GENETICA DE LA OBESIDAD

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CONFLICTOS DE INTERES: NINGUNO

GENETICA DE LA OBESIDAD

- GENETICA DE LA SACIEDAD / INGESTA
- GENETICA DE LA ADICCION
- GENETICA DEL SABOR
- GENETICA DEL ADIPOCITO
- GENETICA DE LA PERDIDA DE PESO
- INTERACCION ENTRE NUTRIENTES Y GENES
- FARMACOGENETICA, NUTRICION Y MEDICINA PERSONALIZADA
- EPIGENETICA DE LA OBESIDAD

GENETICA DE LA OBESIDAD: LAS ENSEÑANZAS DEL PASADO

DESCUBRIMIENTO DE LEPTINA: REVOLUCION EN MEDICINA

Positional cloning of the mouse obese gene and its human homologue.

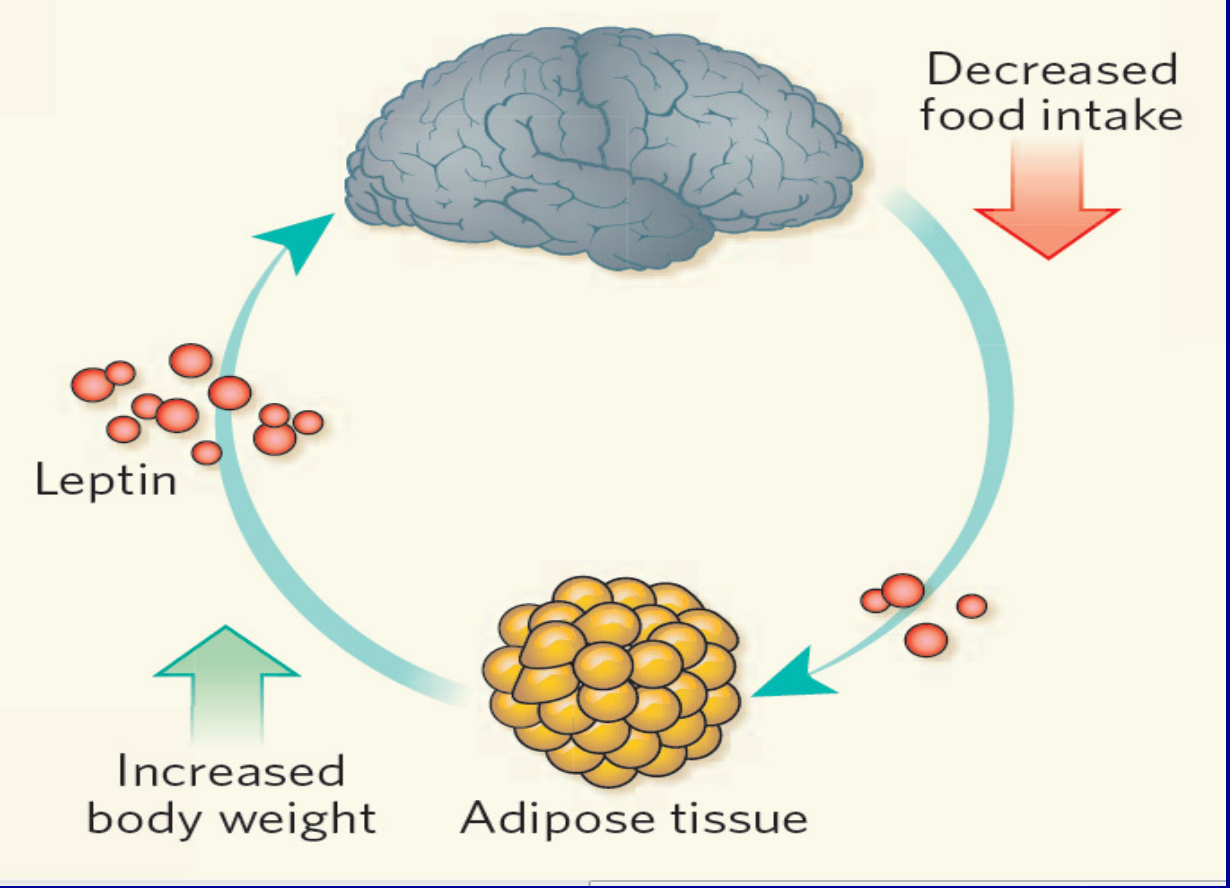
Nature. 1994. Zhang et al.

DESCUBRIMIENTO DE LEPTINA: REVOLUCION EN MEDICINA

DESCUBRIMIENTO DE LEPTINA: REVOLUCION EN MEDICINA

LEPTINA & MASA ADIPOSA

OBESIDAD POLIGENICA → RESISTENCIA A LEPTINA



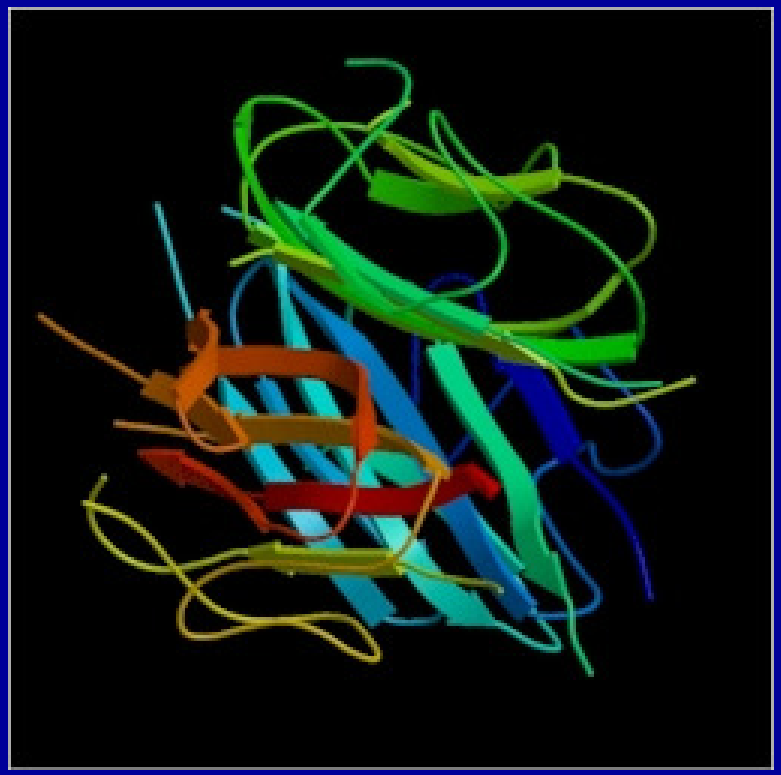
Friedman JM. Nature 2009

DESCUBRIMIENTO DE ADIPONECTINA: REVOLUCION EN MEDICINA

cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1).

Maeda et al. Biochem Biophys Res Commun 1996.

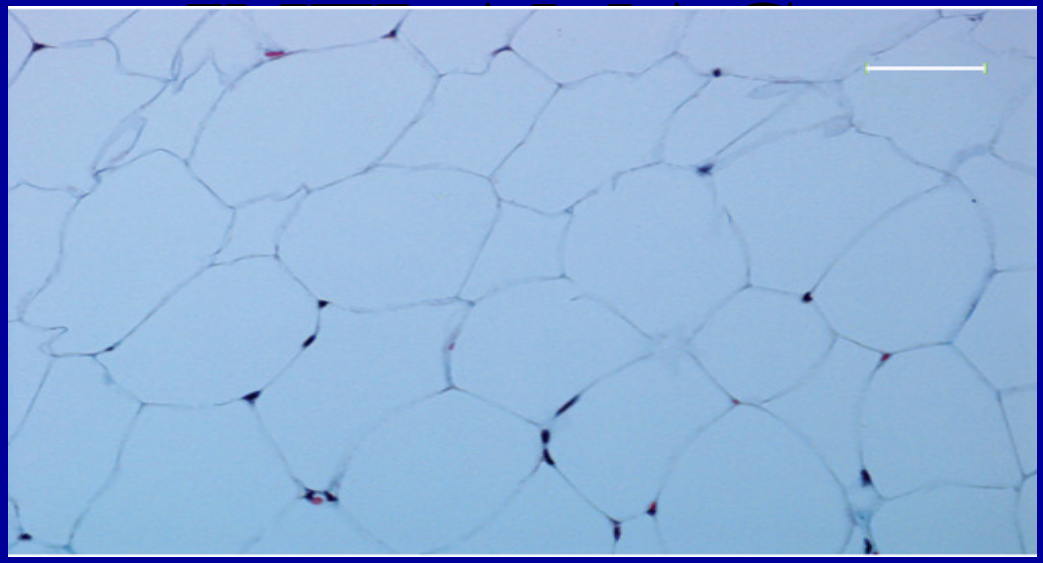
DESCUBRIMIENTO DE ADIPONECTINA: REVOLUCION EN MEDICINA



OBESIDAD ➔INFLAMACION EN GRASA

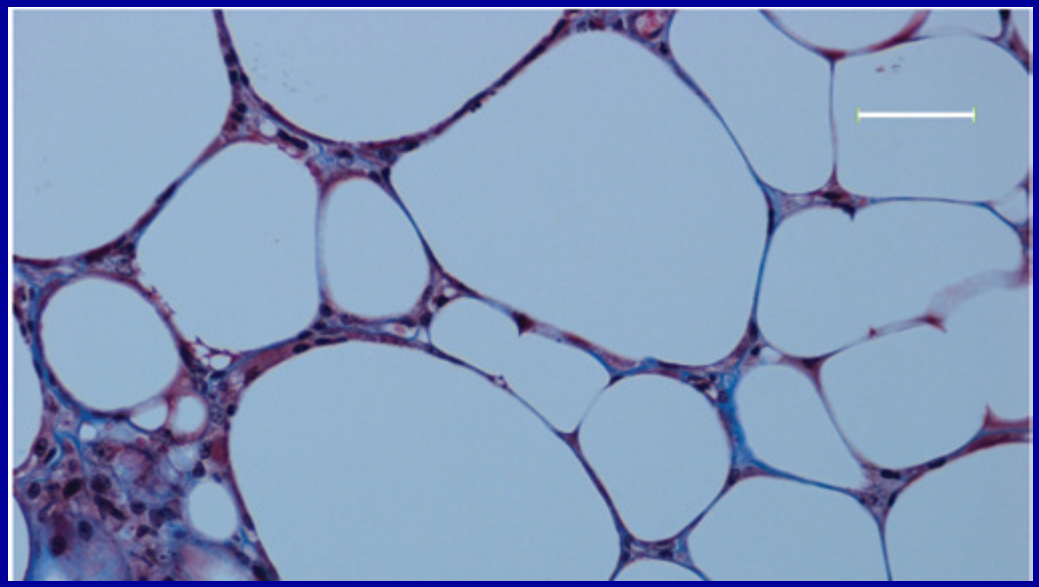
Normopeso

(10% células mononucleares)



Obesidad

(50% células mononucleares)



GENETICA DE LA OBESIDAD: LAS ENSEÑANZAS DEL PASADO

↓

TEJIDO ADIPOSO

=

ORGANO INMUNO-ENDOCRINO-METABOLICO

GENETICA DE LA OBESIDAD: LAS ENSEÑANZAS DEL PASADO

↓

HIPOTALAMO

=

CENTRO REGULADOR

DE LA INGESTA / SACIEDAD

GENETICA DE LA OBESIDAD: PRESENTE

FORMAS DE OBESIDAD

I. OBESIDAD POLIGENICA

II. OBESIDAD MONOGENICA

III. OBESIDAD SINDROMICA

OBESIDAD MONOGENICA

CARACTERISTICAS GENERALES

- **OBESIDAD PRECOZ**
- **OBESIDAD MORBIDA**
- **MANIFEST. CLINICAS LIMITADAS**
- **PATRON DE TRANSMISION HEREDOFAMILIAR**
- **FALLA SEVERA EN UN GEN**

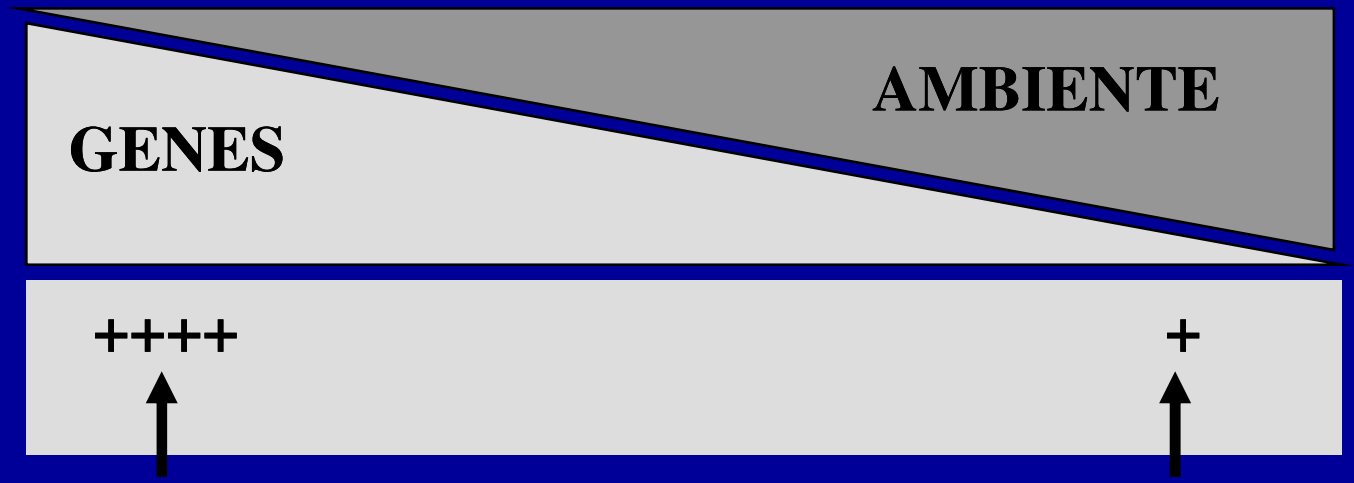
OBESIDAD SINDROMICA

CARACTERISTICAS GENERALES

- **OBESIDAD PRECOZ**
- **OBESIDAD MODERADA A SEVERA**
- **DISMORFIAS + ANOMALIAS COGNITIVAS**
- **PATRON DE TRANSMISION HEREDOFAMILIAR**
- **FALLA SEVERA EN UN GEN/LOCUS**

FORMAS DE OBESIDAD

COMPONENTES GENETICO Y AMBIENTAL



OBESIDAD MONOGENICA

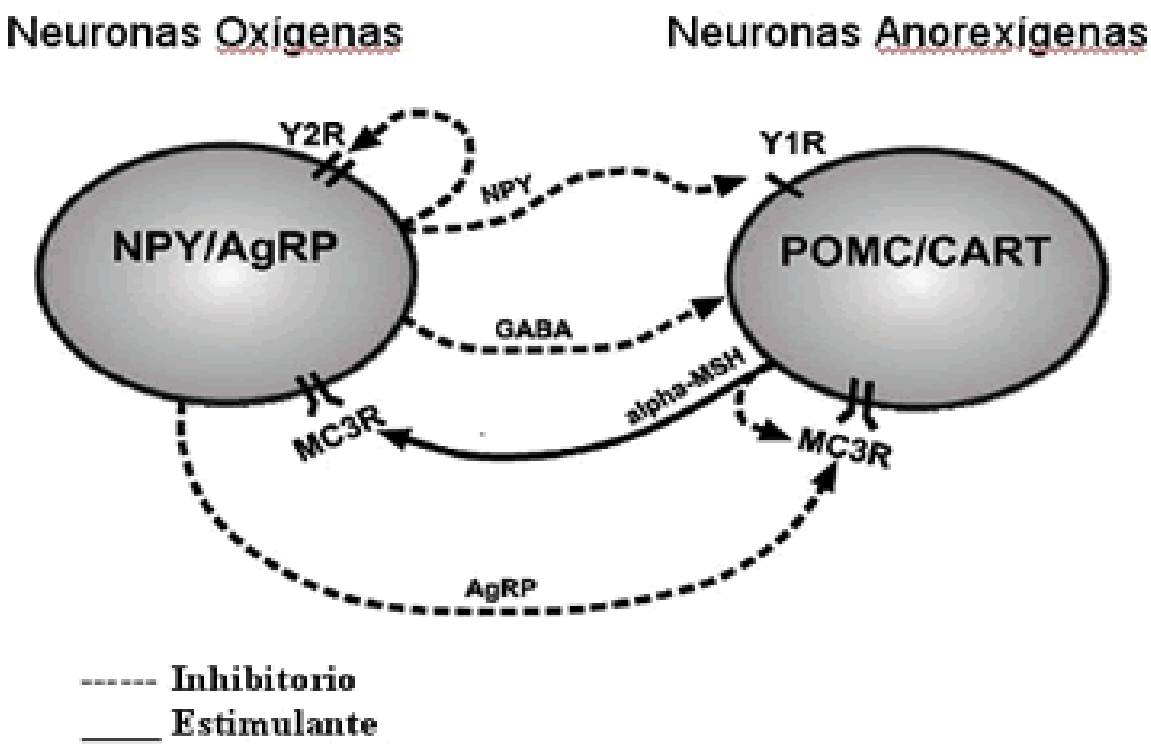
FORMAS Y GENES

GENES PRINCIPALES

GENES	HERENCIA
LEPTINA	RECESIVO
RECEPTOR DE LEPTINA	RECESIVO
PROHORMONA CONVERTASA 1 (PC-1)	RECESIVO
RECEPTOR DE MELANOCORTINA 4 (MC4R)	CODOMIN.
PROOPIOMELANOCORTINA (POMC)	RECESIVO
BDNF	RECESIVO
SIM1	RECESIVO

OBESIDAD MONOGENICA

VIAS OREXIGENICA: NPY & AgRP
VIAS ANOREXIGENAS: POMC & CART



OBESIDAD SINDROMICA

SINDROMES PRINCIPALES

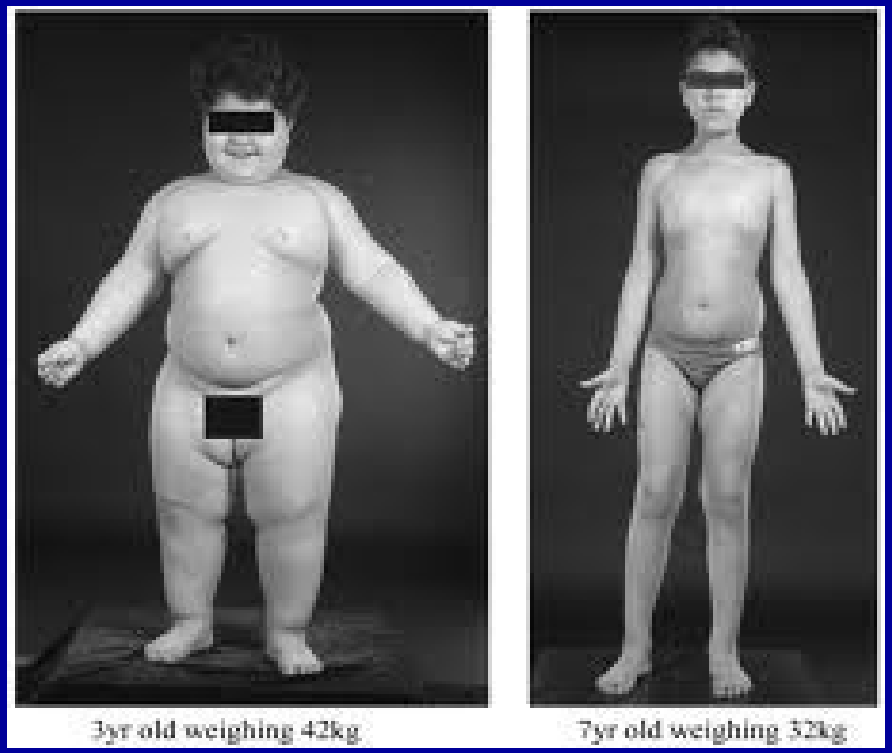
SINDROMES	HERENCIA
SINDROME DE ALSTROM	RECESIVO
SINDROME DE PRADER-WILLI	IMPRINTING
SINDROME BARDET-BIEDL	RECESIVO
SINDROME WAGR	DOMINANTE
DELECION 16p11.2	DOMINANTE

OBESIDAD MONOGENICA / SINDROMICA
PARA QUE SIRVE EL TEST GENETICO?

I. Confirmación diagnóstica
II. Predicción de evolución clínica
III. Orientación terapéutica (Medicina Personalizada)
IV. Diagnóstico precoz en familiares

OBESIDAD MONOGENICA & FARMACOGENETICA

DEFICIENCIA DE LEPTINA
↓
ADMINISTRACION DE LEPTINA RECOMBINANTE



3yr old weighing 42kg

7yr old weighing 32kg

MEDICINA PERSONALIZADA: FARMACOGENETICA

MARCADORES GENETICOS

↓

VARIABILIDAD INTERINDIVIDUAL

EN LA RESPUESTA A AGENTES TERAPEUTICOS

↓

MEDICINA PERSONALIZADA

OBESIDAD POLIGENICA ➔

Interacción entre Genes y Ambiente

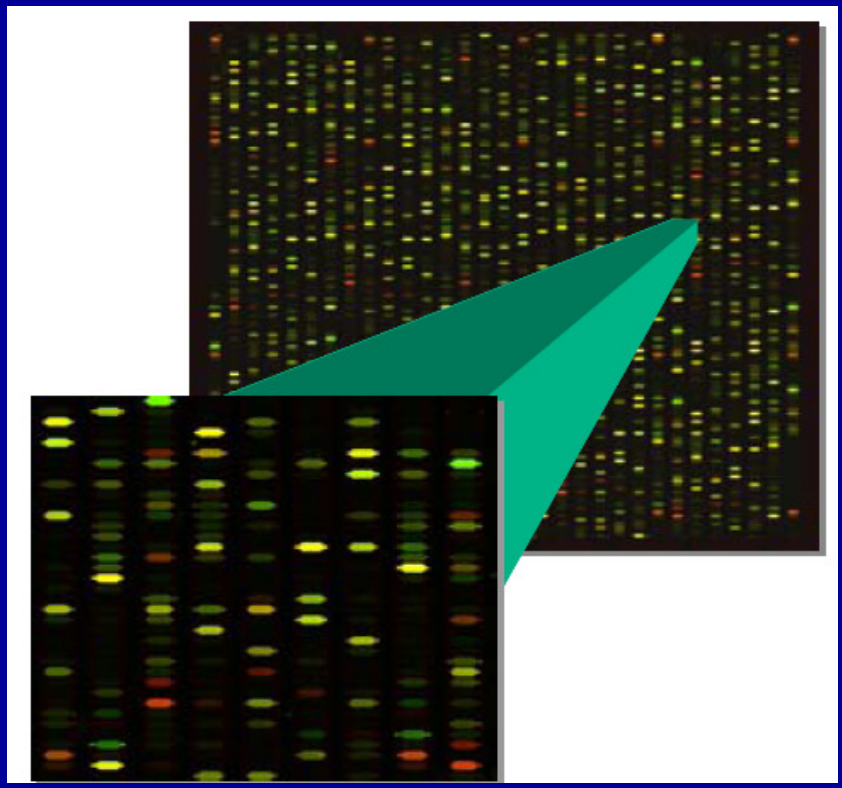
NUTRIGENOMICA


Science
21 December 2007 | 318
BREAKTHROUGH OF THE YEAR
Human Genetic Variation
AAAS

REVOLUCIÓN NANOTECNOLÓGICA: MICROARRAYS (Affymetrix / Illumina)

Genotipificación de > 2.000.000 de mutaciones

Costo: < 500 U$S



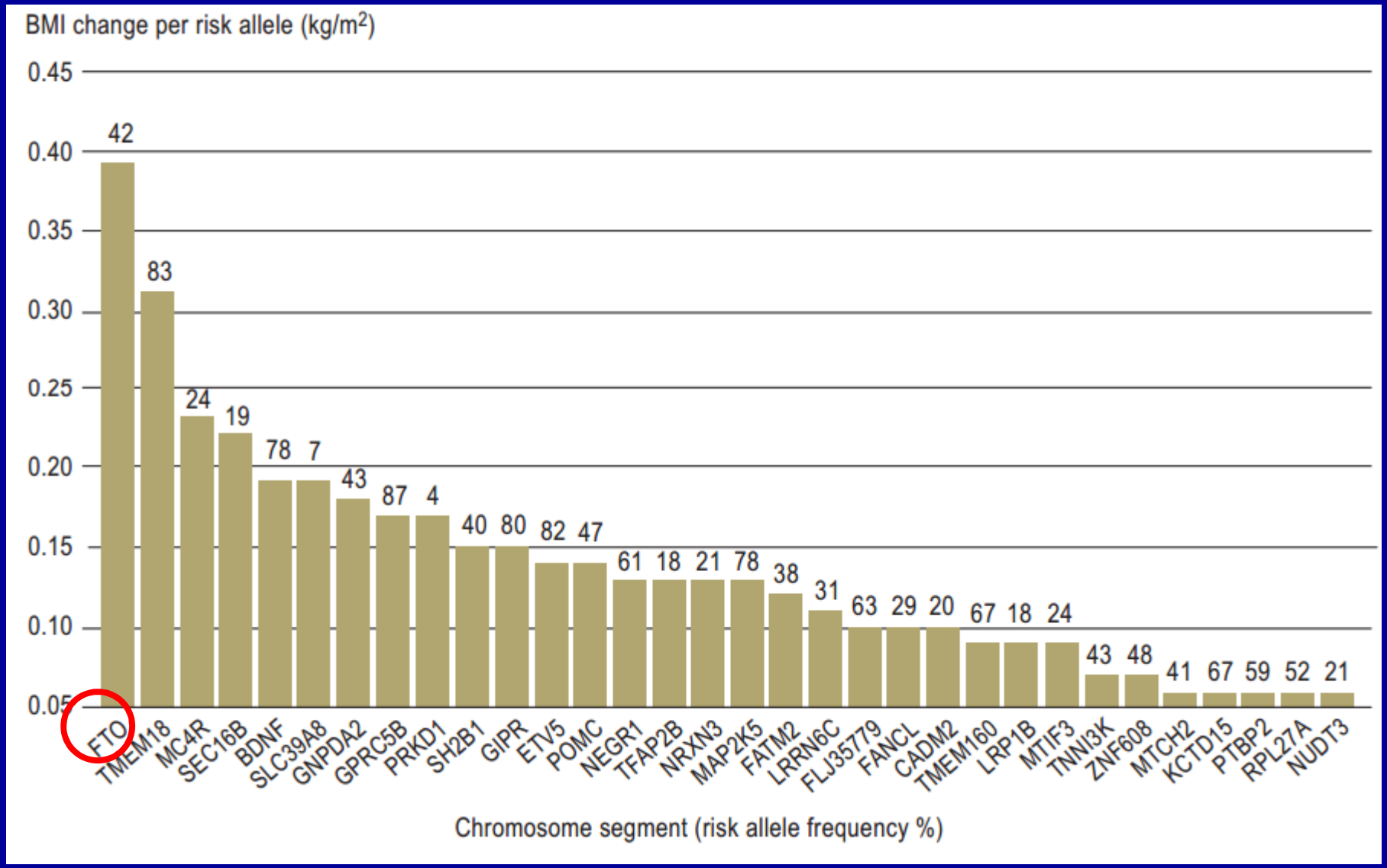
GENETICA & OBESIDAD POLIGENICA

GWAS + MICROARRAYS
(Genome-Wide Association Studies)

↓

RE-NACIMIENTO DE LA GENETICA DE LA OBESIDAD

OBESIDAD POLIGENICA: > 100 GENES



Hebebrand et al. Dtsch Arztebl Int, 2013

MARCADORES GENETICOS DE LA OBESIDAD POLIGENICA VIA GWAS:

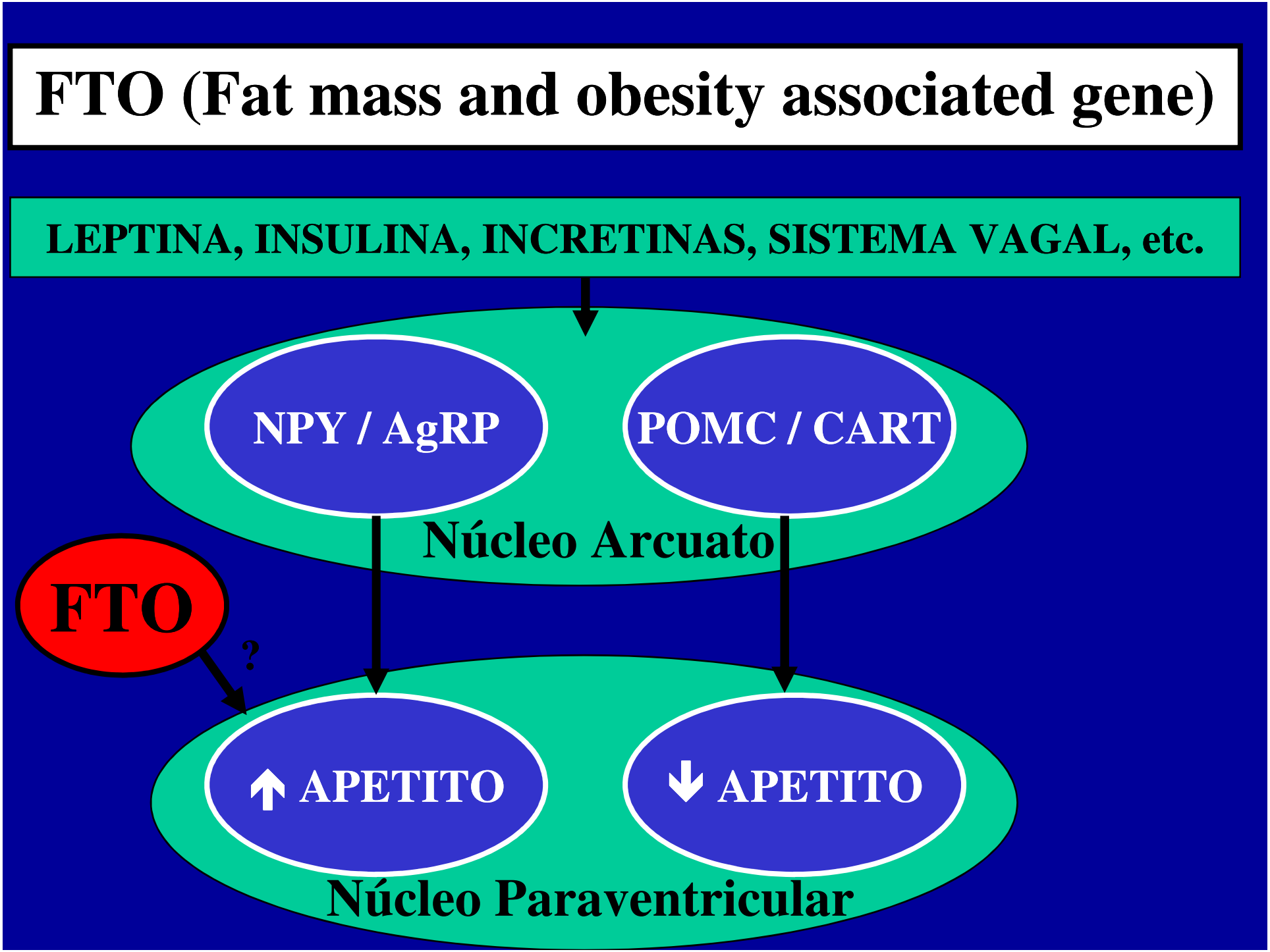
>100 Marcadores Polimórficos (SNPs)

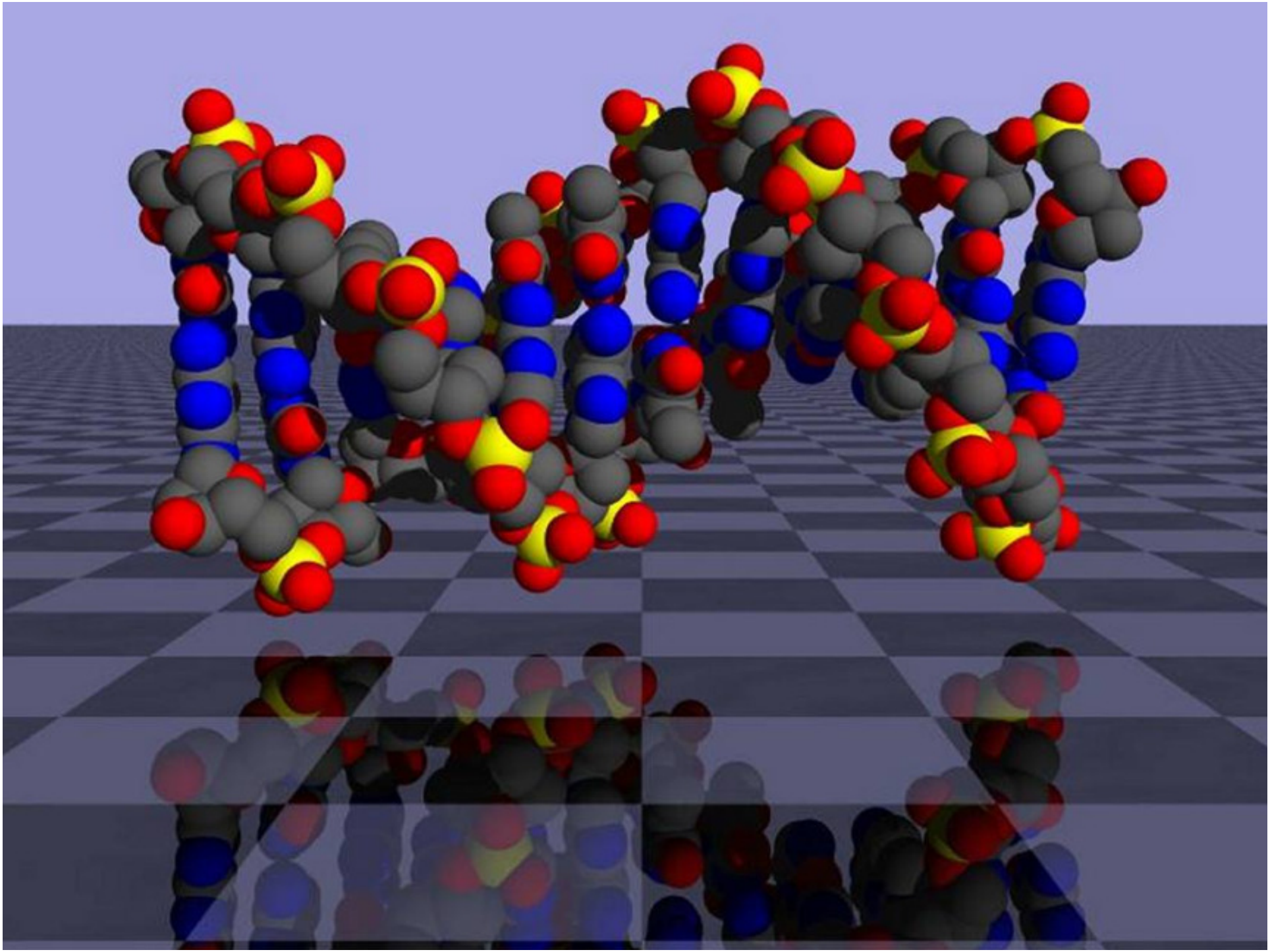
I. IMC / OBESIDAD → GENES DEL SNC

II. DISTRIBUCION GRASA → GENES DEL ADIPOCITO Y DEL METABOLISMO DE LIPIDOS

FTO

FTO (Fat mass and obesity associated gene)





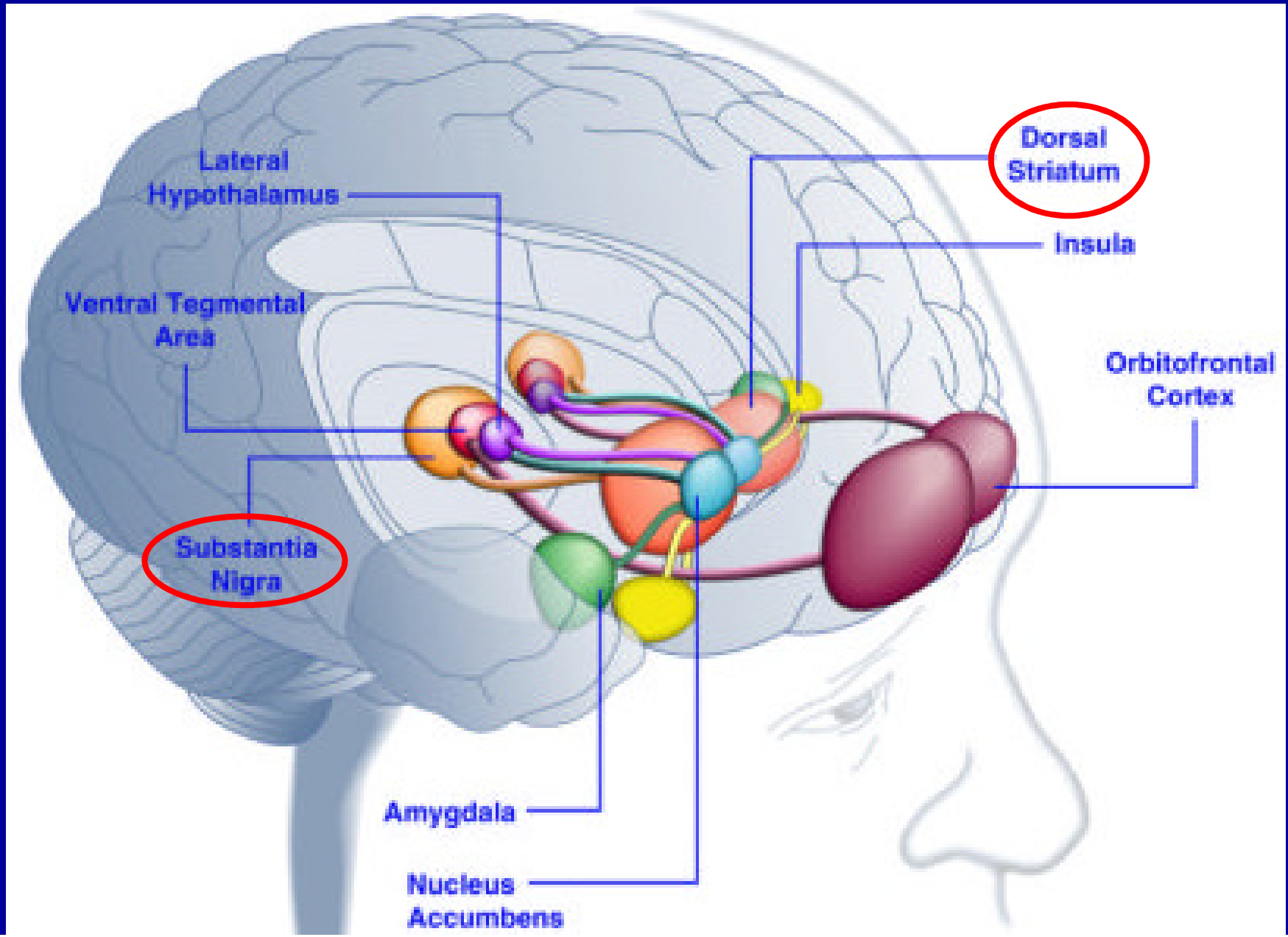
FTO

(*Fat mass and obesity associated gene*)

- **FTO es el único gen, que controla el peso corporal, asociado a DM2**
- **La asociación entre rs99390609 (alelo A) de FTO y Obesidad -DM2 depende del aumento de apetito (Haupt et al. Diabetes 2009)**
- **Homocigotas para SNPs de FTO → + 2,4 kg (Fischer Nature 2009)**
- **SNP de FTO se asoció a insulinorresistencia cerebral (Tschritter. Diabetologia, 2007)**

- FTO regula positivamente la desmetilación del ADN

OBESIDAD & ADICCION



OBESIDAD & ADICCION

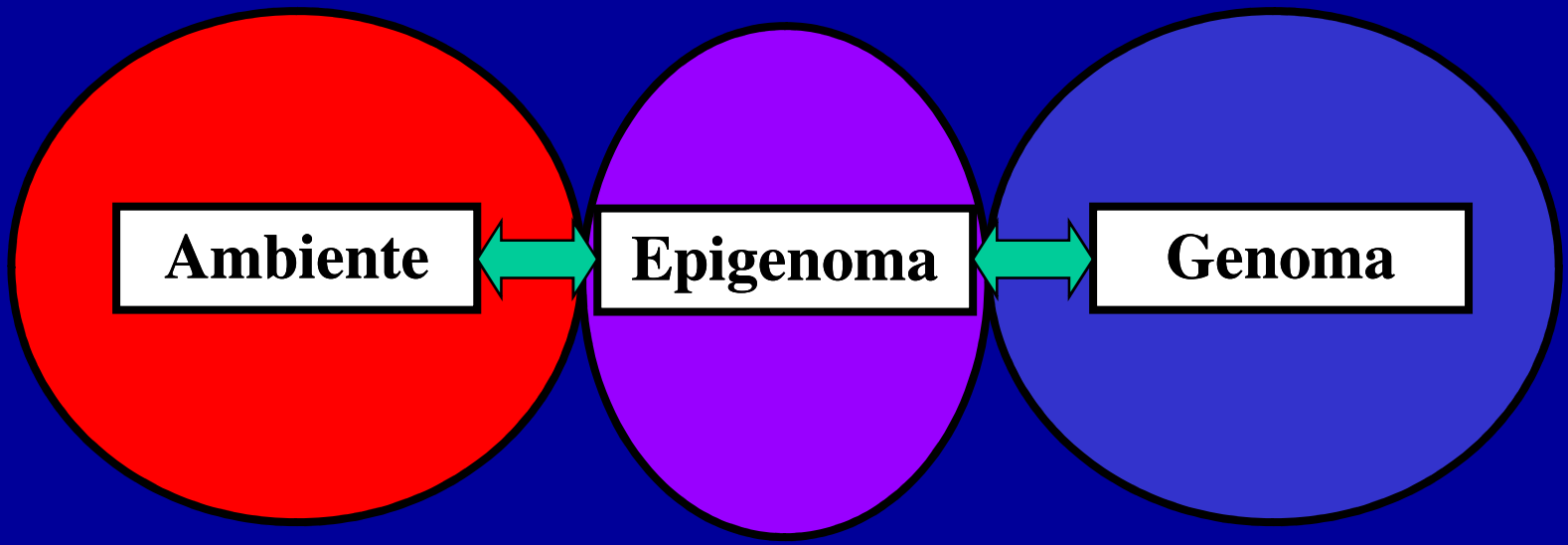
- En obesidad existe reducida activación del núcleo estriado en respuesta a ingesta de alimentos placenteros
- La activación del receptor de dopamina de tipo 2 (DRD2), estimulada por alimentos, se encuentra reducida en la obesidad

GENETICA DE LA OBESIDAD: LAS ESPERANZAS DEL FUTURO

EPIGENOMA

EPIGENOMA

Interfase para Interacciones entre Genoma y Ambiente



- **Epigenoma → conjunto de procesos que regulan la expresión génica (metilación, histonas y micro ARNs)**

CAMBIOS EPIGENETICOS TEMPRANOS (EN LA VIDA INTRAUTERINA) & RIESGO DE OBESIDAD Y ENF. ASOCIADAS

EPIGENOMA

↓

Cambios de Metilación en Genes Específicos + Cambios en Histonas

←

RESTRICCION PROTEICA

RESTRICCION GLOBAL

INGESTA DE MICRONUTR.

EXCESO DE CALORIAS

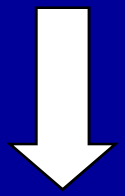
↓

RIESGO PARA OBESIDAD Y TRASTORNOS ASOCIADOS

CAMBIOS EPIGENETICOS TEMPRANOS & RIESGO DE OBESIDAD Y ENF. ASOCIADAS

MUJERES EXPUESTAS A HAMBRUNA DURANTE

LA FASE TEMPRANA DEL EMBARAZO



HIJOS CON INCIDENCIA AUMENTADA DE OBESIDAD

ASOCIADA A REDUCIDA METILACION DE IGF-2

(APORTE REDUCIDO DE DONANTES DE METILO)

Heude et al. JCEM 2007; Heijmans et al. PNAS 2008

HIPOMETILACION DE IGF2 ⇨MAYOR PESO DEL RECIEN NACIDO

Cancer Causes Control (2012) 23:635–645
DOI 10.1007/s10552-012-9932-y

ORIGINAL PAPER

Association of cord blood methylation fractions at imprinted insulin-like growth factor 2 (*IGF2*), plasma IGF2, and birth weight

Cathrine Hoyo · Kimberly Fortner · Amy P. Murtha · Joellen M. Schildkraut · Adelheid Soubry · Wendy Demark-Wahnefried · Randy L. Jirtle · Joanne Kurtzberg · Michele R. Forman · Francine Overcash · Zhiqing Huang · Susan K. Murphy

Received: 4 August 2011 / Accepted: 16 February 2012 / Published online: 6 March 2012

Abstract

Purpose Altered methylation at *Insulin-like Growth Factor 2 (IGF2)* regulatory regions has previously been associated with obesity, and several malignancies including colon, esophageal, and prostate adenocarcinomas, presumably via changes in expression and/or loss of imprinting, but the functional significance of these DNA methylation marks have not been demonstrated in humans. We examined associations among DNA methylation at *IGF2* differentially methylated regions (DMRs), circulating IGF2 protein concentrations in umbilical cord blood (UCB) and birth weight in newborns.

Methods Questionnaire data were obtained from 300 pregnant women recruited between 2005 and 2009. UCB DNA methylation was measured by bisulfite pyrosequencing. UCB plasma concentrations of soluble IGF2 were measured by ELISA assays. Generalized linear regression models were used to examine the relationship between DMR methylation and IGF2 levels.

Results Lower *IGF2* DMR methylation was associated with elevated plasma IGF2 protein concentrations ($\beta = -9.87$, $p < 0.01$); an association that was stronger in infants born to obese women (pre-pregnancy BMI > 30 kg/m^2, $\beta = -20.21$, $p < 0.0001$). Elevated IGF2 concentrations were associated with higher birth weight ($p < 0.0001$) after adjusting for maternal race/ethnicity, pre-pregnancy BMI, cigarette smoking, gestational diabetes, and infant sex. These patterns of association were not apparent at the *H19* DMR.

CAMBIOS EPIGENETICOS TEMPRANOS & RIESGO DE OBESIDAD Y ENF. ASOCIADAS

AMAMANTAMIENTO EN HUMANOS

CORRELACION INVERSA CON OBESIDAD

> 9 MESES ➔ MENOR RIESGO DE OBESIDAD (- 32%)

Harder et al. Am J Epidemiol 2005

HIPERMETILACION DE POMC ⇨OBESIDAD

OPEN ACCESS Freely available online

PLoS GENETICS

An Alu Element–Associated Hypermethylation Variant of the *POMC* Gene Is Associated with Childhood Obesity

Peter Kuehnen[1]*, Mona Mischke[1], Susanna Wiegand[1], Christine Sers[2], Bernhard Horsthemke[3], Susanne Lau[4], Thomas Keil[5], Young-Ae Lee[5,6], Annette Grueters[1], Heiko Krude[1]

1 Institut für Experimentelle Pädiatrische Endokrinologie, Charité - Universitätsmedizin Berlin, Berlin, Germany, **2** Institut für Pathologie, Charité - Universitätsmedizin Berlin, Berlin, Germany, **3** Institut für Humangenetik, Universitätsklinikum Essen, Essen, Germany, **4** Pediatric Allergology, Experimental and Clinical Research Center, Universitätsmedizin Berlin, Berlin, Germany, **5** Institut für Sozialmedizin und Epidemiologie, Charité - Universitätsmedizin Berlin, Berlin, Germany, **6** Max Delbrück Centrum für molekulare Medizin (MDC), Berlin-Buch, Germany

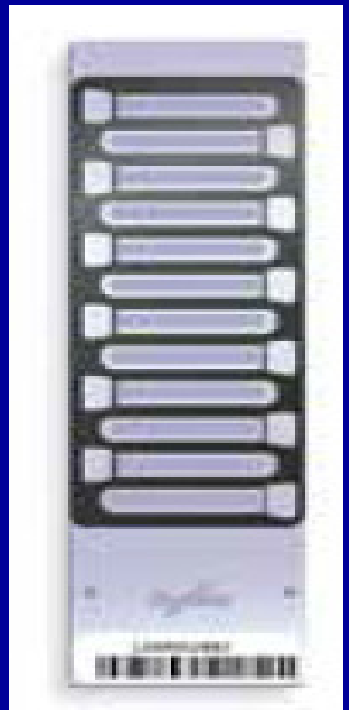
Abstract

The individual risk for common diseases not only depends on genetic but also on epigenetic polymorphisms. To assess the role of epigenetic variations in the individual risk for obesity, we have determined the methylation status of two CpG islands at the *POMC* locus in obese and normal-weight children. We found a hypermethylation variant targeting individual CpGs at the intron2–exon3 boundary of the *POMC* gene by bisulphite sequencing that was significantly associated with obesity. *POMC* exon3 hypermethylation interferes with binding of the transcription enhancer P300 and reduces expression of the *POMC* transcript. Since intron2 contains Alu elements that are known to influence methylation in their genomic vicinity, the exon3 methylation variant seems to result from an Alu element–triggered default state of methylation boundary definition. Exon3 hypermethylation in the *POMC* locus represents the first identified DNA methylation variant that is associated with the individual risk for obesity.

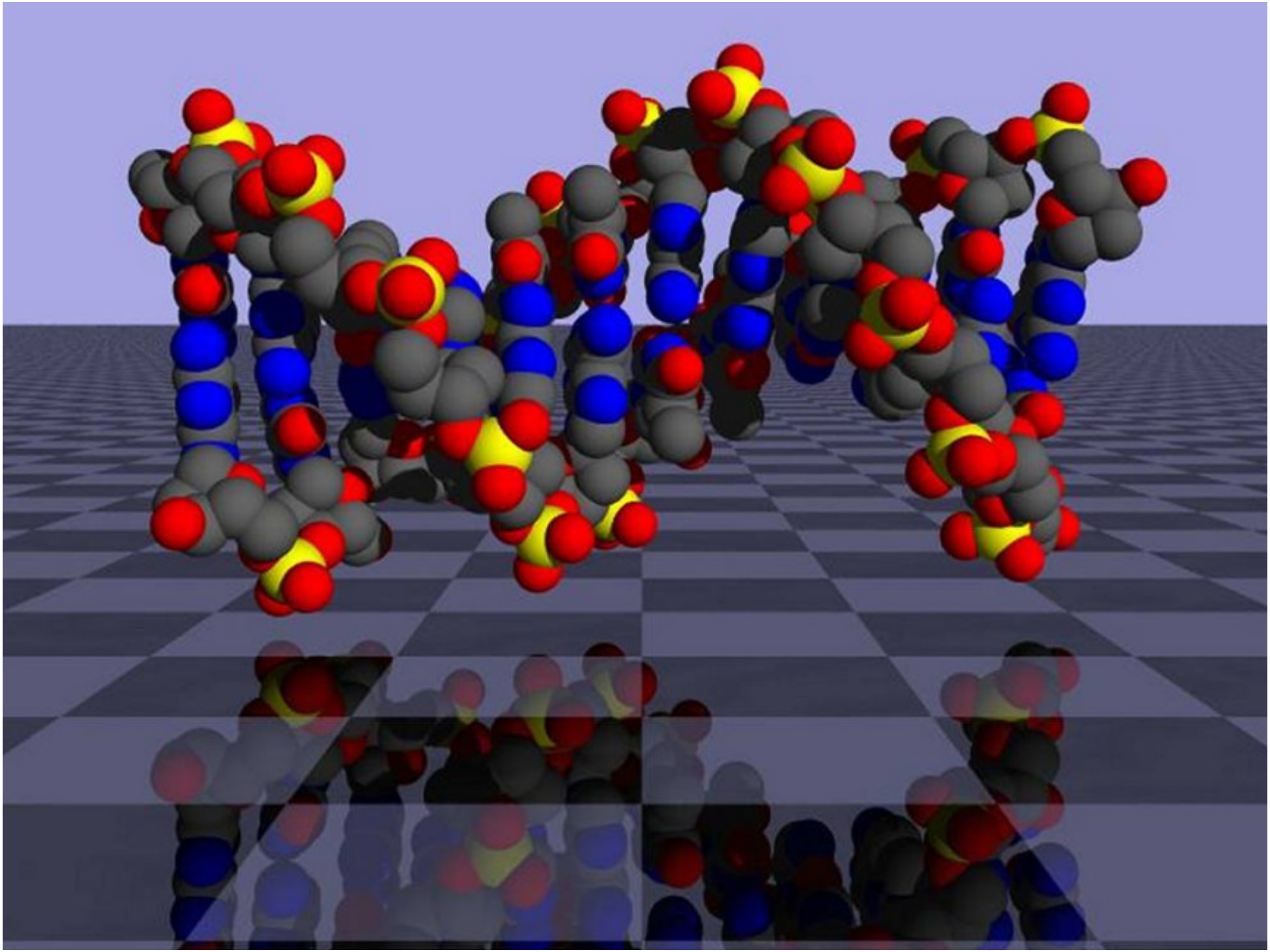
REVOLUCIÓN NANOTECNOLÓGICA: MICROARRAYS PARA CpGs (Illumina) Infinium HumanMethylation27 Beadchip

27.000 regiones de metilación CpGs (14.000 genes)

EWA (*Epigenome Wide Association*)




OBESIDAD
AMBIENTE
GENOMA
EPIGENOMA



OBESIDAD POLIGENICA & FARMACOGENETICA

NUTRICION & MEDICINA PERSONALIZADA

EPIGENOMICA Y NUTRICION PERSONALIZADA

↓ METILACION DE TNF-A & LEP = ↑ Pérdida de Peso

J Physiol Biochem. 2011 Sep;67(3):463-70. Epub 2011 Apr 5.

Leptin and TNF-alpha promoter methylation levels measured by MSP could predict the response to a low-calorie diet.

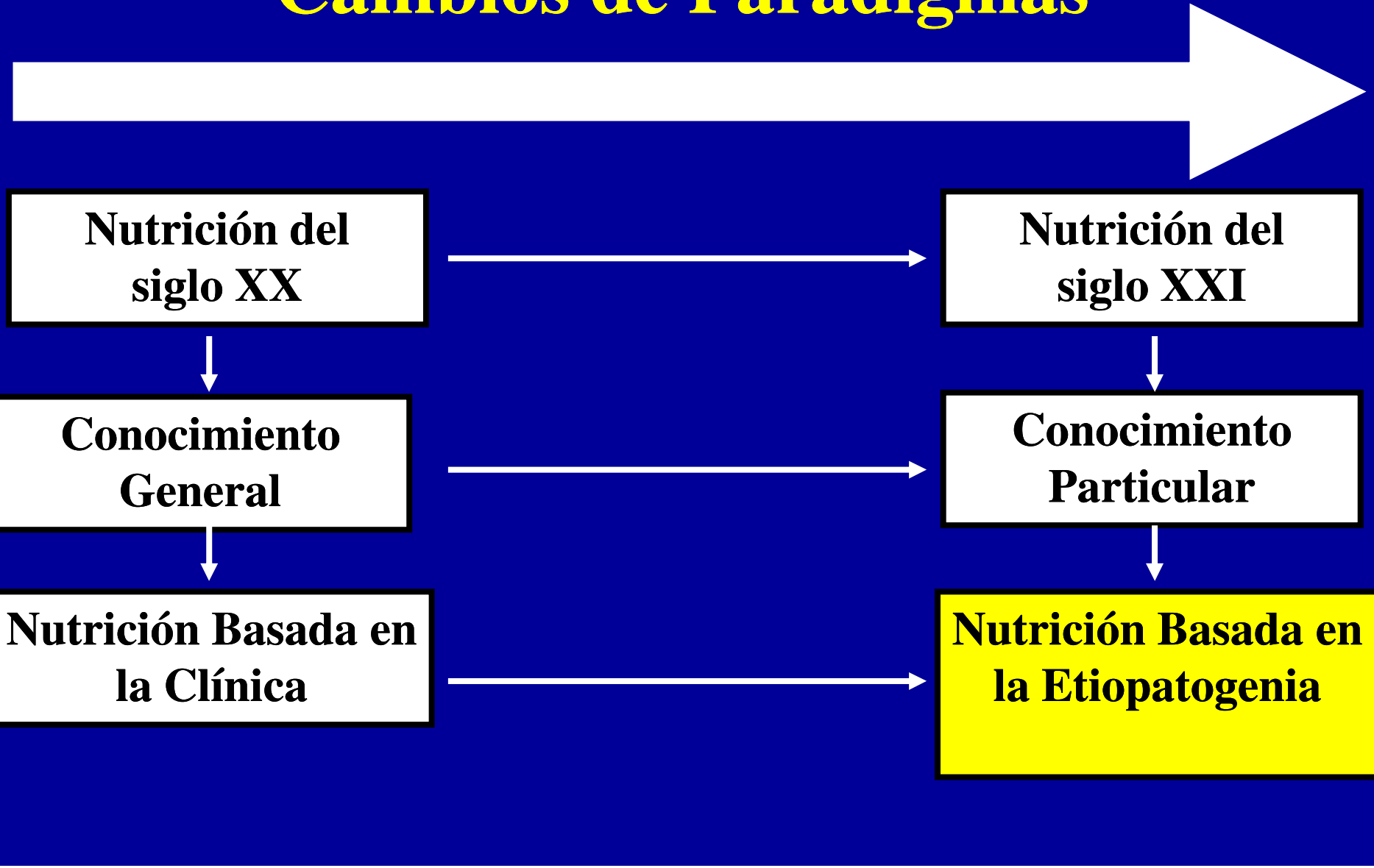
Cordero P, Campion J, Milagro FI, Goyenechea E, Steemburgo T, Javierre BM, Martinez JA.

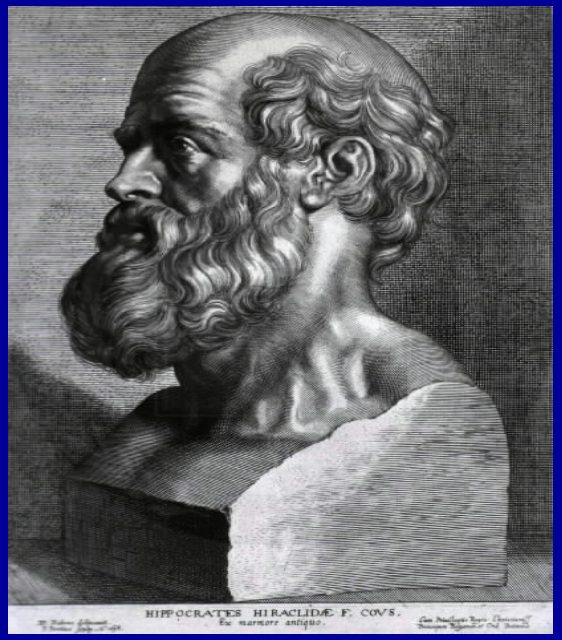
Department of Nutrition and Food Sciences, Physiology and Toxicology, University of Navarra, Pamplona, Spain.

Abstract

Obesity-associated adipose tissue enlargement is characterized by an enhanced proinflammatory status and an elevated secretion of adipokines such as leptin and cytokines such as tumor necrosis factor (TNF)-alpha. Among the different mechanisms that could underlie the interindividual differences in obesity, epigenetic regulation of gene expression has emerged as a potentially important determinant. Therefore, 27 obese women (age, 32-50 years; baseline body mass index, 34.4 ± 4.2 kg/m(2)) were prescribed an 8-week low-calorie diet, and epigenetic marks were assessed. Baseline and endpoint anthropometric parameters were measured, and blood samples were drawn. Genomic DNA and RNA from adipose tissue biopsies were isolated before and after the dietary intervention. Leptin and TNF-alpha promoter methylation were measured by MSP after bisulfite treatment, and gene expression was also analyzed. Obese women with a successful weight loss (≥5% of initial body weight, n=21) improved the lipid profile and fat mass percentage (-12%, $p<0.05$). Both systolic (-5%, $p<0.05$) and diastolic (-8%, $p<0.01$) blood pressures significantly decreased. At baseline, women with better response to the dietary intervention showed lower promoter methylation levels of leptin (-47%, $p<0.05$) and TNF-alpha (-39%, $p=0.071$) than the non-responder group (n=6), while no differences were found between responder and non-responder group in leptin and TNF-alpha gene expression analysis. These data suggest that leptin and TNF-alpha methylation levels could be used as epigenetic biomarkers concerning the response to a low-calorie diet. Indeed, methylation profile could help to predict the susceptibility to weight loss as well as some comorbidities such as hypertension or type 2 diabetes.

GENETICA DE LA OBESIDAD ➔
Cambios de Paradigmas





Hipócrates (Siglo V a. C.)

“Somos lo que comemos”