NuGOweek 2015, 12th edition

MECHANISMS OF A LONG-LIFE HEALTH

Nutritional interventions for weight loss and maintenance based on the genotype

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PERSONALIZED WEIGHT MANAGEMENT

INDIVIDUALIZED NUTRITION

PERSONALIZED NUTRITION BASED ON GENOTYPE

Genetic make-up can determine unique nutritional requirements and responses to different foods.and nutrients

Based on:

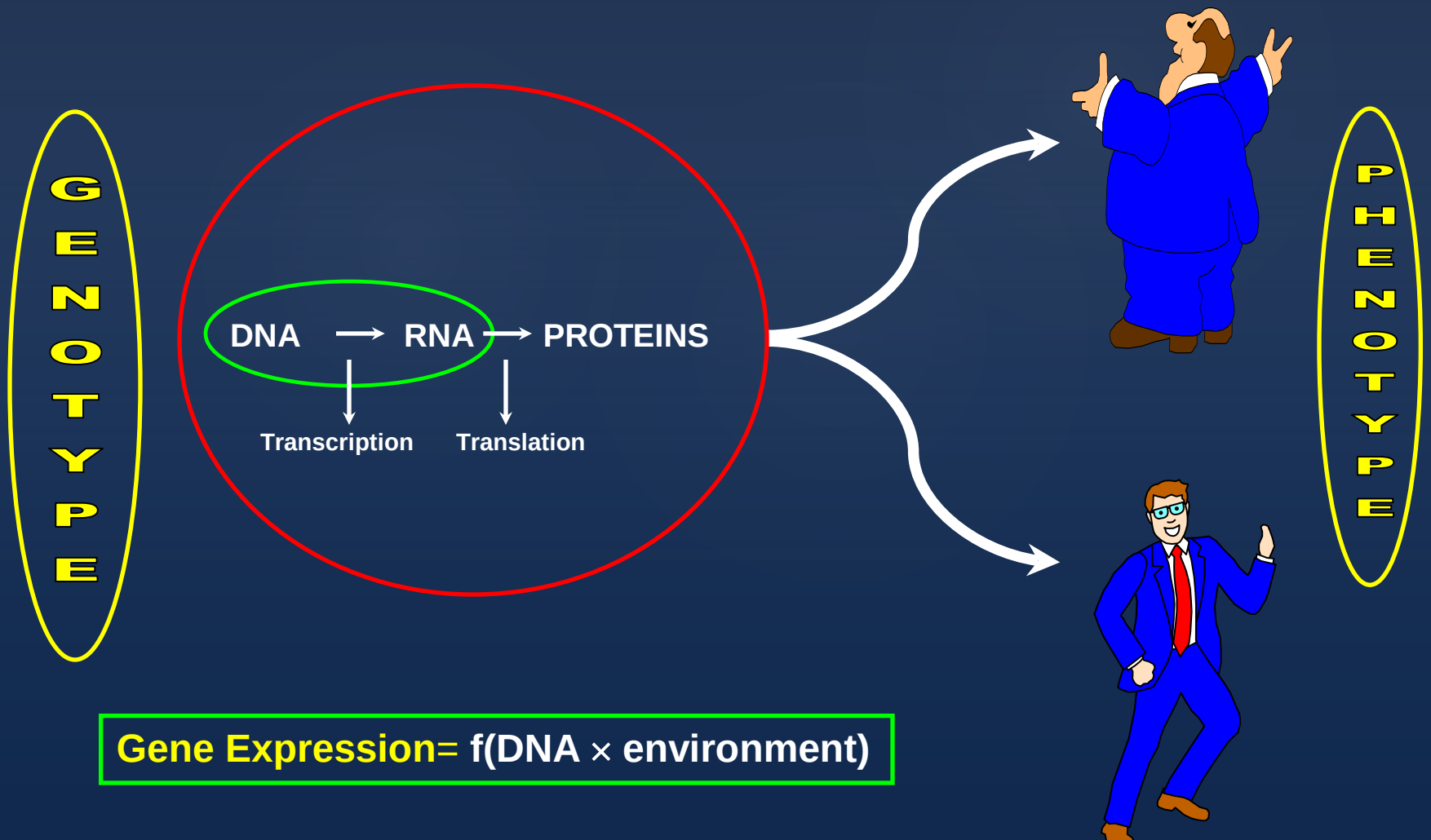
- The sequencing of the human genome,

- subsequent analyses of human genetic variation,

-studies that associate gene variants with disease markers

-Impact of nutrition/nutrients on gene expression

GENOTYPE x NUTRITION → METABOTYPE

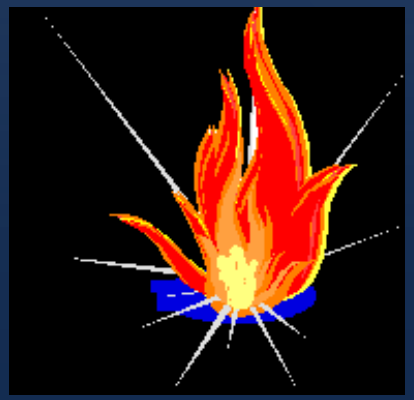


Gene Expression= f(DNA × environment)

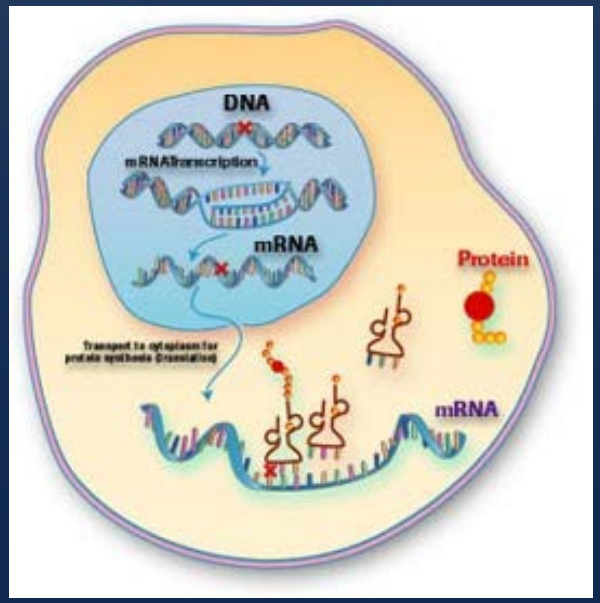
NUTRIENTS FUNCTIONS

Nutrients

Energy

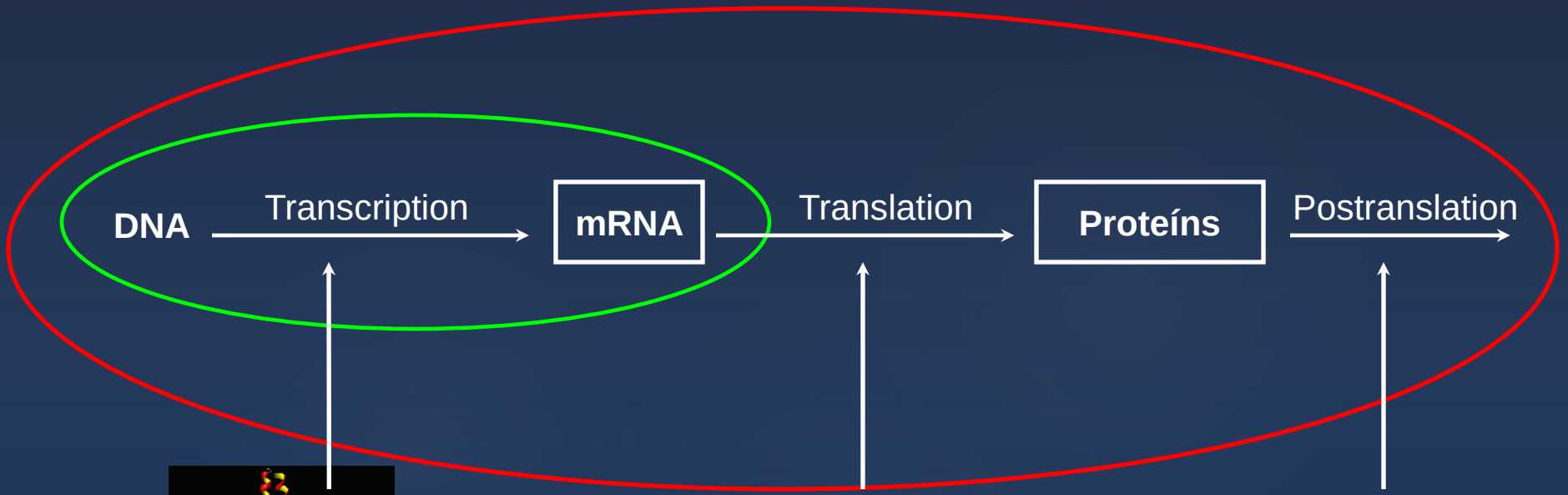


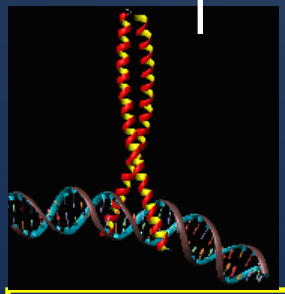
Regulatory Elements



Structural components

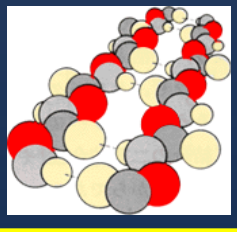
GENE EXPRESSION: NUTRITIONAL CONTROL





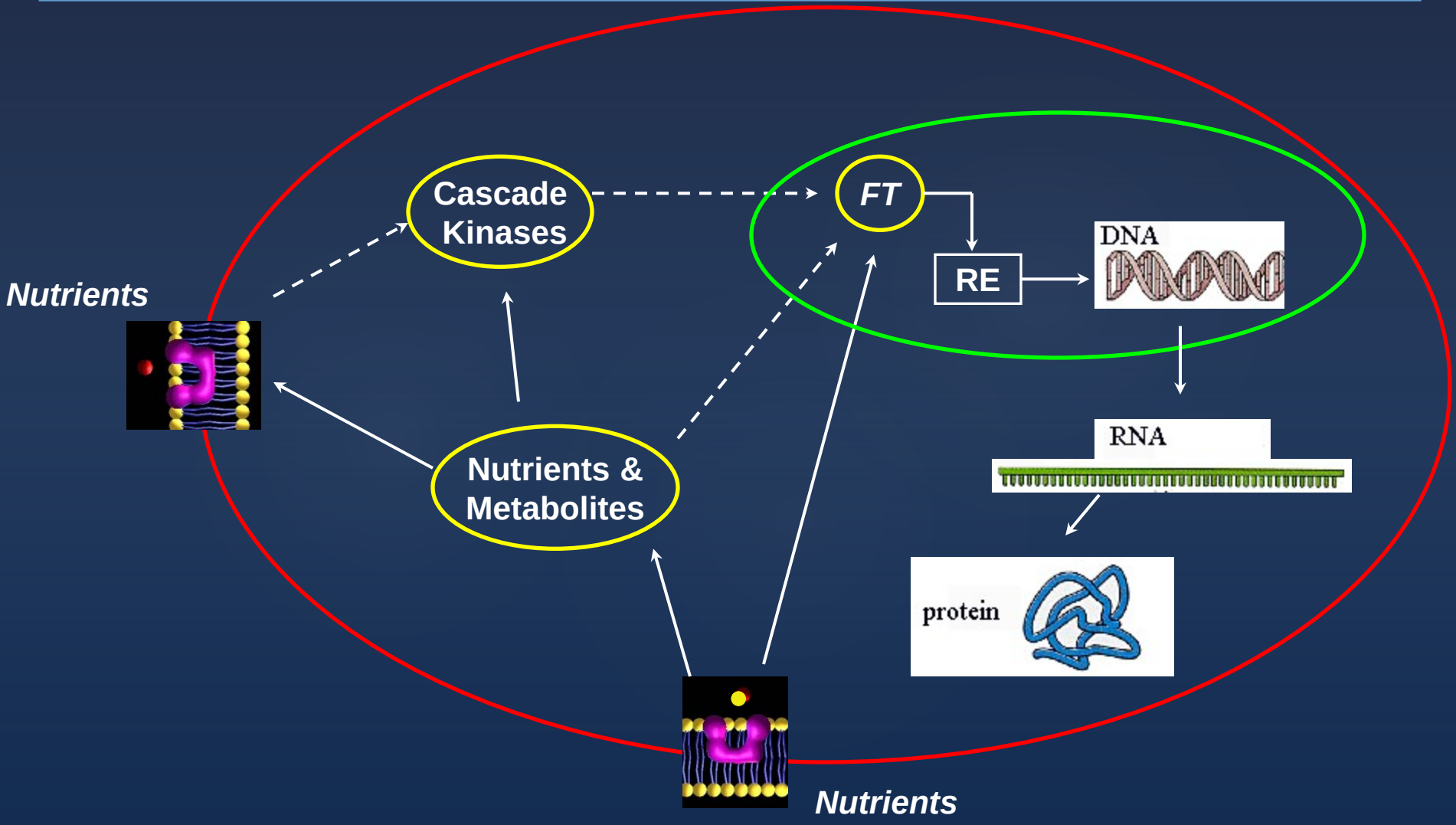
Fatty Acids
Retinoids
Vitamin D
Glucose
Energy

Amino acids
Iron
Selenium



Minerals
Vitamins

GENE EXPRESSION CONTROL: MECHANISMS

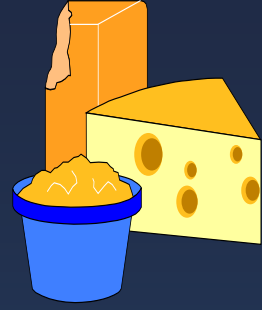


Mechanisms : - Receptors (membrane/nucleus)

- Metabolism intermediate

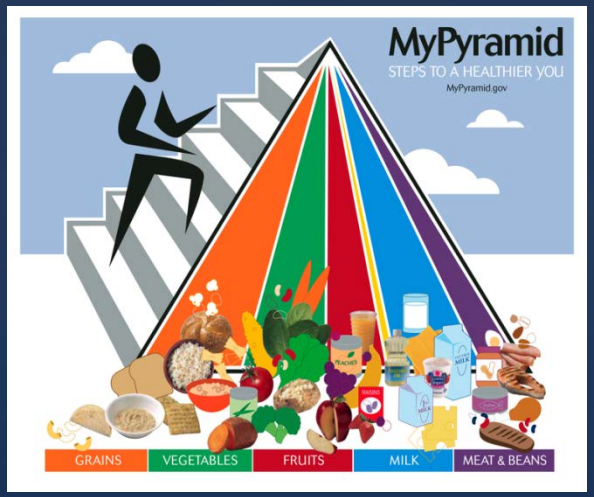
- Transcription Factors (*FT*): affinity & concentrations

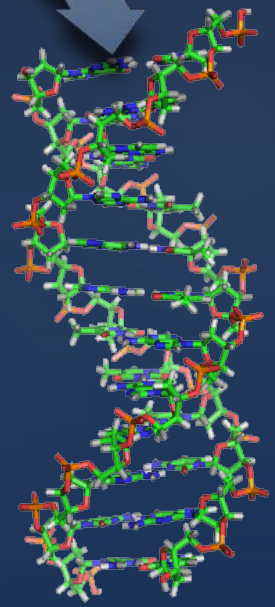
Nutrigenomics and Nutrigetics



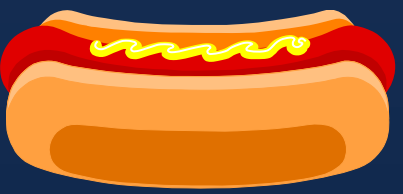
Dietary effects on gene expression

NUTRIGENOMICS



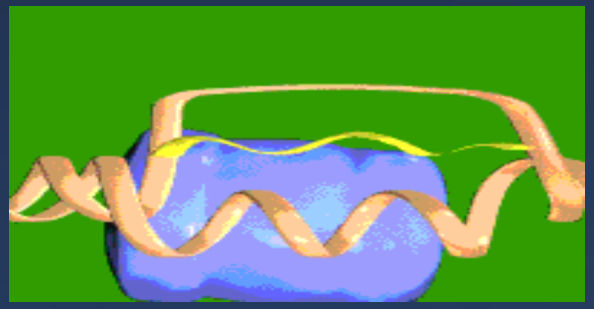


NUTRIGENETICS



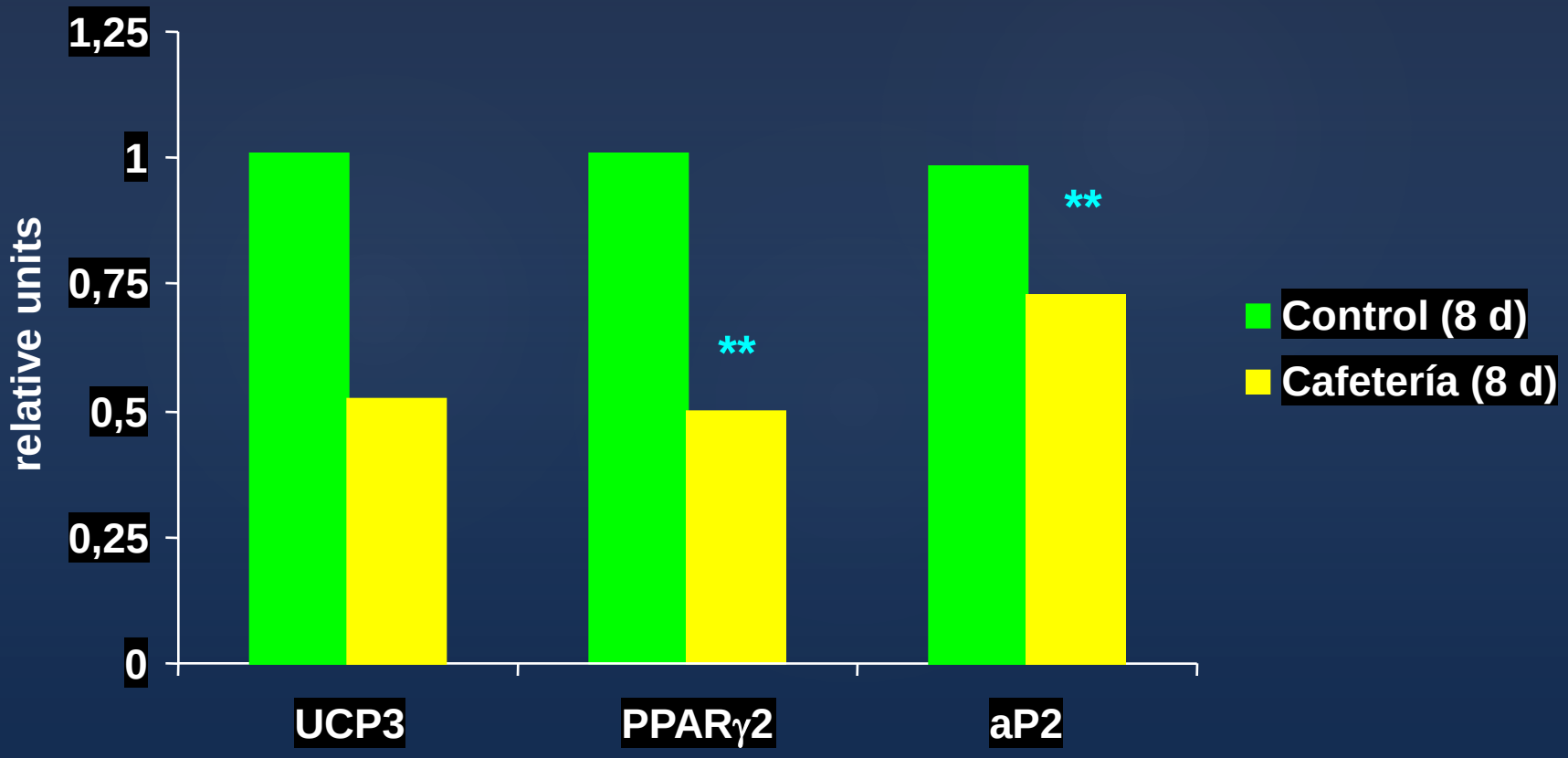
Genotype influences the response related with nutrition and personalised metabolism

NUTRIGENOMIC INTERACTIONS



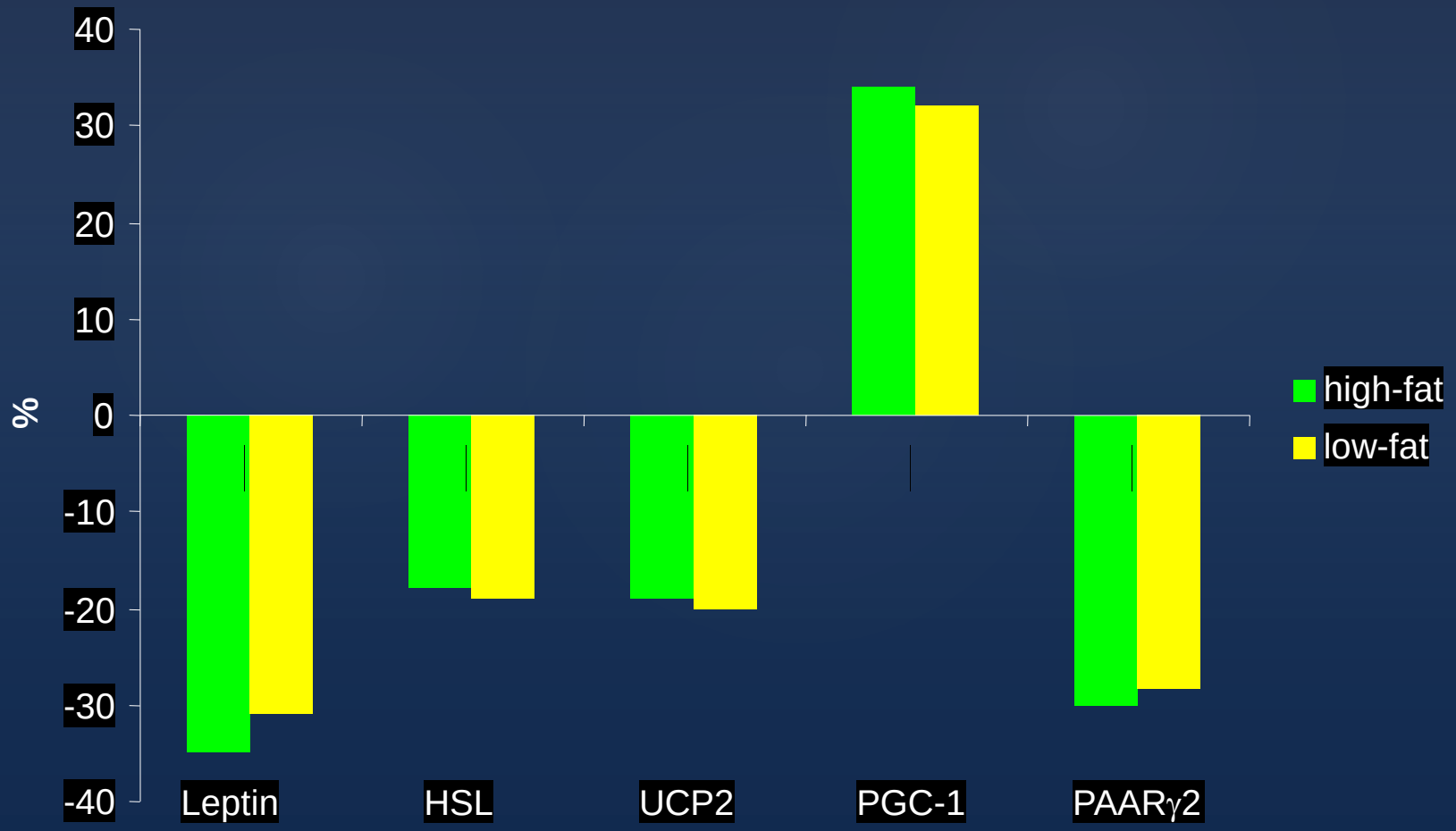
Nutrition → **GENE Expression** → **Phenotype**

DIET DEPENDENT GENE EXPRESSION



Margareto, *et al.* 2001

FAT INTAKE AND mRNA LEVELS AFTER ENERGY RESTRICTION



Viguerie, *et al.* 2005

OMICS A Journal of Integrative Biology
Volume 12, Number 4, 2008

DOI: 10.1089/omi.2008.0001

Differential Expression of Oxidative Stress and Inflammation Related Genes in Peripheral Blood Mononuclear Cells in Response to a Low-Calorie Diet: A Nutrigenomics Study

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Abstract

Nutrigenomics is a new application of omics technologies in nutritional science. Nutrigenomics aims to identify molecular markers of diet-related diseases and mechanisms of interindividual variability in response to food. The aim of this study was to evaluate peripheral blood mononuclear cells (PBMC) as a model system and readily available source of RNA to discern gene expression signatures in relation to personalized therapy of obesity. PBMC were collected from obese men before and after an 8-week low-calorie diet (LCD) to lose weight. Changes in gene expression before and after the LCD were initially screened using a DNA-microarray platform and validated by qRT-PCR. Global gene expression analysis identified 385 differentially expressed transcripts after the LCD. Further analyses showed a decrease in some specific oxidative stress and inflammation genes. Interestingly, expression of these genes was directly related to body weight, while a lower IL8 gene expression was associated with higher fat mass decrease. Collectively, these observations suggest that PBMCs are a suitable RNA source and model system to perform nutrigenomics studies related to obesity and development of personalized dietary treatments. IL8 gene expression warrant further research as a putative novel biomarker of changes in body fat percentage in response to an LCD.

DOI: 10.1111/j.1365-2362.2008.01998.x

ORIGINAL ARTICLE

Sirtuin gene expression in human mononuclear cells is modulated by caloric restriction

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ABSTRACT

Background Sirtuins may provide novel targets for treating some diseases associated with oxidative stress, such as obesity and its comorbidities. However, there are a few *in vivo* studies in humans about the potential role of sirtuins as therapeutic targets among obese patients undergoing caloric restriction. Therefore, the aim of this study was to assess if the gene expression of sirtuins is modulated in peripheral blood mononuclear cells (PBMC) by a hypocaloric diet devised to lose weight in humans.

Materials and methods Gene expression of two sirtuins (SIRT1 and SIRT2) in the PBMC of obese subjects [32·3 ± 5·5 kg m^{-2}] before and following an 8-week hypocaloric diet was investigated. NADH-coenzyme Q reductase (NDUFS2) and cytochrome *c* oxidase assembly protein (COX15) gene expression was selected together with plasma antioxidant power and nitric oxide as markers of antioxidant status. A quantitative real-time polymerase chain reaction approach was performed to assess the nutrigenomics outcome. Moreover, 2-keto[1-^{13}C]isocaproate breath test (KICA-BT) parameters were evaluated to study mitochondrial oxidation *in vivo*.

Results The intervention up-regulated the expression of both sirtuins, being inversely associated with total antioxidant capacity and directly related to nitric oxide, mitochondrial oxidation assessed by the KICA-BT and the expression of the mitochondrial proteins COX15 and NDUFS2.

Conclusion SIRT1 and SIRT2 may serve as key regulators for some obesity comorbidities related to antioxidant status, while PBMC could be a model to study the effect of the sirtuin response in obesity therapy.

Keywords ^{13}C-KICA breath test, caloric restriction, mitochondrial function, oxidative stress, PBMC gene expression, sirtuins.

Eur J Clin Invest 2008; 38 (9): 672–678

Original Paper

Journal of Nutrigenetics and Nutrigenomics

J Nutrigenet Nutrigenomics 0:0:0
DOI: 10.1159/000XXXXXX

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Accepted: January 27, 2009

Expression of Two Inflammation-Related Genes (RIPK3 and RNF216) in Mononuclear Cells Is Associated with Weight-Loss Regain in Obese Subjects

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Key Words
Nutrigenomics · RIPK3 · RNF216 · Gene expression · Obesity · Weight-loss regain · Weight maintenance · Peripheral blood mononuclear cells · Dietary intervention

Abstract
Background/Aims: Nutrigenomics is providing molecular biomarkers concerning the assessment of diet-related diseases. We analyzed the expression of two interacting genes (RIPK3 and RNF216) in obese subjects receiving a low-calorie diet (LCD) and during the subsequent weight changes. *Methods:* Two groups of obese subjects (BMI 32.3 ± 5.5; age 37.7 ± 7.1 years) were selected according to the 6-month weight-regain outcome after the weight-loss induced by an 8-week LCD (n = 12). Body composition and mRNA levels of RIPK3 and RNF216 in peripheral blood mononuclear cells (PBMC) were evaluated by qRT-PCR at three time-points (week 0, week 8 and week 32). *Results:* All subjects lost weight significantly (–5.8 ± 2.3%, $p < 0.001$) and were grouped depending on the successful weight-loss maintenance (weight-loss regain ≤ 10% or >10%). At baseline (week 0), no differences were observed in the mRNA levels between groups ($p > 0.05$). However, at the end of the LCD (week 8), association analysis revealed that higher mRNA levels in PBMC of RIPK3 and RNF216 were able to detect those individuals who are more prone to regain weight 6-month after the nutritional intervention ($p < 0.05$). *Conclusions:* Gene expression of RIPK3 and RNF216 in PBMC could identify those obese subjects, who will regain more weight after a successful initial weight loss. The mRNA levels of these genes could be suggested as nutrigenomic biomarkers for predicting the obesity treatment outcome.

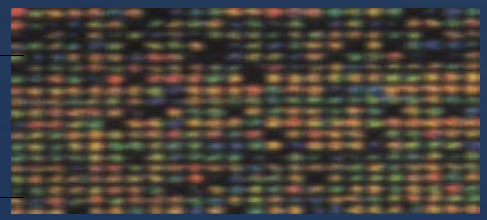
Introduction

Obesity is a multifactorial condition, associated with multiple morbidities, which is showing a rising prevalence worldwide [1, 2]. Weight reduction methods are mainly focused on dietary changes and increased physical activity approaches [3], which often produce successful short-term results. Indeed, weight cycling and relapse are common features after weight-loss treatment of obesity [4]. The failure to maintain weight loss could be partially explained by genetic factors or by the interaction between genes and the environment [5, 6].

In the last years, novel research strategies have been applied to understand the molecular mechanisms involved in the excess fat mass and weight-lowering regulation [7]. In this sense, the nutrigenomics field involves the study of

TOOLS: 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

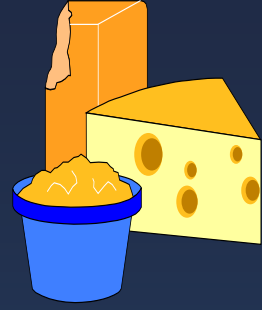
-117.5	S49491	**Proenkephalin**
~-92.3=	J04488	**Prostaglandin D synthetase**
~-47.3	D63772	**Neuronal high affinity glutamate transporter**
~-8.6=	M12450	**Vitamin D binding protein**
-4.1	U57715	**FGF receptor activating protein FRAG1**
-2.8	U48596	**MAP kinase kinase kinase 1 (MEKK1)**
-2.3	L06096	**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**

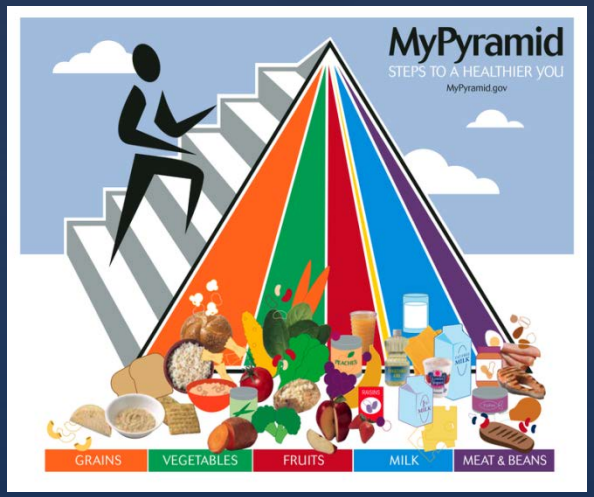
= corresponds to a transcript absent in the obese group (basal line).

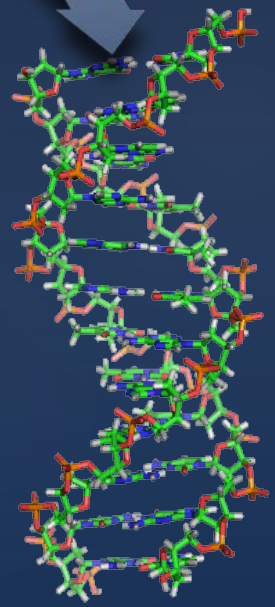
Nutrigenomics and Nutrigetics



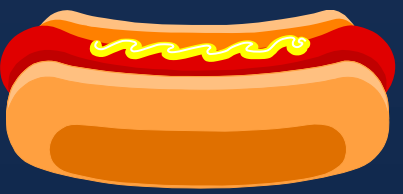
Dietary effects on gene expression

NUTRIGENOMICS



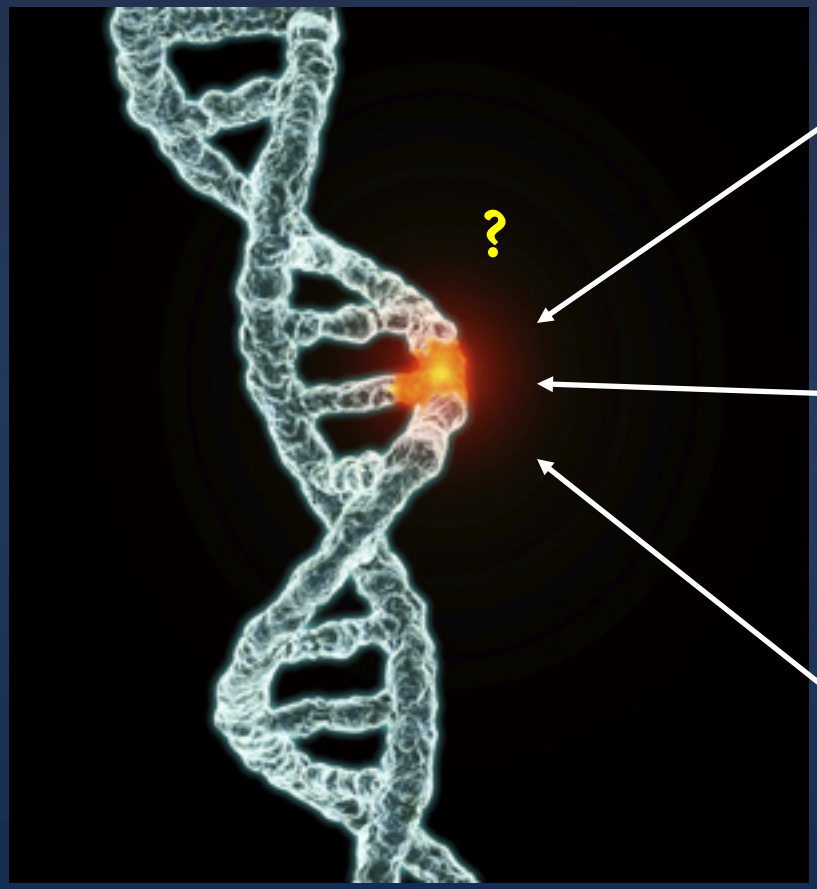


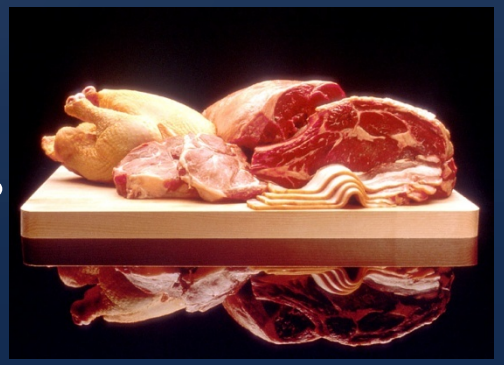
NUTRIGENETICS



Genotype influences the response related with nutrition and personalised metabolism

NUTRIGENETICS: Personalized nutrition based on genotype.





NUTRIGENOMICS is the study of molecular relationships between **nutrition** and the response of **genes** , with the aim of extrapolating how such subtle changes can affect **Human health**.

GENOTYPE & NUTRITION INTERACTIONS

Genotype

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Nutrition

Gene Expression

Phenotype

Nutrition Status

GENOTYPE & NUTRITION INTERACTIONS

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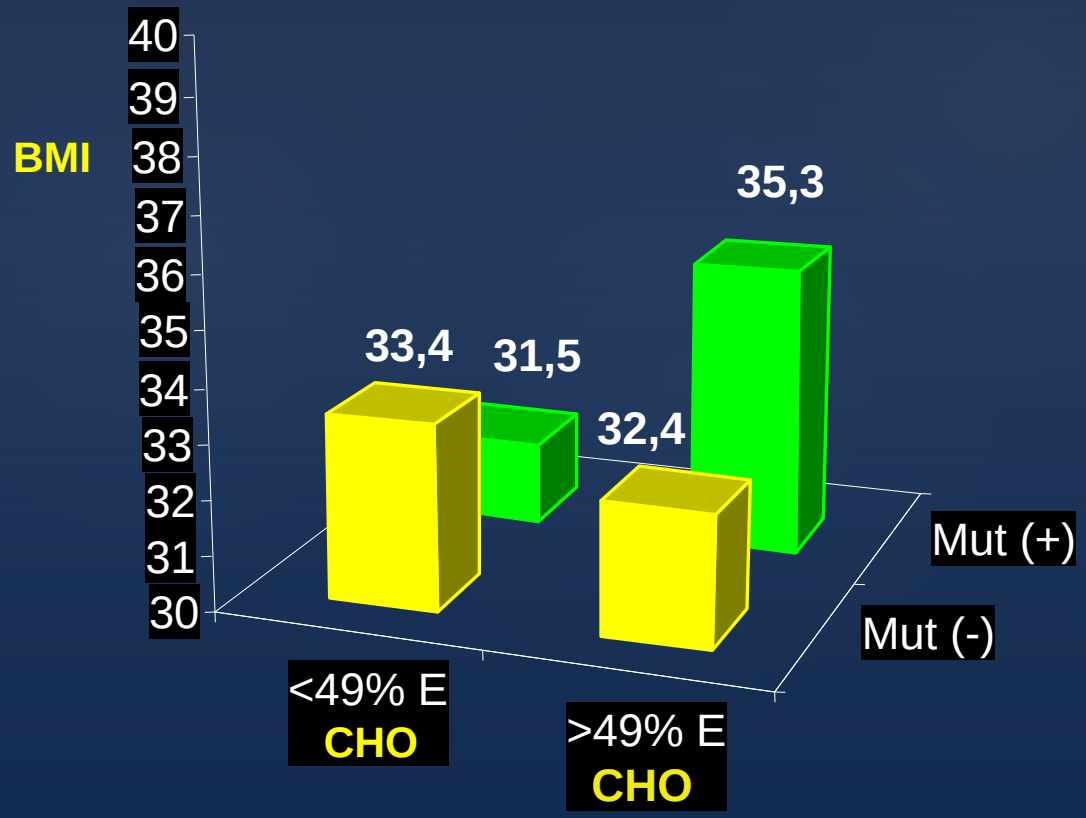
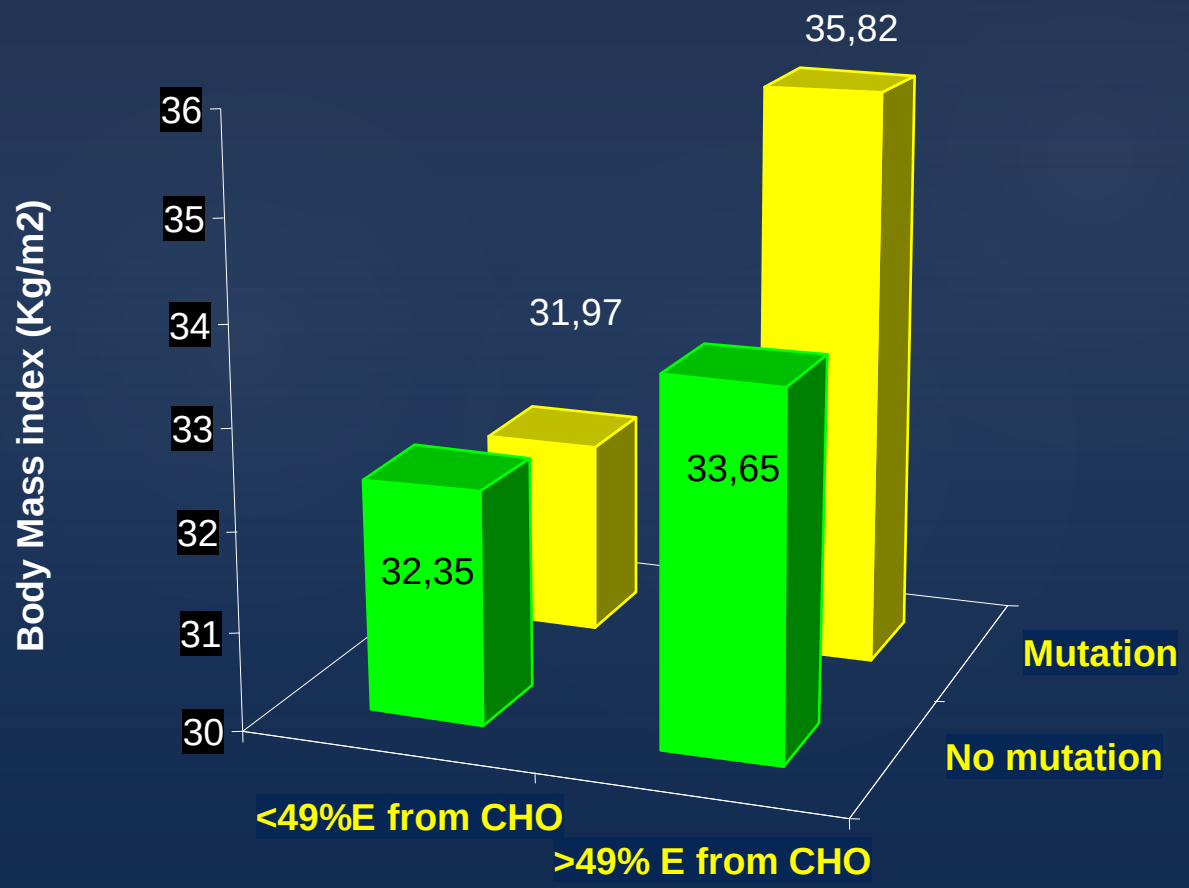


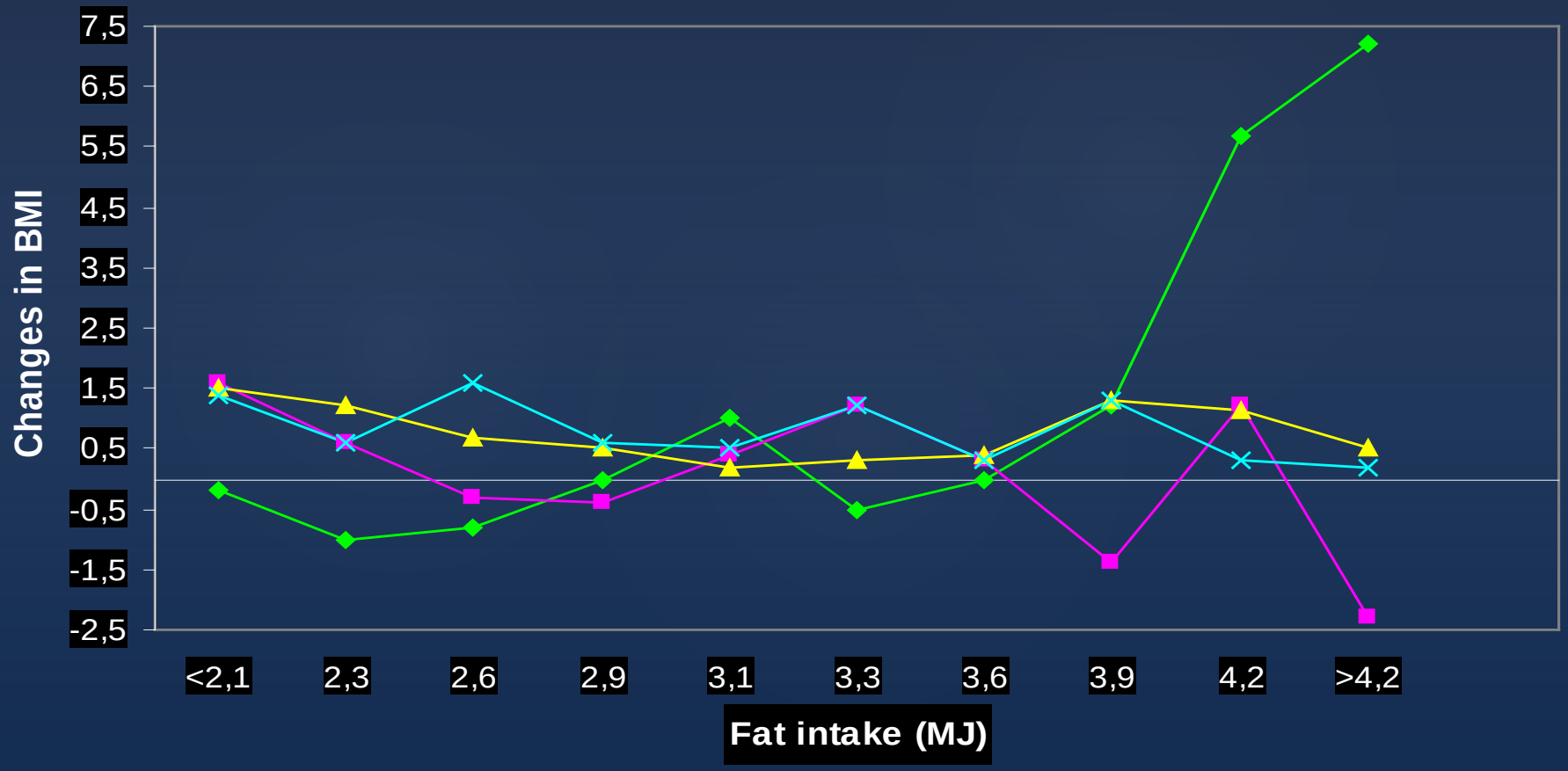
Corbalan, *et al*. 2002

NUTRIGENETICS: β2AR POLYMORPHISM AT GLN27GLN



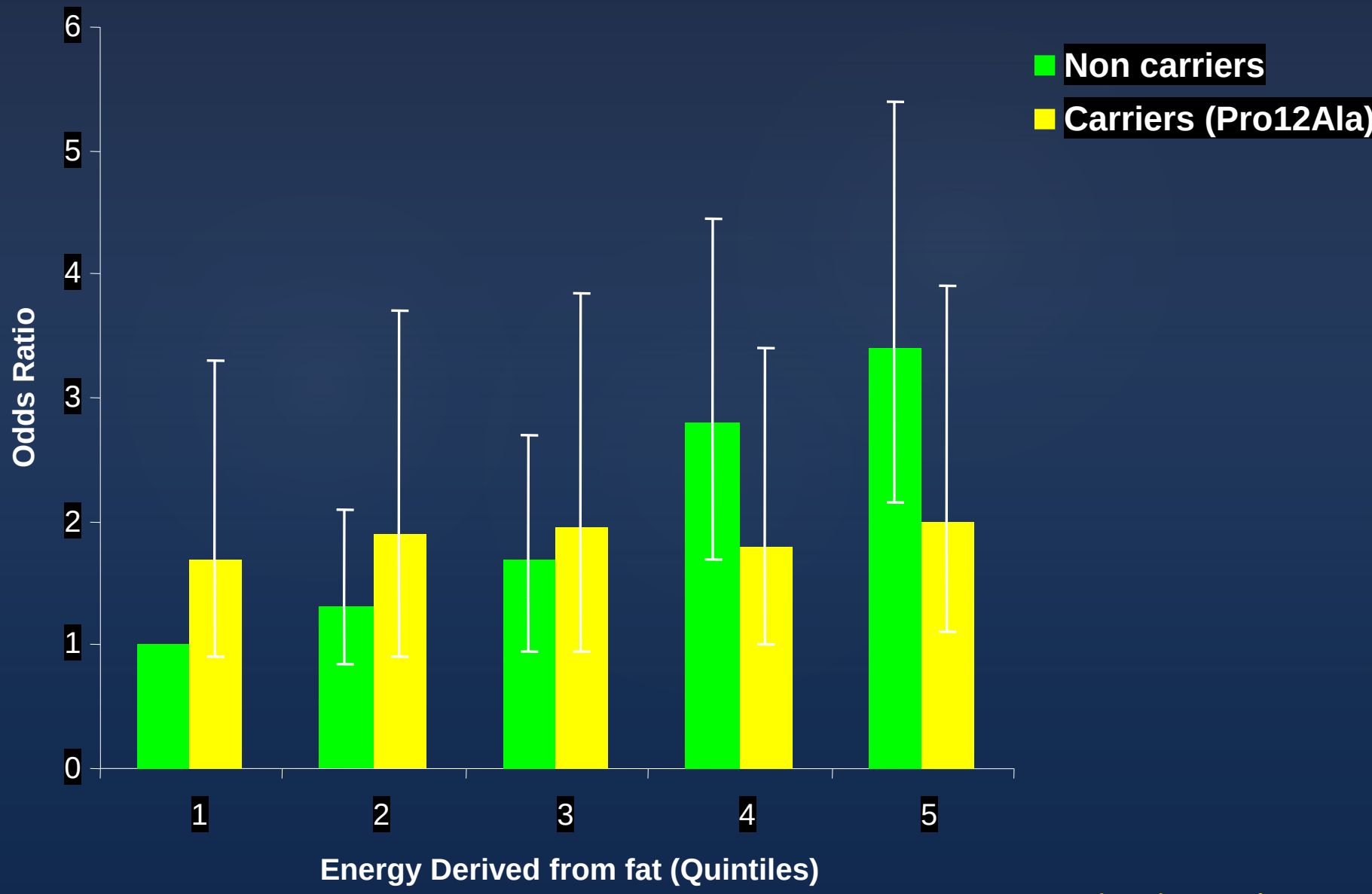
Martínez. *et al.* 2013

BMI, FAT INTAKE AND GENOTYPE INTERACTIONS



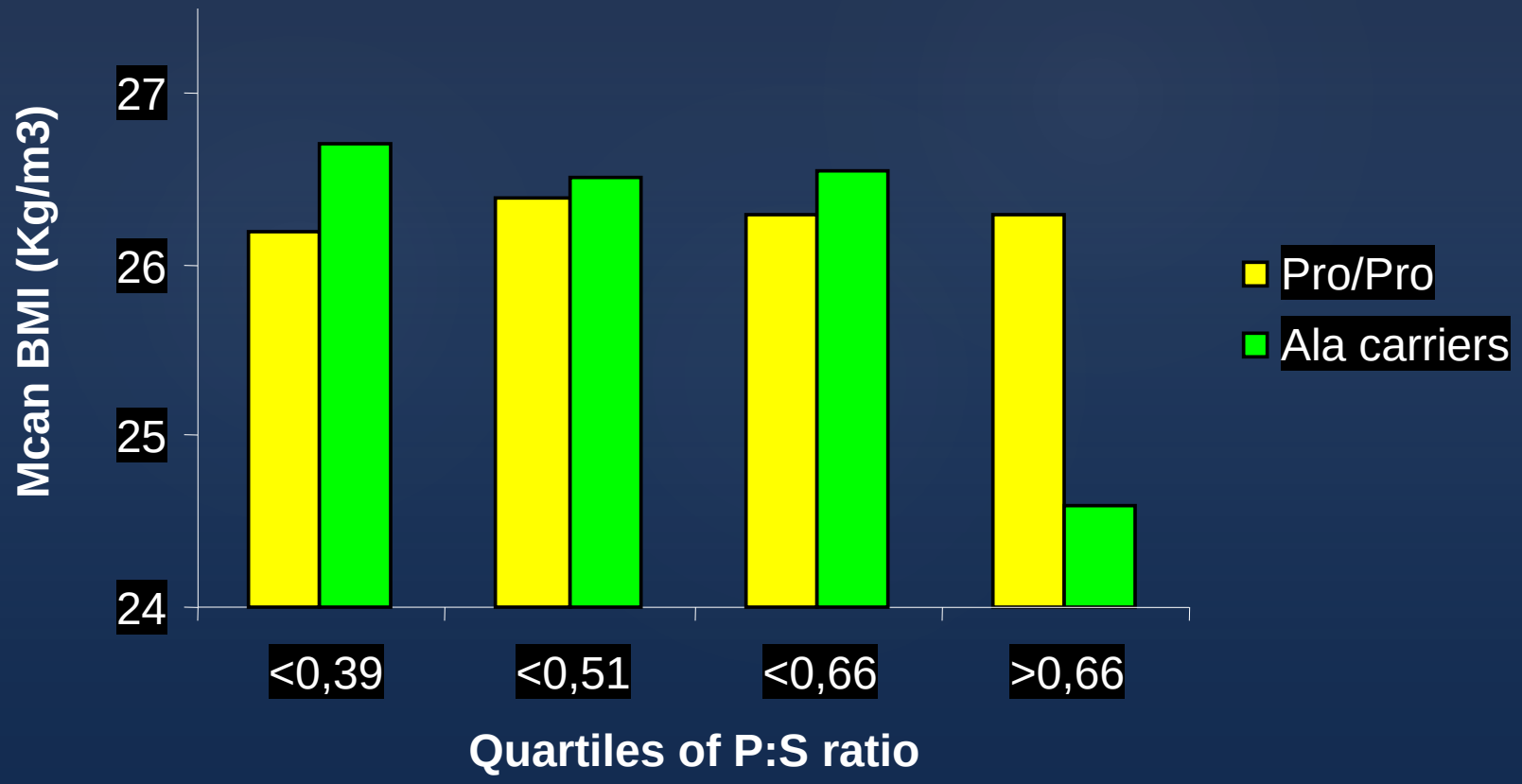
SORENSEN, *et al.* 1997

GENOTYPE X NUTRIENT (FAT) INTERACTIONS



Memisoglu, *et al.* 2003

GENOTYPE & NUTRITION INTERACTIONS



Luan, *et al.* 2001

Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case-control study of children

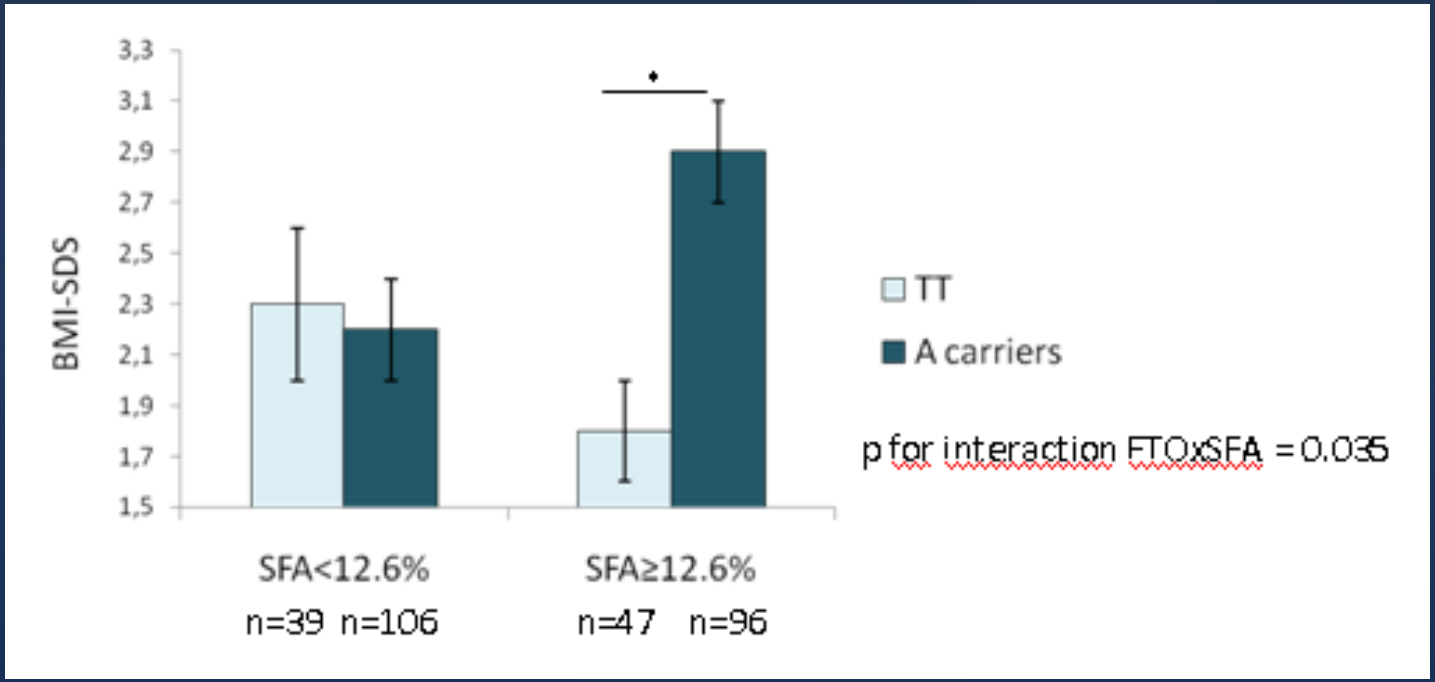
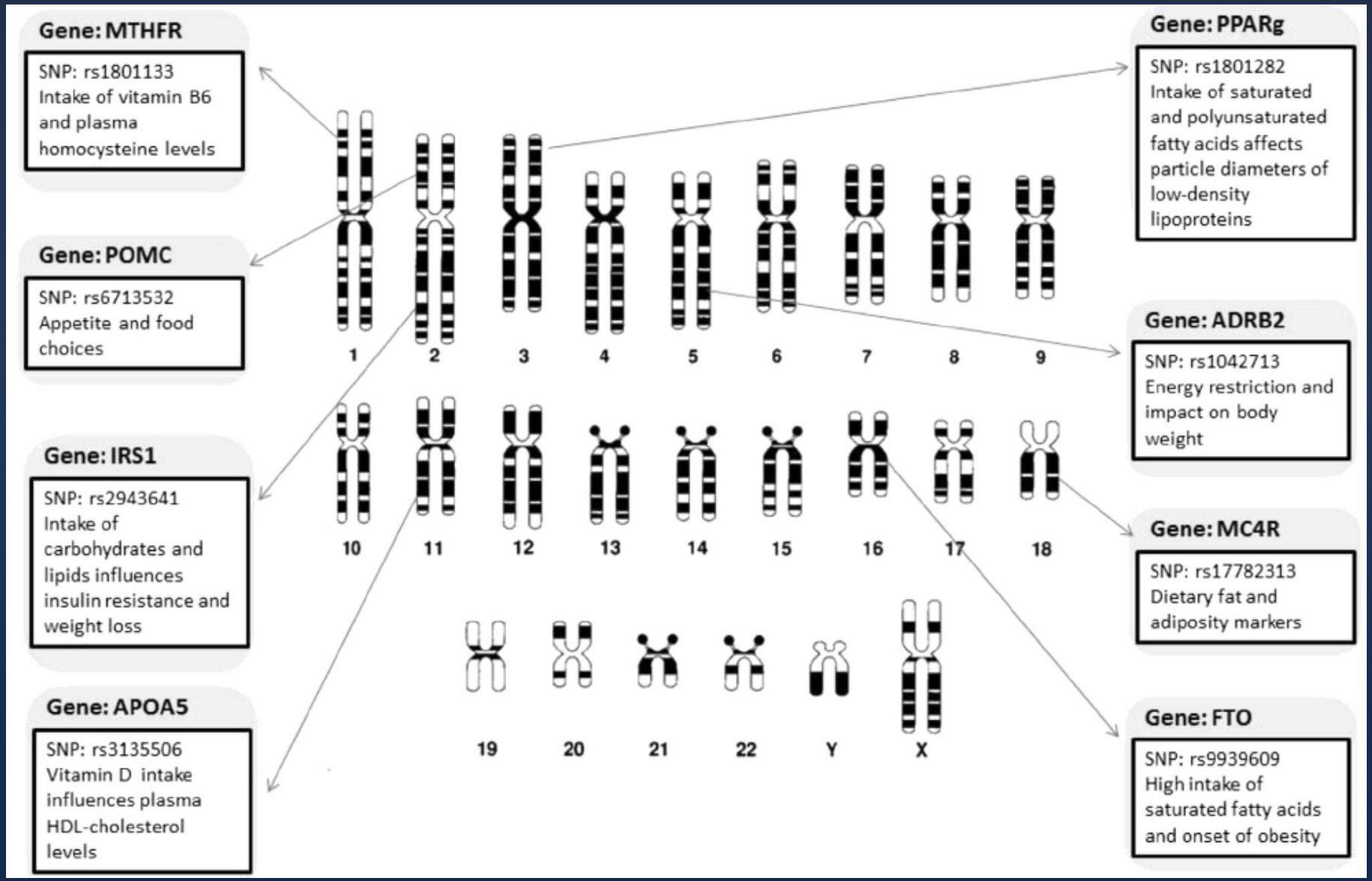


Fig. 2. BMI-standard deviation score (SDS) of children and adolescents according to SFA consumption (percentage of total energy, dichotomised by the median) and the presence of the fat mass and obesity associated (FTO) rs9939609 polymorphism in a dominant model. Values are means, with their standard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

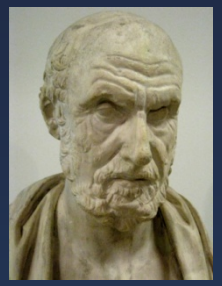
Br J Nutr, 2012; 107 **(4):** 533-8

GENE-NUTRIENT INTERACTIONS



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

Personalized Medicine and Nutrition



Hypocrates (Cos, 460 a. C. - Tesalia 370 a. C.) "…YOUR food is the basis of YOUR health"

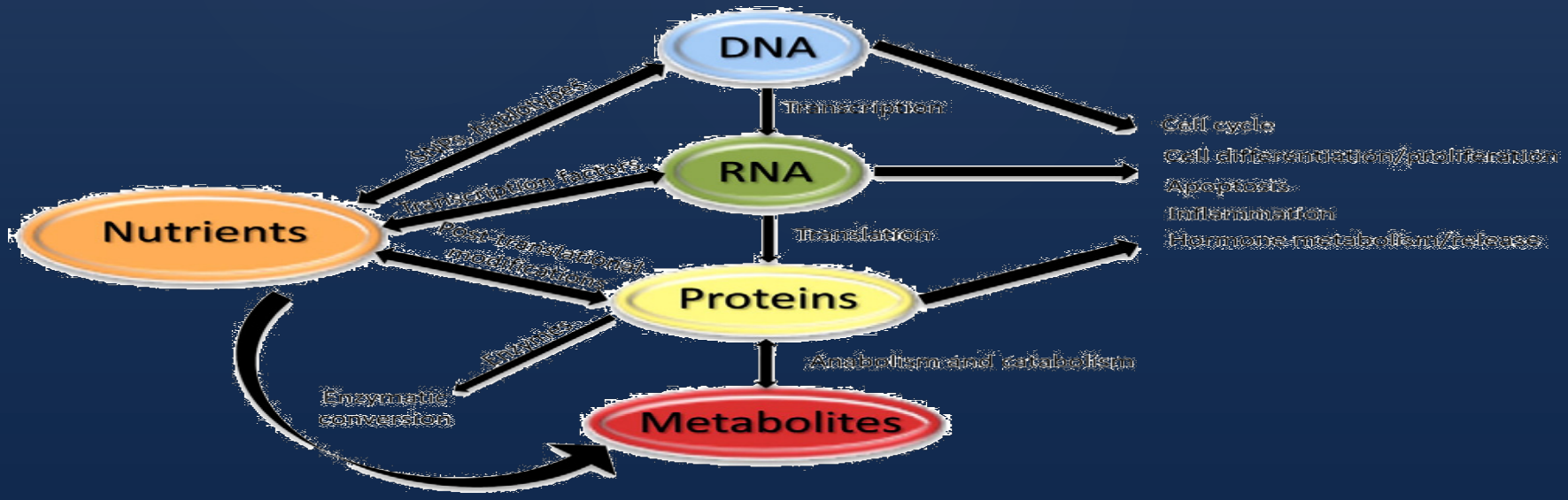
Galeno (Pérgamo, Greece, 130 - Roma, 200) "Personal attitudes and unique response to food"

C. Bernard. (s XIX) "No disease, but patients"

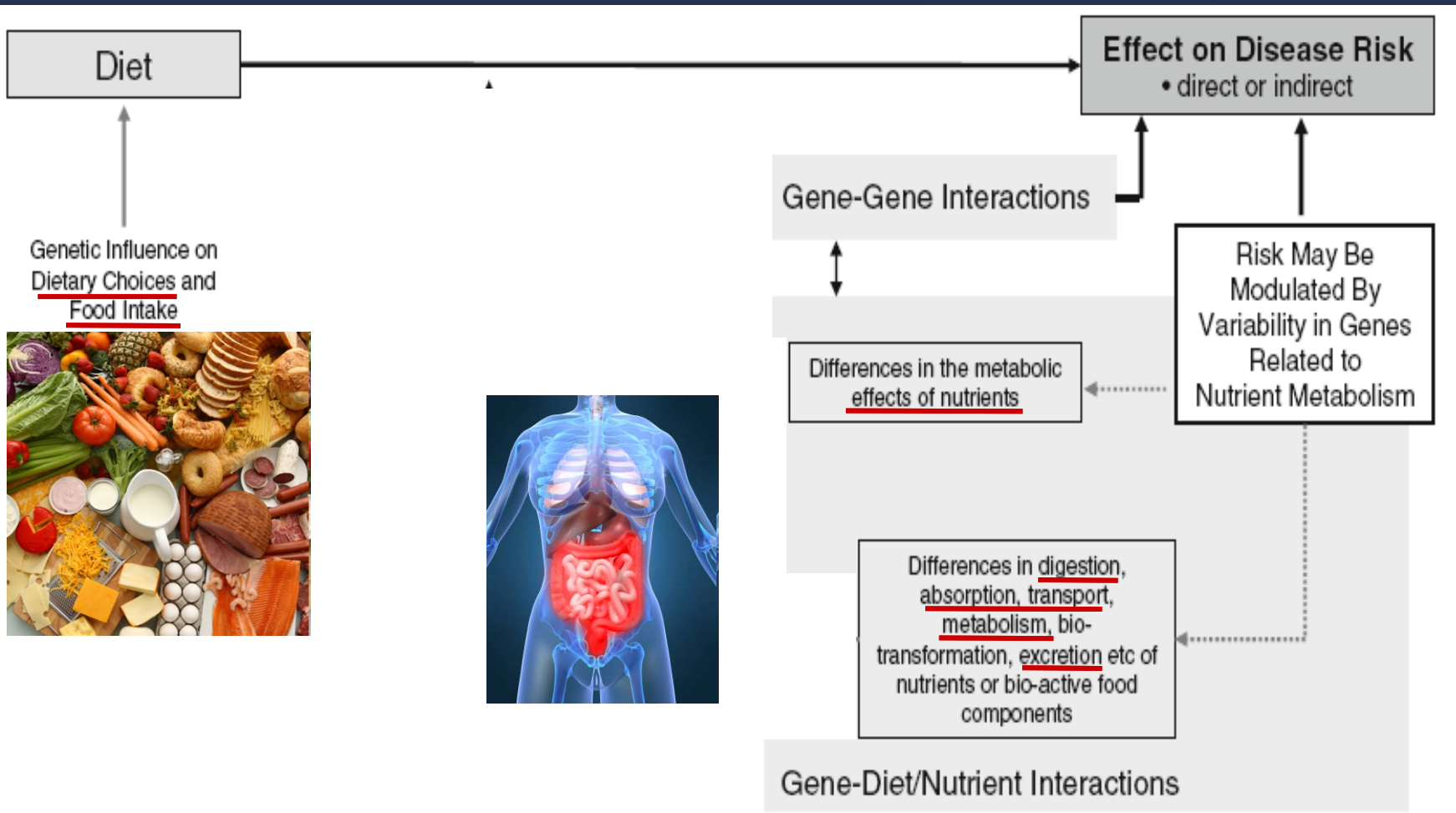
Mendel: (s XIX) Individualized trait transmission among generations

Garrod (early s XX) Nutritional outcomes depend on personal metabolism

Williams (1956): Personal variation in hormonal responses to food



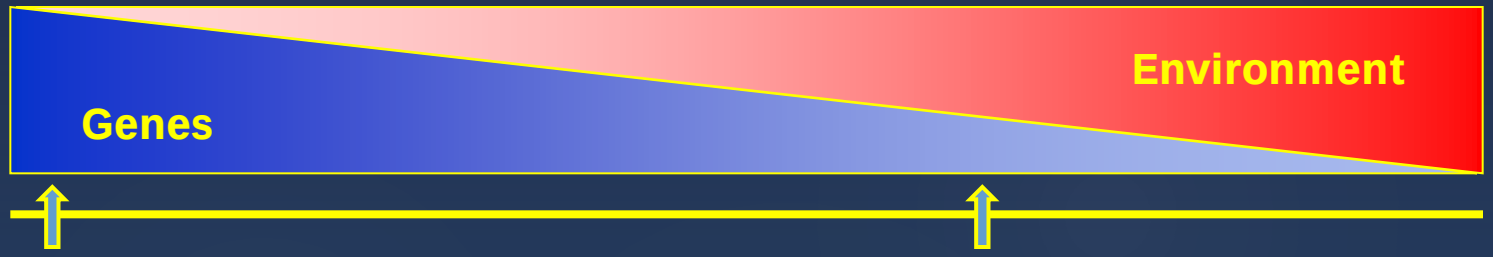
Personalization: Nutrition & Genetic Interactions



Possible interactions of diet with genetic variability to affect disease risk.

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

Genetics of Human Metabolism: gene and environment Interactions



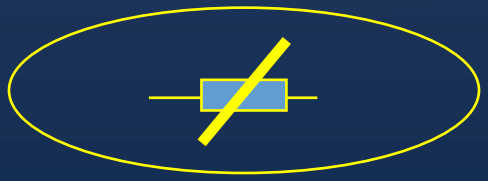
Monogenic

- Rare cases
- Syndromes

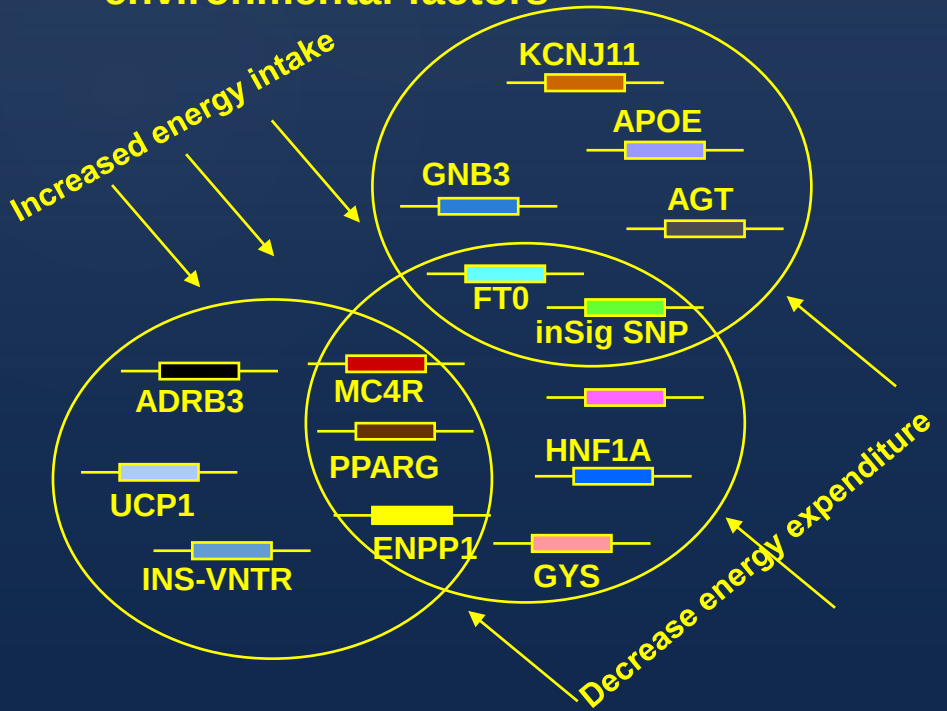
Polygenic

Individual combination in interaction with environmental factors

1 gene 1 disease



LEP, LEPR, POMC,PCSK1
SIM,,



PREDISPOSITION (% RISK) → HAPLOTYPE X ENVIRONMENT

MONOGENIC DISEASES	POLYGENIC DISEASES
Celiac disease Lactose intolerance Familial hypercholesterolemia Phenylketonuria Galactosemia	Obesity Type 2 Diabetes Hyperlipidaemias Cardiovascular disease &Hypertension Osteoporosis Neurodegenerative diseases Cancer

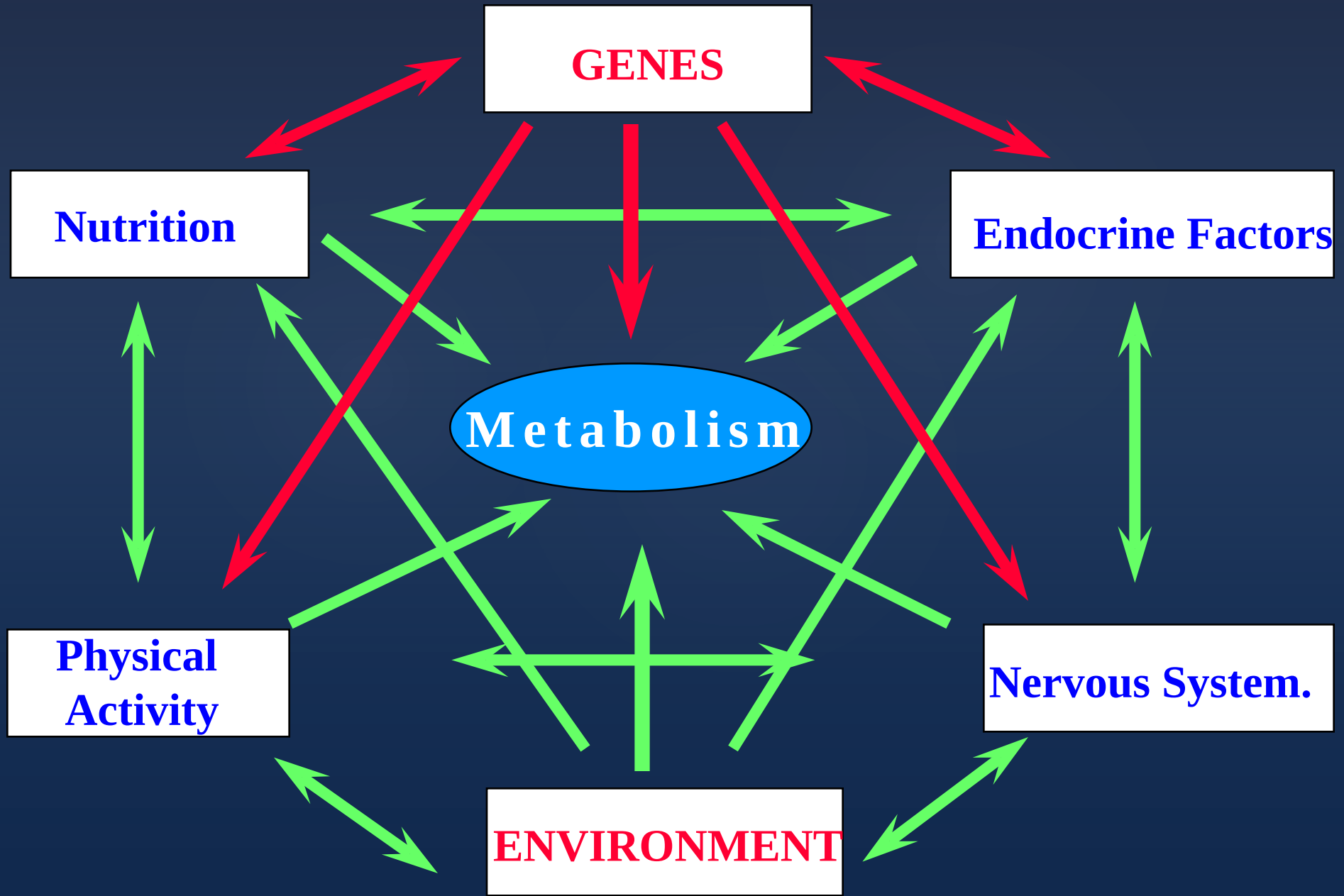
- **Modifiable factors**:

  lifestyle, alcohol, smoking, exercise, dietary habits. sleep

- **Exogenous factors** :

  Toxins. pollutants, microorganisms, allergens

METABOLISM: ETHIOLOGICAL FACTORS



PERSONALIZACION: GENE RESEARCH

- **Genotype:** gene/alleles responsibles for traits
- **Phenotype**: external manifestations of an observable character

Mendelian Syndromes

- Autosomal dominant
- Autosómico recessive
- X-linked

Animal models

- Genetically obese animals
- Transgenic Animals
- Q Trait Loci (QTL)

Association and Linkage Studies

- Candidate genes and GWAS
- Family segregation

MONOGENIC DISORDERS with OBESITY TRAITS

MIM number	Disorder	Locus
Autosomal Dominant		
100800	Achondroplasia (ACH)	4p16.3
122000	Posterior Polymorphous Corneal Dystrophy (PPCD)	20q11
176270	Prader-Willi Syndrome (PWS)	15q11.2-q12
181450	Schinzel syndrome/Ulnar-mammary syndrome (UMS)	12q23-q24.1
Autosomal Recessive		
	Bardet-Biedl Syndrome (BBS)	
209901	BBS1	11q13
209900	BBS2	16q21
600151	BBS3	3p13-p12
600374	BBS4	15q22.3-q23
216550	Cohen Syndrome (CHS1)	
X-LINKED		
301900	Borjeson-Forssman-Lehman Syndrome (BFLS)	Xq26-q27
303110	Choroideremia with deafness and obesity	Xq21
309585	Wilson-Turner Syndrome (WTS)	Xq21.1-q22
312870	Simpson-Golabi-Behmel (SGBS)	Xq26

GENETIC LINKAGE

	Framingham		Canada		Norway	
Phenotype	**BMI**		**BMI/Skinfolds**		**BMI**	
	n	**r^2**	**n**	**r^2**	**n**	**r^2**
Spouses	1163	0,19	3138	0,12	23936	0,12
Parent/child	4027	0,23	7194	0,20	43586	0,20
Sibblings	992	0,28	3924	0,34	19157	0,24

BMI ASSOCIAIONS IN TWEENS

	NAS/NRC	Virginia	Sweden	England
Phenotype	BMI	IMC/Pliegues	BMI	BMI
n	4071	259	311	38
Monozigotes	0,81	0,79	0,70	0,61
Dizigotes	0,42	0,35	0,15	_
h^2	77%	85%	74%	

BMI ASSOCIATIONS between ADOPTEES & FAMILIES

	Denmark		Iowa		Montreal	
Relación	Biológical /	Adoptee	Biológical /	Adoptee	Biológical/	Adoptee
n	3651		357		553	
Parents	0,15	0,00	0,20	0,02	0,17	0,01
Sibblings	0,23	0,14	_	_	0,13	0,07
h^2	34%		_		17%	

ANIMAL GENETIC MODELS

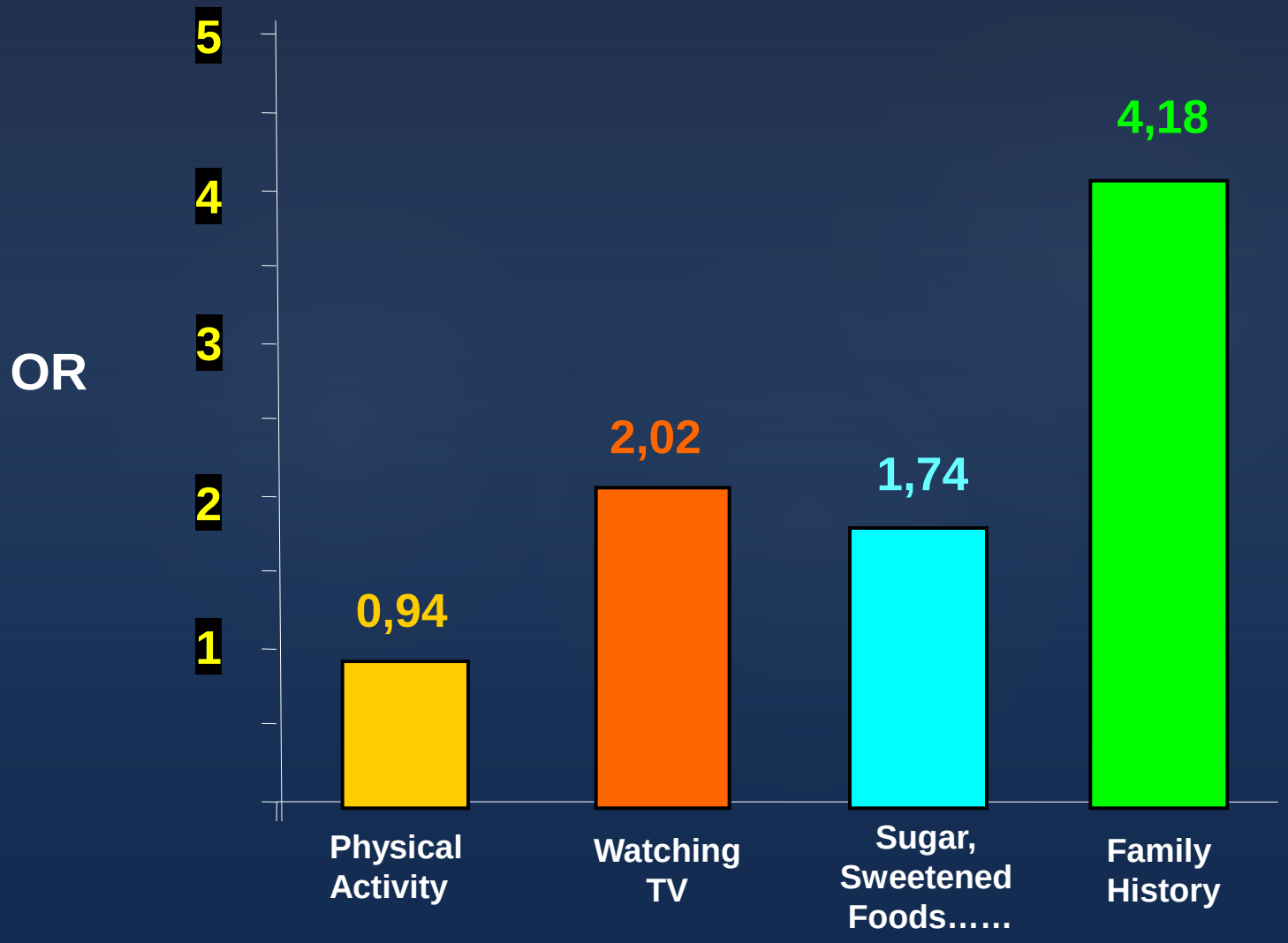
	ANIMAL			HUMANS	
Type	Chr	Loci	Inheritance	Chr	Gene Product
Diabetes (db)	4	Lepr	Recessive	1	leptina receptor
Fat (fat)	8	Cpe	Recessive	4	carboxìpeptidasa E
Obese (ob)	6	Lep	Recessive	7	leptin
Tubby (tub)	7	Tub	Recessive	11	unknown
Agouti yellow	2	Ay	Dominant	20	Agouti protein

TRANSGENIC MODELS

Metabolic alterations

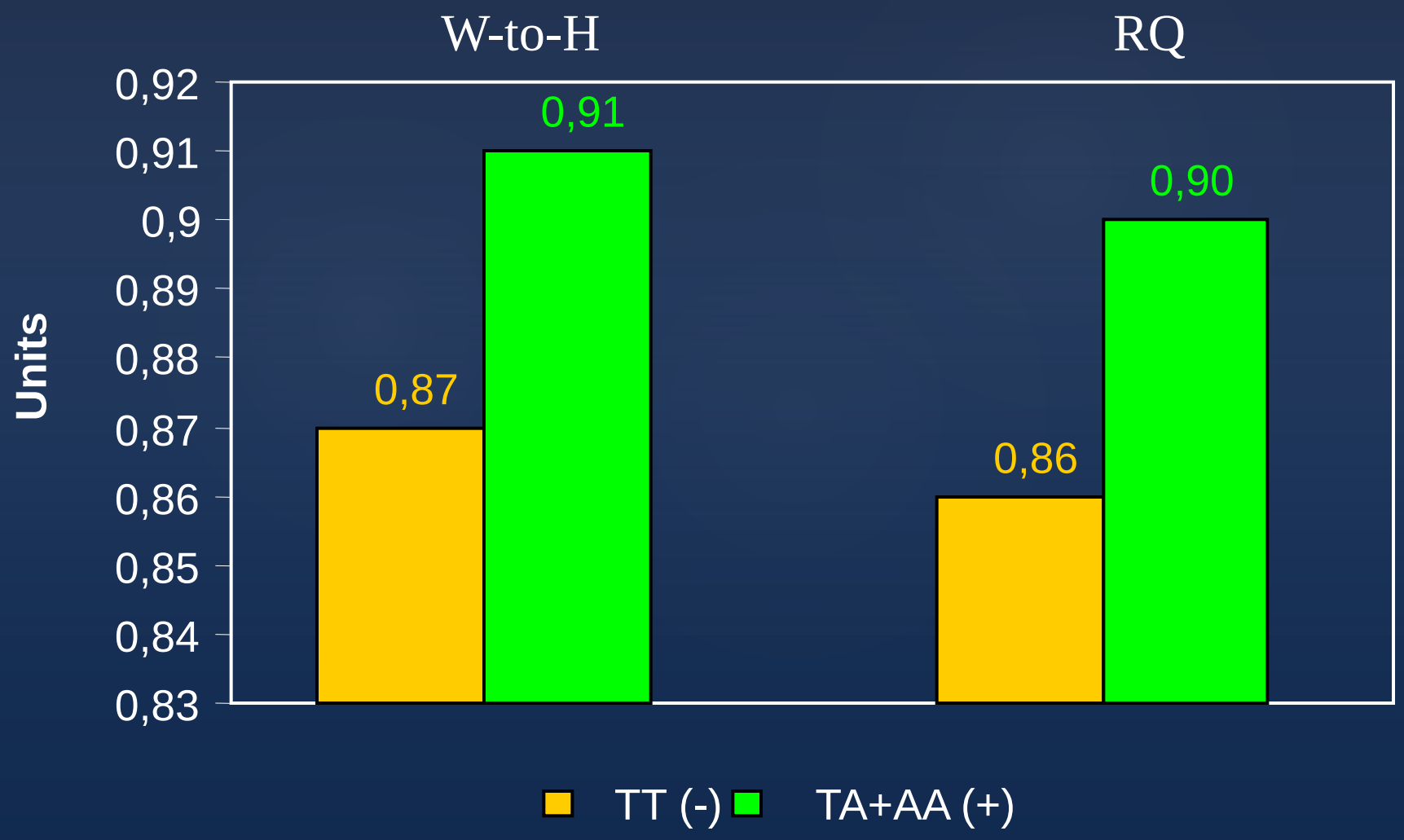
- Knock-out de TNF-α (Glucose tolerance)
- Knock-out de c/EBP (Adipocyte differentiation)
- Knock-out de adrenalin (Thermoregulation)
- Knock-out de LPL (Lipid metabolism)
- Knock-out de BAT (Thermogenesis)

PREDICTOR FACTORS FOR CHILDHOOD OBESITY



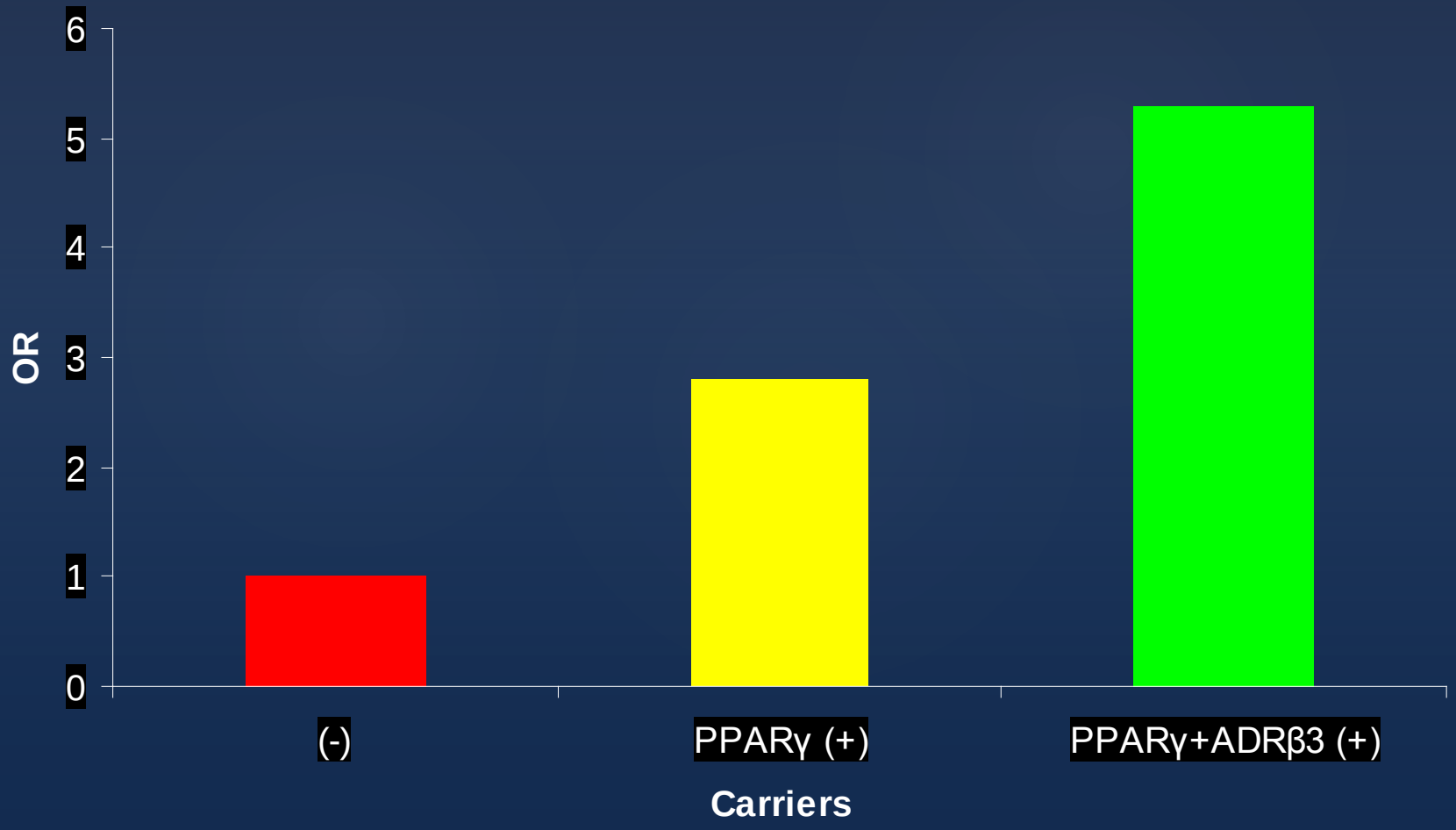
Ochoa, *et al. 2006*

Trp64Arg MUTATION OF THE β_3 ADRENOCEPTOR



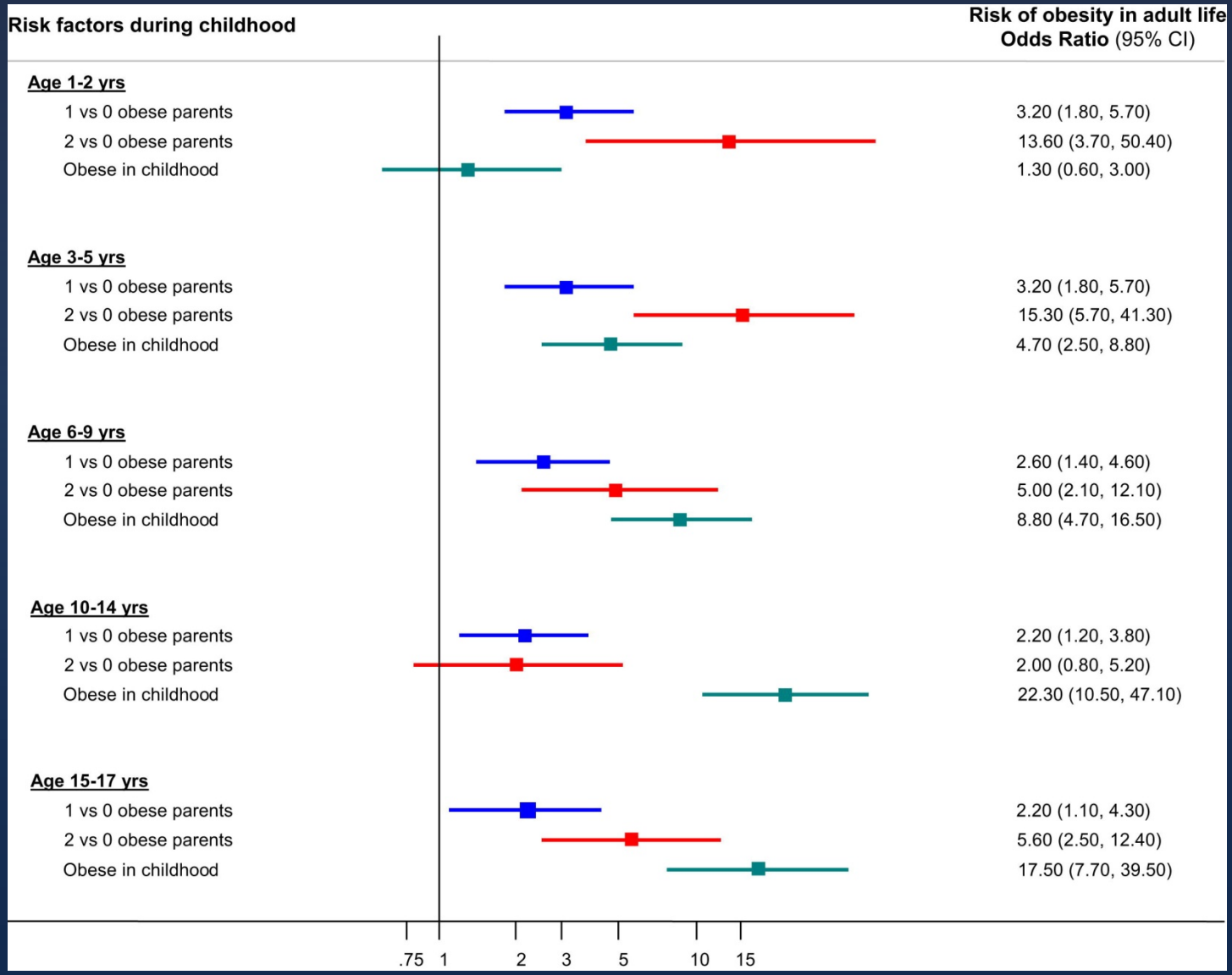
CORBALAN, *et al.* 2000

PPARγ2 x ADRβ3 INTERACTIONS



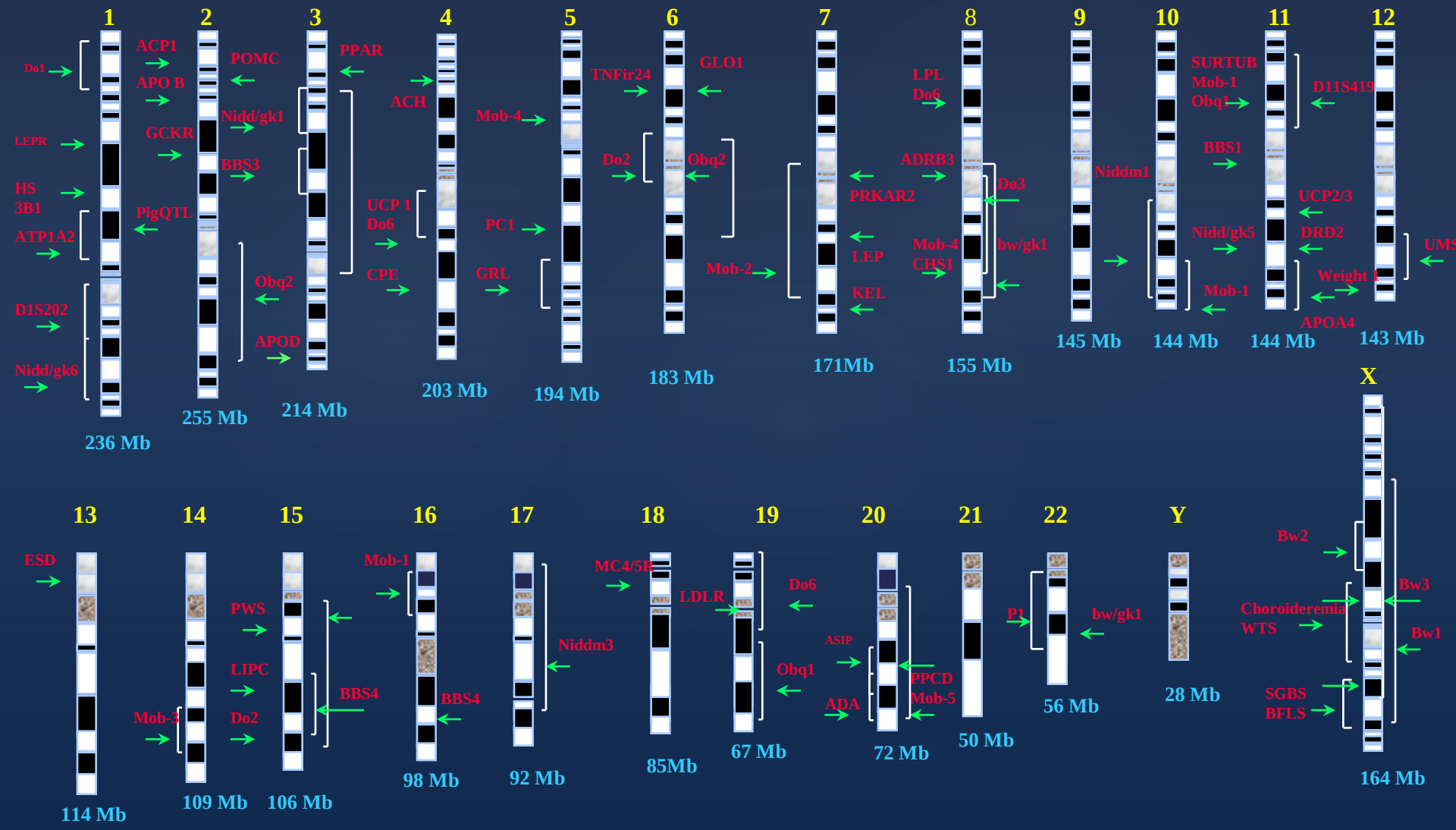
Ochoa, *et al.* 2004

CHILDHOOD OVERWEIGHT AND THE RISK OF OBESITY IN ADULTHOOD

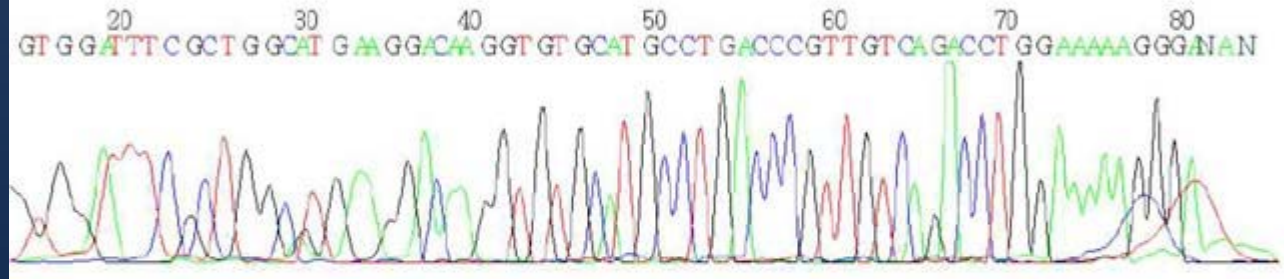


Loos. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2012;26: 211–226

METABOLISM GENOME



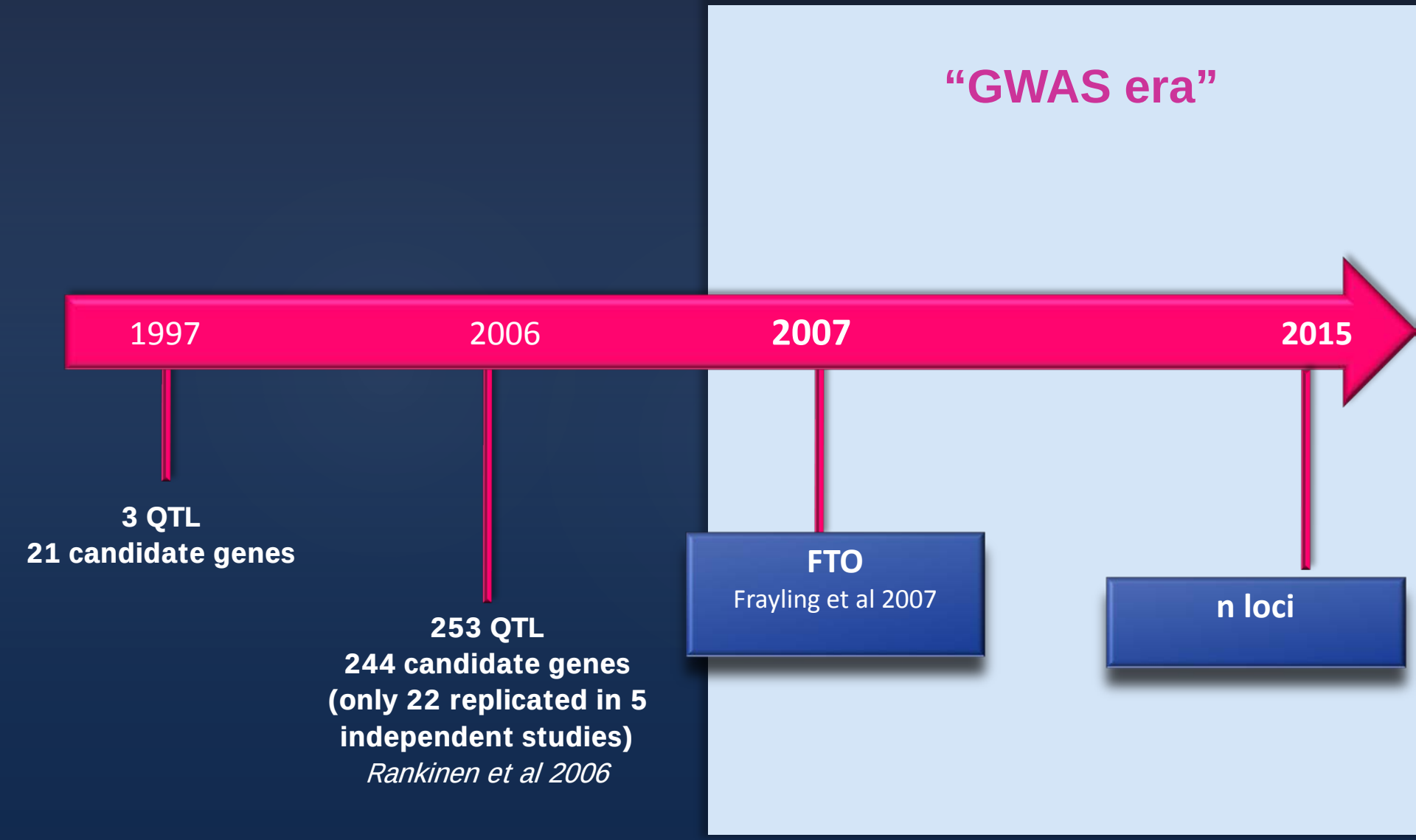
LAST: FTO, MC4R, UCP, POMC, LEP, βAR, PPAR, AP2,….. TNF,...



Sequentiation

microarrays

Milestones in Obesity genetic data acquisition



STRATEGIC APPROACHES IN GENETIC DATA ACQUISITION

CANDIDATE GENE STUDIES

Clinical cases (altered genes associated with disease "Healthy" no alteration)

Screening known gene

Associated SNPs to disease

Cellular/molecular studies
Physiology

GWAS
Genome-Wide Association Studies

Thousands of people

Wide genome scan

Genetic identification

Biochemistry
Genetics
Comparative genomics

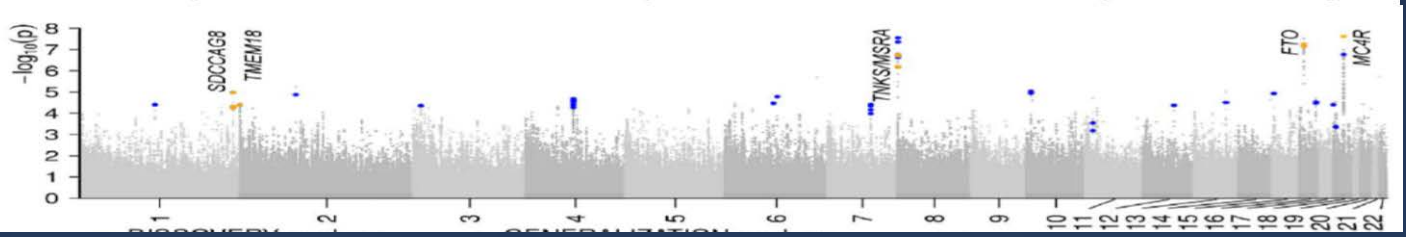
Cellular/mollecular studies
Fisiology

OPEN ACCESS Freely available online

PLoS GENETICS

Two New Loci for Body-Weight Regulation Identified in a Joint Analysis of Genome-Wide Association Studies for Early-Onset Extreme Obesity in French and German Study Groups

André Scherag[1,2]*, Christian Dina[3], Anke Hinney[2], Vincent Vatin[3], Susann Scherag[2], Carla I. G. Vogel[2],

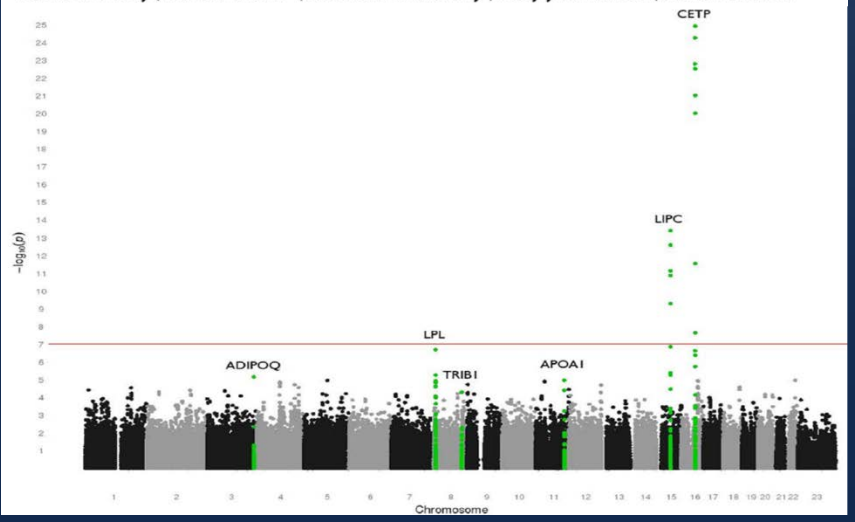


OPEN ACCESS Freely available online

PLoS one

Knowledge-Driven Multi-Locus Analysis Reveals Gene-Gene Interactions Influencing HDL Cholesterol Level in Two Independent EMR-Linked Biobanks

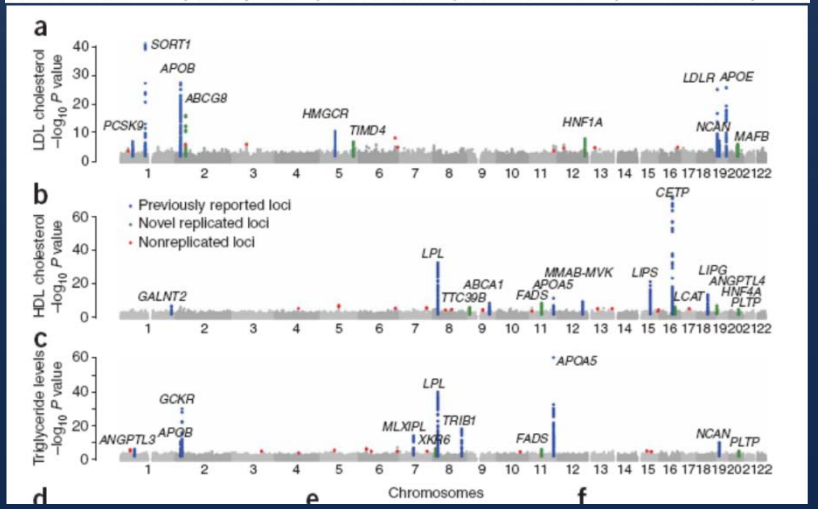
Stephen D. Turner[1], Richard L. Berg[2], James G. Linneman[2], Peggy L. Peissig[2], Dana C. Crawford[1], Joshua C. Denny[3], Dan M. Roden[4,5], Catherine A. McCarty[6], Marylyn D. Ritchie[1], Russell A. Wilke[4]*



nature genetics

Common variants at 30 loci contribute to polygenic dyslipidemia

Sekar Kathiresan*[1–5,37,38], Cristen J Willer[6,37], Gina M Peloso[4,7,37], Serkalem Demissie[4,7,37], Kiran Musunuru[1,2],



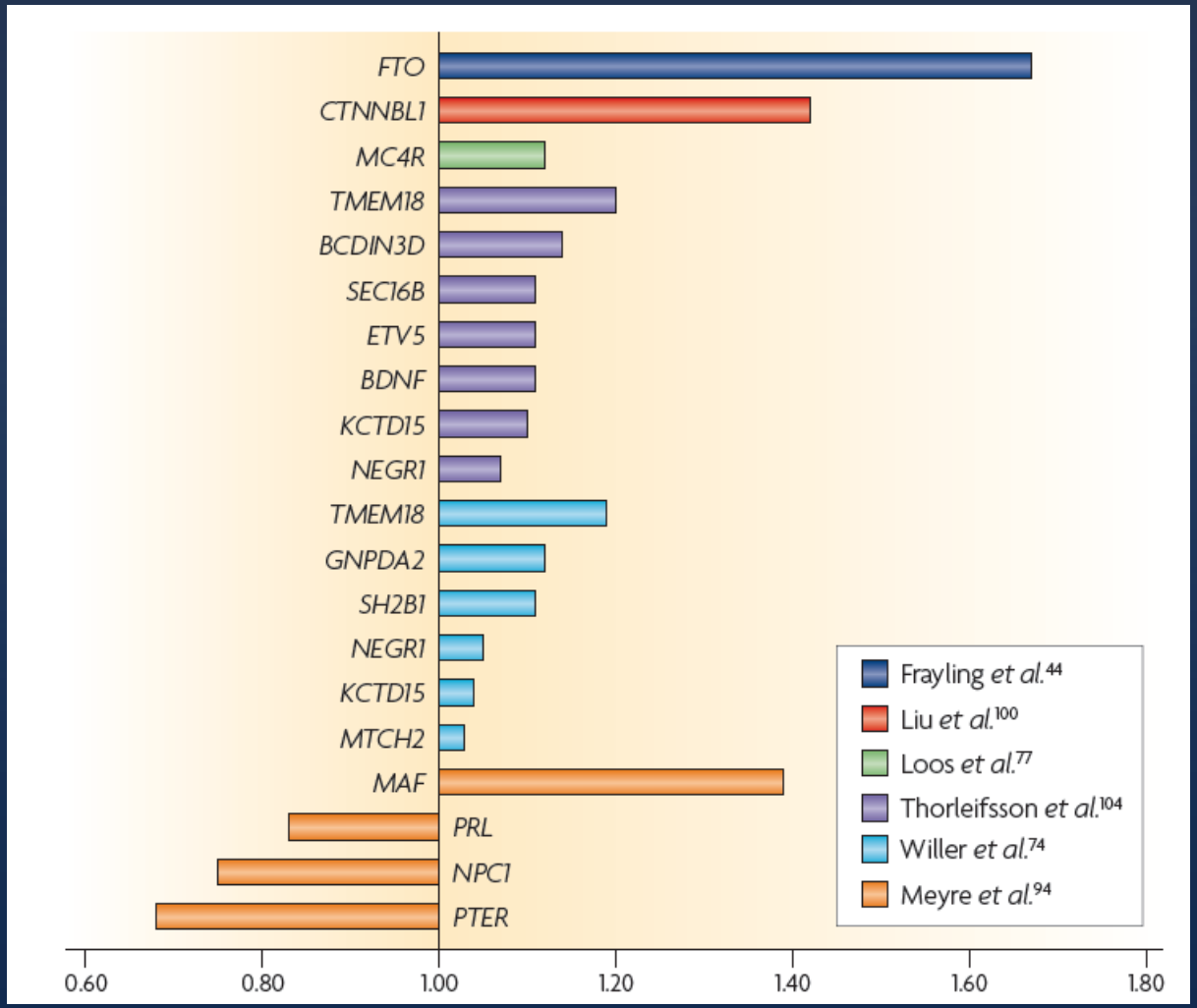
REVIEWS

The genetic contribution to non-syndromic human obesity

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

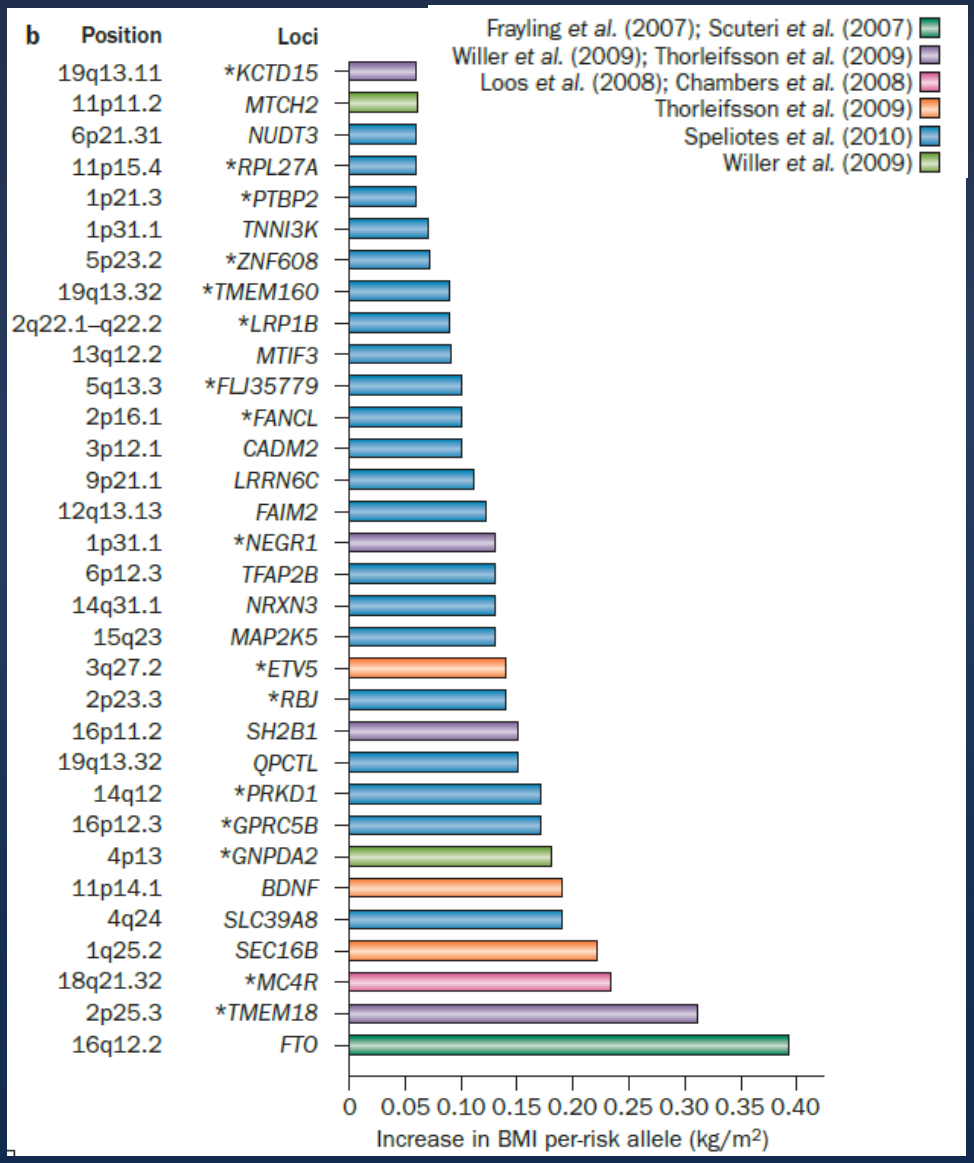
Abstract | The last few years have seen major advances in common non-syndromic obesity research, much of it the result of genetic studies. This Review outlines the competing hypotheses about the mechanisms underlying the genetic and physiological basis of obesity, and then examines the recent explosion 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 ASSOCIATED with HUMAN OBESITY (GWAS)



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

EFFECT SIZES FOR GENETIC VARIANTS ASSOCIATED WITH BMI



*gene closest to the reported association

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

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

8

Genetic determinants of common obesity and their value in prediction

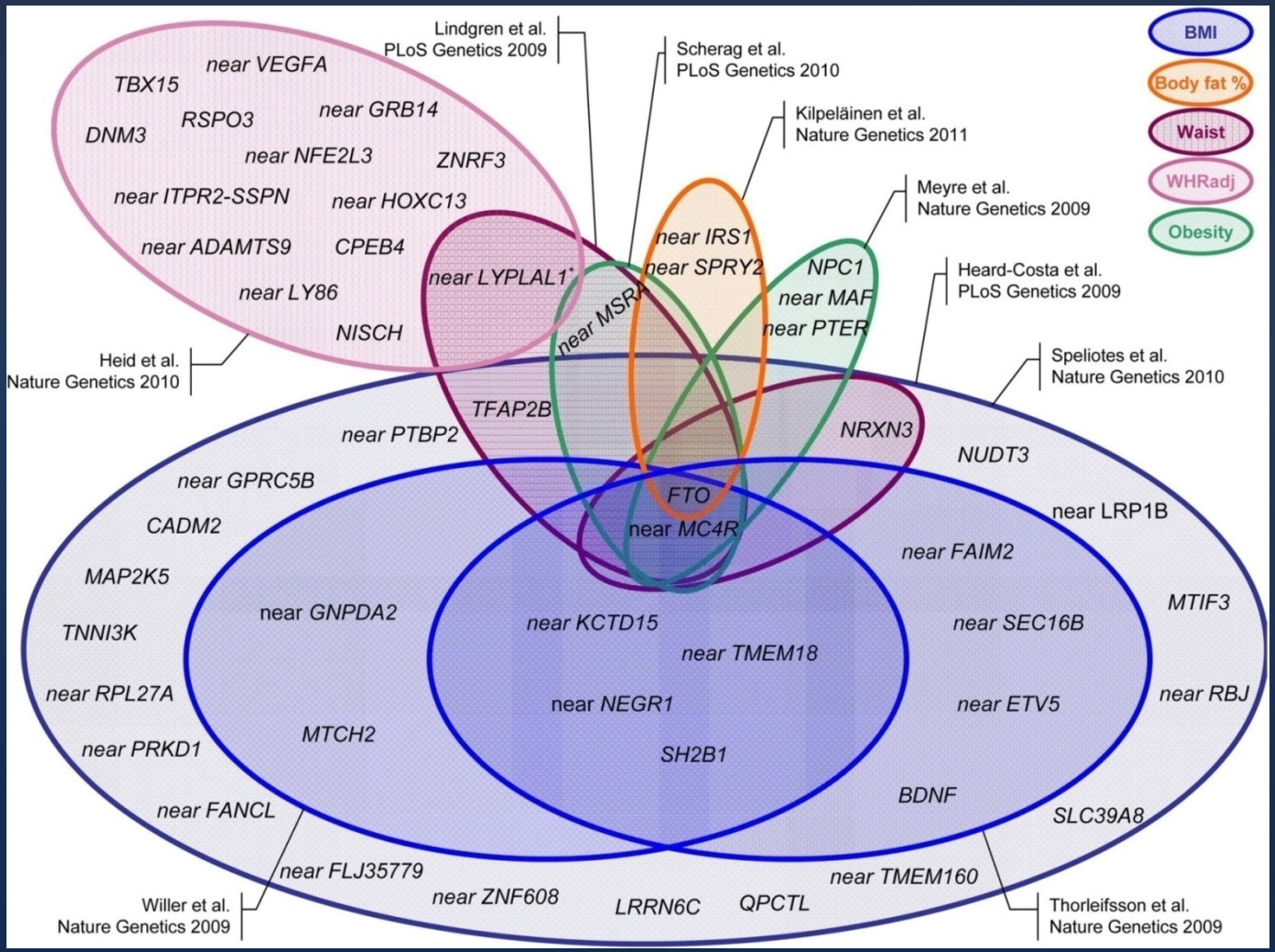
Ruth J.F. Loos, PhD, Programme Leader *

MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Box 285, Cambridge, UK

Keywords:
genome-wide association
obesity
body mass index (BMI)
prediction
personal genome profile

Genome-wide association studies (GWAS) have revolutionised the discovery of genes for common traits and diseases, including obesity-related traits. In less then four years time, 52 genetic loci were identified to be unequivocally associated with obesity-related traits. This vast success raised hope and expectations that genetic information would become soon an integral part of personalised medicine. However, these loci have only small effects on obesity-susceptibility and explain just a fraction of the total variance. As such, their accuracy to predict obesity is poor and not competitive with the predictive ability of traditional risk factors. Nevertheless, some of these loci are being used in commercially available personal genome tests to estimate individuals' lifetime risk of obesity. While proponents believe that personal genome profiling could have beneficial effects on behaviour, early reports do not support this hypothesis. To conclude, the most valuable contribution of GWAS-identified loci lies in their contribution to elucidating new physiological pathways that underlie obesity-susceptibility.

OBESITY GWAS



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

ARTICLE

doi:10.1038/nature14132

New genetic loci link adipose and insulin biology to body fat distribution

A list of authors and their affiliations appears at the end of the paper

Body fat distribution is a heritable trait and a well-established predictor of adverse metabolic outcomes, independent of overall adiposity. To increase our understanding of the genetic basis of body fat distribution and its molecular links to cardiometabolic traits, here we conduct genome-wide association meta-analyses of traits related to waist and hip circumferences in up to 224,459 individuals. We identify 49 loci (33 new) associated with waist-to-hip ratio adjusted for body mass index (BMI), and an additional 19 loci newly associated with related waist and hip circumference measures ($P < 5 \times 10^{-8}$). In total, 20 of the 49 waist-to-hip ratio adjusted for BMI loci show significant sexual dimorphism, 19 of which display a stronger effect in women. The identified loci were enriched for genes expressed in adipose tissue and for putative regulatory elements in adipocytes. Pathway analyses implicated adipogenesis, angiogenesis, transcriptional regulation and insulin resistance as processes affecting fat distribution, providing insight into potential pathophysiological mechanisms.

Genes enriched for WHRadjBMI-associated loci

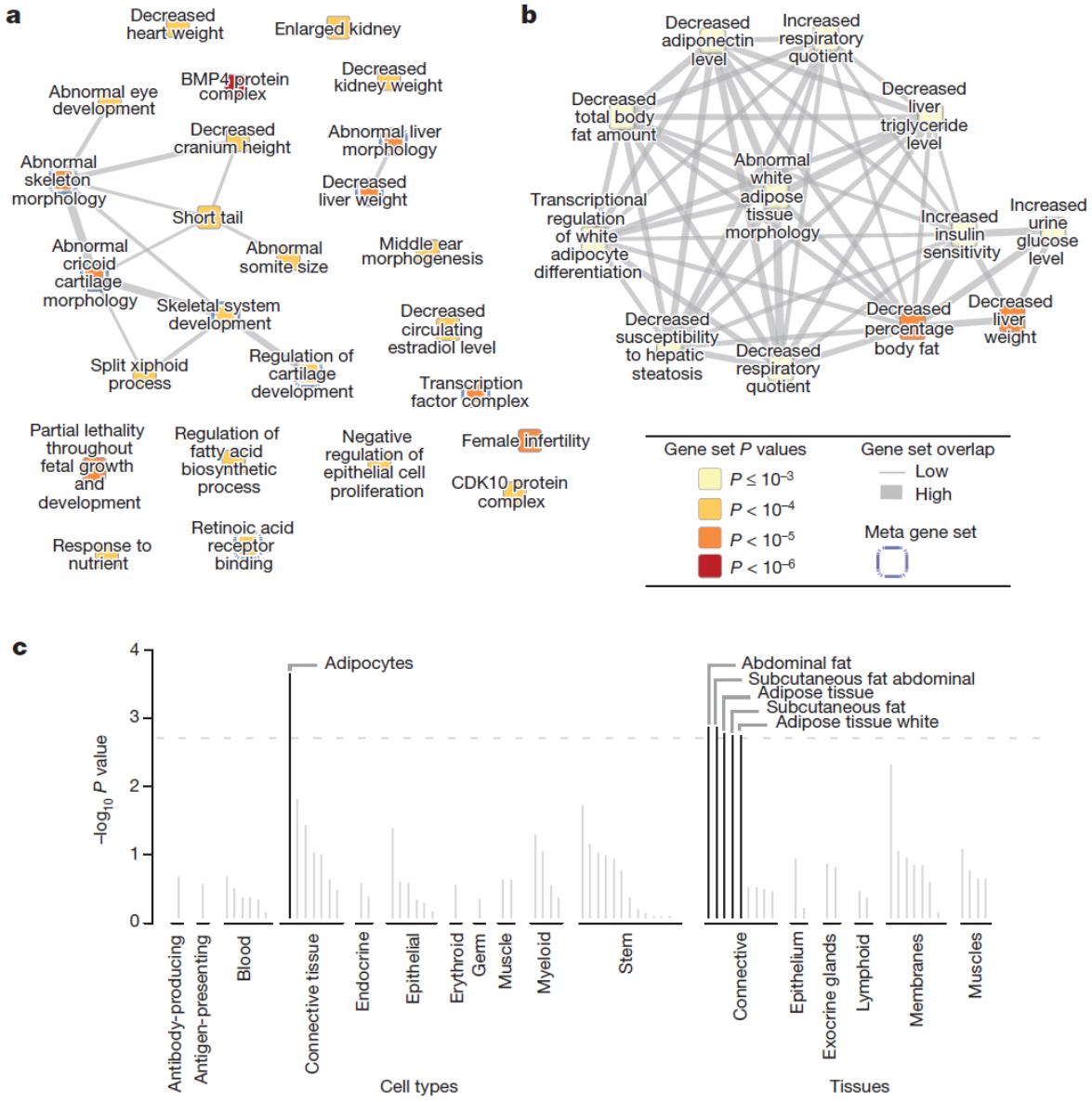


Figure 2 | Gene set enrichment and tissue expression of genes at WHRadjBMI-associated loci (GWAS-only $P < 10^{-5}$). **a**, Reconstituted gene sets found to be significantly enriched by DEPICT (FDR < 5%) are represented as nodes, with pairwise overlap denoted by the width of connecting lines and empirical enrichment *P* value indicated by colour intensity (darker is more significant). **b**, The 'decreased liver weight' meta-node, which consisted of 12 overlapping gene sets, including adiponectin signalling and insulin sensitivity. **c**, On the basis of expression patterns in 37,427 human microarray samples, annotations found to be significantly enriched by DEPICT are shown, grouped by type and significance.

ARTICLE

doi:10.1038/nature14177

Genetic studies of body mass index yield new insights for obesity biology

A list of authors and their affiliations appears at the end of the paper

Obesity is heritable and predisposes to many diseases. To understand the genetic basis of obesity better, here we conduct a genome-wide association study and Metabochip meta-analysis of body mass index (BMI), a measure commonly used to define obesity and assess adiposity, in up to 339,224 individuals. This analysis identifies 97 BMI-associated loci ($P < 5 \times 10^{-8}$), 56 of which are novel. Five loci demonstrate clear evidence of several independent association signals, and many loci have significant effects on other metabolic phenotypes. The 97 loci account for ~2.7% of BMI variation, and genome-wide estimates suggest that common variation accounts for >20% of BMI variation. Pathway analyses provide strong support for a role of the central nervous system in obesity susceptibility and implicate new genes and pathways, including those related to synaptic function, glutamate signalling, insulin secretion/action, energy metabolism, lipid biology and adipogenesis.

Genes enriched for BMI-associated loci

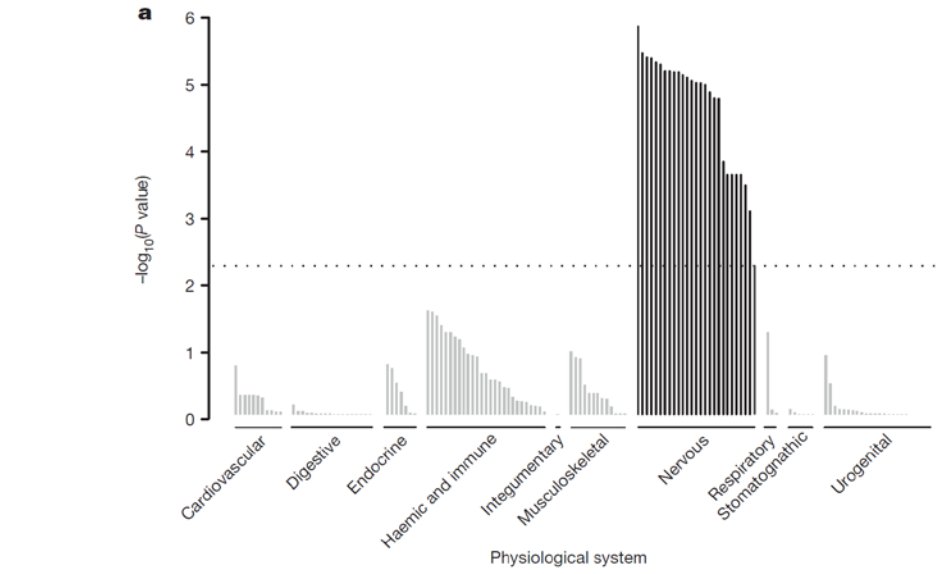
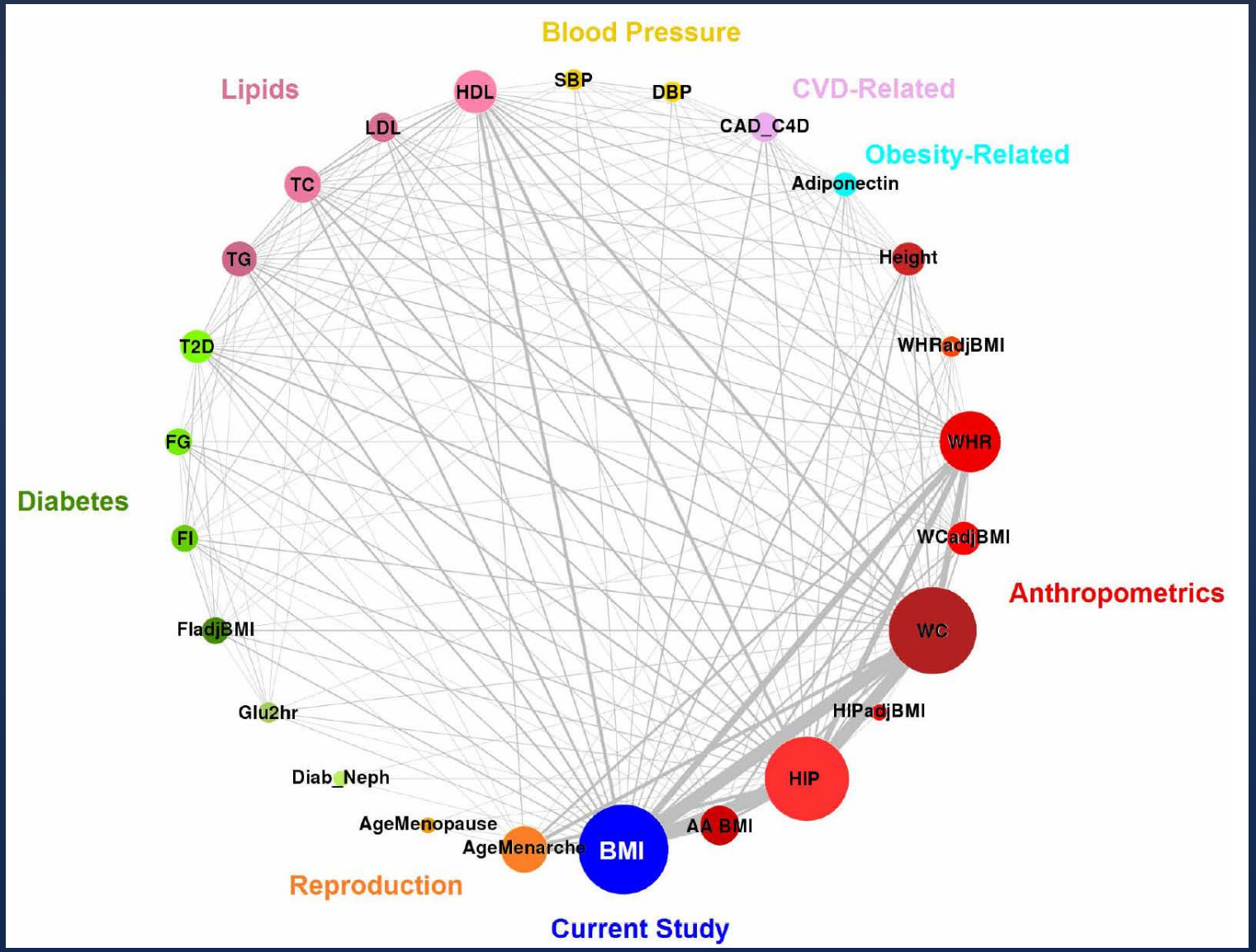


Figure 2 | Tissues and reconstituted gene sets significantly enriched for genes within BMI-associated loci. **a**, DEPICT predicts genes within BMI-associated loci ($P < 5 \times 10^{-4}$) are enriched for expression in the brain and central nervous system. Tissues are sorted by physiological system and significantly enriched tissues are in black; the dotted line represents statistically significant enrichment. **b**, The gene sets most significantly enriched for BMI-associated loci by DEPICT ($P < 10^{-6}$, FDR $< 4 \times 10^{-4}$). Nodes represent reconstituted gene sets and are colour-coded by *P* value. Edge thickness between nodes is proportional to degree of gene overlap as measured by the Jaccard index. Nodes with gene overlap greater than 25% were collapsed into a single 'meta-node' (blue border). **c**, The nodes contained within the most enriched meta-node, 'clathrin-coated vesicle', which shares genes with other gene sets relevant to glutamate signalling and synapse biology. **d**, The 'generation of a signal involved in cell–cell signalling' meta-node represents several overlapping gene sets relevant to obesity and energy metabolism (gene sets with $P < 4 \times 10^{-3}$, FDR < 0.05 shown). For the complete list of enriched gene sets refer to Supplementary Table 21a.

The 97 loci account for ~2,7% of BMI variation

The genetic overlap across traits at BMI susceptibility loci



Genes Nutr (2015) 10:445
DOI 10.1007/s12263-014-0445-z

RESEARCH PAPER

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

Leticia Goni · Marta Cuervo · Fermín I. Milagro · J. Alfredo Martínez

Received: 15 April 2014 / Accepted: 19 November 2014

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-

POLYMORPHISMS INCLUDED IN THE GENETIC RISK 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

Goni L et al. Genes Nutr, 2015

ASSOCIATION BETWEEN THE GENETIC RISK SCORE AND ANTHROPOMETRIC VARIABLES

	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

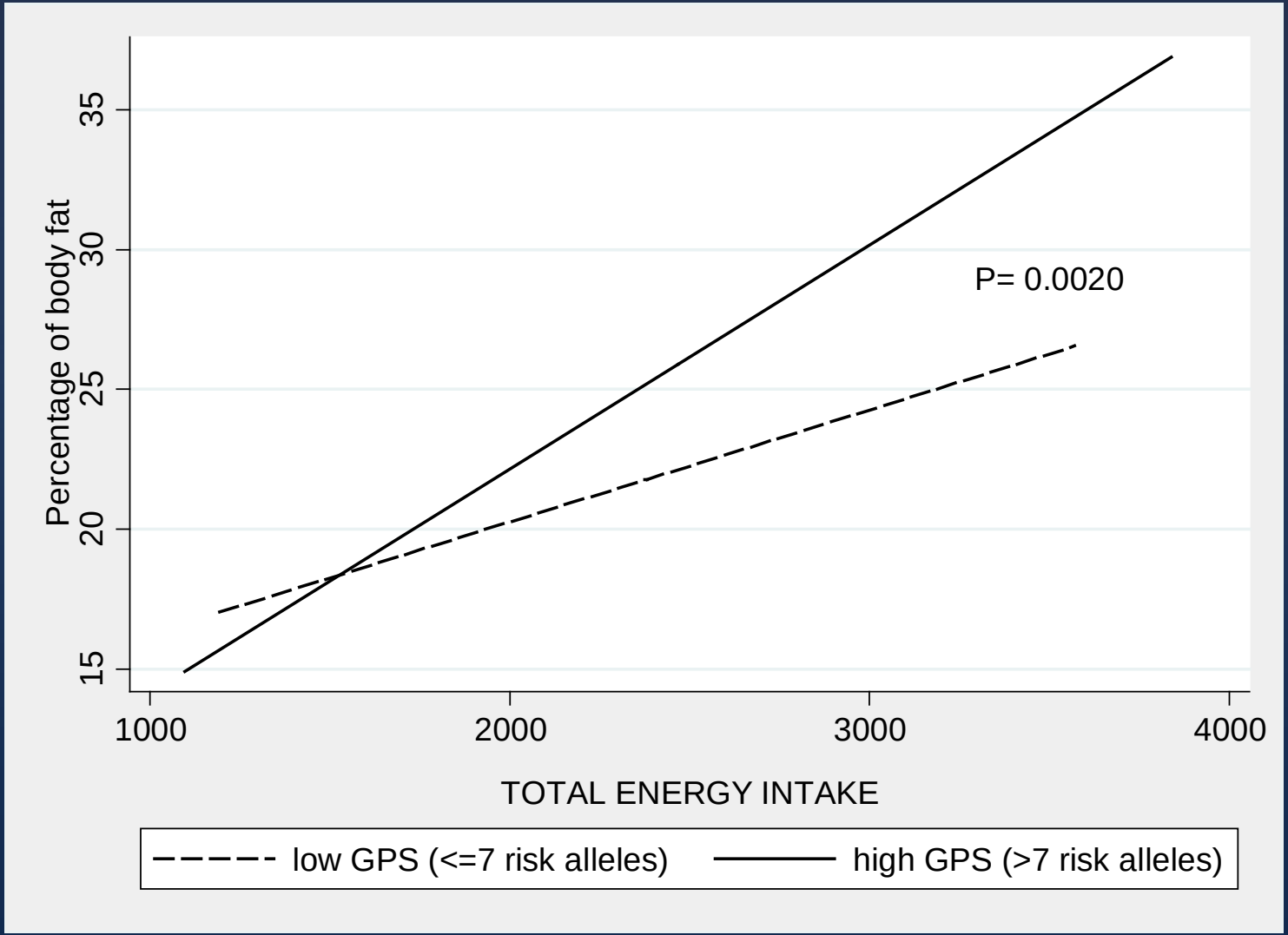
Model 1: Adjusted for gender and age

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

Goni L et al. Genes Nutr, 2015

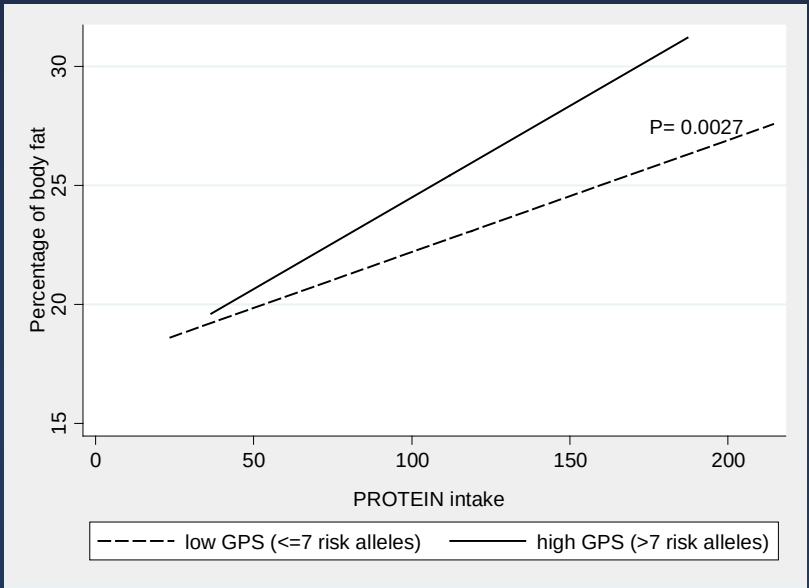
INTERACTION BETWEEN THE GENETIC RISK SCORE AND ENERGY INTAKE

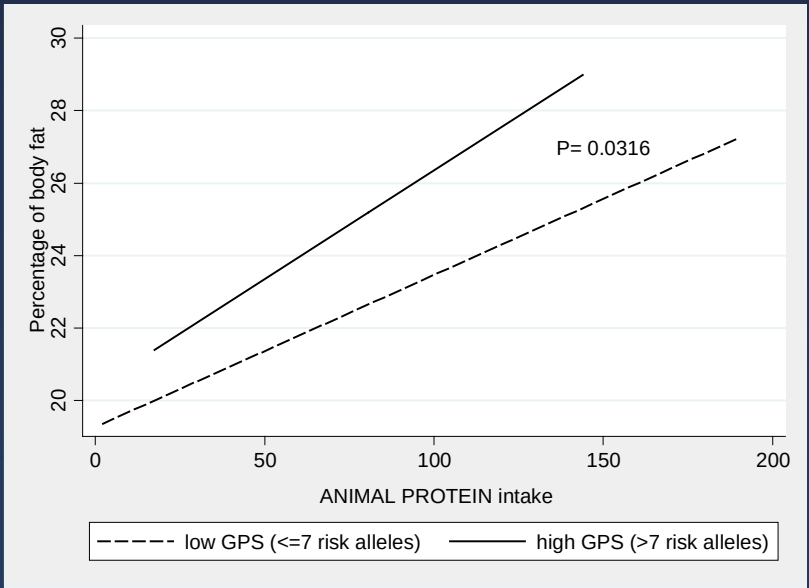


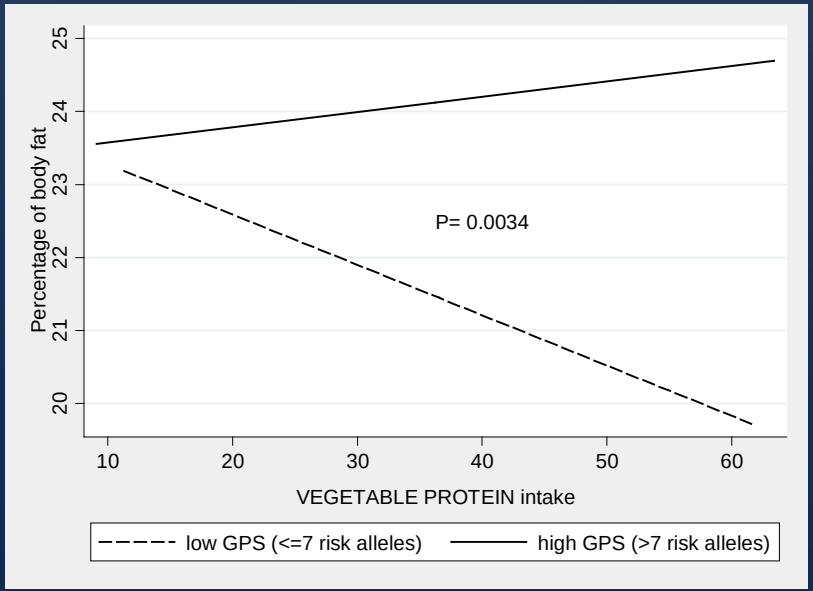
Adjusted for age, gender and physical activity

Goni L et al. Genes Nutr, 2015

INTERACTION BETWEEN THE GENETIC RISK SCORE AND PROTEIN INTAKE



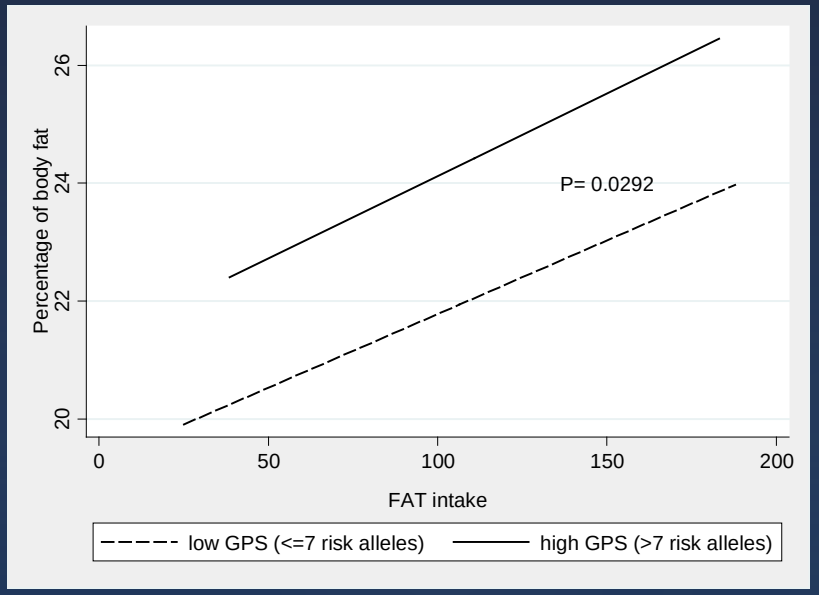


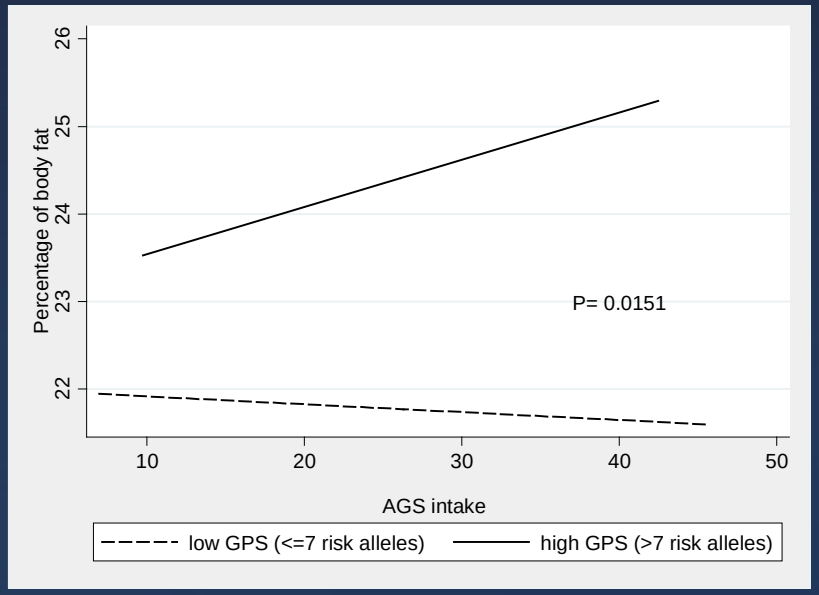


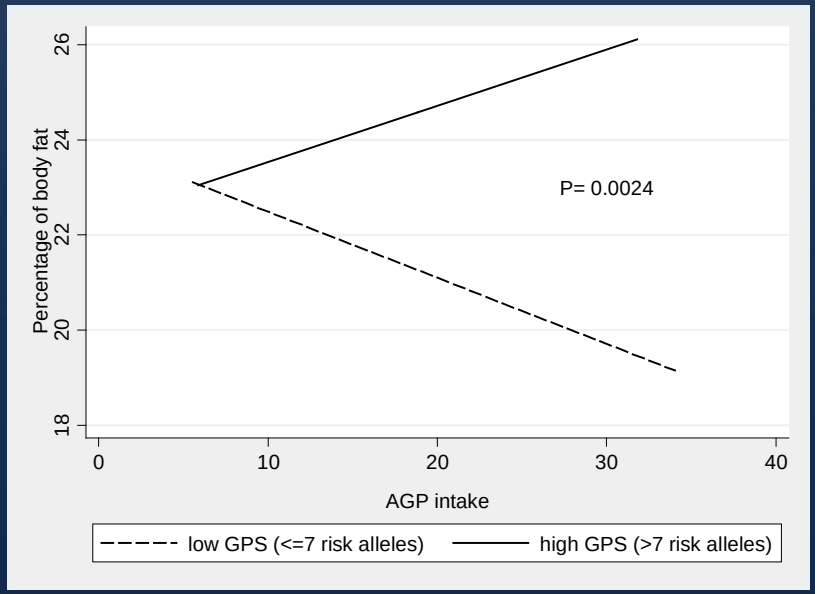
Adjusted for age, gender , physical activity and energy intake

Goni L et al. Genes Nutr, 2015

INTERACTION BETWEEN THE GENETIC RISK SCORE AND DIETARY FAT INTAKE



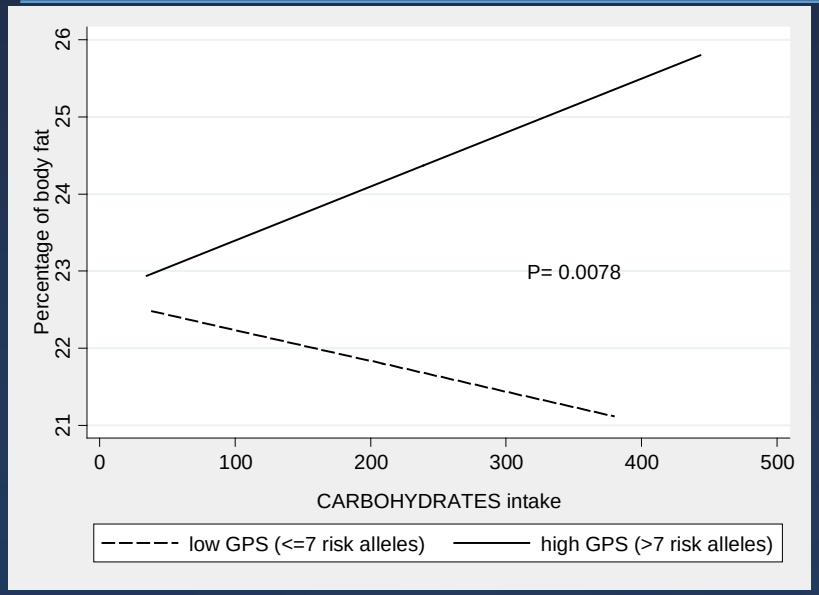


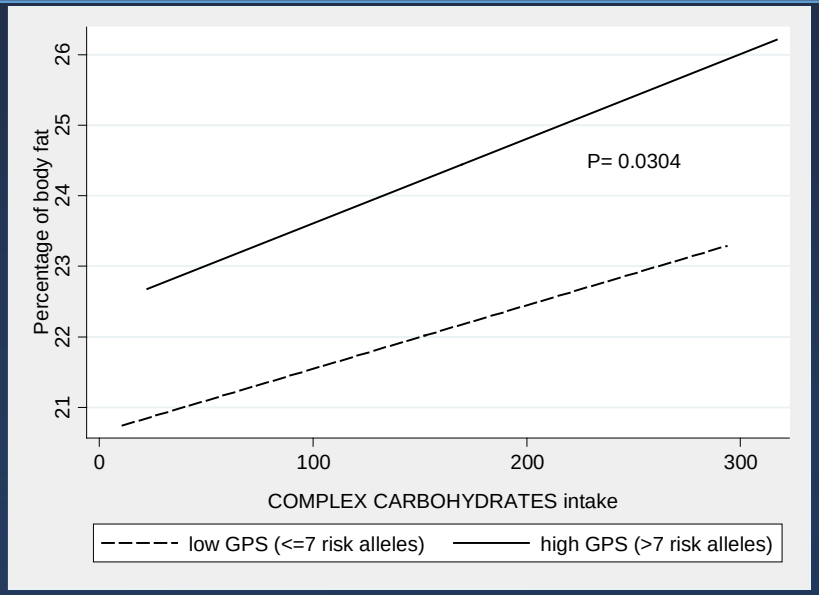


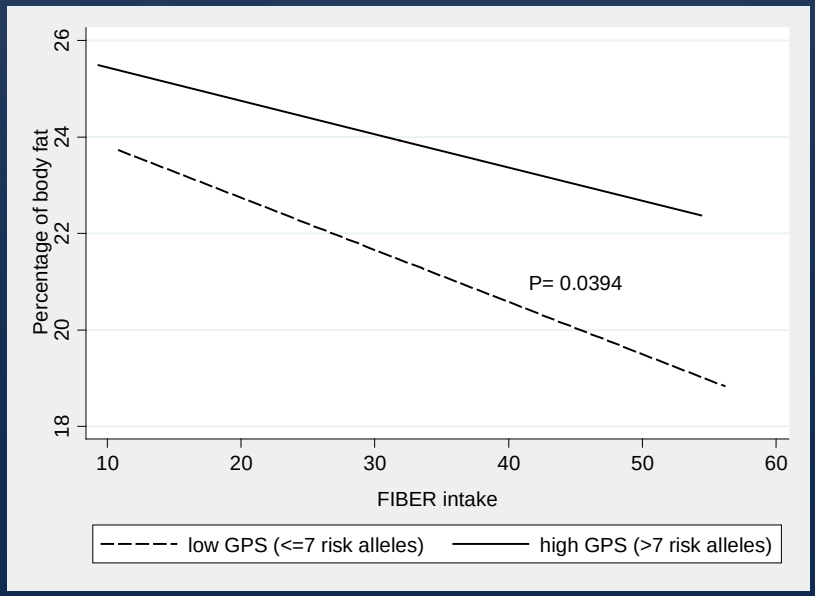
Adjusted for age, gender , physical activity and energy intake

Goni L et al. Genes Nutr, 2015

INTERACTION BETWEEN THE GENETIC RISK SCORE AND CARBOHYDRATE AND FIBER INTAKE







Adjusted for age, gender , physical activity and energy intake

Goni L et al. Genes Nutr, 2015

GENE-NUTRIENT INTERACTIONS IN DETERMINING WEIGHT RELATED PHENOTYPES

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

GENE-NUTRIENT INTERACTIONS IN RELATION TO CENTRAL OBESITY RELATED TRAITS

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

PERSONALIZED APPROACHES AGAINST OBESITY

Nutritional and Diet Theraphy

Drugs Treatments

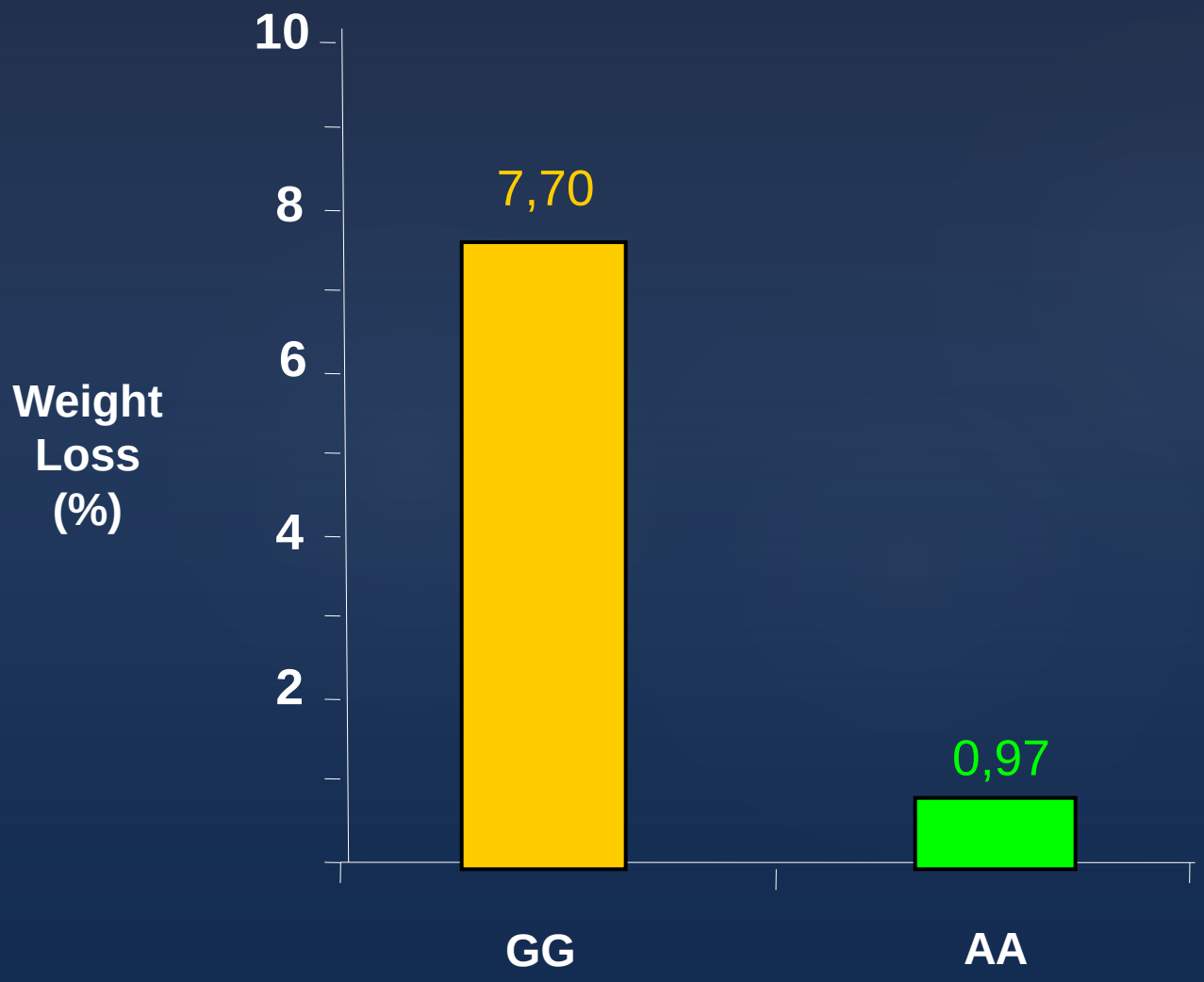
Physical Activity Programmes

Bariatric Surgery

Others: Personalized.....

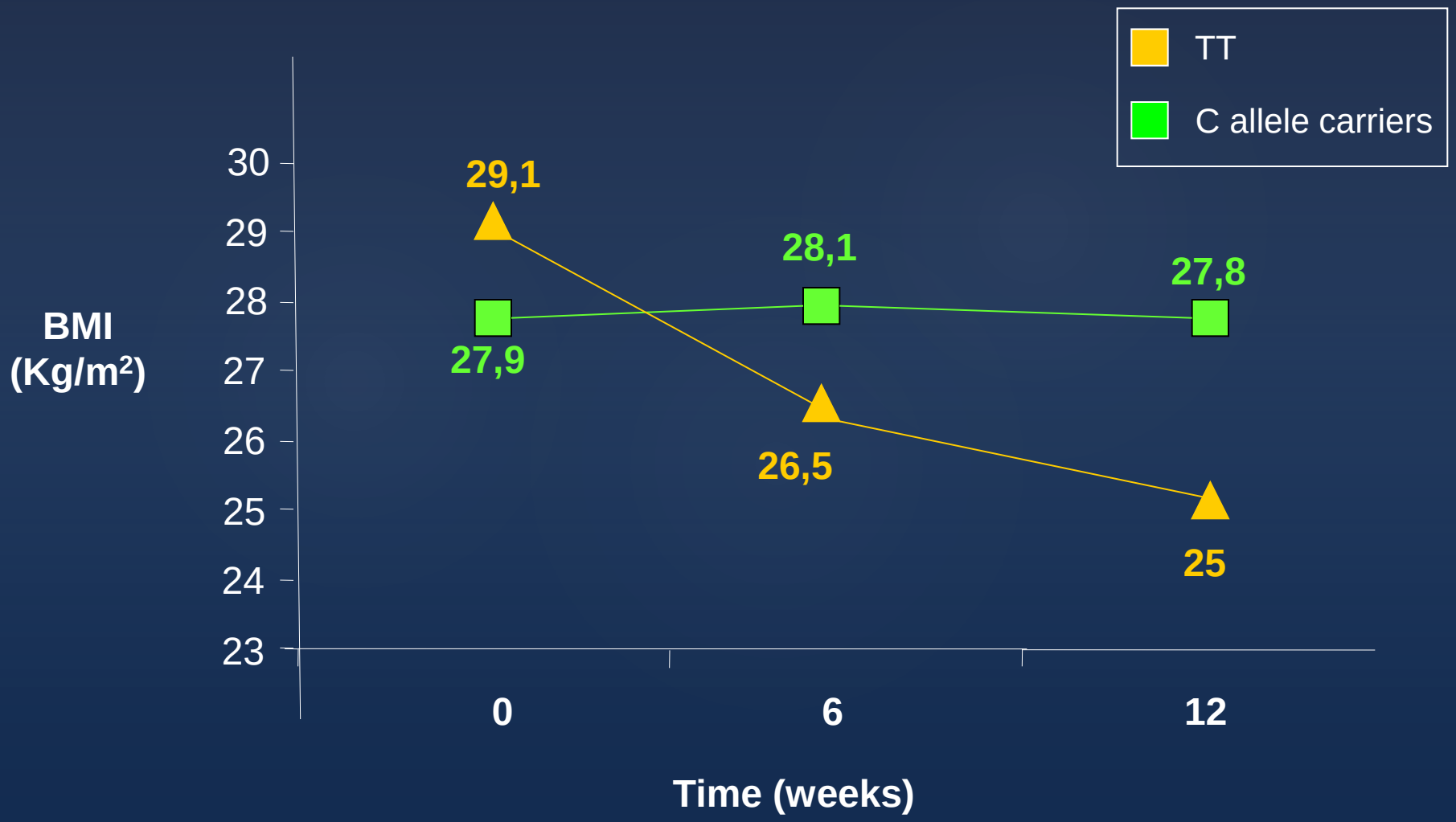
.....Nutrition

PERILIPIN GENE AND WEIGHT LOSS



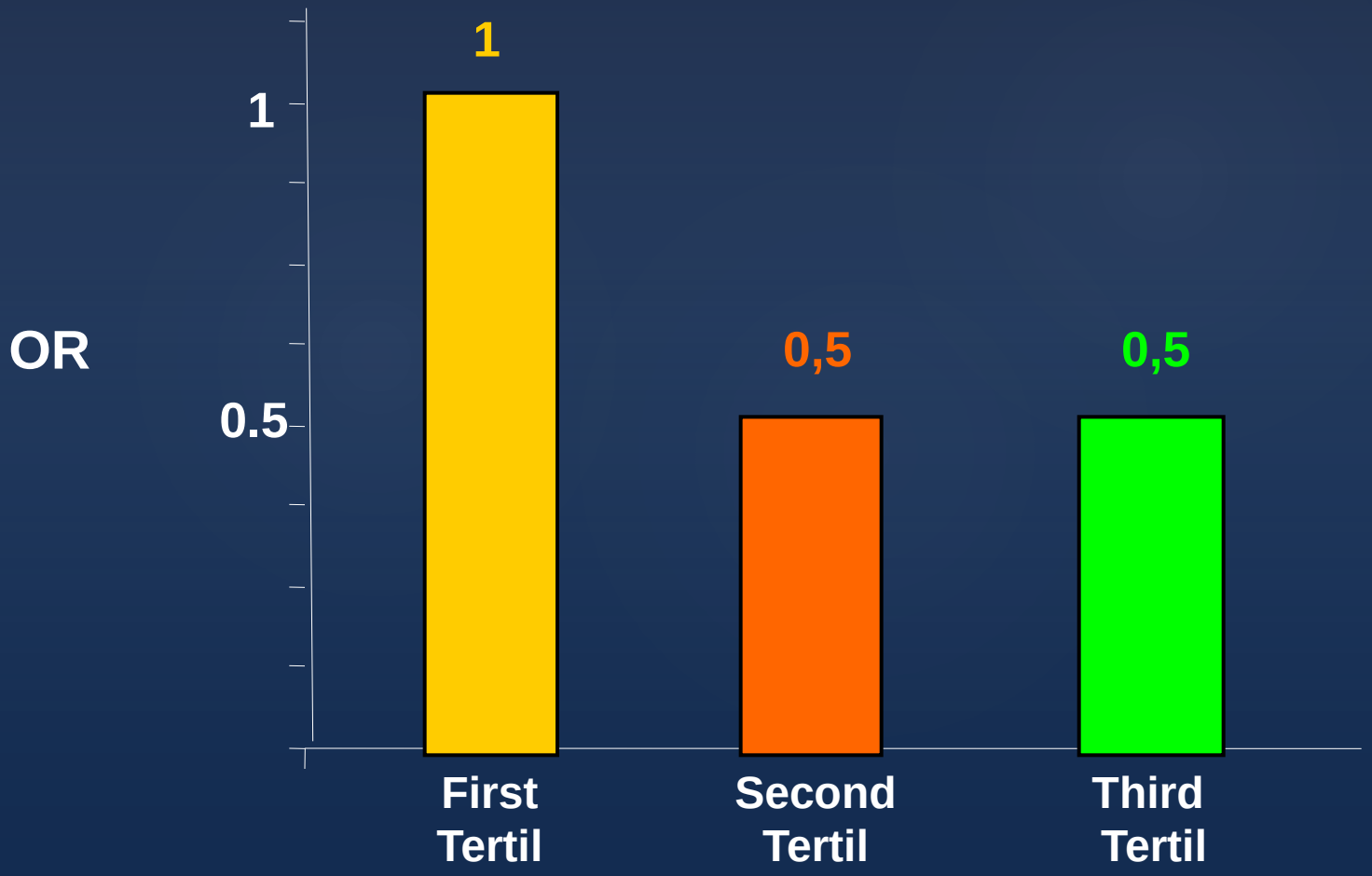
Corella, *et al. 2005*

POLYMORPHISM IN THE APOLIPOPROTEIN A5 GENE



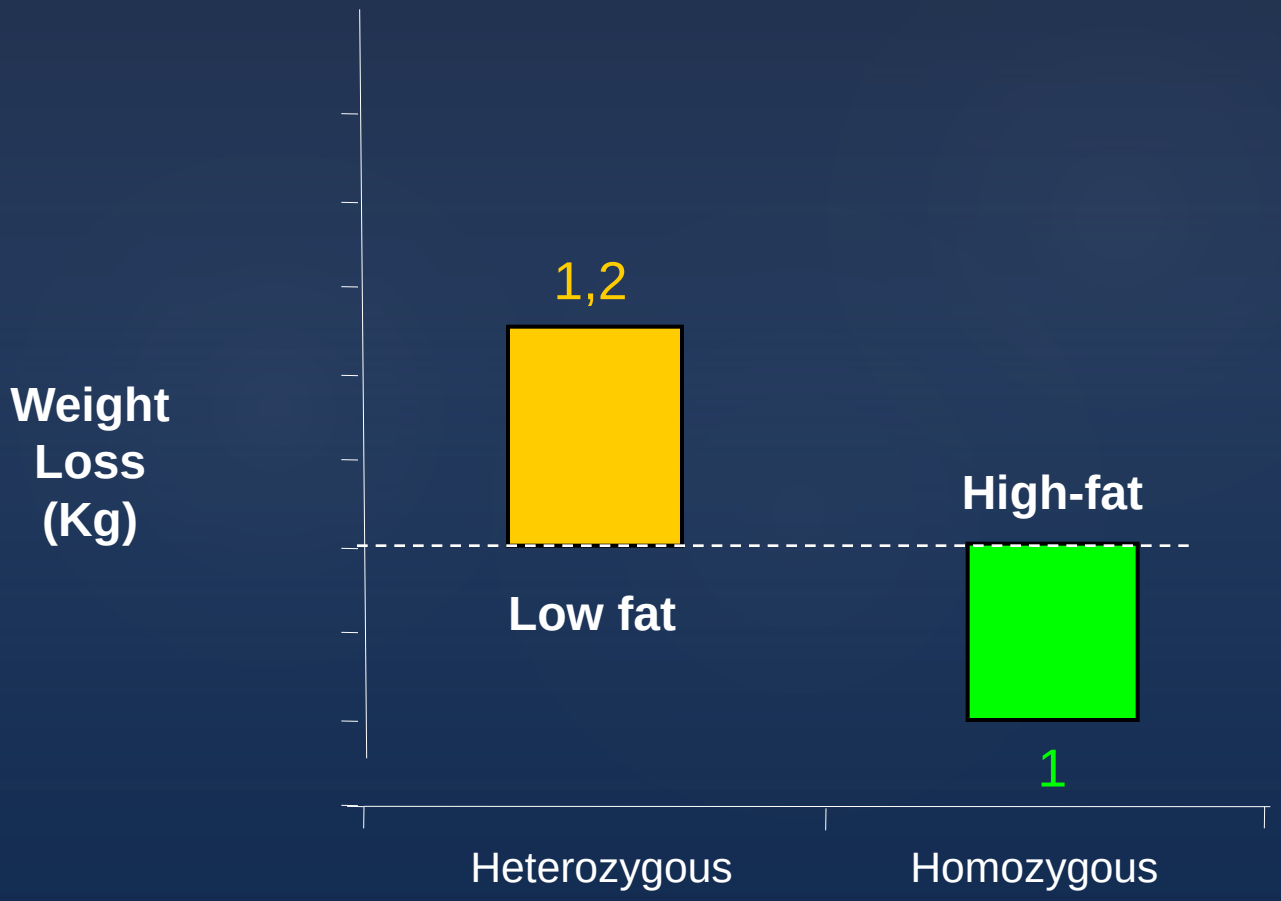
Aberle, *et al. 2005*

LIPC – 514>CT POLYMORPHISM AND FIBRE INTAKE (TERTILES)



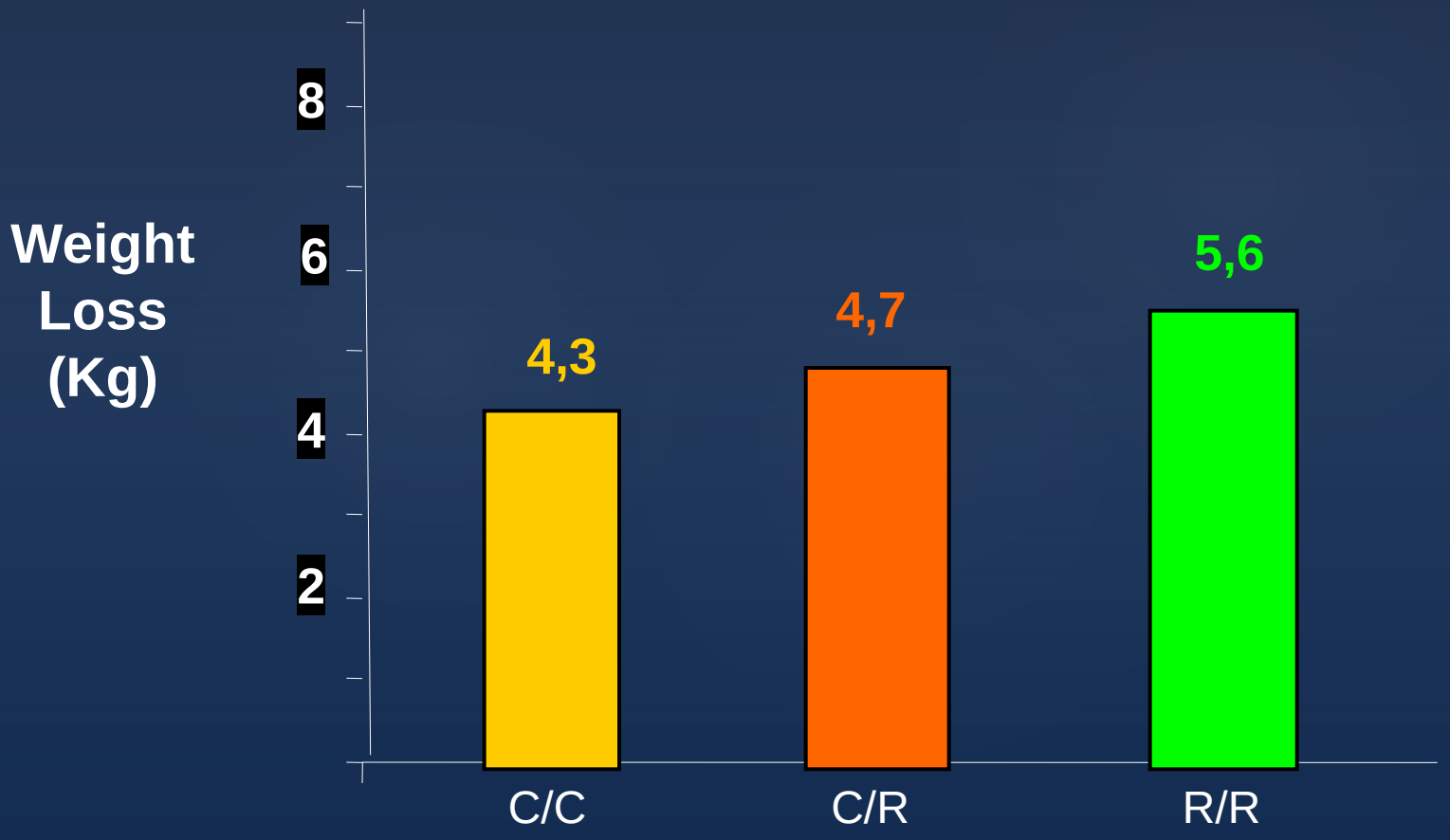
Santos, *et al. 2006*

ADIPOQ – 11377 C>G POLIMORPHISM INFLUENCE ON WEIGHT LOSS



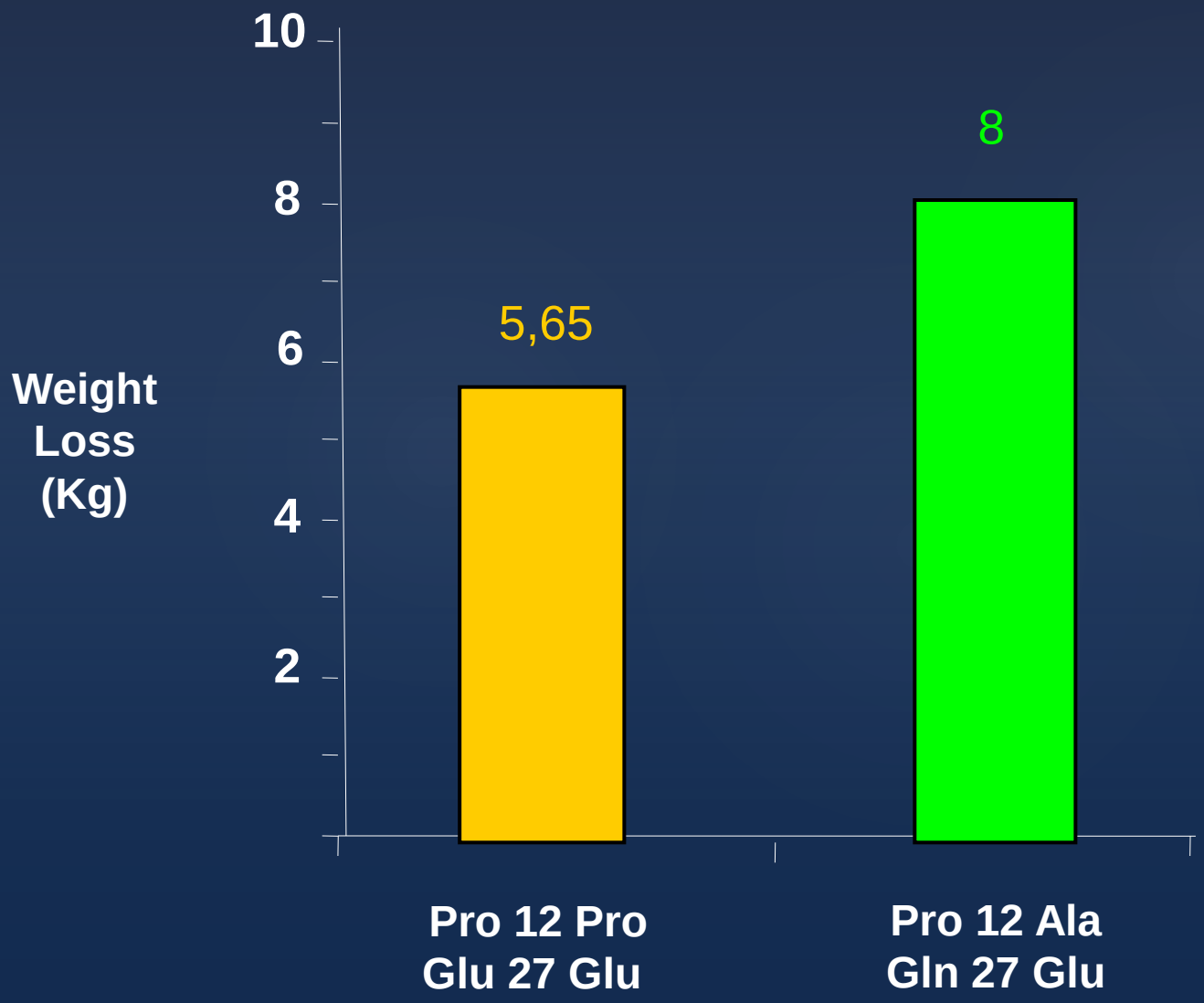
Sorensen, *et al. 2006*

UCP_3 HAPLOTYPES IMPACT ON WEIGHT LOSS



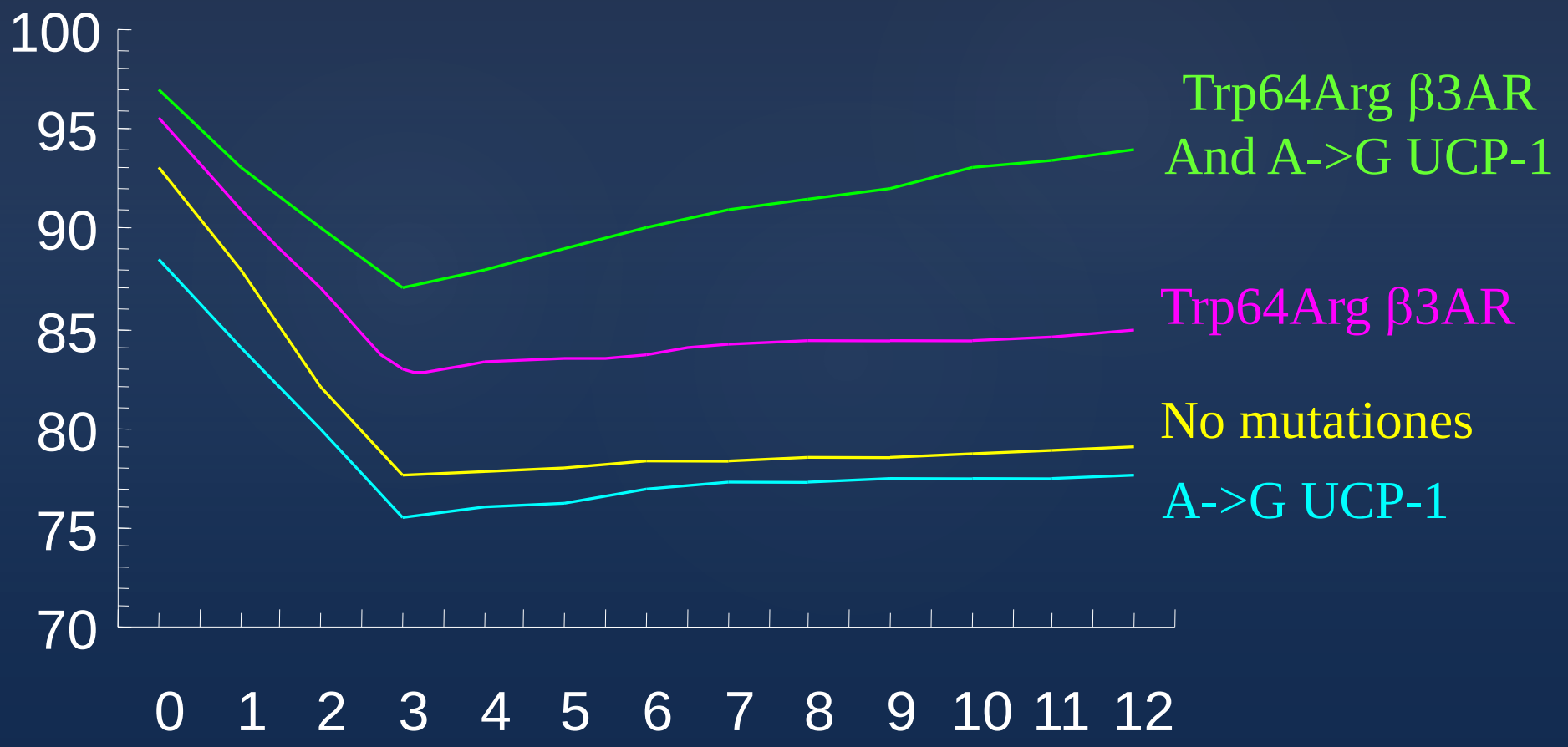
Cha, *et al. 2006*

PPAR x ADRB2 interaction



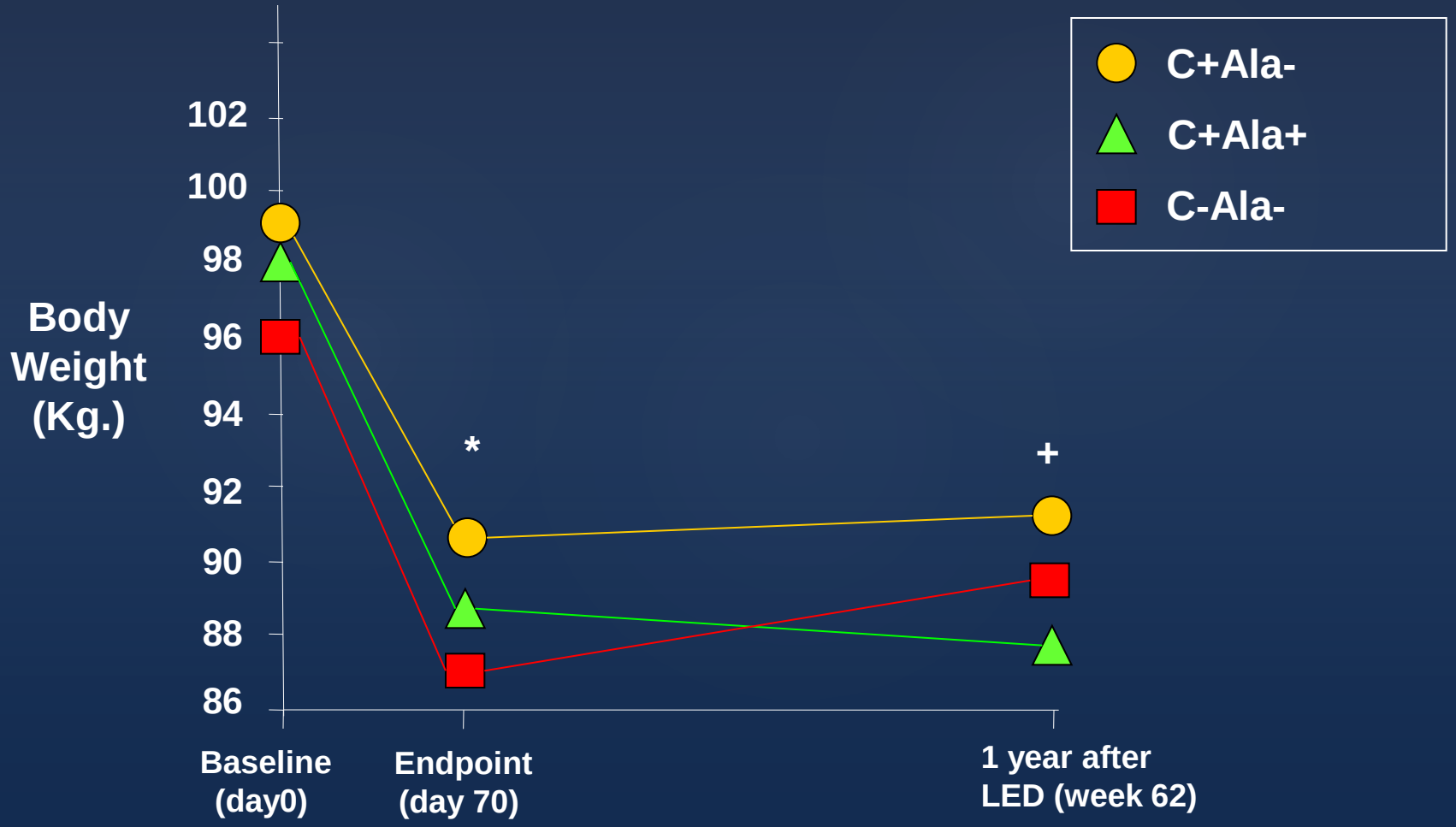
E. L. Rosado, *et al. 2006*

WEIGHT CHANGES AND GENOTYPE



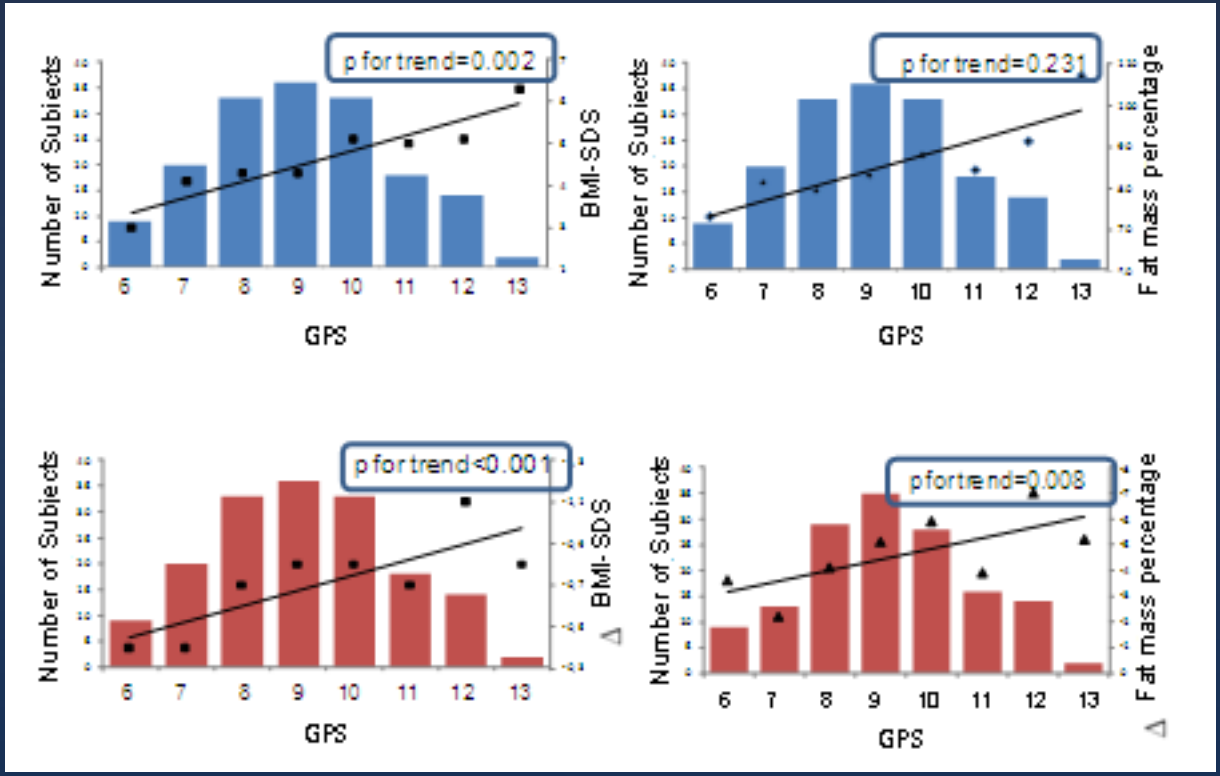
FOGELHOLM, M. *et al.* 1998

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).

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Original Paper

Gene-Gene Interplay and Gene-Diet Interactions Involving the *MTNR1B* rs10830963 Variant with Body Weight Loss

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Key Words
MTNR1B · *FTO* · *MC4R* · Obesity · Body weight loss · Gene-gene interplay · Gene-diet interaction

Abstract
Background/Aims: Investigation of the genetic makeup may facilitate the implementation of more personalized nutritional interventions. The aims were to examine whether the rs10830963 *MTNR1B* polymorphism affects weight loss in response to a hypocaloric diet and to find potential gene-gene interplays and gene-diet interactions. ***Methods:*** 167 subjects enrolled in a personalized nutritional intervention for weight loss (3–6 weeks) were examined for anthropometric measurements, dietary habits and physical activity at baseline and at the first follow-up visit. Three polymorphisms, which have previously been associated with body weight regulation, rs10830963 *(MTNR1B)*, rs9939609 *(FTO)* and rs17782313 *(MC4R)*, were analyzed using the Luminex® 100/200™ System. ***Results:*** After adjusting for covariates, females with the rs10830963 CG/GG genotype showed lower weight loss than those with the CC genotype. In the total population, carriers of variant alleles of both *FTO* and *MC4R* showed a significant association with *MTNR1B* and weight loss outcome. Moreover, among women, higher total protein and animal protein intakes were associated with a lower weight loss in G allele carriers of the *MTNR1B* variant. ***Conclusions:*** Our data evidenced that rs10830963 *MTNR1B* polymorphism could be associated with individual differences in weight loss induced by a hypocaloric diet. This association was influenced by *FTO* and *MC4R* loci and modified by baseline protein intake.

ASSOCIATION BETWEEN *MTNR1B* GENETIC VARIANT AND CHANGES IN WEIGHT AND BMI

Table 2. Linear regression coefficients for the association between *MTNR1B* and anthropometric variables after weight loss intervention

	Δ weight		Δ BMI	
	B (95% CI)	p	B (95% CI)	p
All				
CC	0 (ref.)		0 (ref.)	
CG/GG	−0.11 (−0.64, 0.42)	0.686	−0.08 (−0.27, 0.11)	0.391
Males				
CC	0 (ref.)		0 (ref.)	
CG/GG	0.73 (−1.05, 2.51)	0.409	0.24 (−0.30, 0.79)	0.368
Females				
CC	0 (ref.)		0 (ref.)	
CG/GG	−0.55 (−1.07, −0.03)	0.040	−0.23 (−0.45, −0.03)	0.027

Adjusted for gender, age, energy restriction, time between visits 1 and 2, FTO and MC4R variants and baseline value of the appropriate anthropometric variable.

Goni L et al. J Nutrigenet Nutrigenomics, 2015

INFLUENCE OF *FTO* AND *MC4R* POLYMORPHISMS ON THE ASSOCIATION OF *MTNR1B* POLYMORPHISM AND BMI LOSS

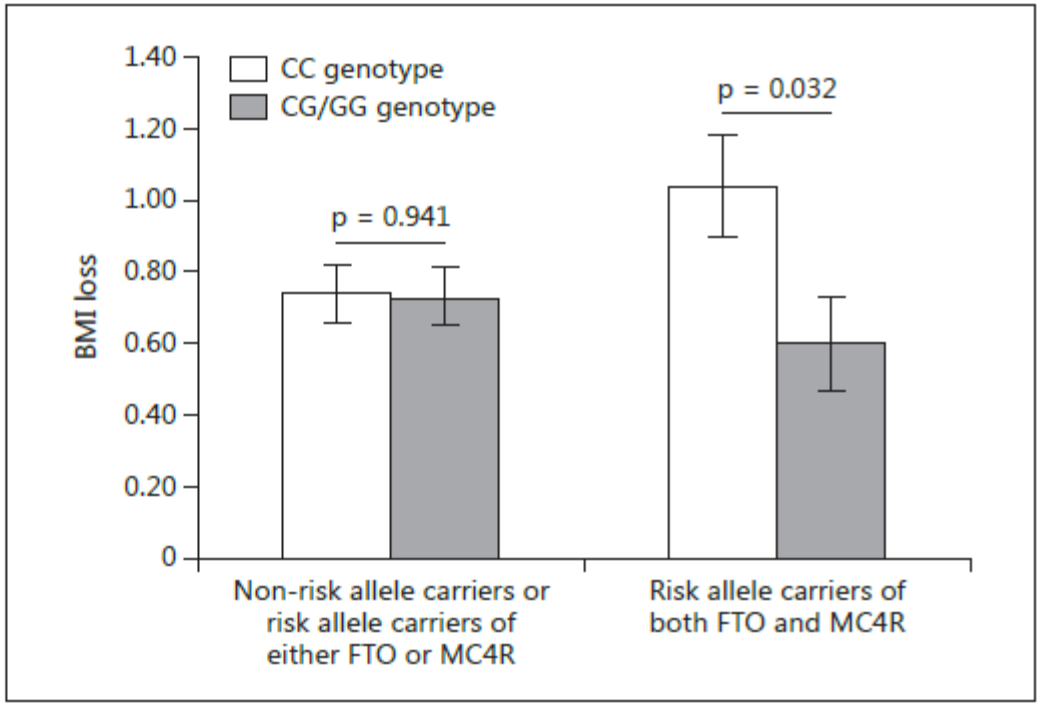

Fig. 1. Influence of obesity loci on the association of *MTNR1B* and BMI loss in the total population. Adjusted for age, energy restriction, time between visits and BMI at baseline.

Goni L et al. J Nutrigenet Nutrigenomics, 2015

INTERACTION BETWEEN MTNR1B POLYMORPHISM AND PROTEIN INTAKE AT BASELINE

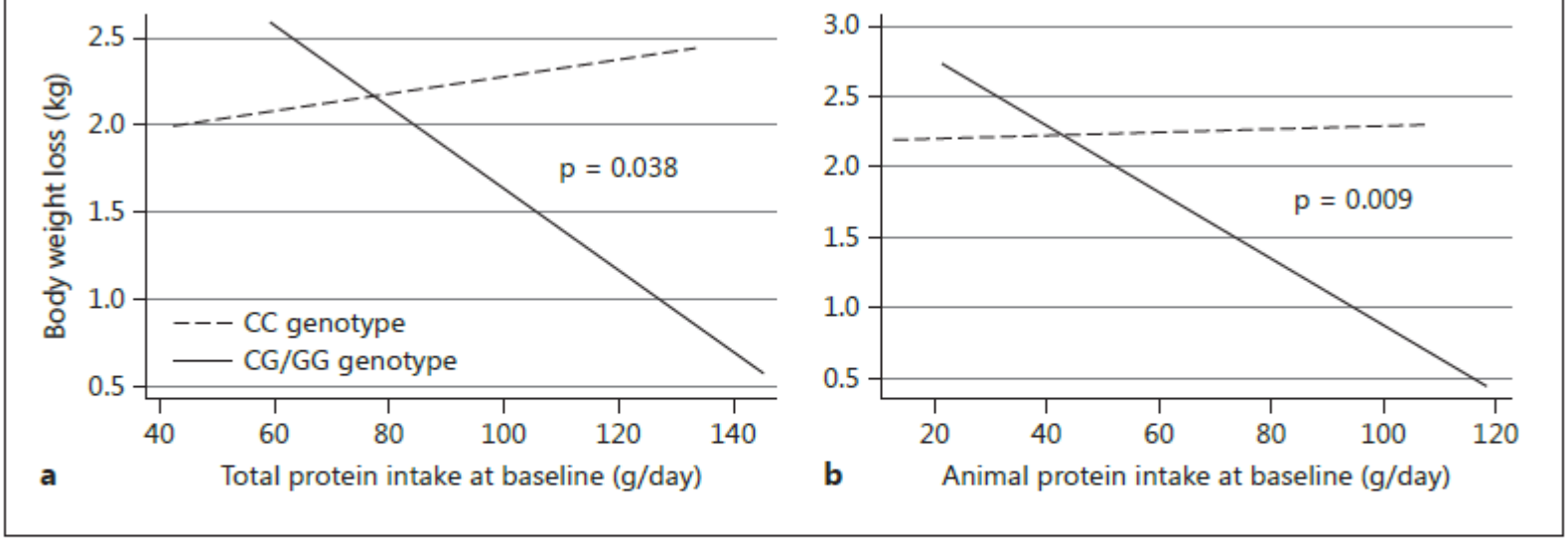

Fig. 2. Interaction between *MTRN1B* and total protein intake at baseline (**a**) and animal protein intake at baseline (**b**) and its effect on body weight loss among women. Adjusted for age, energy restriction, time between visits, *FTO*, *MC4R* and body weight at baseline.

Goni L et al. J Nutrigenet Nutrigenomics, 2015

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Archives of Medical Research ■ (2009) ■

Archives of Medical Research

BRIEF REPORT

Inflammatory State and Stress Condition in Weight-lowering *Lys*109*Arg* LEPR Gene Polymorphism Carriers

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Received for publication November 24, 2008; accepted March 2, 2009 (ARCMED-D-08-00537).

Background and Aims. Carrying variants on the leptin receptor gene (LEPR) may have an impact on inflammatory and stress markers. Thus, the aim of the study was to analyze the role of the *Lys*109*Arg* LEPR gene polymorphism on inflammatory (leptin and IL-6) and stress (cortisol) markers in obese subjects who followed a hypocaloric diet designed to lose weight.

Methods. One hundred and seventy (80 females/90 males) Caucasian subjects (body mass index: 30.8 ± 2.4 kg/m^2), were genotyped for the *Lys*109*Arg* polymorphism by a PCR/RFLP procedure. Anthropometric measurements were assessed and blood samples were drawn in all the volunteers before and after an 8-week energy-restricted diet (−30% E). Plasma levels of leptin as well as interleukin-6 (IL-6) as proinflammatory markers and circulating cortisol concentrations as a stress hormone were measured.

Results. Weight loss (−6.1 ± 2.7%; $p < 0.001$) induced significant changes in anthropometric and biochemical determinations. The *AA* genotype group showed a higher fat mass loss as well as greater total cholesterol decrease compared with the minor allele carriers. Moreover, the *G* allele carriers were associated with a higher basal risk of inflammation (OR = 2.5; $p = 0.042$) and stress (OR = 3.3; $p = 0.011$), which were reduced after weight lowering ($p > 0.05$).

Conclusions. The *Arg* allele carriers of the *Lys*109*Arg* LEPR gene polymorphism were associated with an increased proinflammatory state and stress condition at baseline. These obesity-related markers were importantly decreased after following a hypocaloric diet.

*Key Words: Lys*109*Arg*, Leptin receptor polymorphism, IL-6, Cortisol, Obesity.

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Enhanced short-term improvement of insulin response to a low-caloric diet in obese carriers the *Gly482Ser* variant of the PGC-1α gene

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Insulin resistance
Type 2 diabetes
Obesity
Polymorphism
Weight-loss
Weight regulation

ABSTRACT

Aim: The *Gly482Ser* missense mutation of the transcriptional coactivator, peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) has been involved in insulin function impairments, with conflicting results. The current study investigated the relationships of carrying this polymorphism with insulin resistance (IR) during a short-term weight-loss and the subsequent weight follow-up.

Methods: The *Gly482Ser* was genotyped in 180 Spanish volunteers [body mass index: 31.4 ± 3.2 kg/m^2; age: 35 ± 5 years]. Specific phenotypical measurements were determined at baseline, following an 8-week low-calorie diet (LCD) as well as after 6-month and 1-year of follow-up.

Results: At baseline the *Ser482Ser* genotype was associated with higher HOMA-IR and insulin concentrations than the other genotypes ($p < 0.05$), which was accompanied by an increased higher risk of IR (OR: 2.97; 95% CI: 1.24–7.15). After following the LCD, such increased risk of insulin insensitivity in *Ser482Ser* carriers was toned down ($p > 0.05$). This outcome was sustained after 6-month and 1-year of follow-up ($p > 0.05$).

Conclusions: These data show an increased risk of IR in obese carrying the rs8192673 *Ser482Ser* genotype. This risk was markedly reduced by an energy-restricted diet, which was sustained 6 months and 1 year after the diet therapy. This observation allows identifying obese subjects who might personally profit most from an energy-restrictive treatment concerning insulin response and lead to more individualized prognostic and therapeutic decisions.

British Journal of Nutrition (2006), **96**, 965–972
DOI: 10.1017/BJN20061901

Weight regain after slimming induced by an energy-restricted diet depends on interleukin-6 and peroxisome-proliferator-activated-receptor-γ2 gene polymorphisms

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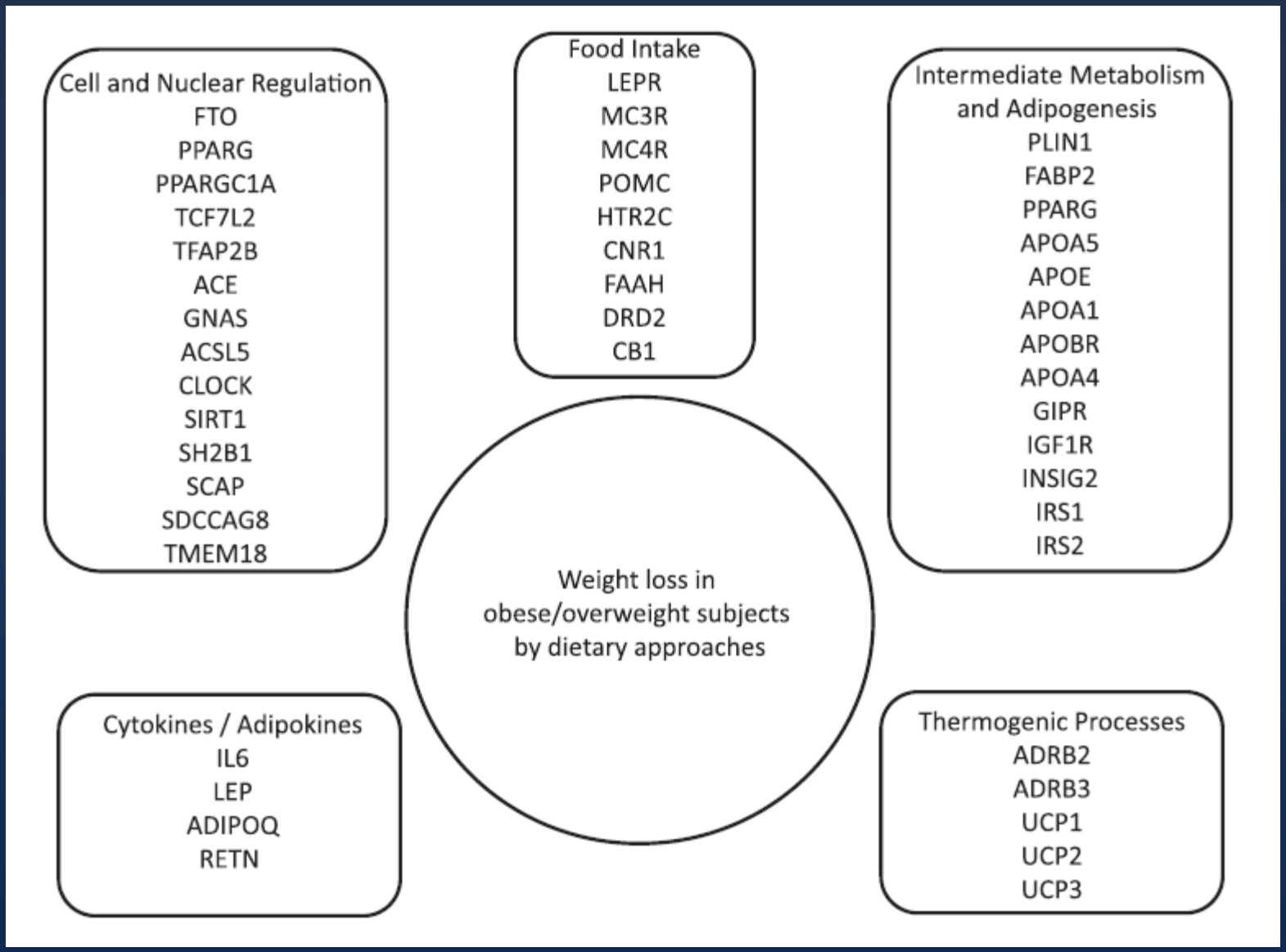
(Received 28 February 2006 – Revised 24 May 2006 – Accepted 7 June 2006)

Weight-loss maintenance after following an energy-restricted diet is a major problem that a number of studies are trying to characterise. The aim of the present study was to investigate the role of IL-6 -174G > C and PPAR-γ2 Pro12Ala variants on weight regulation in obese subjects receiving a low-energy diet and at 1 year after the acute slimming period. Sixty-seven volunteers (age 34·7 (SD 7·0) years; BMI 35·8 (SD 4·8) kg/m^2) were enrolled in a 10-week dietary intervention and were contacted again 1 year after the end of this period. Body composition was measured at three times during the study. Also, PPAR-γ2 Pro12Ala and IL-6 -174G > C polymorphisms were analysed in the participants. No statistical differences were observed depending on the genetic variants at baseline for anthropometric variables, or after the intervention. However, the C allele of the -174G > C IL-6 gene polymorphism was more frequently observed (P=0·032) in subjects with successful weight maintenance (< 10 % weight regain). In fact, the C allele partially protected against weight regain (odds ratio 0·24; P=0·049), while the conjoint presence of both gene variants (C + and Ala +) further improved the ability for weight maintenance (odds ratio 0·19; P=0·043). The present study demonstrates that the C allele of the -174G > C polymorphism gives protection against regain of weight lost. Moreover, the presence of the Ala allele of the PPARγ-2 together with the C allele strengthens this protection. These findings support a role for these polymorphisms on weight regulation and suggest a synergetic effect of both variants on weight maintenance after following a diet to lose weight.

GENES IN WHICH THERE ARE POLYMORPHISMS RELATED TO BODY WEIGHT LOSS



Martínez JA et al. Trends Food Sci Technol, 2015

Personalization for weight management

Courtesy John Mathers, UNew

Background

Personalised nutrition: the concept?

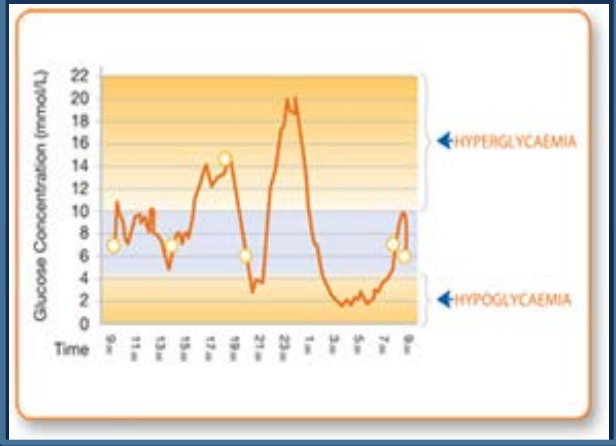
"Personalised nutrition is the tailoring of dietary advice to suit an individual based on their genetic make-up."

2000

Phenotyping devices

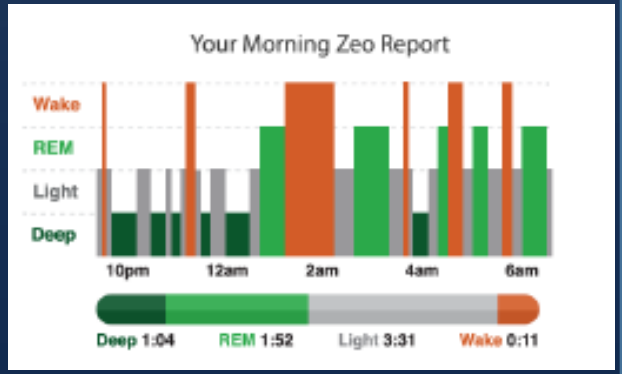
Continuous glucose monitoring system

Sensor tail 5 mm



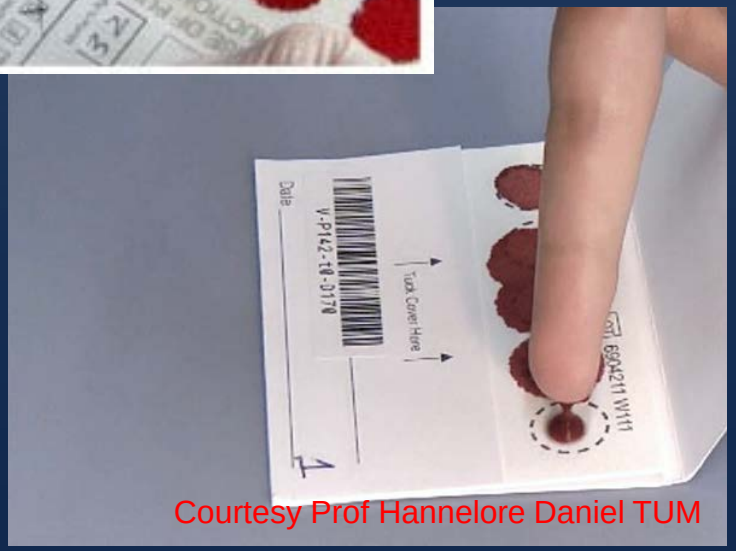
Direct Life Activity Monitor

The Zeo sleep Manager (Oram)



GPS: Biochemical and Genetic analysis

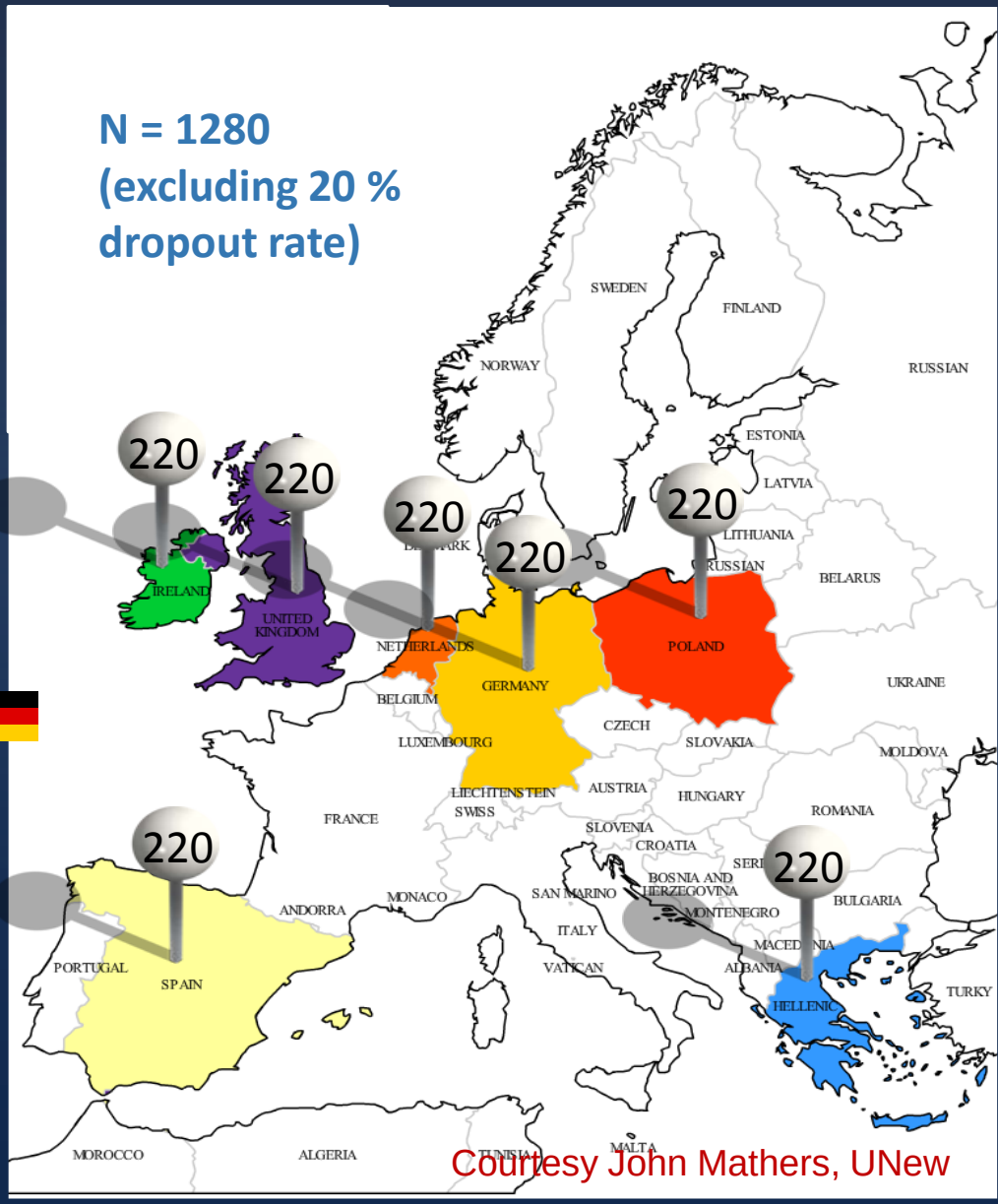
30 – 100 µl per spot



Courtesy Prof Hannelore Daniel TUM

FOOD4ME: Recruiting centres for Study

1. University College Dublin (Ireland)
2. Maastricht University (The Netherlands)
3. University of Navarra (Spain)
4. University of Reading (UK)
5. National Food and Nutrition Institute Warsaw (Poland)
6. Harokopio University Athens (Athens)
7. Technische Universitaet Muenchen (Germany)



Courtesy John Mathers, UNew

Objectives

- To explore the **scientific**, **business** and **consumer** aspects of personalised nutrition

- To determine whether dietary advice based on a person's genes, could deliver consumer benefits

ETHICAL ISSUES!

Appetite 66 (2013) 67–74

Contents lists available at SciVerse ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

Research report

Factors influencing European consumer uptake of personalised nutrition. Results of a qualitative analysis ☆

Barbara Stewart-Knox [a], Sharron Kuznesof [b], Jenny Robinson [a], Audrey Rankin [a], Karen Orr [a], Maresa Duffy [a], Rui Poínhos [c], Maria Daniel Vaz de Almeida [c], Anna Macready [d], Caroline Gallagher [e], Aleksandra Berezowska [f], Arnout R.H. Fischer [f], Santiago Navas-Carretero [g], Martina Riemer [h], Iwona Traczyk [i], Ingrid M.F. Gjelstad [j], Christina Mavrogianni [k], Lynn J. Frewer [b,*]

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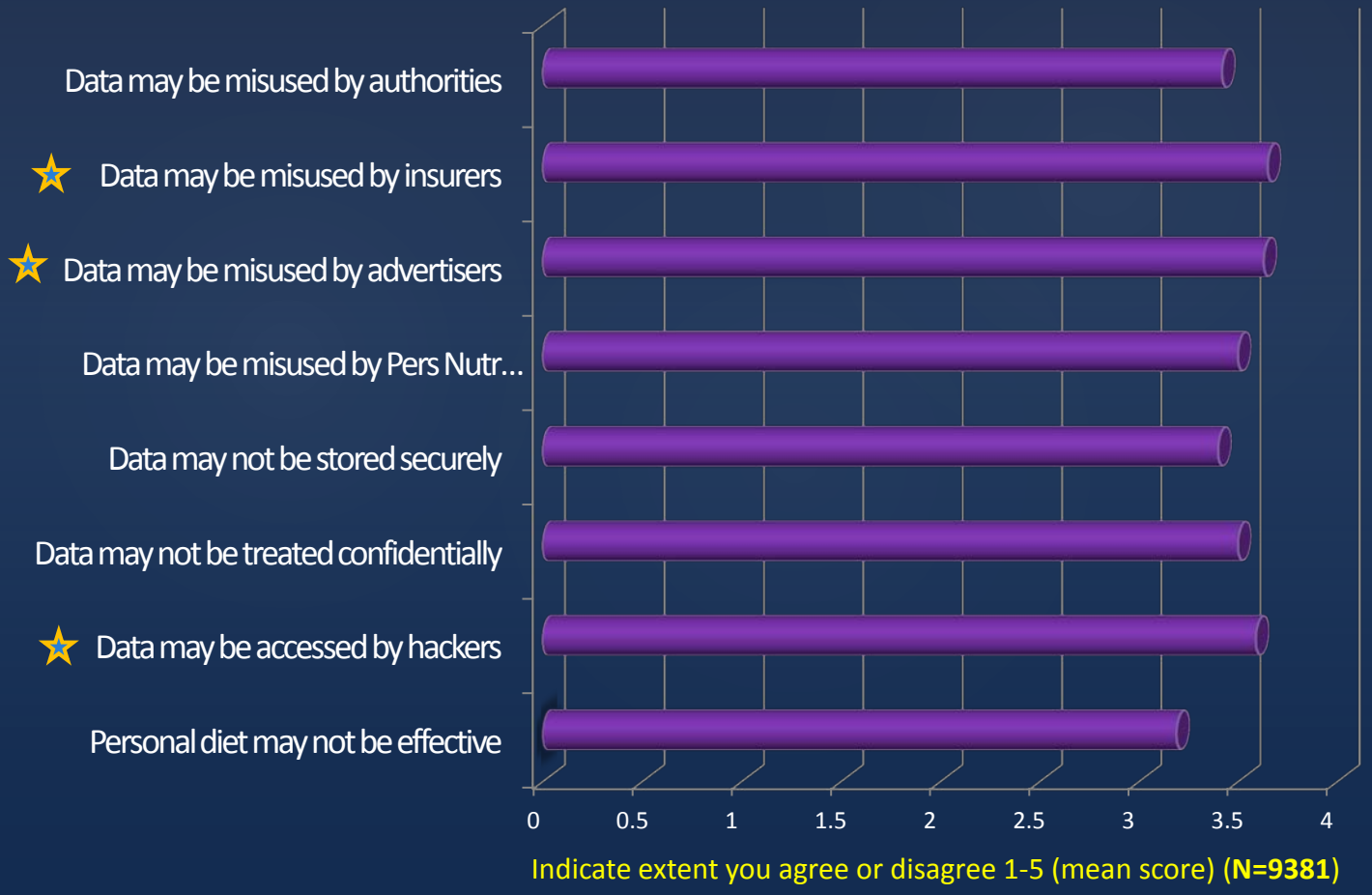
Consumer
Qualitative
Barriers
Acceptance
Focus group
Food4Me

ABSTRACT

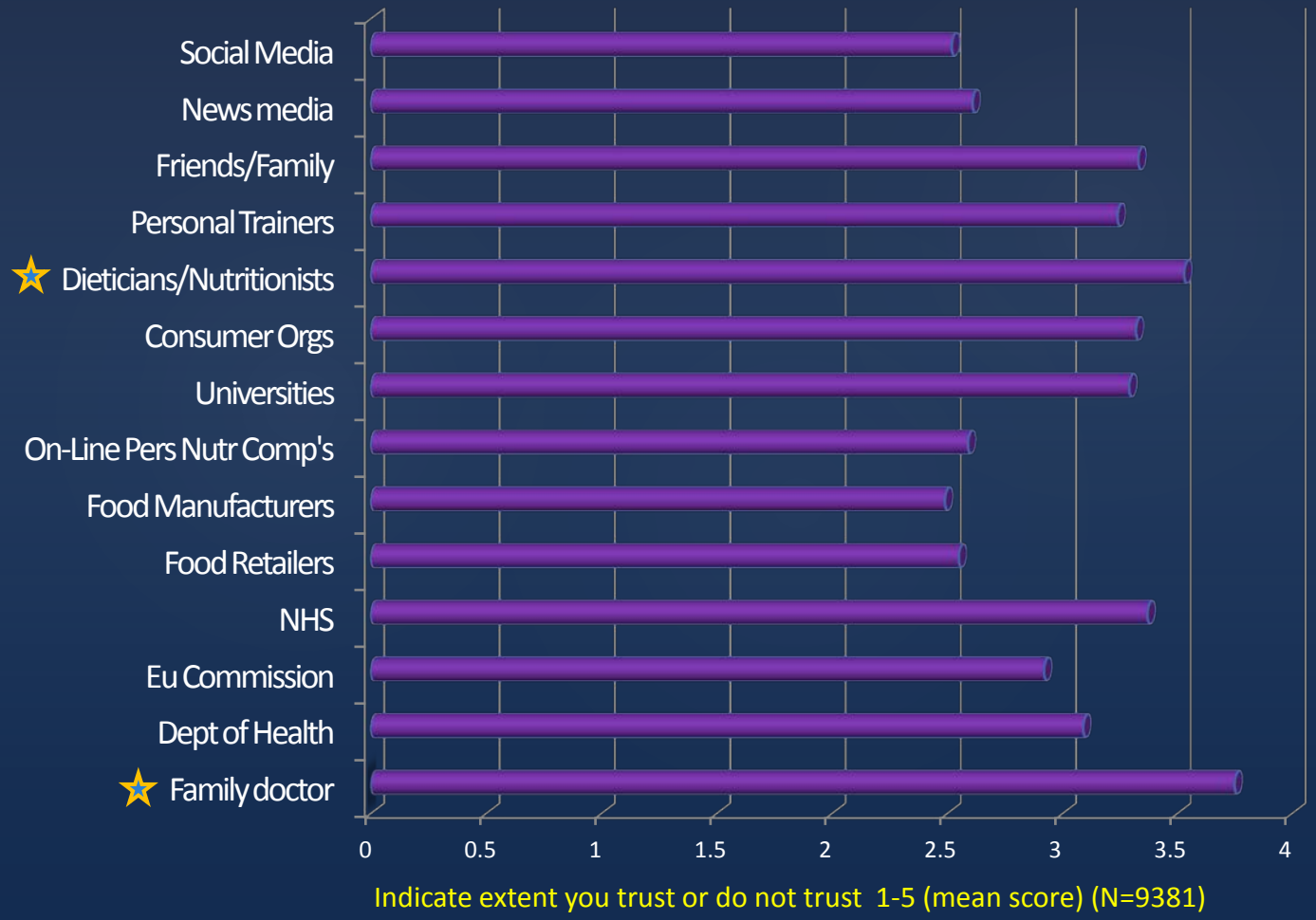
The aim of this research was to explore consumer perceptions of personalised nutrition and to compare these across three different levels of "medicalization": lifestyle assessment (no blood sampling); phenotypic assessment (blood sampling); genomic assessment (blood and buccal sampling). The protocol was developed from two pilot focus groups conducted in the UK. Two focus groups (one comprising only "older" individuals between 30 and 60 years old, the other of adults 18–65 yrs of age) were run in the UK, Spain, the Netherlands, Poland, Portugal, Ireland, Greece and Germany ($N = 16$). The analysis (guided using grounded theory) suggested that personalised nutrition was perceived in terms of benefit to health and fitness and that convenience was an important driver of uptake. Negative attitudes were associated with internet delivery but not with personalised nutrition *per se*. Barriers to uptake were linked to broader technological issues associated with data protection, trust in regulator and service providers. Services that required a fee were expected to be of better quality and more secure. An efficacious, transparent and trustworthy regulatory framework for personalised nutrition is required to alleviate consumer concern. In addition, developing trust in service providers is important if such services to be successful.

WHAT WORRIES THE PUBLIC ABOUT PERSONALISED NUTRITION?



Courtesy Barbara Stewart-Knox, UU

WHO DO THE PUBLIC TRUST TO PROVIDE PERSONALISED NUTRITION?



Courtesy Barbara Stewart-Knox, UU

FROM THE ACADEMY
Position Paper

Position of the Academy of Nutrition and Dietetics: Nutritional Genomics

ABSTRACT

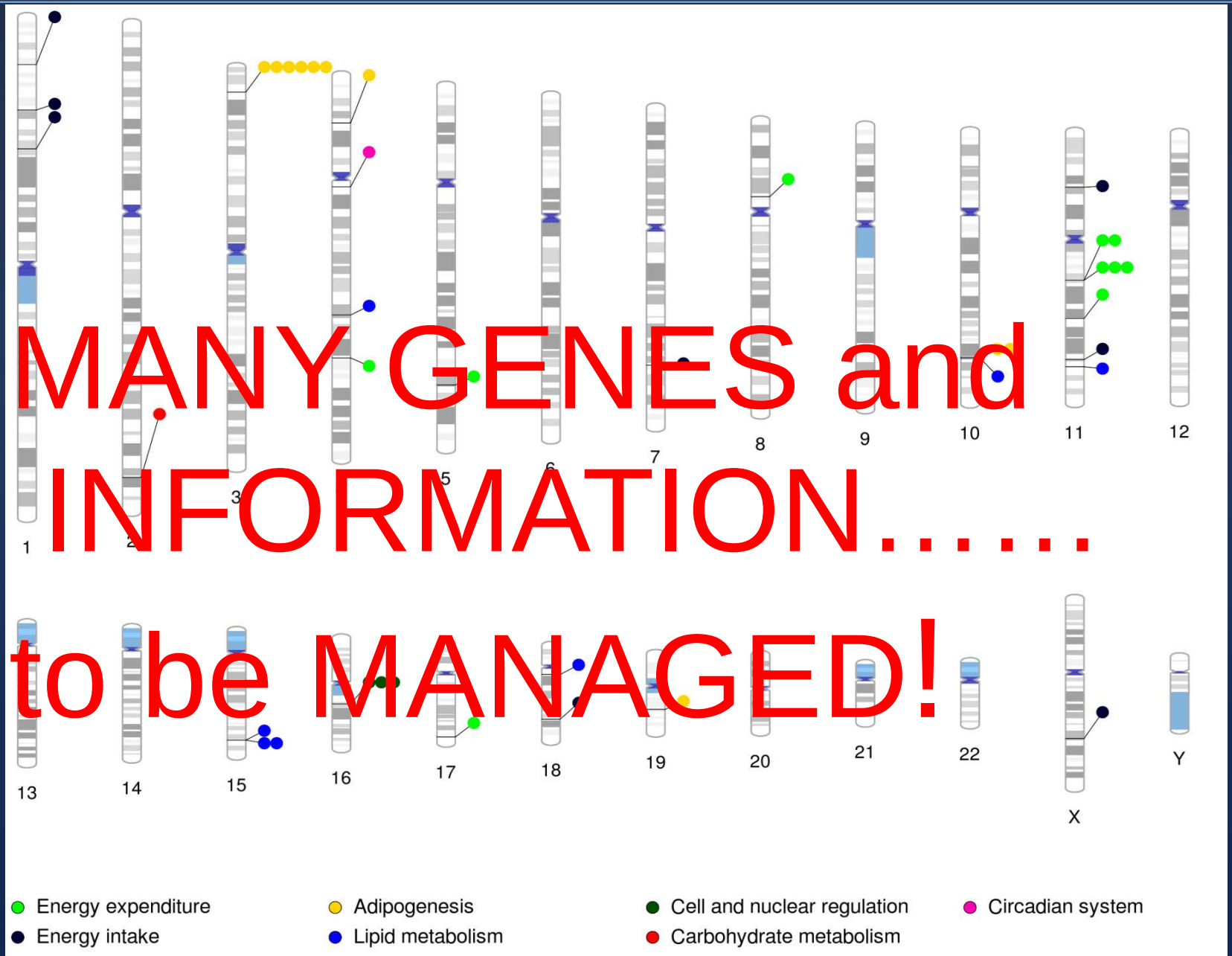
It is the position of the Academy of Nutrition and Dietetics that nutritional genomics provides insight into how diet and genotype interactions affect phenotype. The practical application of nutritional genomics for complex chronic disease is an emerging science and the use of nutrigenetic testing to 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

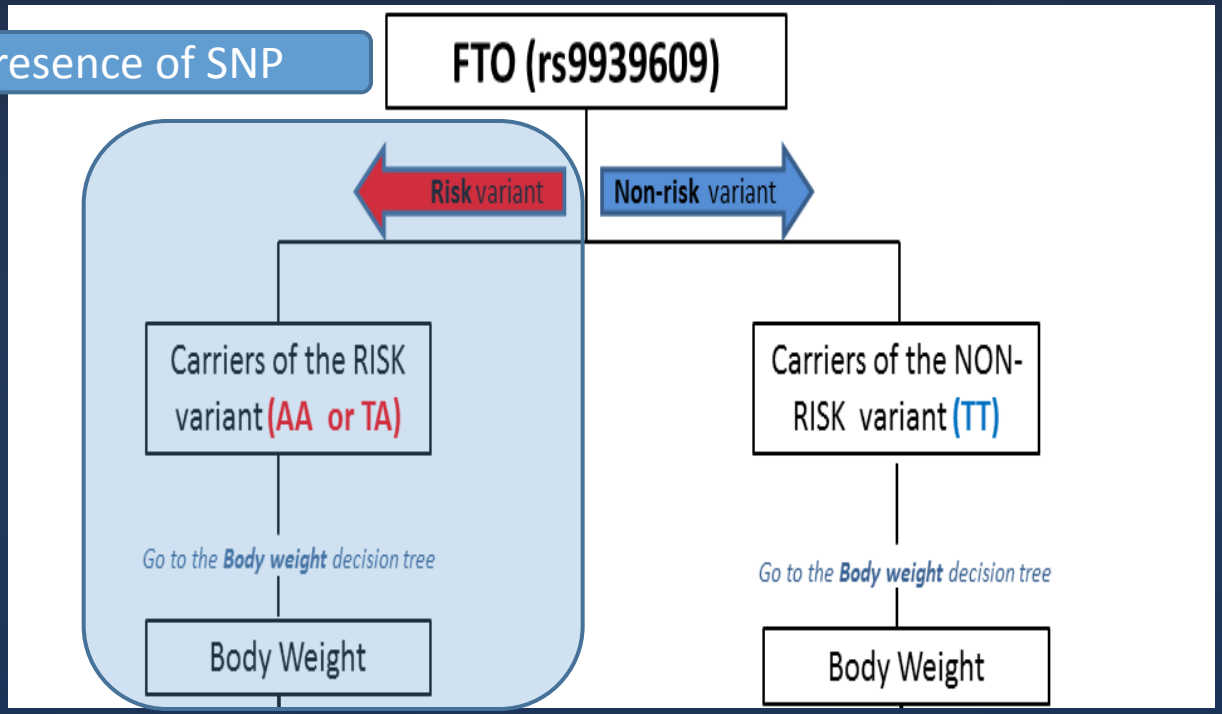
It is the position of the Academy of Nutrition and Dietetics that nutritional genomics provides insight into how diet and genotype interactions affect phenotype. The practical application of nutritional genomics for complex chronic disease is an emerging science and the use of nutrigenetic testing to 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.

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

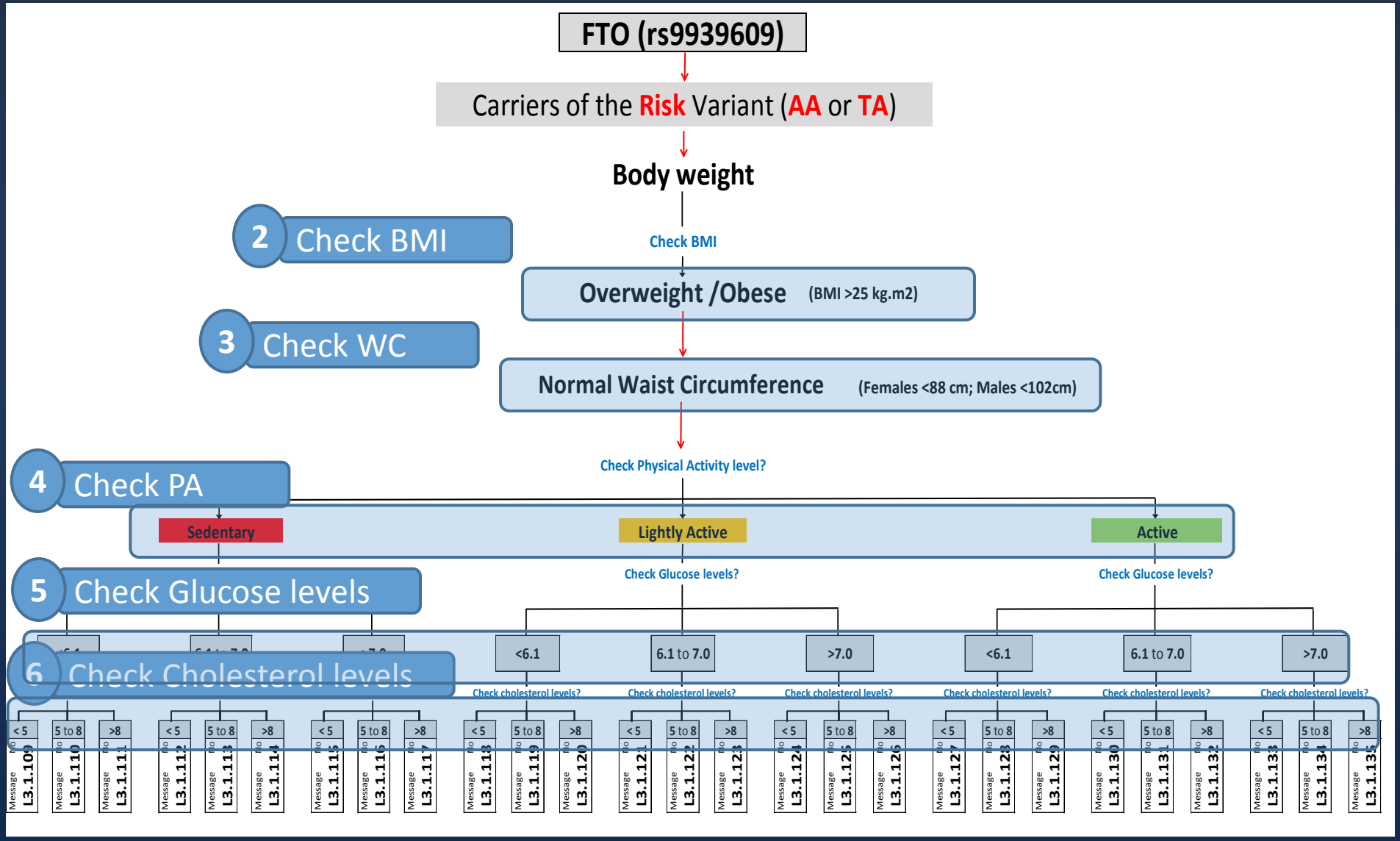


BODY WEIGHT: *FTO* SNP

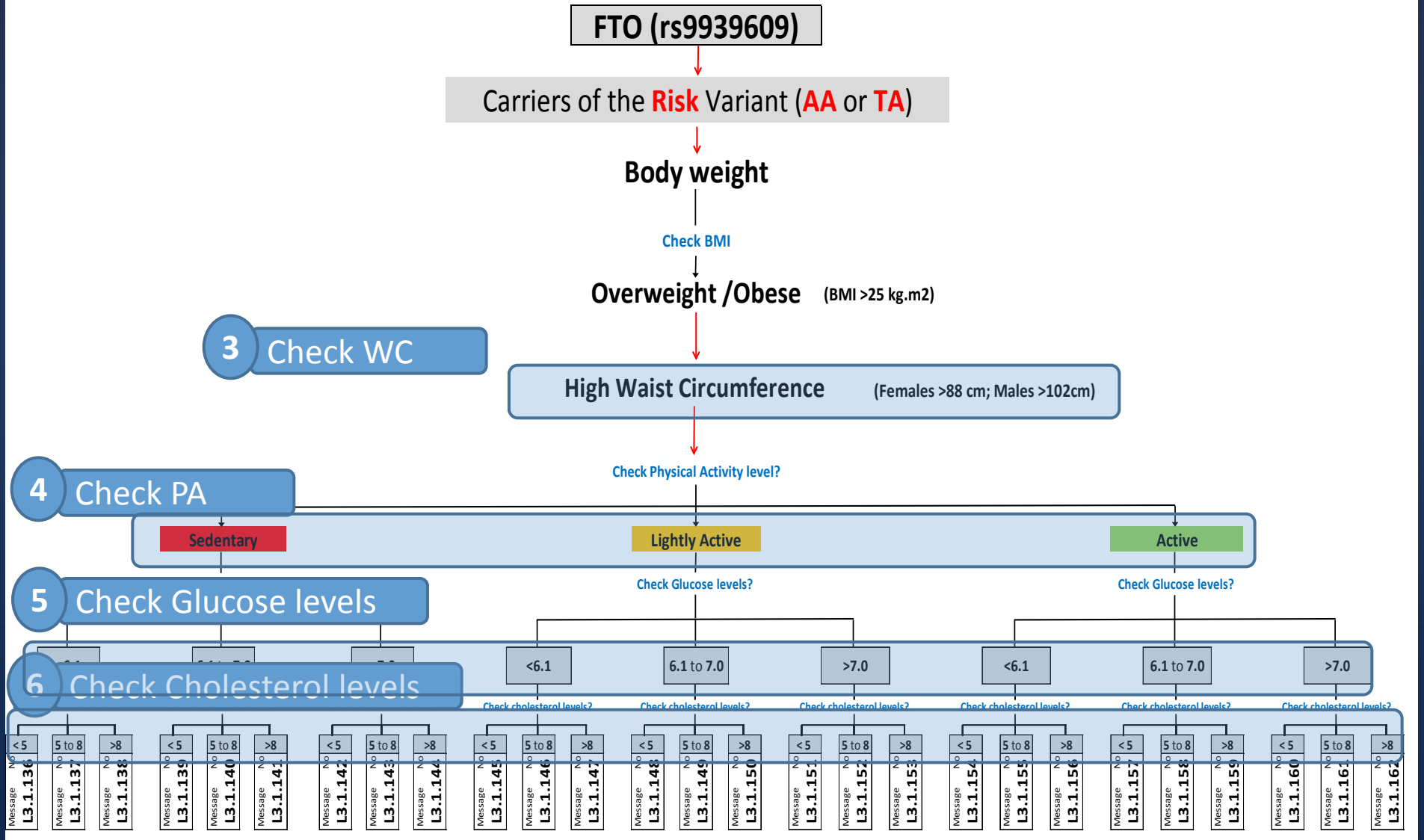
1 Check the presence of SNP



BODY WEIGHT: *FTO* SNP



BODY WEIGHT: *FTO* SNP



OPEN ACCESS Freely available online

PLOS | ONE

TFAP2B Influences the Effect of Dietary Fat on Weight Loss under Energy Restriction

Tanja Stocks[1,2*9], Lars Ängquist[1*9], Ka
Peter Arner[6], Jean-Michel Oppert[7], J. A
Dominique Langin[11], Stephan Rössner[
Andreas F. H. Pfeiffer[14,15], Marie Kunes
Oluf Pedersen[3,20,21], Arne Astrup[22], Th

Pathophysiology/Complications

BRIEF REPORT

Genetic Predictors of Weight Loss and
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RESEARCH Open Access

C677T gene polymorphism of *MTHFR* and metabolic syndrome: response to dietary intervention

COSTS!

Laura Di Renzo[1*], Luigi Tonino Marsella[2], Frances arlo[ ], Sold[ ], anto ratten[ ], ovi Abenavoli[6] and Antonino De Lorenzo[1,7,8]

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OPEN ACCESS Freely available online

PLoS one

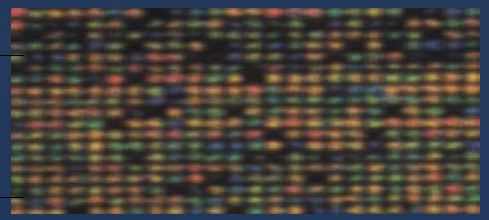
Ghrelin, Sleep Reduction and Evening Preference: Relationships to CLOCK 3111 T/C SNP and Weight Loss

Marta Garaulet[1*], Carmen Sánchez-Moreno[1], Caren E. Smith[2], Yu-Chi Lee[2], Francisco Nicolás[4], Jose M Ordovás[2,3]

TOOLS: 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

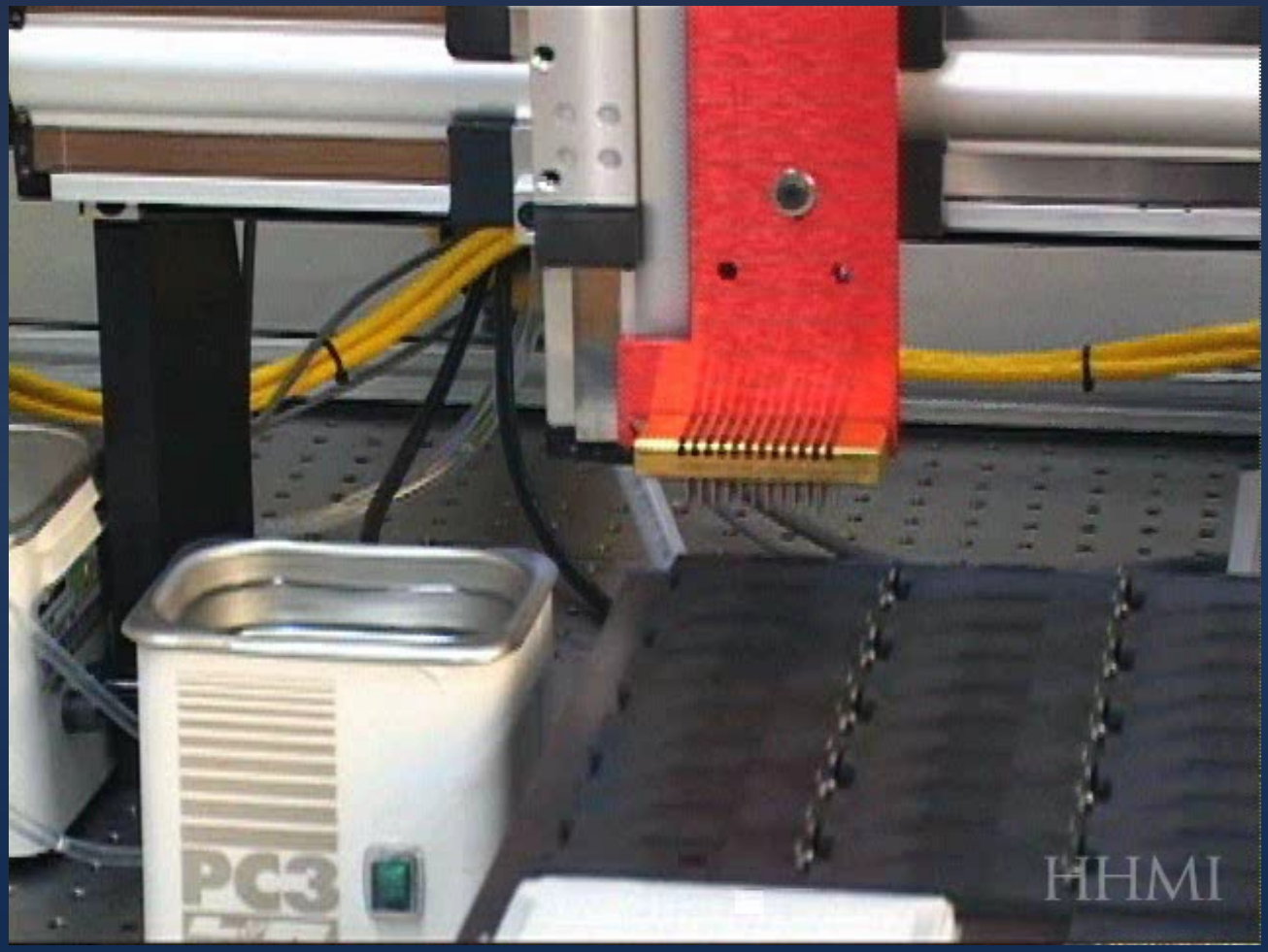
-117.5	S49491	**Proenkephalin**
~-92.3=	J04488	**Prostaglandin D synthetase**
~-47.3	D63772	**Neuronal high affinity glutamate transporter**
~-8.6=	M12450	**Vitamin D binding protein**
-4.1	U57715	**FGF receptor activating protein FRAG1**
-2.8	U48596	**MAP kinase kinase kinase 1 (MEKK1)**
-2.3	L06096	**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).

MICROARRAY/SEQUENCING



INTERPRETATION!

Leading Edge
Review

Cell

The Hunger Genes: Pathways to Obesity

Agatha A. van der Klaauw[1] and I. Sadaf Farooqi[1,*]
[1]University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Wellcome Trust-MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
*Correspondence: isf20@cam.ac.uk
http://dx.doi.org/10.1016/j.cell.2015.03.008

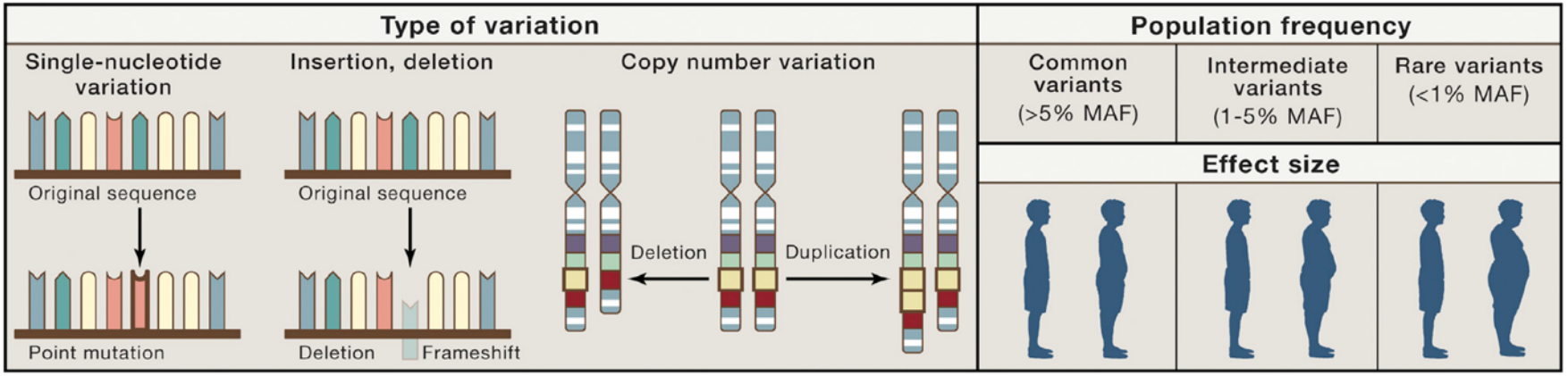
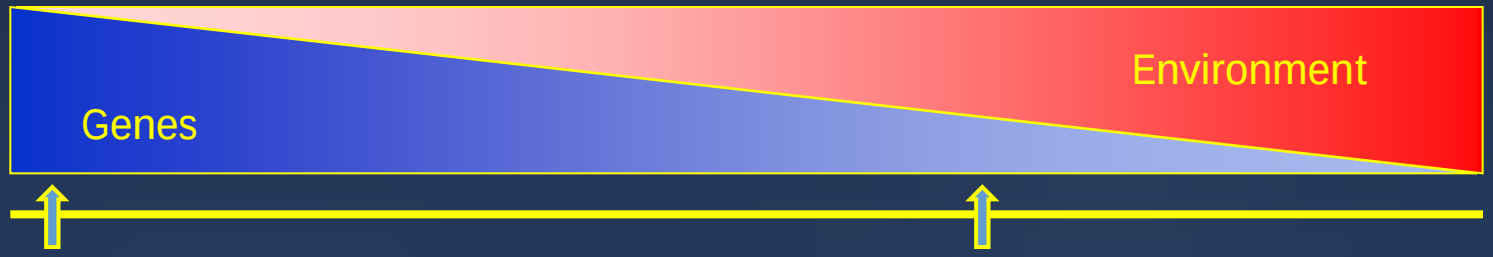


Figure 4. Types of Genetic Variation Contributing to Body Weight Regulation

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.

Genetics of Human Metabolism



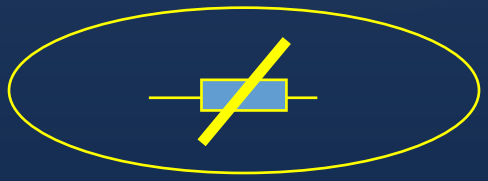
Monogenic

- Rare cases
- Syndromes

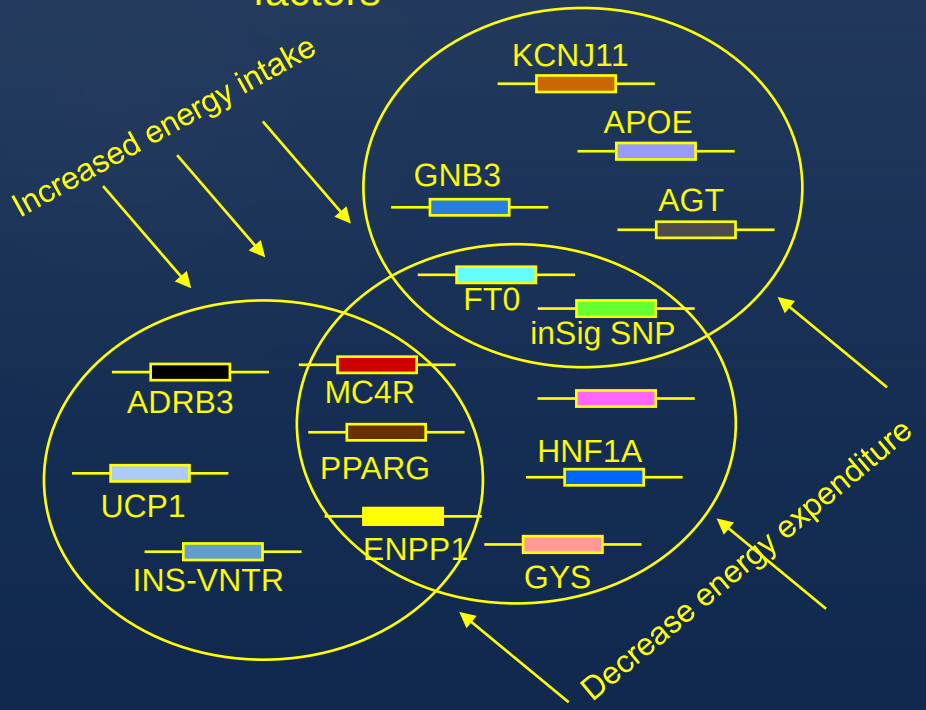
Polygenic

Individual combination in interaction with environmental factors

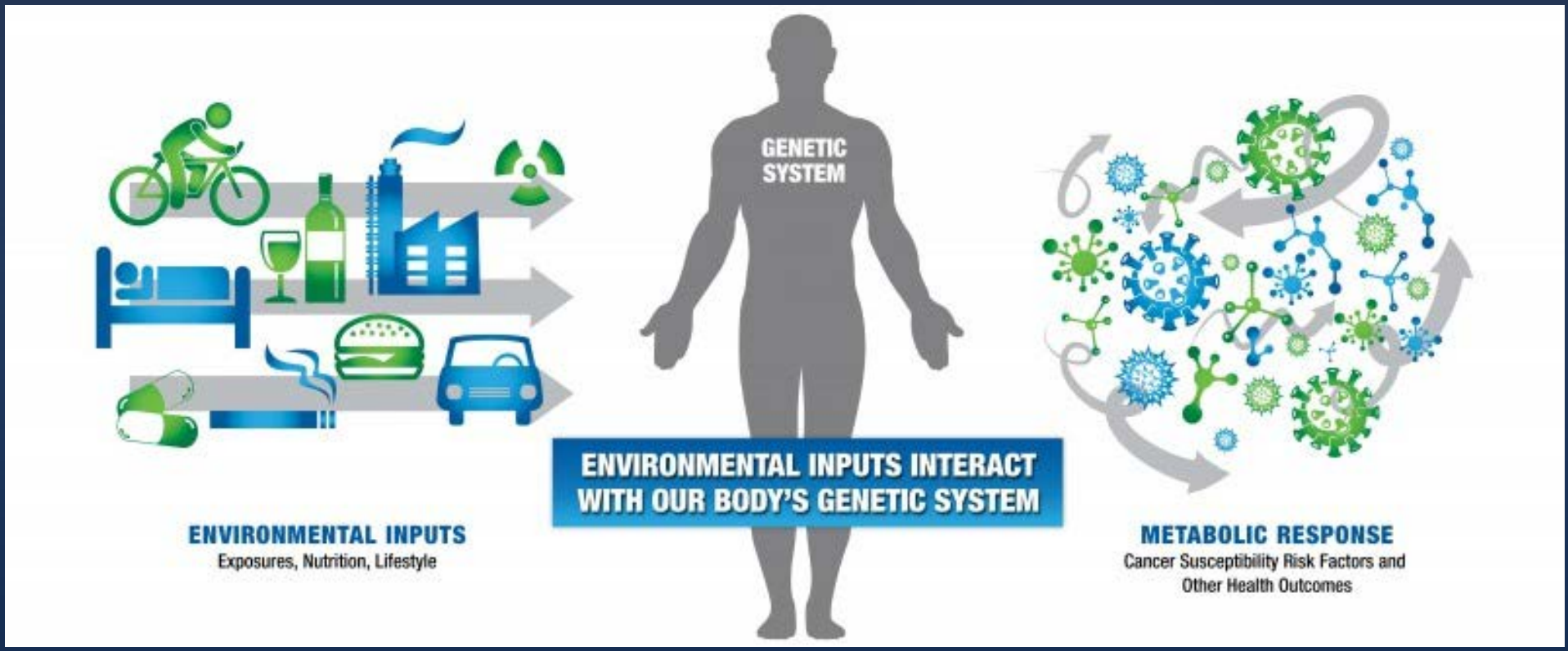
1 gene 1 disease



LEP, LEPR, POMC,PCSK1
SIM,,



GENE-ENVIRONMENTAL INPUTS INTERACTION



GENETIC TESTS

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)

GPS based on computing risk alleles

GENETIC TESTS

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**

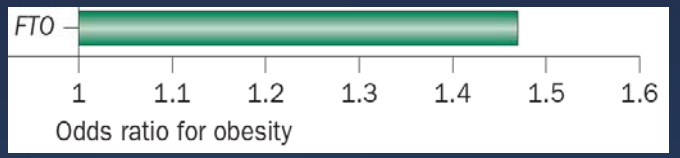
GENETIC TESTS
GENE-DIET INTERACTIONS

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.

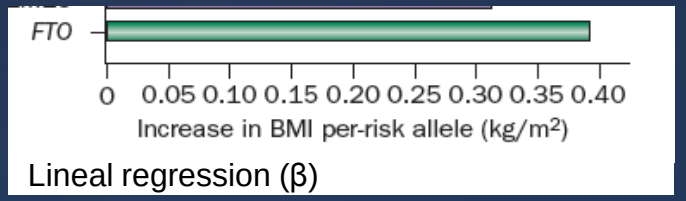
GENE CONTRIBUTION TO BODY WEIGHT MANAGEMENT

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

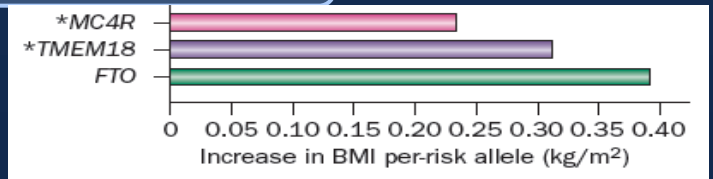
$Weighted\ GPS = (\beta_1 x OR_1 + \beta_2 x OR_2 + \ldots \beta_n x OR_n)$

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

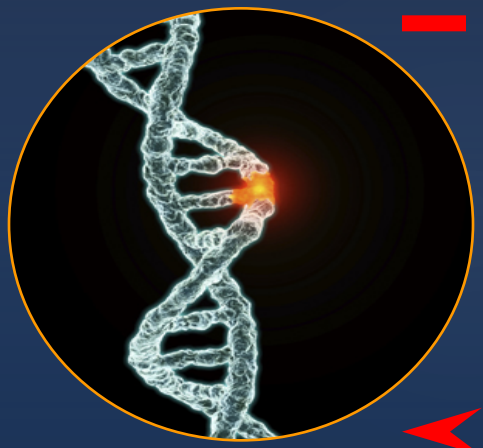
5. Propensity score matching ?



MOLECULAR NUTRITION

Nutrigenetic

Polimorphism



Genes

Nutrients

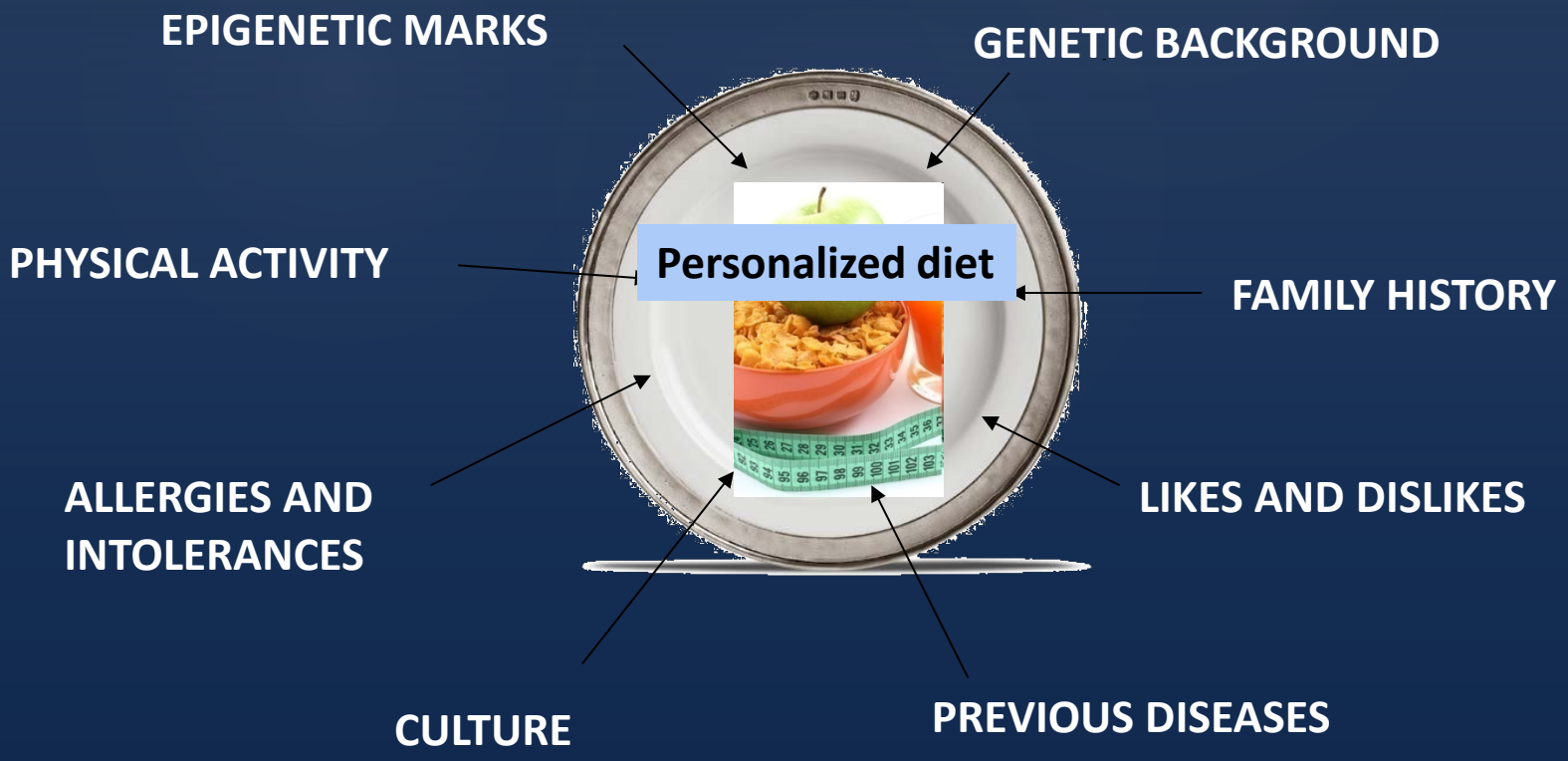
Nutrigenomic

Gene expression

PERSONALISED NUTRITION

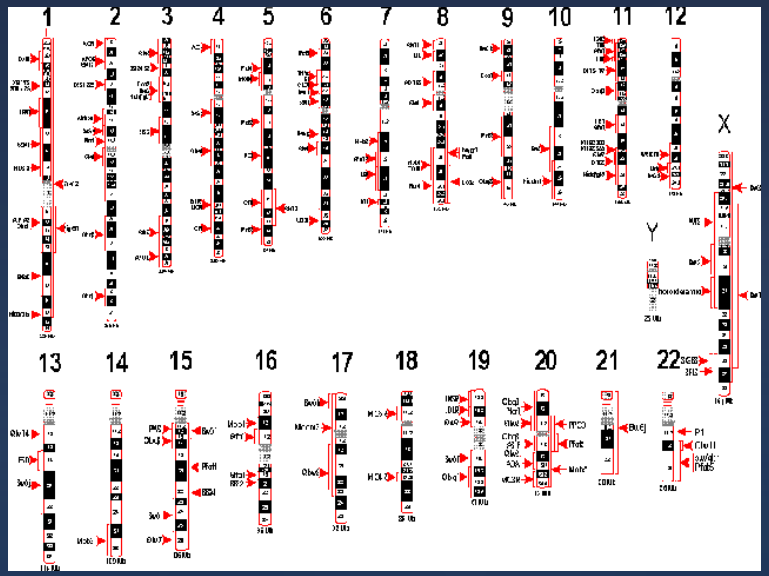
Personalized Nutrition

Rather than existing an 'optimal' diet, there is a range of adequate diets depending on genetic, biological and cultural variation.



Conclusions

GENOMA



Genome: **30.000 genes (more than 30% have polimorphisms)**

Gene expression = f (DNA ✕ nutrition, physical activity environment,…..)

Diagnosys:
- **Nutrient requirements**
- **Predisposition to nutrition related diseases**
- **Prescription of diets (Prophylaxis/therapy)**

Universidad de Navarra

ASOCIACIÓN DE AMIGOS

ciberobn

PERSONALIZED WEIGHT MANAGEMENT

INDIVIDUALIZED NUTRITION