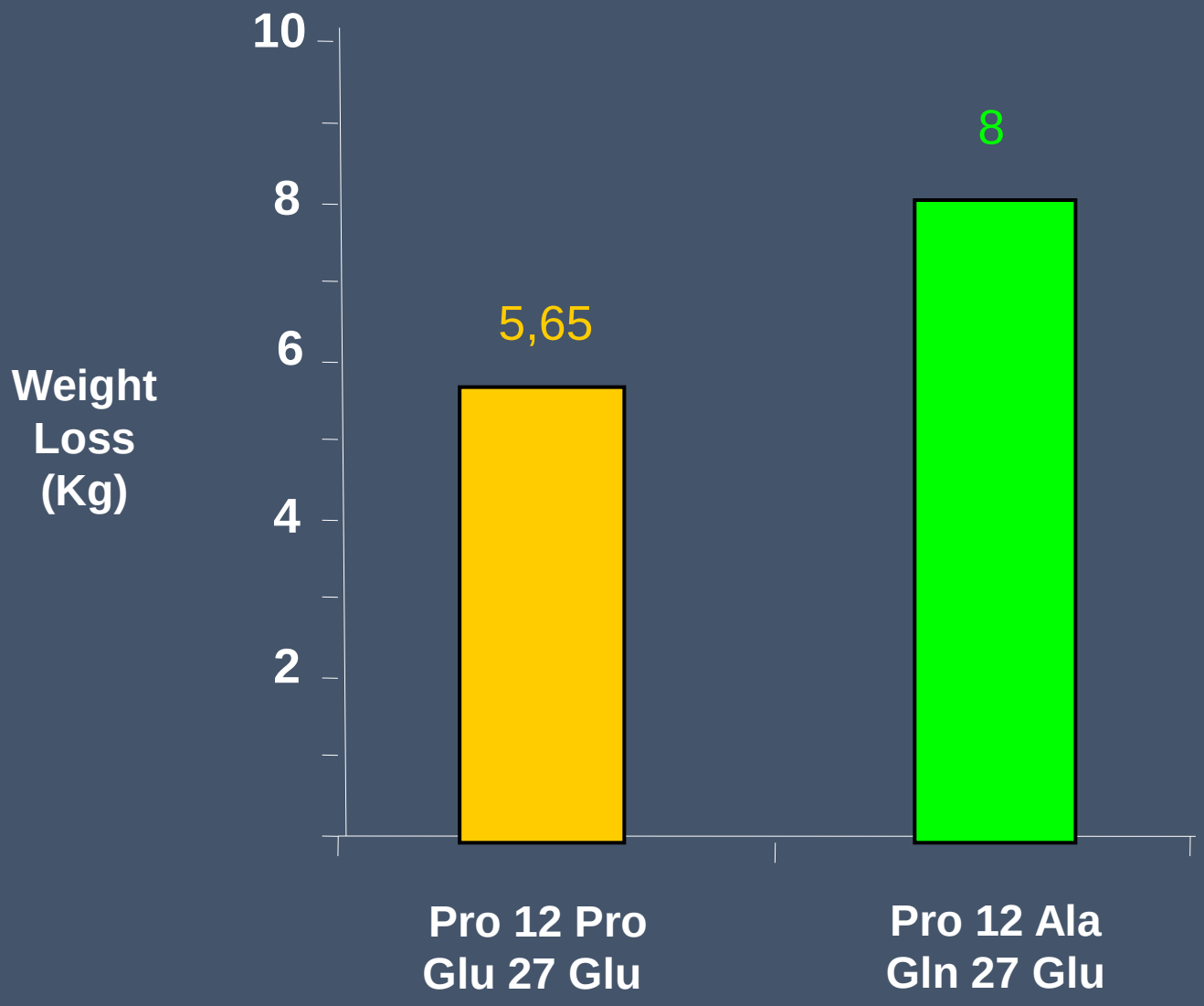
Corella, *et al. 2005*

POLYMORPHISM IN THE APOLIPOPROTEIN A5 GENE



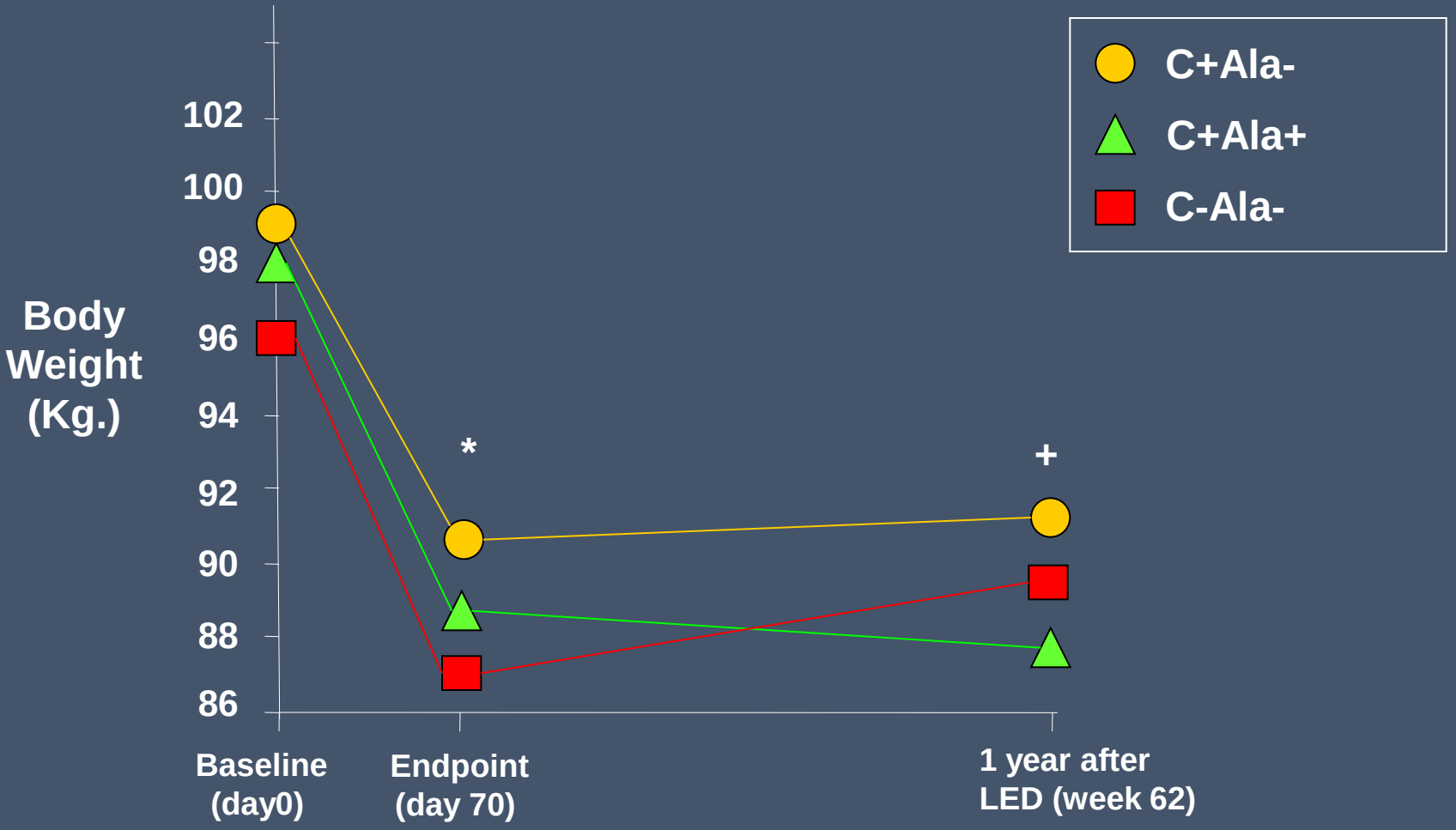
Aberle, *et al. 2005*

PPAR x ADRB2 interaction



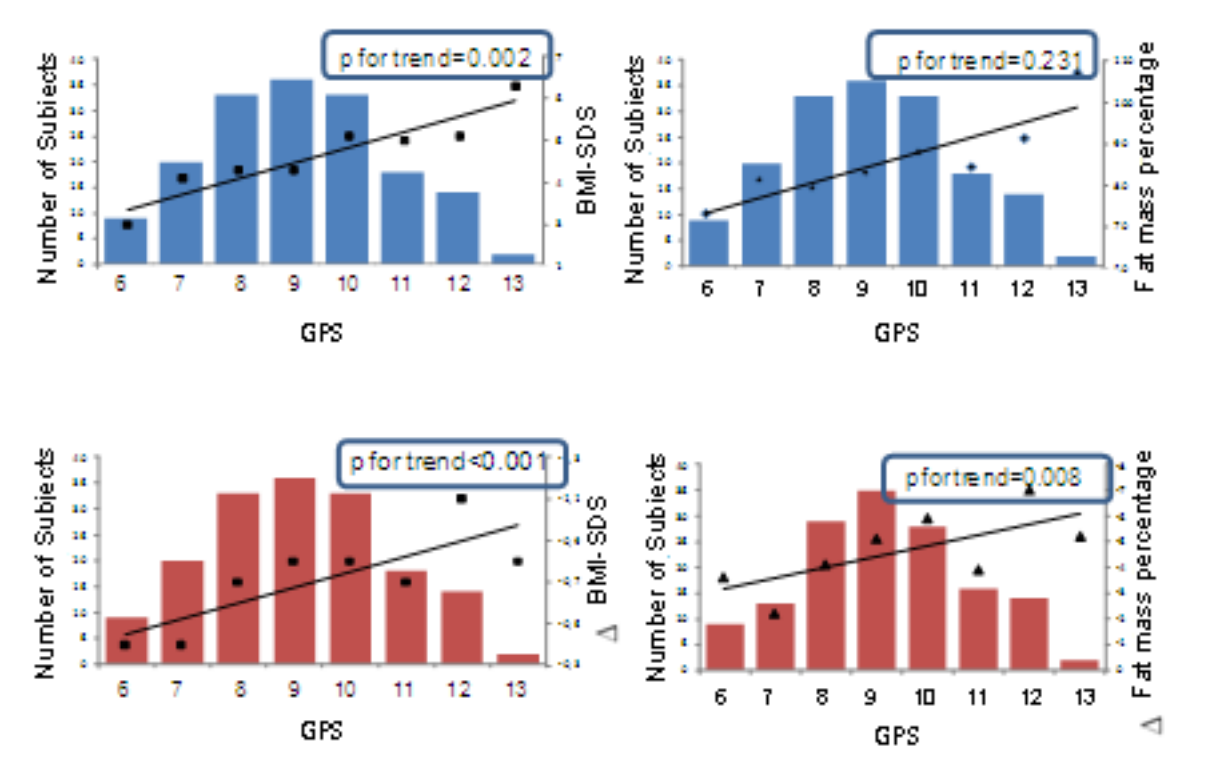
E. L. Rosado, *et al. 2006*

BODY WEIGHT REDUCTION AND GENETIC VARIANTS: IL-6 AND PPAR-Γ2



Goyenechea, *et al. 2006*

Obesity Susceptibility Loci on Body Mass Index and Weight Loss in Spanish Adolescents after a Lifestyle Intervention



Supplementary Figure 2 (online): Distribution of the Genetic Predisposition Score (GPS), trend and cumulative effects on BMI-SDS and fat mass percentage in the adolescent population A.) At baseline and B.) After 10 weeks of multidisciplinary intervention. Left axis: Prevalence. Right axis: A) BMI-SDS or Fat mass percentage (baseline) and B) BMI-SDS or Fat mass percentage variation (after the intervention).

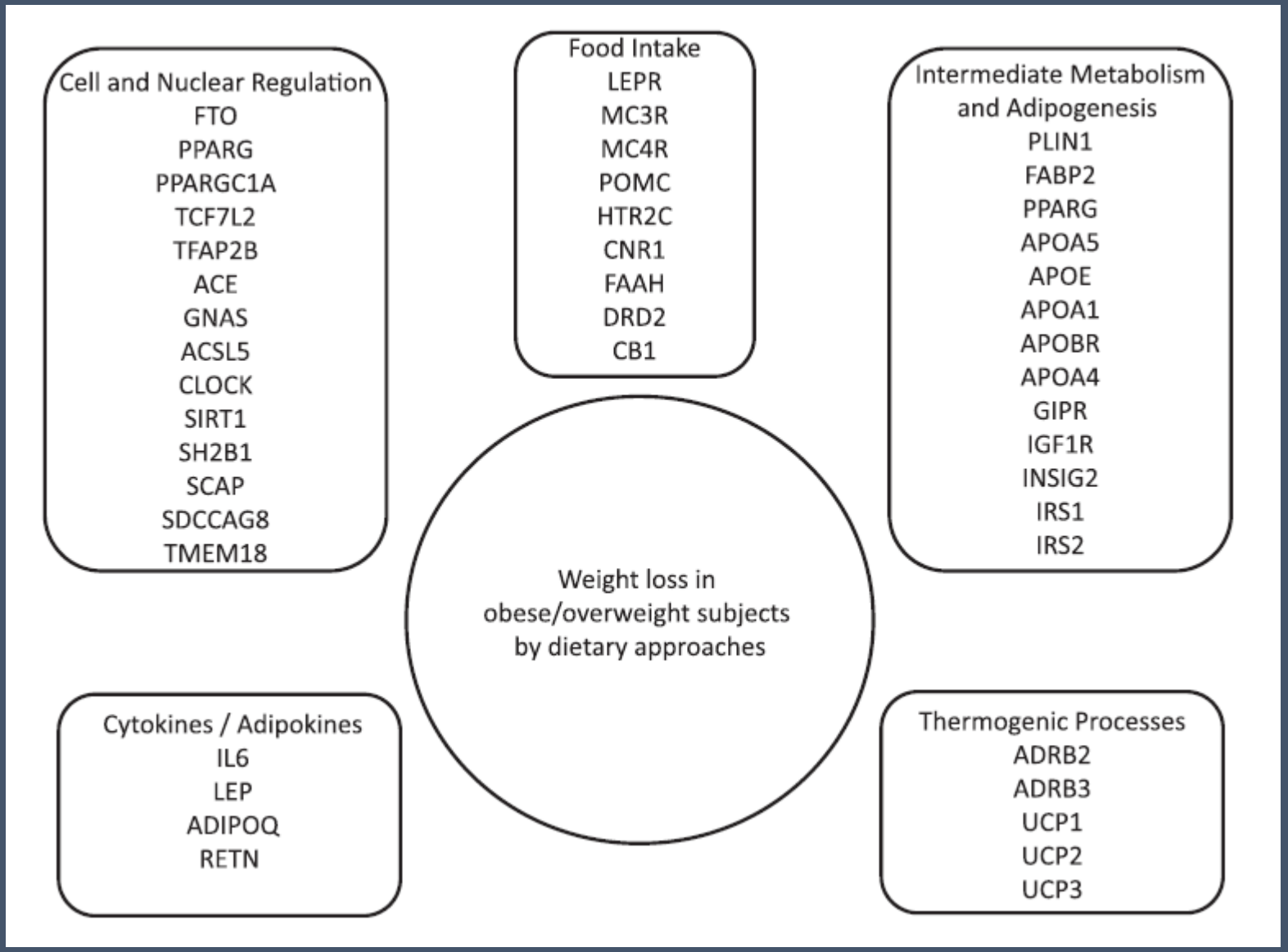
J Pediatr, 2012 Sept 161: 466-470.e2

GENE-NUTRIENT INTERACTIONS ON BODY WEIGHT LOSS

Reference	Gene	Polymorphism	Study design	Participants	Outcome
Grau *et al.* (2010)[98]	*TCF7L2*	rs7903146	10 weeks energy restriction (low-fat vs high-fat)	771 adults with obesity	Individuals homozygous for the T allele are more responsive to low-fat diets than other genotypes (–2.6 additional kg lost, $P=0.009$)
Kim & Lee (2010)[100]	*UCP1* and *ADRB3*	3826A/G and Trp64Arg	Two low-calorie rice-based diets with different fibre compositions	40 women with obesity	The AA *UCP1* genotype produced significant weight loss ($P=0.041$) in the high-fibre group but *ADRB3* genotype had no effect
Haupt *et al.* (2010)[99]	*TCF7L2*	rs7903146	9 month lifestyle intervention with fat reduction and fibre increase	304 adults with obesity	Dietary fibre modulated the association between *TCF7L2* variance and weight loss ($P=0.0034$)
Mattei *et al.* (2012)[96]	*TCF7L2*	rs12255372	Dietary intervention with four diets (low or high fat and low or high protein) for 2 years	591 adults with overweight	Individuals with the TT genotype lost more fat mass while consuming a diet low in lipids ($P<0.05$)
Qi *et al.* (2012)[95]	*GIPR*	rs2287019	Intervention with four diets (low or high fat and low or high protein) for 3 years	757 adults with overweight	The T allele was associated with increased weight loss when consuming a low-fat diet ($\beta \pm SE$; $-1.05 \pm 0.56\%$; $P=0.06$)
Stocks *et al.* (2012)[97]	*TFAP2B*	rs987237	8 weeks energy-restricted diet (low-fat versus high-fat)	771 adults with obesity	Individuals with the AA genotype had improved weight loss in response to low-fat diets (1.0 kg, 95% CI 0.4–1.6 kg), whereas individuals with the GG genotype had improved weight loss in response to high-fat diets (2.6 kg, 95% CI 1.1–4.1 kg)
Zhang *et al.* (2012)[94]	*FTO*	rs1558902	Intervention with four diets (low or high fat and low or high protein) for 2 years	742 adults with obesity	High-protein diet might have specific benefits for weight loss ($P<0.05$ for all interactions) in individuals with the risk allele (A)
Cameron *et al.* (2013)[101]	*DRD2*	TAqIARFLP	Caloric restriction and resistance training for 6 months	127 postmenopausal women with obesity	Carriers of the A1 allele lost significantly less body weight ($P<0.05$), but this effect seemed to be exercise-dependent

Martínez JA et al. Nat Rev Endocrinol, 2015

GENES IN WHICH THERE ARE POLYMORPHISMS RELATED TO BODY WEIGHT LOSS



Martínez JA et al. Trends Food Sci Technol, 2015

FROM THE ACADEMY
Position Paper

Position of the Academy of Nutrition and Dietetics: Nutritional Genomics

ABSTRACT

It is the position of the Academy of Nutrition and Dietetics that nutritional genomics provides insight into how diet and genotype interactions affect phenotype. The practical application of nutritional genomics for complex chronic disease is an emerging science and the use of nutrigenetic testing to provide dietary advice is not ready for routine dietetics practice. Registered dietitian nutritionists need basic competency in genetics as a foundation for understanding nutritional genomics; proficiency requires advanced knowledge and skills. Unlike single-gene defects in which a mutation in a single gene results in a specific disorder, most chronic diseases, such as cardiovascular disease, diabetes, and cancer are multigenetic and multifactorial and therefore genetic mutations are only partially predictive of disease risk. Family history, biochemical parameters, and the presence of risk factors in individuals are relevant tools for personalizing dietary interventions. Direct-to-consumer genetic testing is not closely regulated in the United States and may not be accompanied by access to health care practitioners. Applying nutritional genomics in clinical practice through the use of genetic testing requires that registered dietitian nutritionists understand, interpret, and communicate complex test results in which the actual risk of developing a disease may not be known. The practical application of nutritional genomics in dietetics practice will require an evidence-based approach to validate that personalized recommendations result in health benefits to individuals and do not cause harm.

J Acad Nutr Diet. 2014;114:299-312.

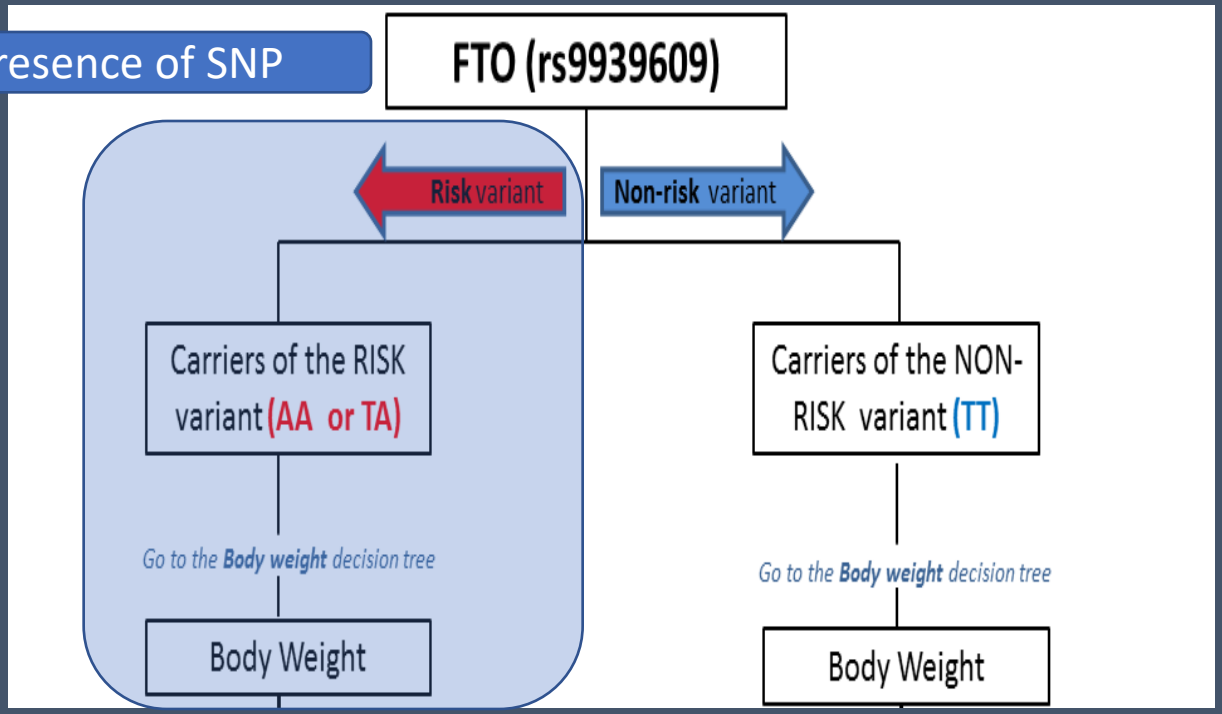
POSITION STATEMENT

It is the position of the Academy of Nutrition and Dietetics that nutritional genomics provides insight into how diet and genotype interactions affect phenotype. The practical application of nutritional genomics for complex chronic disease is an emerging science and the use of nutrigenetic testing to provide dietary advice is not ready for routine dietetics practice. Registered dietitian nutritionists need basic competency in genetics as a foundation for understanding nutritional genomics; proficiency requires advanced knowledge and skills.

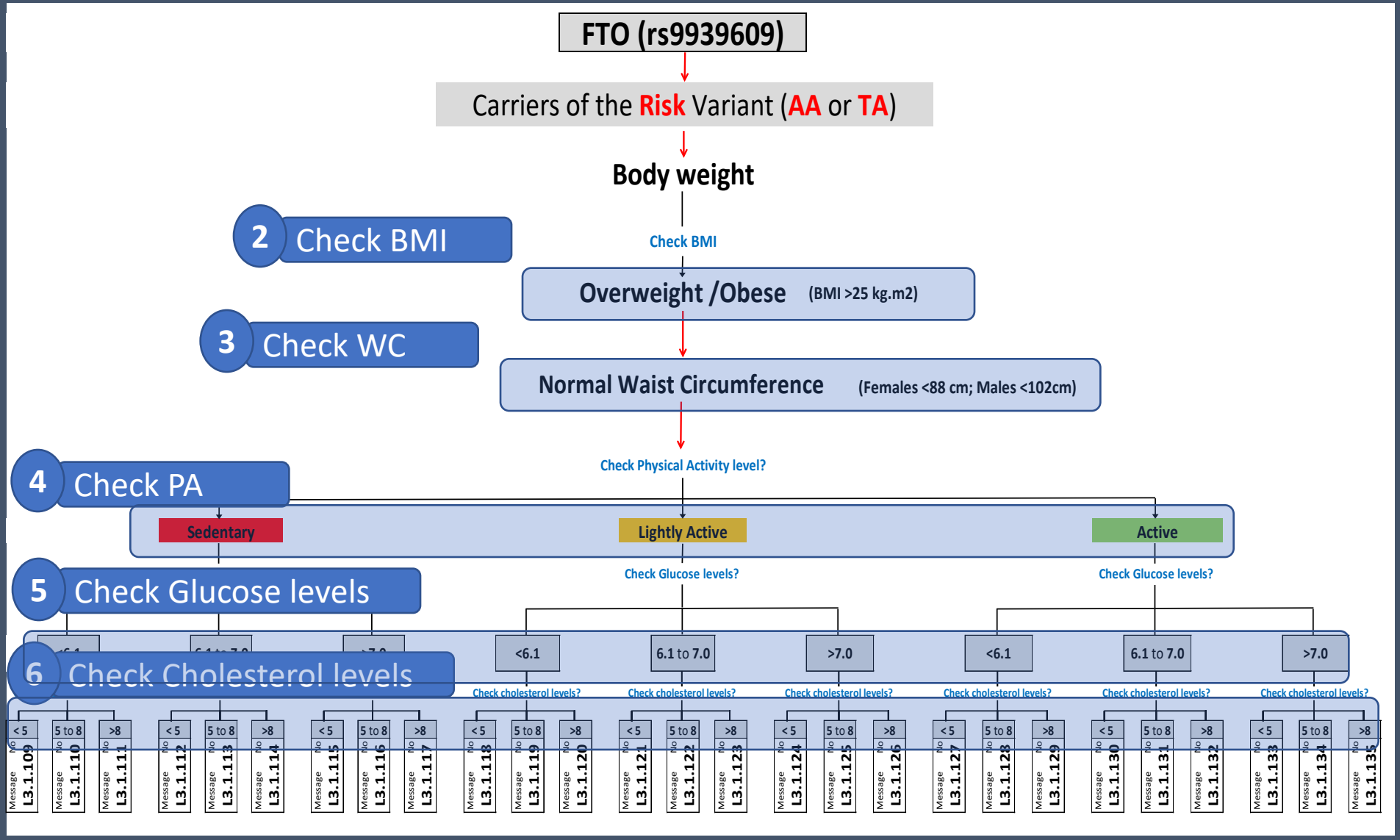
APLICACIONES

BODY WEIGHT: *FTO* SNP

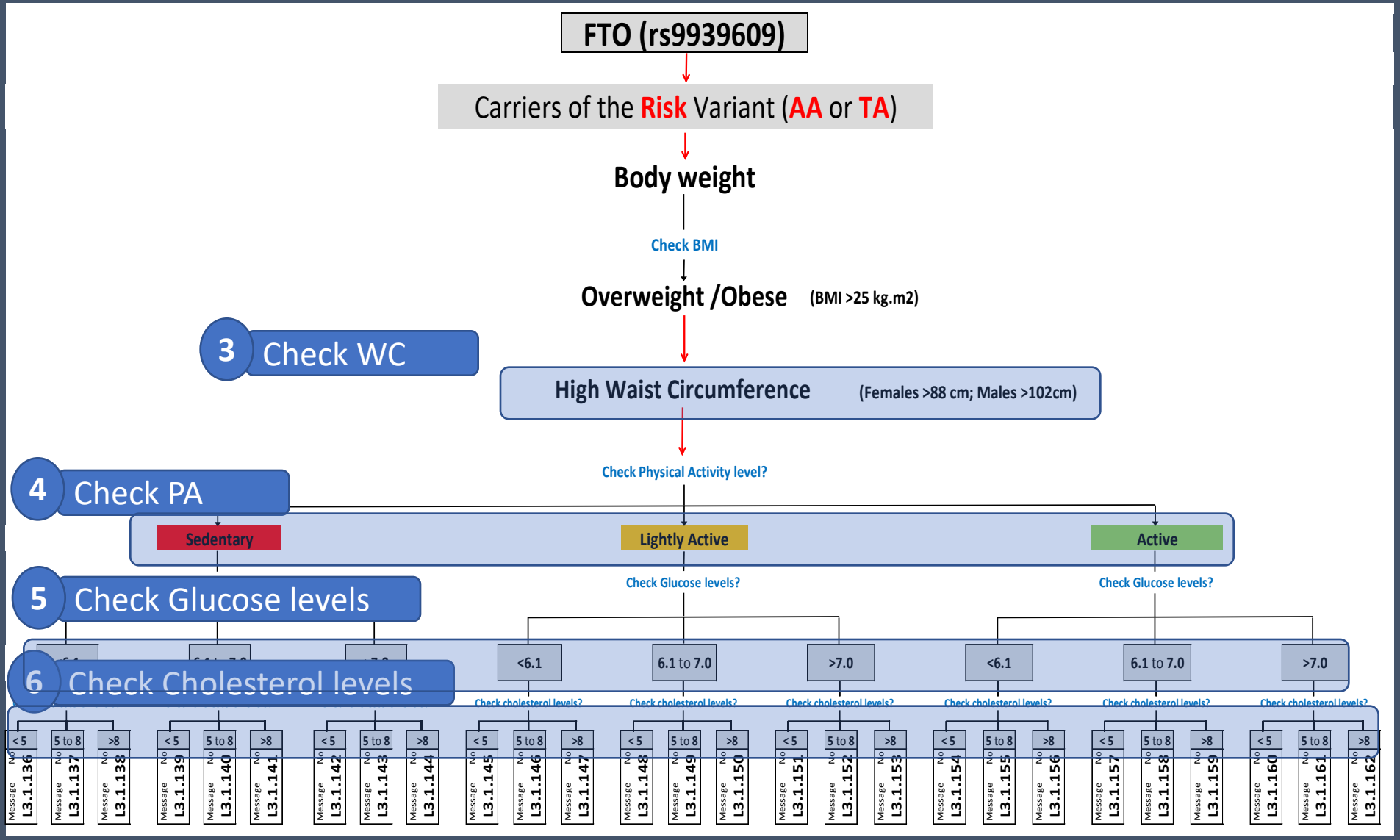
1 Check the presence of SNP



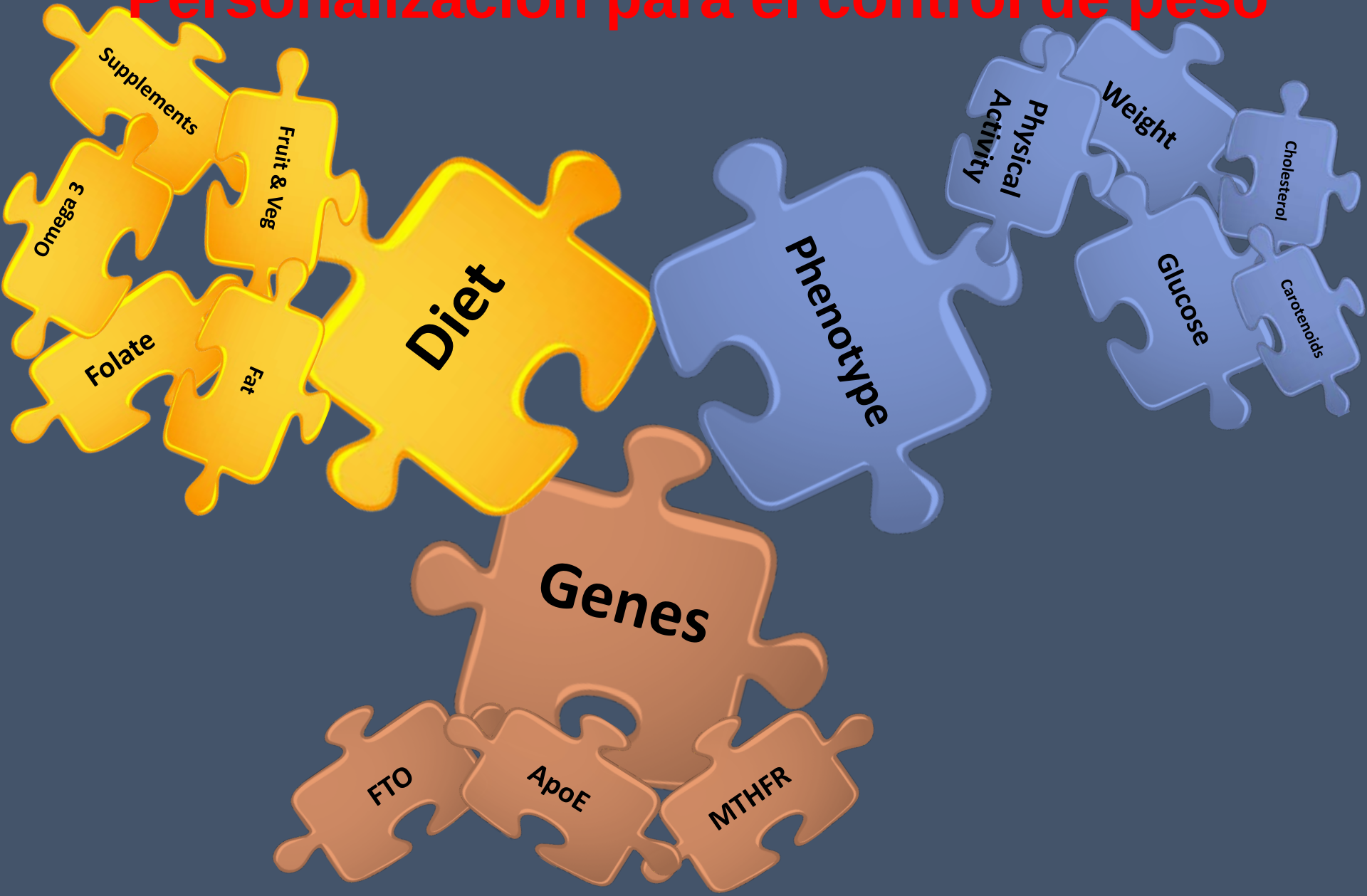
BODY WEIGHT: *FTO* SNP



BODY WEIGHT: *FTO* SNP



Personalización para el control de peso



Courtesy John Mathers, UNew

NUTRICIÓN MOLECULAR

Nutrigenetica

Polimorfismo

Genes

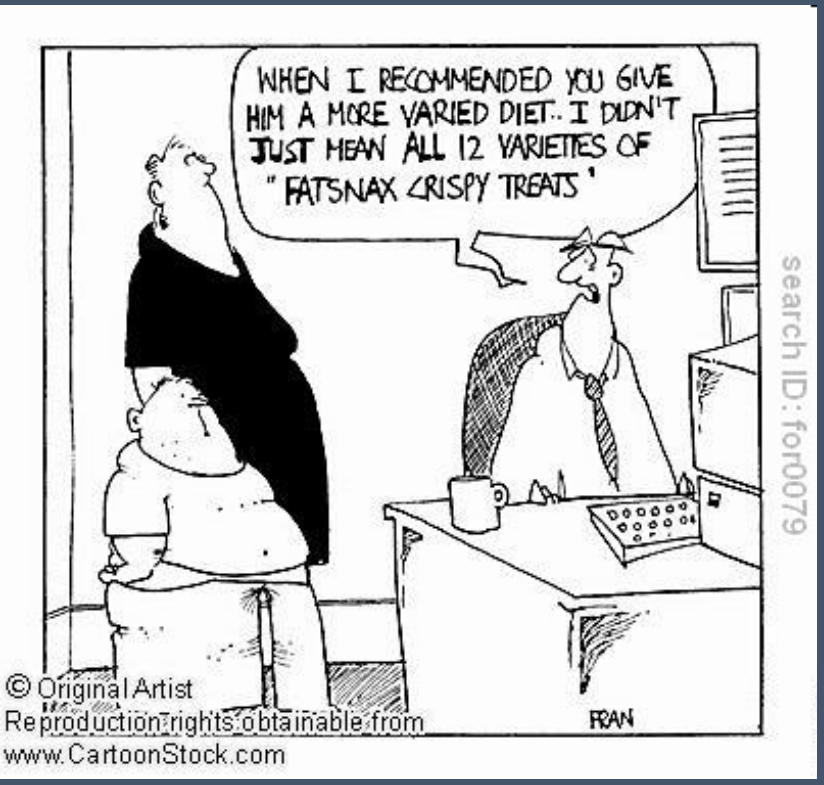
Nutrientes

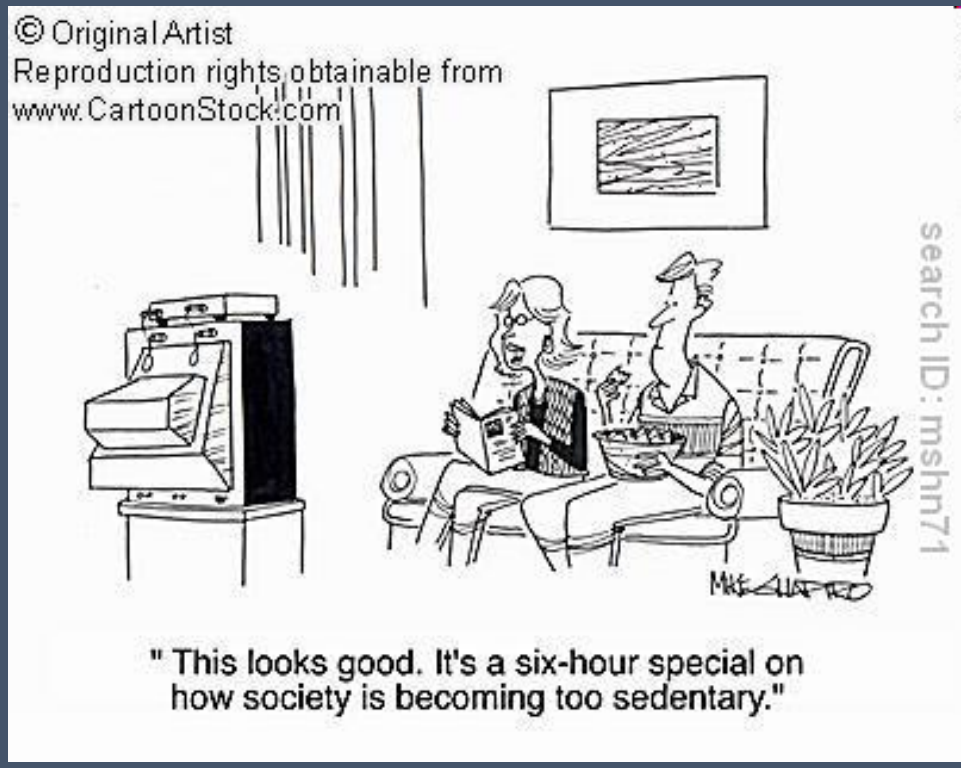
Nutrigenómica

Expresion génica

NUTRICIÓN PERSONALIZADA

Nutrición y Salud



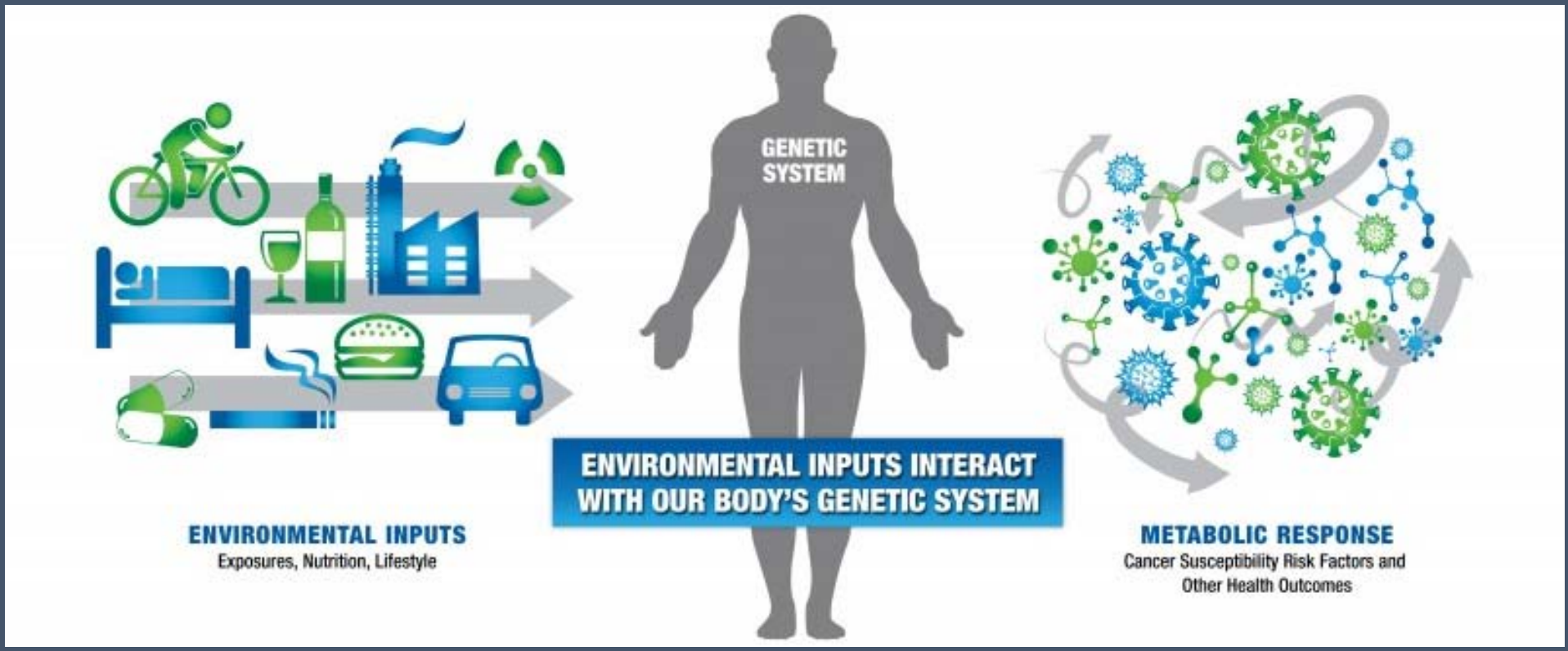


Pero genética/epigenética es sólo la punta del iceberg

Conclusión?

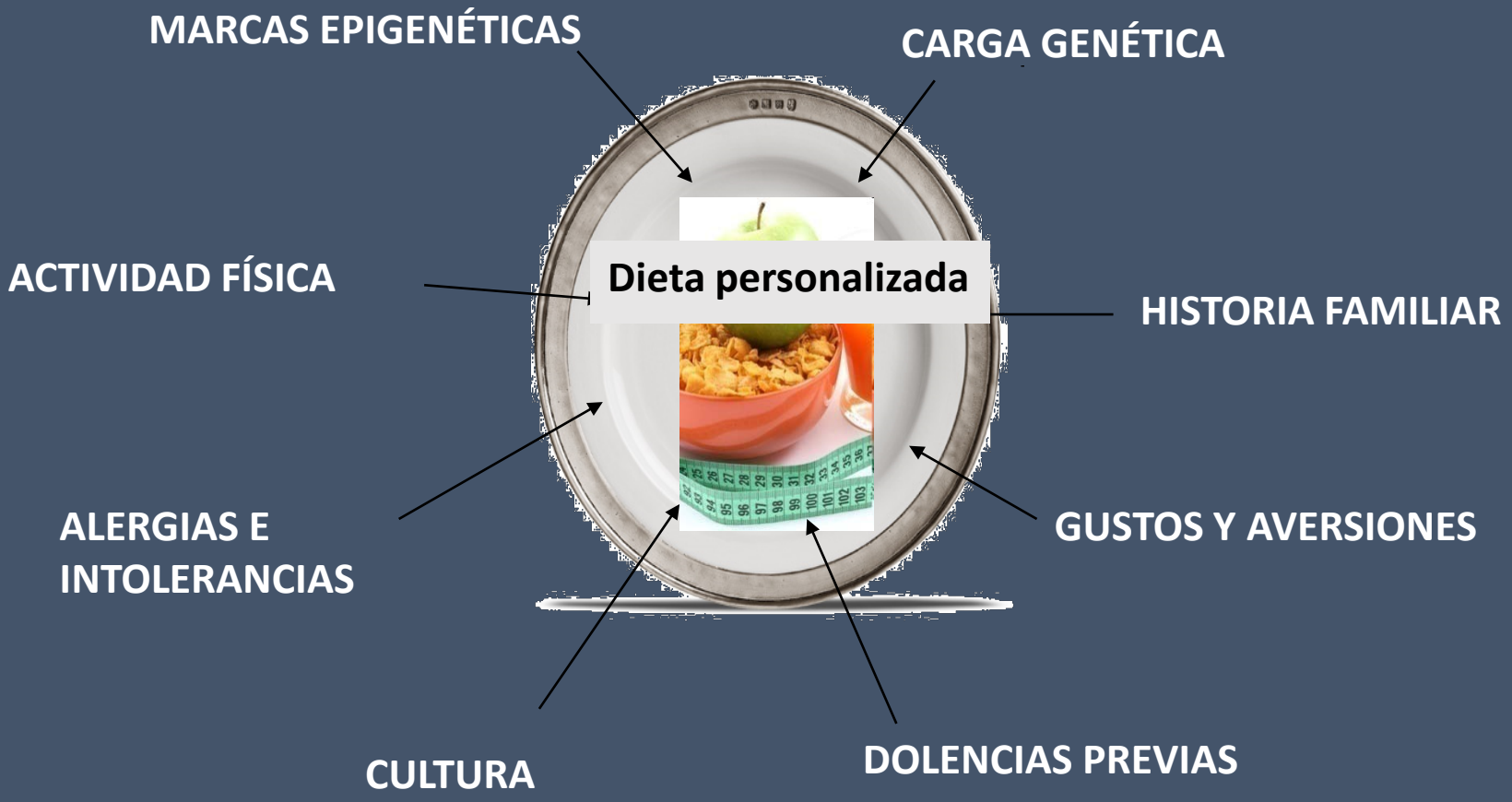
If they ask you anything you don't know, just just say it's due to epigenetics.

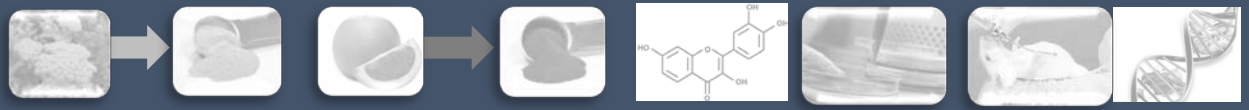
GENE-ENVIRONMENTAL INPUTS INTERACTION



¡Nutrición de Precisión!

Mas que existir una “dieta óptima”, existe un rango de dietas adecuadas en función de la diversidad genética, fenotípica y cultural.





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