The Power of Food Science and Technology and Nutrition for Sustainable Planet Health

OMICS Applications on Precision Nutrition in fighting the Obesity Pandemics

Prof J.Alfredo Martínez

16 November, 08:00 – 12:45 UTC
17 November, 15:00 – 18:15 UTC
Precision Medicine and Nutrition

Hypocrates (s V b.C) “YOUR food is basis of YOUR health”
Galeno (Pérgamo, s II) “Personal attitudes and unique response to food”
C. Bernard and others (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
Ley and others (2006): Individual’s microbiota related to diet and health
Precision Nutrition v.4.0 (s XXI): Integrated Metabolomics personalization
Gene Expression (Phenotype) = f (DNA & microbiota x environment)
Precision Nutrition and OMICS

DNA → Genes → mRNA → HS protein → Metabolites

Genome → Transcriptome → Proteome → Metabolome

Genomics → Transcriptomics → Proteomics → Metabolomics

Biochemical processes
Personalization: Nutrition & Genetic Interactions

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

Trp64Arg MUTATION OF THE $\beta_3$ ADRENOCEPTOR

CORBALAN, et al. 2000
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 Scherag¹,²,§, Christian Dina³, Anke Hinney², Vincent Vatin³, Susann Scherag², Carla I. G. Vogel²,

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

Stephen D. Turner¹, Richard L. Berg⁵, James G. Linneman¹, Peggy L. Peissig³, Dana C. Crawford¹, Joshua C. Denny², Dan M. Roden⁴, Catherine A. McCarty⁵, Marylyn D. Ritchie¹, Russell A. Wilke⁶,

Common variants at 30 loci contribute to polygenic dyslipidemia

Sekar Kathiresan¹,³,³, Cristen J Willer⁶,³, Gina M Peloso⁴,³, SerkaDemissie⁴,³,³, Kiran Masunuru²,³
EFFECT SIZES FOR GENETIC VARIANTS ASSOCIATED WITH BMI


*gene closest to the reported association

Frayling et al. (2007); Scuteri et al. (2007)
Willer et al. (2009); Thorleifsson et al. (2009)
Loos et al. (2008); Chambers et al. (2008)
Thorleifsson et al. (2009)
Speliotes et al. (2010)
Willer et al. (2009)
LAST: FTO, MC4R, TMEM, UCP, POMC, LEP, βAR, PPAR, AP2, TNF,.. (2021).
Dietary effects on gene expression

Nutrigenomics and Nutrigenetics

NUTRIGENOMICS

Dietary effects on gene expression

NUTRIGENETICS

Genotype influences the response related with nutrition and personalised metabolism
PRECISION NUTRITION: NUTRIGENOMIC INTERACTIONS

Nutrition → GENE Expression → Phenotype

% high-fat and low-fat levels for Leptin, HSL, UCP2, PGC-1, PAARγ2

Viguerie, et al. 2005
PRECISION NUTRITION: NUTRIGENETIC INTERACTIONS

Genotype

×

Nutrition

Gene Function

Phenotype

Nutrition Status

Corbalan, et al. 2002
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 © Springer-Verlag Berlin Heidelberg 2014

Abstract There is evidence that genetic risk score (GRS)-diet interaction may impact total energy intake on obesity. To further evaluate the impact of genetic risk score on dietary intake on obesity, we used a trigonometric regression model to assess body composition measures and physical activity. The results indicated that the combination of genetic risk score and dietary intake modifies the relationship between body composition measures and physical activity. The findings suggest that genetic risk score and diet may not only influence energy intake but also other health outcomes. The results of this study may guide the development of personalized nutrition interventions.
INTERACTION BETWEEN THE GENETIC RISK SCORE AND MACRONUTRIENT INTAKE

Adjusted for age, sex, physical activity and energy intake

Goni L et al. Genes Nutr, 2015
PRECISION NUTRITION: GENE-NUTRIENT INTERACTIONS

**Gene: MTHFR**
- SNP: rs1801133
- Intake of vitamin B6 and plasma homocysteine levels

**Gene: POMC**
- SNP: rs6713532
- Appetite and food choices

**Gene: IRS1**
- SNP: rs2943641
- Intake of carbohydrates and lipids influences insulin resistance and weight loss

**Gene: APOA5**
- SNP: rs3135506
- Vitamin D intake influences plasma HDL-cholesterol levels

**Gene: PPARg**
- SNP: rs1801282
- Intake of saturated and polyunsaturated fatty acids affects particle diameters of low-density lipoproteins

**Gene: ADRB2**
- SNP: rs1042713
- Energy restriction and impact on body weight

**Gene: MC4R**
- SNP: rs17782313
- Dietary fat and adiposity markers

**Gene: FTO**
- SNP: rs9939609
- High intake of saturated fatty acids and onset of obesity

PERSONALIZED APPROACHES AGAINST OBESITY

Nutritional and Diet Therapy
Drugs Treatments
Physical Activity Programmes
Bariatric Surgery
Others: Personalized.........

...........................................Nutrition
POLYMORPHISM IN THE APOLIPOPROTEIN A5 GENE

Aberle, et al. 2005

BMI (Kg/m\(^2\))

- TT allele carriers
- C allele carriers

Time (weeks)

- 0 weeks: 29.1
- 6 weeks: 28.1
- 12 weeks: 27.8

Aberle, et al. 2005
BODY WEIGHT REDUCTION AND GENETIC VARIANTS: IL-6 AND PPAR-Γ2

Goyenechea, et al. 2006
BODY WEIGHT: FTO SNP

FTO (rs9939609)

Carriers of the Risk Variant (AA or TA)

Body weight

Check BMI

Overweight /Obese (BMI >25 kg.m²)

Check BMI

Normal Waist Circumference (Females <88 cm; Males <102 cm)

Check Physical Activity level?

Check BMI

Check Glucose levels?

Check Cholesterol levels?

Check Activity level?

Check Glucose levels?

Check Cholesterol levels?

Check Activity level?

Check Glucose levels?

Check Cholesterol levels?
GENES WITH POLYMORPHISMS RELATED TO BODY WEIGHT LOSS

Cell and Nuclear Regulation
- FTO
- PPARG
- PPARGC1A
- TCF7L2
- TFAP2B
- ACE
- GNAS
- ACSL5
- CLOCK
- SIRT1
- SH2B1
- SCAP
- SDCCAG8
- TMEM18

Food Intake
- LEPR
- MC3R
- MC4R
- POMC
- HTR2C
- CNR1
- FAAH
- DRD2
- CB1

Intermediate Metabolism and Adipogenesis
- PLIN1
- FABP2
- PPARG
- APOA5
- APOE
- APOA1
- APOB
- APOA4
- GIPR
- IGF1R
- INSIG2
- IRS1
- IRS2

Cytokines / Adipokines
- IL6
- LEP
- ADIPOQ
- RETN

Thermogenic Processes
- ADRB2
- ADRB3
- UCP1
- UCP2
- UCP3

Weight loss in obese/overweight subjects by dietary approaches

Weight loss prediction based on Precision Nutrition

PARTICIPANT/USUARIO/PACIENT

- Sex
- Age
- Initial BW
- SNPs
- Energy (kcal)
- Physical activity (Mets)

Exchanges DIET 1

EQUATION

Exchanges DIET 2

Prescriptio
Person 1

Diet 1

Pérdida de peso con DIETA 1 = Edad + Peso inicial + rs2605100_LYPLAL1 + rs4929949_STK33 + rs3813929_HTR2C + rs1801133_MTHFR + rs659366_UCP2 + rs11030104_BDNF + INTrs180133xEdad

Diet 2

Pérdida de peso con DIETA 2 = Calorías consumidas + Peso inicial + Sexo + rs1800544_ADRA2A + rs3813929_HTR2C + rs1800592_UCP1 + rs662799_APOA5 + rs1042713_ADRB2 + rs10182181_RB1_ADCY3 + rs12502572_UCP1 + INTrs2502572xSexo + INTrs1042713xSexo

Person 2

Diet 1

Pérdida de peso con DIETA 1 = Edad + Peso inicial + rs2605100_LYPLAL1 + rs4929949_STK33 + rs3813929_HTR2C + rs1801133_MTHFR + rs659366_UCP2 + rs11030104_BDNF + INTrs180133xEdad

Diet 2

Pérdida de peso con DIETA 2 = Calorías consumidas + Peso inicial + Sexo + rs1800544_ADRA2A + rs3813929_HTR2C + rs1800592_UCP1 + rs662799_APOA5 + rs1042713_ADRB2 + rs10182181_RB1_ADCY3 + rs12502572_UCP1 + INTrs2502572xSexo + INTrs1042713xSexo
Precision Nutrition and OMICS

DNA → Genes → mRNA → HS protein → Metabolites

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Genomics → Transcriptomics → Proteomics → Metabolomics

Biochemical processes
Epigenetics literally means “in addition to changes in genetic sequence”.

**DNA Methylation and Histone modification**

- **DNA methylation**: Methyl marks added to certain DNA bases repress gene activity.
- **Histone modification**: A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.
PRECISION NUTRITION: Epigenetic Modifications

DNA Methylation

Histone Modifications

miRNA

Enzyme modulation

Chromatin Packaging Alterations

DNA Packaging around Nucleosomes
Epigenetic Biomarkers In Weight Loss

8 weeks of hypocaloric diet

Illumina Microarray

Milagro FI et al. FASEB J (2011)
Methylation changes induced by an energy restricted diet

**Microarray**

**Changes by the diet**

**Before vs. After diet**

- 70 CpG hypermethylation
- 100 CpG hypomethylation

(20 % variation  p < 0.05)

***

APOA5     PTEN          GNAS        H19           IL26

(% methylation)

Epigenetic Biomarkers In Weight Loss

Low vs. High responders before diet

(>20 % variation, p < 0.05)

602 CpG hypermethylation

432 CpG hypomethylation

IL10 AR GNAS SIRT1 CASP8

(% methylation)

High-Throughput Sequencing of microRNAs in Peripheral Blood Mononuclear Cells: Identification of Potential Weight Loss Biomarkers

Fermin I. Millagro¹, Jonatan Miranda², Maria P. Portillo², Alfredo Fernandez-Quintela², Javier Campión¹, J. Alfredo Martinez¹*

¹ Department of Nutrition, Food Sciences and Physiology, University of Navarra, Pamplona, Spain, ² Department of Nutrition and Food Sciences, University of the Basque Country UPV/EHU, Vitoria, Spain

Abstract

Introduction: MicroRNAs (miRNAs) are being increasingly studied in relation to energy metabolism and body composition homeostasis. Indeed, the quantitative analysis of miRNAs expression in different adiposity conditions may contribute to understand the intimate mechanisms participating in body weight control and to find new biomarkers with diagnostic or prognostic value in obesity management.

Objective: The aim of this study was the search for miRNAs in blood cells whose expression could be used as prognostic biomarkers of weight loss.

Methods: Ten Caucasian obese women were selected among the participants in a weight-loss trial that consisted in following an energy-restricted treatment. Weight loss was considered unsuccessful when <5% of initial body weight (non-responders) and successful when >5% (responders). At baseline, total miRNA isolated from peripheral blood mononuclear cells (PBMC) was sequenced with SOLID v4. The miRNA sequencing data were validated by RT-PCR.

Results: Differential baseline expression of several miRNAs was found between responders and non-responders. Two miRNAs were up-regulated in the non-responder group (miR-935 and miR-4772) and three others were down-regulated (miR-223, miR-224 and miR-376b). Both miR-935 and miR-4772 showed relevant associations with the magnitude of weight loss, although the expression of other transcripts (miR-874, miR-199b, miR-766, miR-589 and miR-148b) also correlated with weight loss.

Conclusions: This research addresses the use of high-throughput sequencing technologies in the search for miRNA expression biomarkers in obesity, by determining the miRNA transcriptome of PBMC. Basal expression of different miRNAs, particularly miR-935 and miR-4772, could be prognostic biomarkers and may forecast the response to a hypocaloric diet.
High-Throughput Sequencing of microRNAs in Peripheral Blood Mononuclear Cells: Identification of Potential Weight Loss Biomarkers

Figure 1. miRNAs differentially expressed between responders and non-responders at baseline (adjusted P-value < 0.1). The data correspond to the mean of the transcripts sequenced in each group ± SEM. doi:10.1371/journal.pone.0054319.g001
Precision Nutrition and OMICS

DNA → Genes → mRNA → HS protein → Metabolites

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Genomics → Transcriptomics → Proteomics → Metabolomics

Biochemical processes
Urinary metabolomic profile following the intake of meals supplemented with cocoa extract in middle-aged obese subjects

Ibero-Baraibar I ¹,², Romo-Hualde A ², Gonzalez-Navarro CJ ², Zulet MA ¹,²,³,⁴, Martinez JA ¹,²,³,⁴

¹ Department of Nutrition, Food Science and Physiology, University of Navarra, Pamplona, Spain
² Centre for Nutrition Research. Faculty of Pharmacy. University of Navarra, Pamplona, Spain
³ Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain
⁴ Physiopathology of Obesity and Nutrition, CIBERobn. Carlos III Health Research Institute, Madrid, Spain
Laboratory procedures

**Preparation of urine samples**

- **HPLC-TOF**
- **Data acquisition**
- **Feature selection and identification**

**Pathway analysis**

Gika *et al.*, 2007; Llorach *et al.*, 2010

**Procedure**

**Metabolite selection**

- **Urine metabolite profile**
  - 1095 features ESI+
  - 1154 features ESI-
  - Metabolites different among the 3 groups (p<0.01)
  - 26 putative metabolites
  - 20 putative metabolites
  - Metabolites with p<0.001 between control and cocoa
  - 3 putative metabolites
  - 5 putative metabolites

Ibero-Baraibar I *et al.*, Food & Function (2016)
Principal component analysis

Ibero-Baraibar I et al., in Food & Function (2016)
Positive association between HVA and BDI (depression)

Cocoa:
\[ \beta = -0.39 \]
\[ p = 0.029 \]
\[ R^2 = 0.39 \]

Abbreviations: BDI, Beck depression inventory; HVA, homovanillic acid
Gut microbiota “new organ” within our organism

- 10^{11} - 10^{12} cells/mL in colon
- ≥ 150 times more genes than the human genome

- Classified from phylum to species levels
- Regulates key “host” functions
  - Immunity
  - Nutrient production/availability
  - Energy harvesting

Recent attention

FIRMICUTES (60-80%)
BACTEROIDETES (20-40%)

Bäckhed et al., 2005
**Metabolic functions**
- Production of vitamins
- Antimicrobial secretion
- Fermentation of non-digestible polysaccharides
  - Production of SCFAs
  - Energy source and energy harvest
- Epithelial cell growth and differentiation regulation
- Intestinal villi and crypts development
- TJPs and mucus layer properties regulation
- Colonization resistance

**Structural & protective functions**

**Immune functions**
- Innate and adaptive immunity activation
  - Inflammatory cytokine regulation
- Immune system development
  - B- and T-cell development

Gut microbiota exerts important functions for health.

Villanueva-Millan et al., 2015; Prakash et al., 2011
OBESITY & GUT MICROBIOTA

HEALTH

- Diverse and abundant microbiota
- *Firmicutes, Bacteroidetes* and *Actinobacteria* dominant
- Healthy levels of SCFA production
- Intact mucosal barrier
- No overt inflammation

DISBIOSYS
(Bacterial imbalance in the gut)

- Diversity reduced
- Elevated *Enterobacteriaceae*/opportunistic pathogens
- Skewed SCFA profile
- Disruption of mucosal barrier
- Host response inflammatory response initiated

Adapted from A.W. Walker et al., 2012
Phylogenetic diversity curves for microbiota of lean vs obese individuals
Turnbaugh et al., 2009 (Nature)

Cecal microbiota in lean vs obese mice
Ley et al., 2005 (PNAS)
Low-grade systemic inflammation

**Changes in Intestinal Microbiota**

Overweight adolescents (13-15 years)

**Connection**

Santacruz et al., 2009

**Correlation of different bacterial groups with weight loss (kg)**

n=36
10 weeks

Increased **Bacteroides fragilis**
Decreased **Clostridium coccoides**

Low weight-loss group (˃2 Kg)
High weight-loss group (˃4 kg)

No significant differences

Increased **B. fragilis** & **Lactobacillus**
Decreased **C. coccoides**

Correlation of different bacterial groups with weight loss (kg)

Santacruz et al., 2009

**OBESITY & GUT MICROBIOTA**
NUTRIOMICS
GENE-ENVIRONMENTAL INPUTS, METABOLOMOMIC and MICROBIOTA INTERACTIONS
Nutrition and Health

When I recommended you give him a more varied diet, I didn’t just mean all 12 varieties of FatSnax crispy treats.

“This looks good. It’s a six-hour special on how society is becoming too sedentary.”

© Original Artist
But genetics/epigenetics is only the tip of the iceberg
If they ask you anything you don’t know, just just say it’s due to epigenetics.
Dietary, Phenotypical and Metabolomic Data

Courtesy Prof Hannelore Daniel TUM
PRECISION NUTRITION: Manipulation of the gut microbiota

Diet (Polyphenols)

ANTIMICROBIALS

PREBIOTICS, PROBIOTICS & SYMBIOTICS

FAECAL MICROBIOTA TRANSPLANT

Scott et al., 2015; Aguirre et al., 2015
Personalization for weight management
Rather than existing an ‘optimal’ diet, there is a range of adequate diets depending on genetic, biological and cultural variation.

Precise Nutrition based on Omics

- **OMICS & EPIGENETIC MARKS**
- **GENETIC BACKGROUND**
- **PHYSICAL ACTIVITY**
- **ALLERGIES AND INTOLERANCES**
- **CULTURE**
- **LIKES AND DISLIKES**
- **FAMILY HISTORY**
- **PREVIOUS DISEASES**

**Personalized diet**
IUNS-ICN
NOW DECEMBER 2022 !!!
Personalization for weight management

Diet
- Supplements
- Omega 3
- Folate
- Fruit & Veg
- Fat

Genes
- FTO
- ApoE
- MTHFR

Phenotype
- Weight
- Physical Activity
- Cholesterol
- Glucose
- Carotenoids
Acknowledgments

Universidad de Navarra

ASOCIACIÓN DE AMIGOS

CENTRO DE INVESTIGACIÓN EN NUTRICIÓN

ciberobn
Algoritmo de decisión en función de pérdida de peso

PARTICIPANTE/USUARIO/PACIENTE

Sexo, Edad, Peso inicial, SNPs, Energía (kcal), Ejercicio físico (Mets)

Intercambios de DIETA 1
Pérdida de peso > 1 kg en dieta 1 con respecto a dieta 2

Calculo de pérdida de peso con ECUACIÓN para dieta 1 y con dieta 2

Intercambios de DIETA 2
Pérdida de peso > 1 kg en dieta 2 con respecto a dieta 1

Diferencias entre dietas menores de 1Kg

Elección de dieta según preferencias individuales (intercambios de dieta 1 o 2)
**Etapas de toda de decisión**

1. **Participante**
2. **Test genético**
3. **Predicción pérdida de peso**
4. **Comparación resultados**
5. **Prescripción dietética**

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**Individuo 1**

Pérdida de peso con DIETA 1 = Edad + Peso inicial + rs2605100_LYPLAL1 + rs4929949_STK33 + rs3813929_HTR2C + rs1801133_MTHFR + rs659366_UCP2 + rs11030104_BDNF + INTrs180133xEdad

Pérdida de peso con DIETA 2 = Calorías consumidas + Peso inicial + Sexo + rs1800544_ADRA2A + rs3813929_HTR2C + rs1800592_UCP1 + rs662799_APOA5 + rs1042713_ADRB2 + rs10182181_RB1_ADCY3 + rs12502572_UCP1 + INTrs2502572xSexo + INTrs1042713xSexo

**Individuo 2**

Pérdida de peso con DIETA 1 = Edad + Peso inicial + rs2605100_LYPLAL1 + rs4929949_STK33 + rs3813929_HTR2C + rs1801133_MTHFR + rs659366_UCP2 + rs11030104_BDNF + INTrs180133xEdad

Pérdida de peso con DIETA 2 = Calorías consumidas + Peso inicial + Sexo + rs1800544_ADRA2A + rs3813929_HTR2C + rs1800592_UCP1 + rs662799_APOA5 + rs1042713_ADRB2 + rs10182181_RB1_ADCY3 + rs12502572_UCP1 + INTrs2502572xSexo + INTrs1042713xSexo

**Diagrama**

- **Test genético**
- **Predicción pérdida de peso**
- **Comparación resultados**
- **Prescripción dietética**

---

**Grafico**

<table>
<thead>
<tr>
<th>Dieta 1</th>
<th>Dieta 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pérdida</td>
<td>-3.50</td>
</tr>
<tr>
<td>Dieta 1</td>
<td>-12.61</td>
</tr>
<tr>
<td>Pérdida</td>
<td>-3.63</td>
</tr>
<tr>
<td>Dieta 2</td>
<td>-13.50</td>
</tr>
</tbody>
</table>

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**Prescripción dietética**
TNF-α Promoter Methylation as a Predictive Biomarker for Weight-loss Response

Javier Campión, Fermin I. Milagro, Estibaliz Goyenechea and J. Alfredo Martínez

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine which is commonly elevated in obese subjects and whose promoter is susceptible to be regulated by cytosine methylation. The aim of this research was to analyze whether epigenetic regulation of human TNF-α promoter by cytosine methylation could be involved in the predisposition to lose body weight after following a balanced hypocaloric diet. Twenty-four patients (12 women/12 men) with excessive body weight-for-height (BMI: 30.5 ± 0.32 kg/m²; age: 34 ± 4 years old) followed an 8-week energy-restricted diet. Blood mononuclear cell DNA, isolated before the nutritional intervention, was treated with bisulfite and a region of TNF-α gene promoter (from −360 to +50 bp) was sequenced. Obese men with successful weight loss (25% of initial body weight) showed lower levels of total TNF-α promoter methylation \( (r = 0.74; P = 0.021) \), especially in the positions −170 bp \( (r = 0.75, P = 0.005) \) and −120 bp \( (r = 0.70, P = 0.011) \). Baseline TNF-α circulating levels were positively associated with total promoter methylation \( (r = 0.84, P = 0.005) \) and methylation at position −245 bp \( (r = 0.75, P = 0.020) \). TNF-α promoter methylation could be a good inflammation marker predicting the hypocaloric diet-induced weight-loss, and constitutes a first step toward personalized nutrition based on epigenetic criteria.