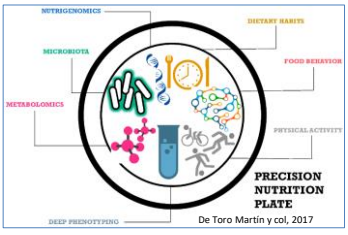
Alimentación del futuro. **Nutrición personalizada**.
Nutrigenómica, nutrigenética y epigenética

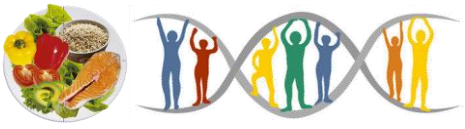
Nutrición de precisión



De Toro Martín y col, 2017

Del *Prêt-à-porter* al traje a medida;
O cuando los genes deciden lo que hay que comer

Precision Nutrition
Precision Medicine
Precision Health



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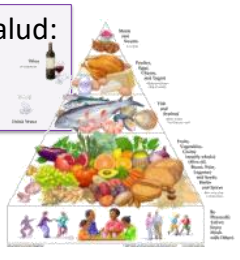
Objetivo final de la Investigación Nutricional:

Mejorar la calidad de vida, minimizando morbilidad y maximizando longevidad

Pautas y normas para garantizar un óptimo estado de salud:
- IDR, Objetivos Nutricionales, Guías Alimentarias

Programas y políticas alimentarias y nutricionales



Prevención

Falta de intervenciones efectivas en enfermedad crónica

Nutrición personalizada

Dieta-salud: La transición nutricional

Inicios empíricos

Sobrevivir → Satisfacer hambre/sed → Disfrute y satisfacción → Prevenir la enfermedad crónica → Siglo XXI: Máxima calidad de vida y longevidad

Modificado de Verschuren, 2001

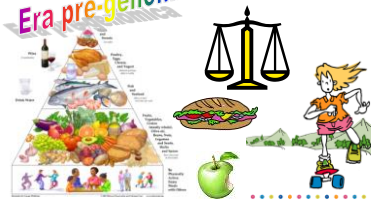
Dieta equilibrada y suficiente
Energía y 50 nutrientes (N)
[IDR] (Erradicación de la enfermedad deficitaria)

Dieta mediterránea

Dieta prudente y palatable
***"Dieta total"**: [ON-GABA]*
(N + nuevas funciones + no N)
+ actividad física

Nutrición óptima
Concepción holística
Modelo dietético +
estilo de vida + genética
Dieta personalizada
Nutrición de precisión

Era pre-genómica



Era post-genómica

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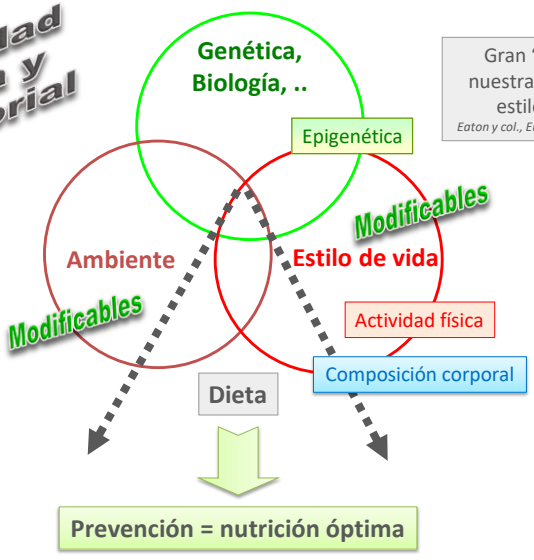
Enfermedades crónicas (ECV, cáncer, diabetes, obesidad, ..)

Enfermedad Compleja y Multifactorial

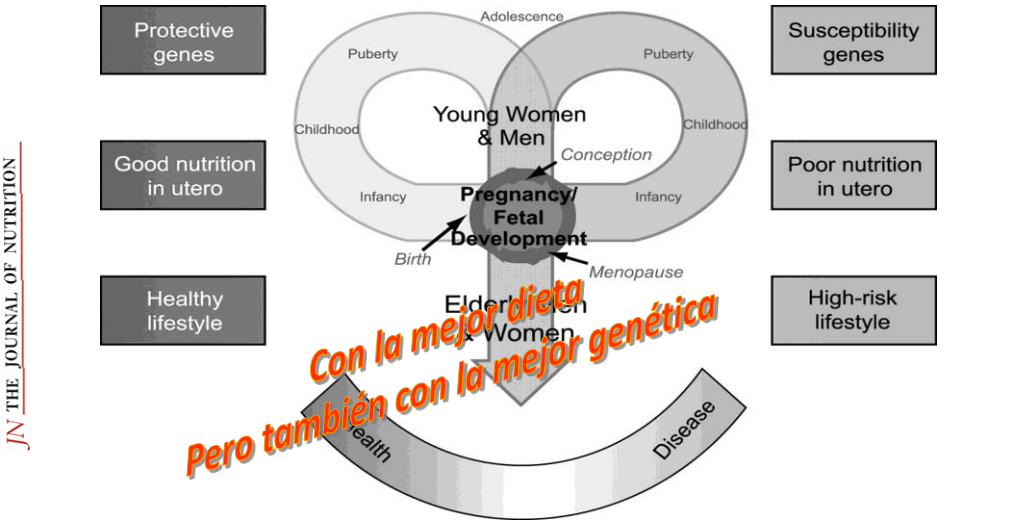


Gran "desajuste" entre nuestra genética y nuestro estilo de vida (S XXI)
Eaton y col., Eur J Clin Nutr (1997) 51, 207±216

Ángeles Carbajal Azcona. Dpto de Nutrición y Ciencia de los Alimentos. Fac. Farmacia. Universidad Complutense de Madrid. https://www.ucm.es/nutricioncarbajal

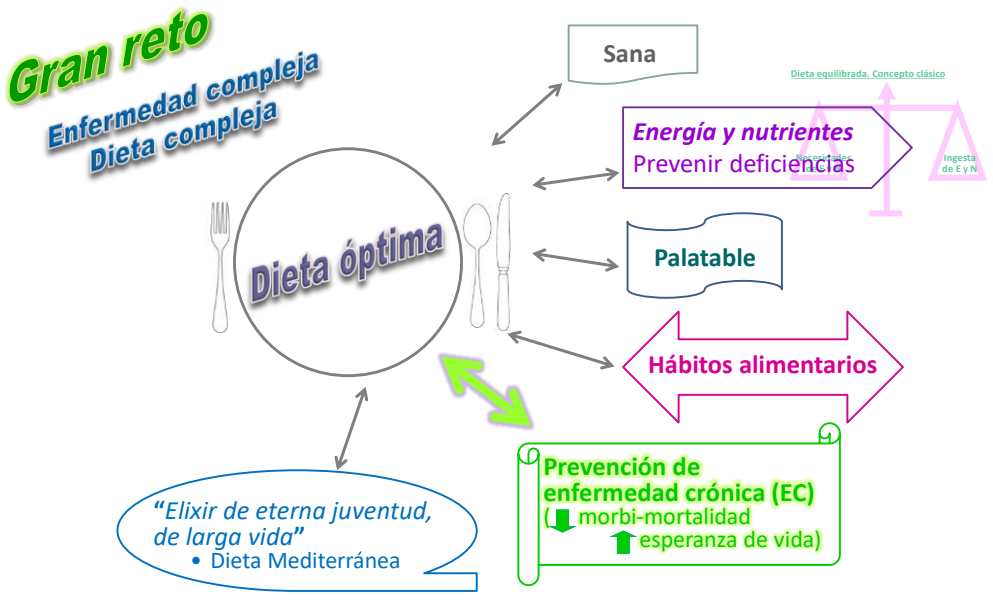
La prevención es posible

Development of dietary guidelines at various stages of individual life cycle from conception, infancy, adolescence to aging, related to individual genotype and phenotype in health promotion and disease prevention.



JN THE JOURNAL OF NUTRITION

Go V L W et al. J. Nutr. 2005;135:3016S-3020S



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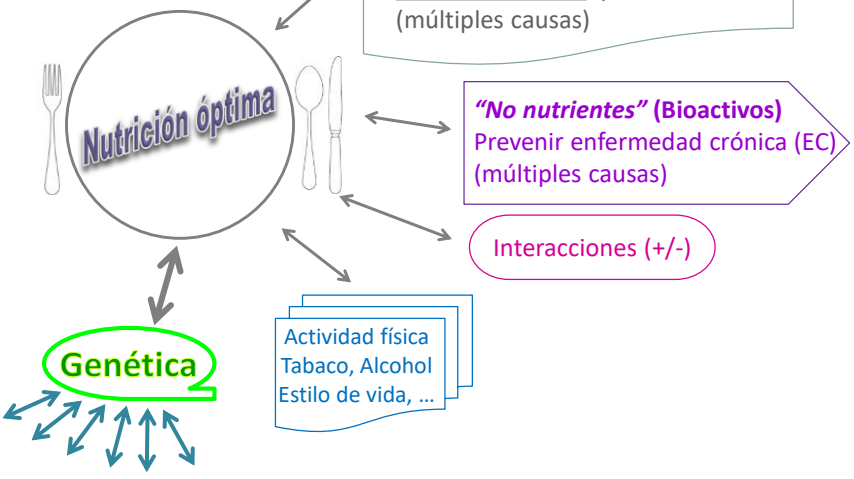
Concepto de dieta total



Era post-genómica
Nutrición personalizada

Nutrición de precisión

D. Corella, J. Ordovás, A. Martínez, M. Garaulet

Prevenir la enfermedad crónica:
⇩ morbi-mortalidad
⇧ esperanza de vida

The **Human Genome Project (HGP)** [1990 →2003; HapMap: 2005]
One of the sciences strongly influenced by this project was **nutrition**, through the consolidation of **nutritional genomics**.

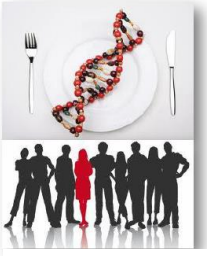
International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. Nature. 2004;431(7011):931–45.
En: Cominetti et al. Nutrire (2017) 42:10 - https://nutrirejournal.biomedcentral.com/articles/10.1186/s41110-017-0033-2
https://www.ucm.es/innovadieta/n

Human Nutrition — University of Reading

Personalised Nutrition

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

2000



Rosalind Fallaize - Food Matters Live 2014

https://pdfs.semanticscholar.org/presentation/fa13/8df514834bacb0eab8b40581fc380bd5e101.pdf
https://www.genome.gov/10001772/all-about-the--human-genome-project-hgp/
http://edit.um.es/campusdigital/santiago-grisolia-el-bioquimico-que-dirigio-el-proyecto-genoma-humano-de-la-unesco-2/
http://bioinformatica.uab.es/base/base3.asp?sitio=ensayosgenetica&anar=pgh&item=

Rather than there being an 'optimal' human diet, there are a range of adequate diets which depend upon individual biological and cultural variation:

Nutrición personalizada, basada en:

- ✓Secuenciación genoma humano
- ✓Análisis de variabilidad genética
- ✓Estudios de asociación entre variantes genéticas y marcadores de enfermedad
- ✓Impacto de nutrientes sobre la expresión génica

http://www.portalfarma.com/jornadas-congresos/ii-jornada-profesional-alimentacion/Documents/Alfredo-Martinez.pdf

Nutrición personalizada:
Desarrollar pautas nutricionales específicas para cada individuo según su **genética**.

The **hypolactasia** diagnosis, the **celiac disease** ruling out or the **phenylketonuria** screening, have allowed the implementation of tailored nutritional advices based on genetic makeup for years, i.e., avoiding lactose-, gluten- and phenylalanine-containing products to at-risk individuals.

De las ingestas recomendadas a la nutrición personalizada
http://www.ucm.es/data/cont/docs/458-2017-11-17-carbajal-IR-Nutr-personalizada-GENUTREN-26-Abril-2012.pdf

Nutrición de precisión

Desarrollar pautas efectivas basadas en la combinación de factores genéticos y epigenéticos, perfil metabólico, hábitos alimentarios, microbiota, actividad física, ambiente, estilo de vida, … teniendo en cuenta que todos ellos pueden cambiar a lo largo del tiempo.
Lo que hacemos y dónde estamos puede ser más importante que lo que somos.

Actualmente no existe una base racional para una nutrición verdaderamente personalizada para la mayoría de las personas, basada en las diferencias interindividuales.

Por el contrario, la **nutrición de precisión** basada en el "estilo de vida" ambiental y / o de comportamiento de cada persona puede proporcionar una base más sólida para ajustar la dieta de forma dinámica, adaptándola a las diferentes demandas y requisitos fisiológicos a lo largo del tiempo.

Betts y González, 2016
https://onlinelibrary.wiley.com/doi/pdf/10.1111/nbu.12238
De Toro Martín y col, 2017
http://www.mdpi.com/2072-6643/9/8/913/htm

Limitaciones actuales:
- Falta de resultados robustos y reproducibles,
- Alto coste de tecnologías ómicas y aspectos metodológicos en el diseño,
- Análisis e interpretación de datos (Big-data)

Nutrición de precisión

The Road to Tailored Dietary Advices

One of the ultimate goals of the promising field of **precision nutrition** is the design of tailored nutritional recommendations to treat or prevent metabolic disorders. More specifically, precision nutrition pursuits to develop more comprehensive and dynamic nutritional recommendations based on shifting, interacting parameters in a person's internal and external environment throughout life. To that end, **precision nutrition** approaches include, in addition to genetics, other factors such as dietary habits, food behavior, physical activity, the microbiota and the metabolome. Following the completion of the mapping of the Human Genome, a cumulative number of association studies have been performed in order to identify the genetic factors that may explain the inter-individual variability of the metabolic response to specific diets. In this sense, while numerous genes and polymorphisms have been already identified as relevant factors in this heterogeneous response to nutrient intake, clinical evidence supporting these statistical relationships is currently too weak to establish a comprehensive framework for personalized nutritional interventions in most cases. Thus, although most of findings on this topic are still relatively far from giving their fully expected potential in terms of translation and application of this knowledge to precision nutrition, some of them have been successfully developed in both the public and the private sectors. On one hand, the hypolactasia diagnosis, the celiac disease ruling out or the phenylketonuria screening, have allowed the implementation of tailored nutritional advices based on genetic makeup for years, i.e., avoiding lactose-, gluten- and phenylalanine-containing products to at-risk individuals. On the private sector, many companies are already offering genetic tests to customize diets based on the individual response to specific nutrients. For instance, that is the case of genetic tests based on the specific metabolism of caffeine (slow or fast metabolizers), the predisposition to weight gain by saturated fat intake, or the increased risk of developing hypertension by high salt intake, among others. Together, these nutritional recommendations solely based on genetic background represents a straightforward approach to the concept of personalized nutrition. Although quite similar to the concept of precision nutrition, and sometimes interchangeable, the latter makes reference to a conceptual framework covering a wider set of individual features allowing an effective and dynamic nutritional approach. Thus, while personalized nutrition based on genes is already being implemented successfully based on numerous research studies, such as the ones above mentioned, precision nutrition may still lack sufficient evidence for full implementation given its complexity, as will be reviewed below.

http://www.mdpi.com/2072-6643/9/8/913/htm

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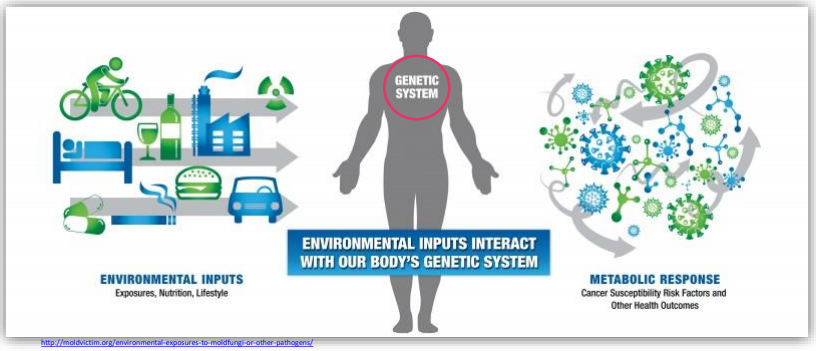
Nutrición de precisión

Interacción Gen – Ambiente



http://moldvictim.org/environmental-exposures-to-moldfungi-or-other-pathogens/

La nutrición personalizada, entendida como la adecuación del consejo nutricional a las necesidades específicas del individuo, incluyendo las interacciones nutrigenéticas y nutrigenómicas, ha marcado la investigación en nutrición del Siglo XXI. El concepto de "Nutrición de Precisión", de gran importancia en investigación y en el ámbito clínico, considera que la prevención o el tratamiento de enfermedades metabólicas debe abordarse de un modo integral, teniendo en cuenta al individuo y a su entorno, y no sólo a nivel fenotípico o molecular, sino también a nivel subjetivo, emocional y conductual. Proyecto Europeo Food4Me.

S Navas-Carretero, Director de la Línea de Investigación de Nutrición Personalizada, Centro de Investigación en Nutrición. Universidad de Navarra
http://www.sennutricion.org/es/2017/12/28/nutricin-de-precisin-la-personalizacin-integral-de-la-dieta-como-medio-de-prevencin-de-enfermedades

Ángeles Carbajal Azcona. Dpto de Nutrición y Ciencia de los Alimentos. Fac. Farmacia. Universidad Complutense de Madrid. https://www.ucm.es/nutricioncarbajal

Precision Nutrition and Type 2 Diabetes Management: Is It Ready for Prime Time?

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

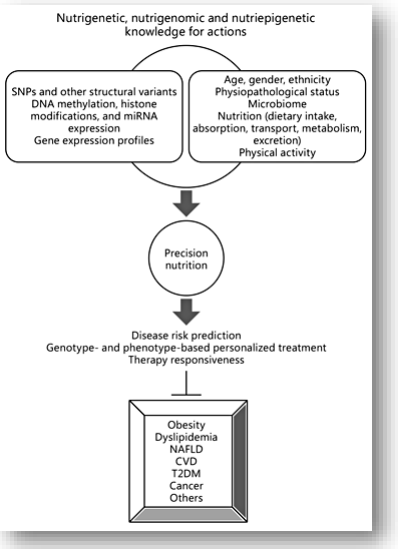
When it comes to the prevention and management of type 2 diabetes, a combination of regular exercise, maintaining a healthy body weight, and following evidenced-based dietary recommendations remains sound guidance for the general population. However, in combination with recent technological advances, the e
offers a novel approach to tailor prevention and treatm
characteristics—such as genetic background or gut mi
applying precision nutrition effectively in our clinical a
disease affecting nearly 425 million adults worldwide?

What is precision nutrition?

Precision nutrition, or personalized nutrition is a method of tailoring nutrition recommendations based on a person's DNA, unique microbiome, health history, various environmental exposures such as diet or lifestyle habits, and an emerging area of research called metabolomics. (Metabolomics studies metabolites, or small molecules that are created from reactions in cells, such as the digestion of food. All of the metabolites in a person's body produce their "metabolome," which can potentially reveal dietary patterns.)

https://www.hsph.harvard.edu/nutritionsource/2018/02/09/precision-nutrition-type-2-diabetes-management-is-it-ready-for-prime-time/
https://www.hsph.harvard.edu/news/features/precision-nutrition-hype-or-hope/

Nutrigenetic, nutrigenomic, and nutriepigenetic approaches for precision nutrition to the prevention and management of obesity and associated chronic diseases.

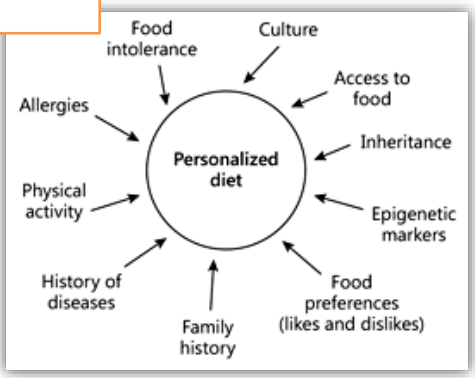


Ramos-López y col., Guide for Current Nutrigenetic, Nutrigenomic, and Nutriepigenetic Approaches for Precision Nutrition Involving the Prevention and Management of Chronic Diseases Associated with Obesity. J Nutrigenet Nutrigenomics 2017;10:43-62 - https://www.karger.com/Article/FullText/477729

Precision Nutrition. The interplay between genetic background, biological, cultural and environmental variations on personalized nutrition.

The response of an individual to nutrient intake results from the interaction of metabolic, environmental, social and genetic factors (fig). Analysis of an individual's genome can distinguish responders from nonresponders to dietary interventions and treatments. Personalized nutrition depends on the genetic background plus biological and cultural variations, including food intolerances, preferences and allergies, where knowledge and integration will allow precision nutrition.

The traditional concept of personalized nutrition is to adapt the diet according to individual needs and preferences. With the evolution of high-throughput technologies, precision nutrition can finally contribute to the reduction and prevention of disease by using genetic information to predict whether someone is going to respond to specific nutritional patterns or not. Personalized nutrition is based on the principle that particular foods or nutrient quantities may alter disease risk more or less, depending on the individual's DNA sequence.

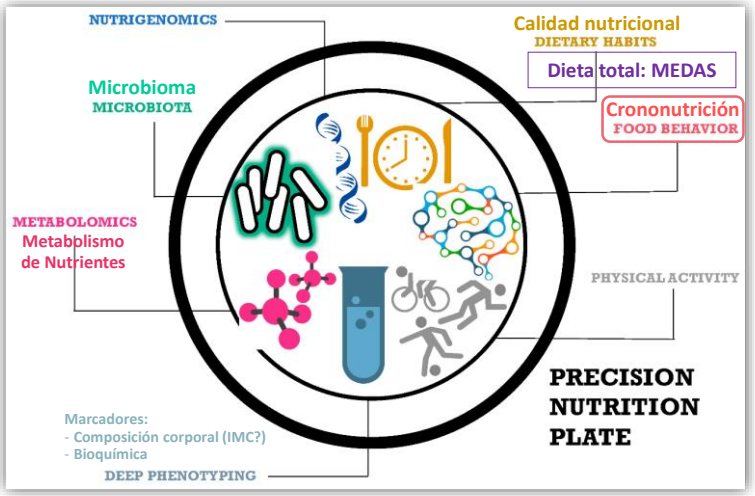


Precision nutrition can be considered as occurring at three levels: (1) conventional nutrition based on general guidelines for population groups by age, gender and social determinants; (2) individualized nutrition that adds phenotypic information about the person's current nutritional status (e.g. anthropometry, biochemical and metabolic analysis, physical activity, among others), and (3) genotype-directed nutrition based on rare or common gene variation. The ultimate goal is to integrate such sources of information to ensure that health-care professionals, including dietitians, physicians, pharmacists and genetic counselors, know sufficient concepts about nutrigenetics and nutrigenomics to decide on the most appropriate level of care to achieve a precision nutrition which integrates phenotypical and genotypical issues as well as social, environmental and metabolic factors.

Martinez JA, Navas-Carretero S, Saris WH, Astrup A: Personalized weight loss strategies-the role of macronutrient distribution. Nat Rev Endocrinol 2014;10:749-760.
Ramos-López y col., Guide for Current Nutrigenetic, Nutrigenomic, and Nutriepigenetic Approaches for Precision Nutrition Involving the Prevention and Management of Chronic Diseases Associated with Obesity. J Nutrigenet Nutrigenomics 2017;10:43-62 - https://www.karger.com/Article/FullText/477729

The precision nutrition plate. A schematic representation of the main factors worth to consider when approaching precision nutrition.

"the scientific community generally agrees that the future of precision nutrition will not be solely based on nutrigenetics"



Modificado de: Toro-Martín y col. Precision Nutrition: A Review of Personalized Nutritional Approaches for the Prevention and Management of Metabolic Syndrome. Nutrients 2017, 9(8), 913. http://www.mdpi.com/2072-6643/9/8/913/htm
Betts & Gonzalez. Personalised nutrition: What makes you so special? Nutr. Bull. 2016, 41, 353–359.

Cómo aplicar la Nutrigenética y la Epigenética de nuestro reloj interno a la práctica clínica de la nutrición
M. Garaulet - https://www.youtube.com/watch?v=jgQw-uVZDqc
Los relojes de tu vida: https://tv.um.es/canal?cod=a1&serie=20801

PREDIMED y Food4me

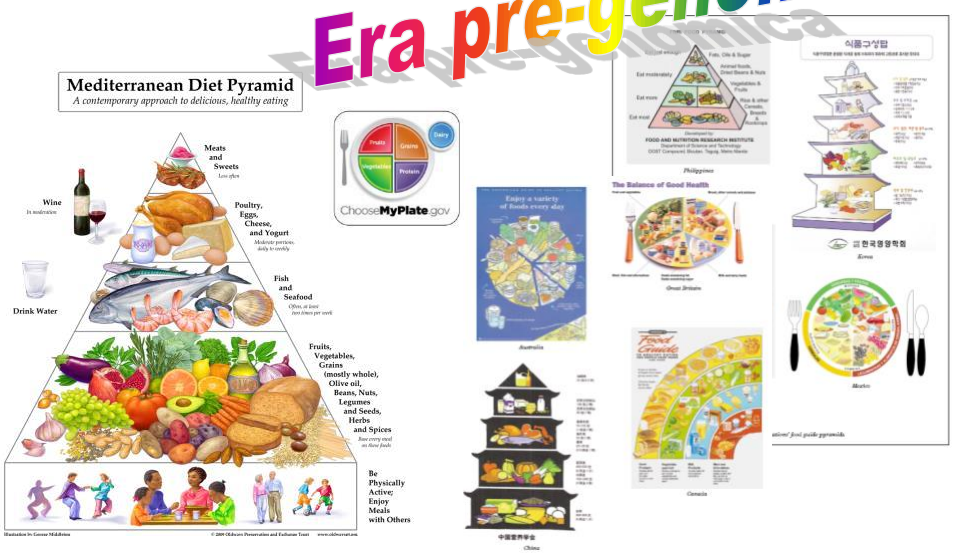
http://www.food4me.org/es/

http://www.predimed.es/

http://www.mdpi.com/2072-6643/9/8/913/htm

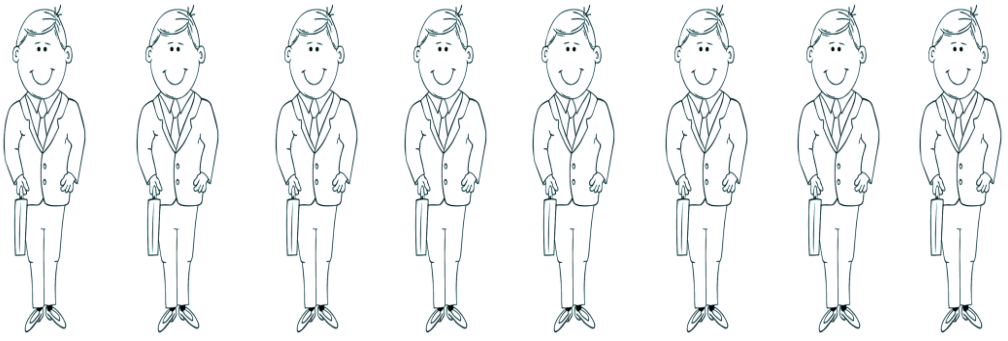
Up to date, the PREDIMED study and the Food4Me project could be considered as state-of-the-art trials in the field of precision nutrition, and two of the most stimulating wide-scale approaches in this field, that will hopefully provide guidance about how precision nutrition could be used to successfully prevent and manage cardiometabolic disorders. As already mentioned, such integrated approaches have the potential to improve dietary behaviors in an individualized or in a group-based manner, and to generate new and innovative tools, methods and procedures.

Era pre-genómica



Enfoque tradicional:

La misma dieta para todos !



- Se asume que los miembros de un grupo tienen las características medias del grupo en conjunto.
- Se asume que los grupos son homogéneos.

¿Por qué …

Esta comida es sana para unos y para otros supone un riesgo de hipercolesterolemia?

Normal Cholesterol

High Cholesterol

Not FAIR!!

?

¿Por qué …

Café & enfermedad coronaria

- Resultados inconsistentes:
  - Beber café aumenta el riesgo de enfermedad coronaria
  - La cafeína NO tiene efecto
  - El consumo moderado de café tiene efectos cardio-protectores

Recent research has indicated that part of the interindividual variability in cardiovascular responses to caffeine has a genetic basis.
Moving towards Specific Nutrigenetic. Recommendation Algorithms: Caffeine, Genetic Variation and Cardiovascular Risk.
J Nutrigenet Nutrigenomics 2016;9:106-115 - https://doi.org/10.1159/000446801

This study had a limited sample size to assess outcome events.

Practical Implications
Heavy coffee drinkers (>814 ml) with the low-activity COMT rs4680 AA genotype should be advised to limit their coffee drinking (grade IIb, LOE B).

"gran variabilidad individual en la respuesta", "susceptibilidad individual", …

Keys (1965): Las "*características intrínsecas*" del individuo son las que motivan la diferente respuesta lipídica a la misma intervención dietética

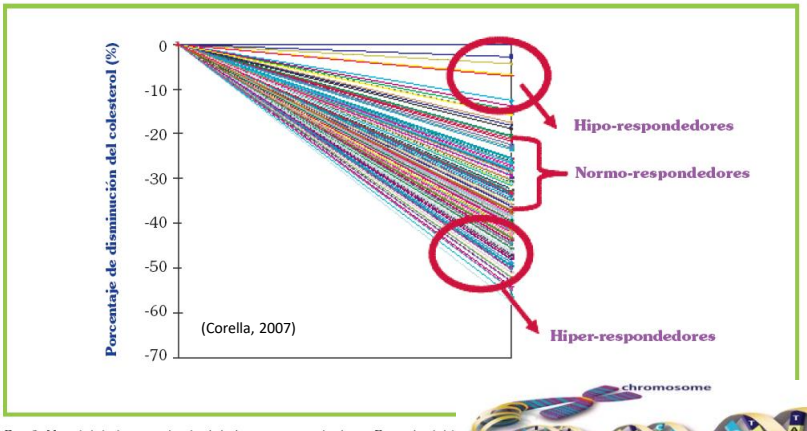
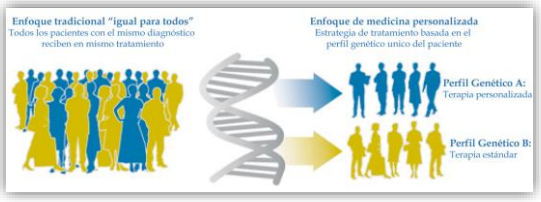


Fig. 2. Variabilidad interindividual de la respuesta a la dieta. Ejemplo del % duos sometidos a la misma dieta durante el mismo tiempo.

Enfoque actual:

Somos distintos!: Dieta individualizada !



http://biogenic-colombia.blogspot.com.es/2012/05/medicina-personalizada-una-medicina.html

Siglo XXI

Era post-genómica

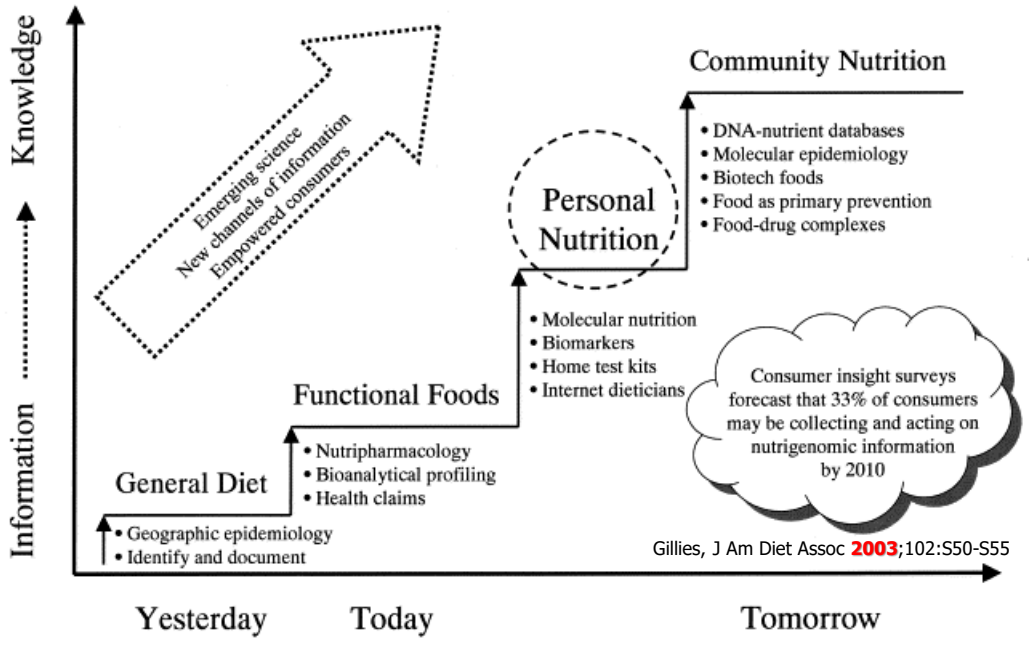
Nutrición personalizada

alimentación del futuro

Optimizar la prevención

Genética

(modificado de Corella, 2007)



Ciencia que estudia la interacción funcional entre los alimentos y sus componentes y el genoma

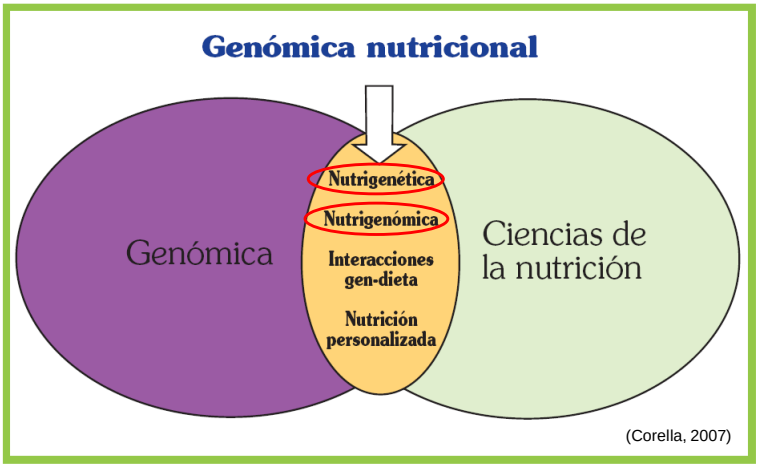


Fig. 1. Genómica nutricional como integración de la genómica en las ciencias de la nutrición.

Medicina y Nutricion personalizadas

Hipócrates (Cos, 460 a. C. - Tesalia 370 a. C.) "…que el alimento sea tu medicina y la medicina tu alimento"

Galeno (Pérgamo, Grecia, 130 - Roma, 200) "ninguna causa puede ser eficiente sin una aptitud del cuerpo"….los individuos heredan respuestas únicas a los alimentos → susceptibilidades únicas a enfermedades crónicas

C. Bernard (Mediados. s XIX) manifiesta " no hay enfermedades sino enfermos".

Garrod (ppios. s XX) sugiere que dieta influye en enfermedad de manera diferente según el individuo.

Williams (1956): Diversos estudios muestran amplias variaciones en los niveles de insulina, colesterol, iones….

Nizel, AE (1972) Personalized nutrition counseling. ASDC J Dent Child 39, 353-360

A Martínez. Presente y Futuro de la Nutrición Personalizada
http://www.portalfarma.com/jornadas-congresos/ii-jornada-profesional-alimentacion/Documents/Alfredo-Martinez.pdf

Antecedentes relevantes

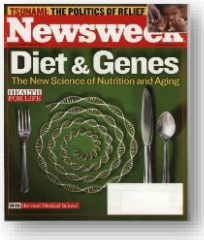
-El término **nutrigenética** fue acuñado por **Brennan RO** en **1975** en su libro ***"Nutrigenetics: New Concepts for Relieving Hypoglycemia"*, M. Evans Inc., New York, USA. (1975).**

-La influencia de la interrelación genoma-dieta en los requerimientos nutricionales fue contemplada por Holtzman NA en 1998 en su artículo:
Genetic variation in nutritional requirements and susceptibility to disease: policy implications. Am J Clin Nutr 1988; 48:1510-6.

-El término nutrigenómica o genómica nutricional fue utilizado por primera vez por : DellaPenna D en su artículo
"Nutritional genomics: manipulating plant micronutrients to improve human health. Science 1999;285:375-9.
(intersección entre el área de la bioquímica de plantas, la genómica y la nutrición para mejorar la salud humana)

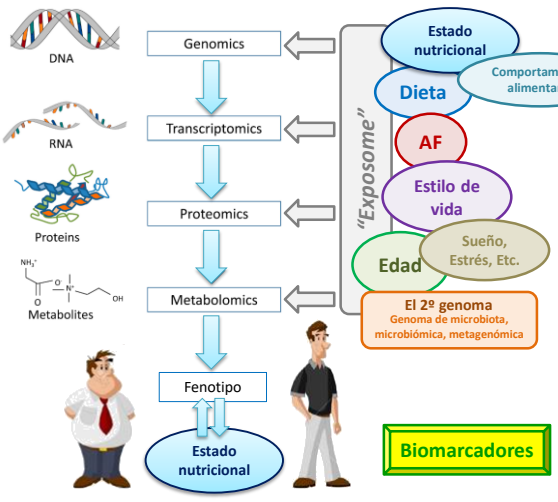
(Corella, 2007)

2004



El Proyecto Genoma Humano (2001) y el HapMap (2005) han aportado las herramientas y la información necesarias para entender la interacción gen-nutriente

The omics cascade. Metabolomics is the final step in the cascade, and thus studies information closer to the phenotype than the preceding omics.
http://www.mdpi.com/2218-1989/7/2/18/htm



Martínez, MOOC Nutrición, genes y salud - 2.1. Nutrición personalizada
https://www.youtube.com/watch?v=_7v9HWGW9QI&feature=youtu.be

EXPOSOMICS

Exposome. Wild, Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):1847-50.
https://www.ncbi.nlm.nih.gov/pubmed/16103423
https://academic.oup.com/ije/article/41/1/24/650703
https://www.sciencedirect.com/science/article/pii/S1438463916301304

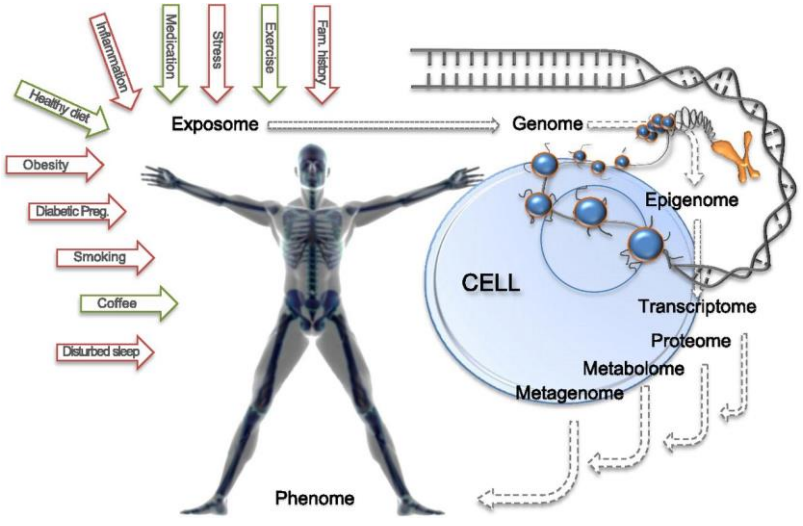
The suffix 'omics' means 'global' and is used as a modifier for a wide range of endeavors such as the comprehensive analysis of:

- Genes (genomics),
- DNA modifications (epigenomics) (DNA methylation, …),
- Messenger RNA (mRNA) or transcripts (transcriptomics),
- Proteins expression (proteomics),
- Metabolites changes (metabolomics),
- Lipids (lipidomics),
- Food (foodomics),
- Microbiota (microbiomics, metagenomics).

https://www.karger.com/Article/FullText/445350
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121546/
http://circgenetics.ahajournals.org/content/9/3/291
http://www.gutmicrobiotaforhealth.com/es/glossary/proyecto-de-microbioma-humano/

Ángeles Carbajal Azcona. Dpto de Nutrición y Ciencia de los Alimentos. Fac. Farmacia. Universidad Complutense de Madrid. https://www.ucm.es/nutricioncarbajal

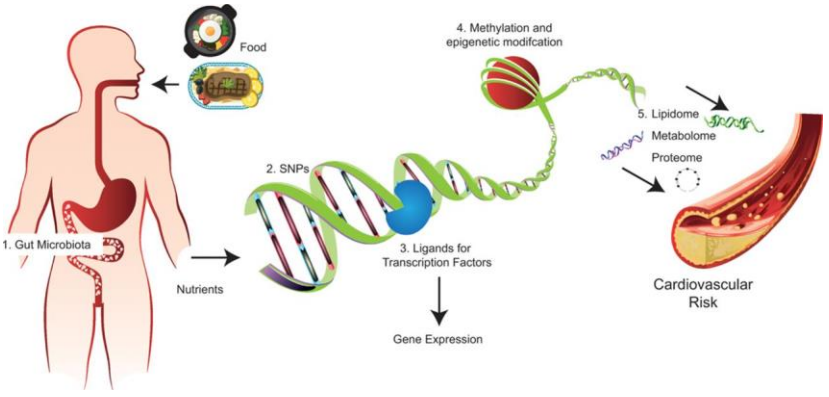
The future of research on stratified diabetes medicine: a systems epidemiology approach to the discovery of interactions between the exposome (all nongenetic elements to which we are exposed) and the quantifiable elements of the human physiome.



Paul W. Franks et al. Dia Care 2013;36:1413-1421
http://care.diabetesjournals.org/content/36/5/1413

American Diabetes Association.

Potential molecular mechanisms for nutrigenomic/nutrigenetic interactions in cardiovascular disease (CVD) risk.



Jane F. Ferguson et al. Circ Cardiovasc Genet. 2016;9:291-313
http://circgenetics.ahajournals.org/content/9/3/291

American Heart Association.

3. Biomarcadores en nutrición personalizada

Tanto en medicina como en nutrición, existe una necesidad de identificar nuevos biomarcadores que sean robustos e indiquen de manera sencilla pero clara la existencia o no de enfermedad, el riesgo o predisposición a sufrirla en el futuro, o el mejor tratamiento dietético o farmacológico. Los biomarcadores nutricionales (bioquímicos, funcionales o moleculares) están revolucionando nuestra comprensión de la función de los nutrientes en la salud, y pueden ser de gran ayuda para la prevención, detección temprana, diagnóstico y tratamiento de las enfermedades. Los biomarcadores pueden ser utilizados, además de para el diagnóstico, para evaluar la ingesta alimentaria de un individuo, para obtener información sobre las respuestas biológicas o fisiológicas a una dieta determinada o a procesos patogénicos, para evaluar la respuesta a diversas intervenciones terapéuticas, y para proporcionar datos sobre las diferencias interindividuales en la respuesta a la dieta y la nutrición.

La nutrición personalizada a través de la epigenómica, Milagro y Martínez, 2015
http://www.publicacionescajamar.es/publicaciones-periodicas/mediterraneo-economico/mediterraneo-economico-27-nutricion-y-salud/740/

http://foodmetabolome.org/biomarkers_def

Table II
Classification of new omic-based biomarkers

Genetic biomarkers	Based on changes in DNA, mainly polymorphisms of a single nucleotide (SNP). Examples: Polymorphisms in the lactase gene (LCT) as proxies of milk consumption in Mendelian randomization analyses.
Epigenetic biomarkers	Biomarkers based on the main epigenetic regulators: DNA methylation, histone modification and non-coding RNAs. Examples: DNA hypermetylation or hypomethylation of specific genes depending on food intake; Levels of circulating microRNAs associated with several nutrion-related diseases.
Transcriptomic biomarkers	Biomarkers based on RNA expression (whole transcriptome or differences in expression of selected genes). Example: Differences in the gene expression profile in subjects following a Mediterranean diet in comparison with control subjects.
Proteomic biomarkers	Biomarkers based on the study of the proteome. Example: Analysis of the proteome of participants fed control diets with the proteome of participants fed low folate diets.
Lipidomic biomarkers	Biomarkers based on the study of the lipidome. Lipidomic profile of human plasma in type 2 diabetic subjects on a high-fat diet versus a high carbohydrate diet.
Metabolomic biomarkers	Biomarkers based on the study of the proteome. Example: The 1H NMR urinary profile in subjects following a traditional Mediterranean diet in comparison with the urinary profile of subject on a low fat diet.

Biomarkers: background, classification and guidelines for applications in nutritional epidemiology, 2015
www.aulamedica.es/nh/pdf/8765.pdf

Table 2. Classification of new omic-based biomarkers.

Omic-Based Biomarkers	Description	References
Genetic biomarkers	Based on changes in DNA, single nucleotide polymorphisms (SNP). Examples:	
	SNPs in the lactase gene (LCT) as proxies of milk consumption in Mendelian randomization analyses.	[52]
	SNPs in the lipoprotein lipase (LPL) gene as biomarkers of genetic risk of stroke.	[40]
Epigenetic biomarkers	Biomarkers based on the main epigenetic regulators: DNA methylation, histone modification, and non-coding RNAs. Examples:	
	DNA hypermetylation or hypomethylation of specific genes depending on food intake; Levels of circulating microRNAs associated with several nutrition-related diseases.	[53,54]
Transcriptomic biomarkers	Biomarkers based on RNA expression (whole transcriptome or differences in the expression of selected genes). Example:	[55]
	Differences in the gene expression profile in subjects following a Mediterranean diet in comparison with control subjects.	[56]
Proteomic biomarkers	Biomarkers based on the study of the proteome.	[57]
Lipidomic biomarkers	Biomarkers based on the study of the lipidome (comprehensive analysis of the molecular lipid species).	[58]
Metabolomic biomarkers	Biomarkers based on the study of the metabolome [the entire small molecule (metabolite) component of a system]. Metabolites (including peptides, lipids, nucleotides, carbohydrates, amino acids, and many other classes of small molecules) are generally defined as having an atomic mass of less than 1.5 kDa and can be exogenous, endogenous, or derived from the microbiome. Example:	[59]
	The ^{1}H NMR urinary profile in subjects following a traditional Mediterranean diet in comparison with the urinary profile of subject on a low fat diet.	[60]

Fito y col. Int. J. Mol. Sci. 2016, 17(9), 1469; doi:10.3390/ijms17091469
http://www.mdpi.com/1422-0067/17/9/1469/htm

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Nutrición molecular, genómica nutricional
Interacción gen-nutriente

El genoma humano es sensible al entorno nutricional en un doble sentido

Modificado de Gillies, J Am Diet Assoc 2003;102:S50-S55
Pérez-Martínez y col., 2008

Some 'omics' technologies could be used to develop optimal, customized diets to promote health maintenance and disease prevention for each individual, thus expanding into effective public health strategies on diet therapy.

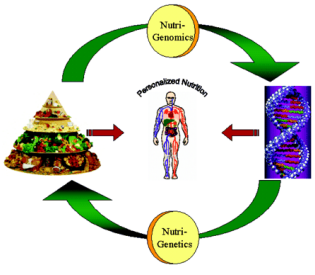
With this perspective, the omics tools most immediately relevant to personalized nutrition include nutrigenetics, nutrigenomics and nutriepigenetics.

Nutrigenetics investigates the influence of the genotype (variants of the DNA sequence) on the response to nutritional change and on the risk of nutrition-related disease.

Nutrigenomic studies investigate the effect of nutrition on gene expression and, consequently, on the proteome and the metabolome.

Nutriepigenetic studies explore the chromatin structure and DNA modifications that do not alter the underlying DNA sequence, but affect gene expression.

Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 - Fields of Precision Nutrition, 2016 - https://www.karger.com/Article/FullText/445350



Mutch et al. (2005) *FASEB Journal* 19:1602-1616.

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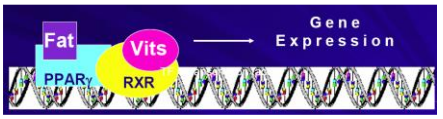
Los nutrientes modulan la expresión de los genes



NUTRIGENÓMICA:

- Analiza el efecto de los componentes bioactivos de la dieta (nutrientes y no nutrientes) en la EXPRESIÓN GENÉTICA (en los genes).

- *Objetivos:*
  - *Identificar los genes regulados por la dieta (genes candidatos responsables de un fenotipo concreto).*

Muller M & Kersten S. (2003) *Nature Reviews Genetics* 4:315-322
https://www.ncbi.nlm.nih.gov/pubmed/12671662

Nutrigenomics

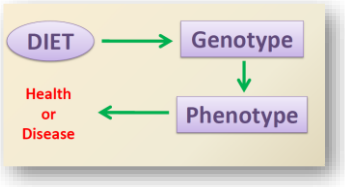
Nutrients and food components can affect and regulate gene activity both directly and indirectly, including acting as ligands of transcription factors and playing a regulatory role in intermediate metabolites of signaling pathways, with positive or negative effects.
Hence, nutrigenomics seeks to show how dietary factors influence gene expression and subsequently impact protein and metabolite levels.

A common approach is the examination of individual mRNA levels relative to intake of certain food components.

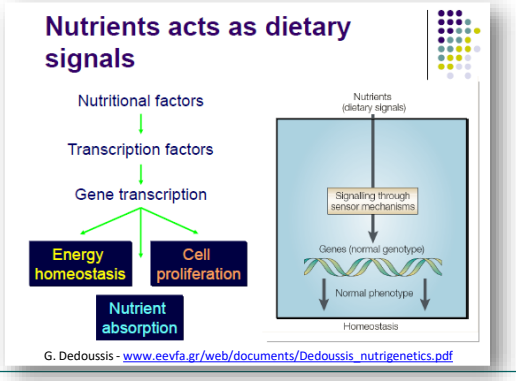
Nutrigenomic strategies thus include analysis of gene expression and biochemical profiles. Early examples of such research strategies include the finding that dietary cholesterol inhibits transcription of the 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) gene, and that long-chain omega-3 polyunsaturated fatty acids reduce gene transcription of platelet-derived growth factor and interleukin-1β.

Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 - Fields of Precision Nutrition, 2016 - https://www.karger.com/Article/FullText/445350

- From a nutrigenomic perspective bioactive food components are **dietary signals** that are detected by the cellular sensor systems (e.i. PPARγ and RXR receptors) that influence gene expression, protein synthesis and metabolite production.
- From this point of view **genes** are **dietary targets**.
- **Patterns of gene expression, protein synthesis and metabolite production** in response to particular nutrients can be considered as **dietary signatures**.
- Nutrigenomics seeks to examine **these dietary signatures** in specific cells, tissues and organisms and to understand how nutrition influences homeostasis.
- Nutrigenomics aims also to **identify the genes that influence the risk of diet-related diseases on a genome -wide scale** and to understand the mechanisms that underlie these genetic predispositions.



Muller M & Kersten S. (2003) *Nature Reviews Genetics* 4:315-322
https://www.ncbi.nlm.nih.gov/pubmed/12671662



G. Dedoussis - www.eevfa.gr/web/documents/Dedoussis_nutrigenetics.pdf

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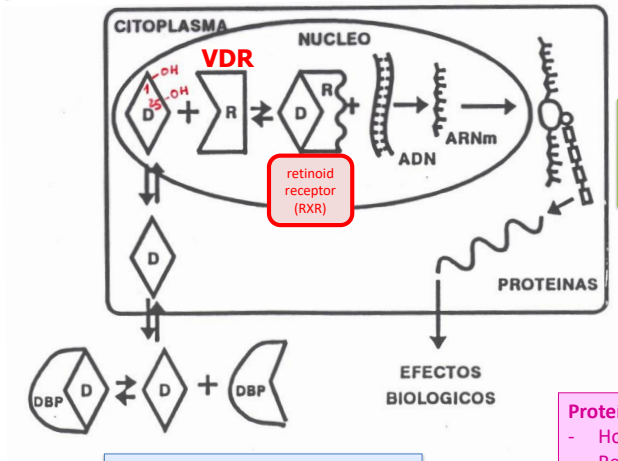
Nutrigenómica

Primer ejemplo de nutrientes que modulan la expresión génica

Célula diana



D=1,25(OH)2D
R=receptor

> 30 tejidos con VDR (intestino, riñón, hueso, corazón, músculo, piel, ...)
> 50 genes regulados por vit. D
Regula la síntesis de:

CaBP = CALBINDINA
Fibronectina
Osteocalcina
c-fos
c-fms
Interleuquina-2
-Interferón
GM-CSF

Proteínas relacionadas con:
- Homeostasis calcio/fósforo
- Respuesta inmune
- Diferenciación/proliferación celular
- .....

Vitamin D receptor (VDR)
Polimorfismos (nutrigenética)

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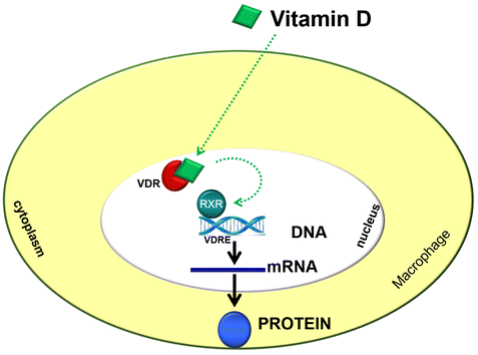


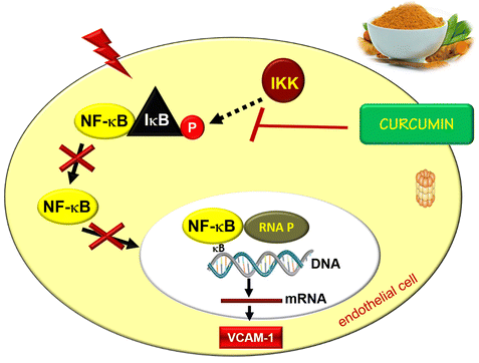
Fig. 2. Example of a direct nutrigenomic mechanism mediated by calcitriol. Modified from Nagpal et al. [30]. VDR vitamin D receptor, RXR retinoid X receptor, VDRE vitamin D response element.

The action of calcitriol, the vitamin D active form, represents an example of a direct nutrigenomic mechanism in which this molecule acts as a ligand for the nuclear receptor, the vitamin D receptor (VDR). Binding to this nuclear receptor causes vitamin D to associate with another protein, retinoid X receptor (RXR), which results in the formation of RXR-VDR heterodimer. In turn, this complex interacts with specific nucleotide sequences in the DNA, called vitamin D response element (VDRE). VDRE activation allows other transcription factors to bind to this complex, which then modulates transcriptional activity of target genes.

https://nutrirejournal.biomedcentral.com/articles/10.1186/s41110-017-0033-2

Regarding **indirect mechanisms** that control gene expression, nutrients or food components activate signaling pathways, which in turn promote the translocation of specific transcription factors from the cytoplasm to the cell nucleus. Transcription factor binds to the promoter region of specific genes inducing gene transcription. Curcumin, a yellow pigment found in the rhizome of *Curcuma longa* and known as turmeric, represents an example of a food component that induces an indirect mechanism of gene expression regulation. Several studies have characterized the anti-inflammatory actions of curcumin, combined with its antibacterial, antiviral, antifungal, and antitumoral effects. Curcumin modulates several in vitro molecular targets, including the NF-kB, and the expression of genes induced by this transcription factor, such as those encoding cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), vascular cell adhesion molecule 1 (VCAM-1), intracellular adhesion molecule 1 (ICAM-1), TNF-α, interleukin (IL)-1, IL-6, IL-8, IL-12, and interferon gamma (IFN-γ). In addition, this molecule also inhibits the production of TNF-α induced by phorbol-12-myristate-13-acetate (PMA) and hydrogen peroxide. Thus, it has been suggested that the anti-inflammatory effects of curcumin may be attributed, in part, to its ability to trap reactive oxygen species radicals.

Fig. 3. Example of an indirect mechanism mediated by curcumin. Adapted from Aggarwal [38]. NF-kB nuclear factor-kappa B, IkB kappa B inhibitor, IKK IkB kinase, P phosphorylation, RNA P RNA polymerase, kB kB sites, VCAM-1 vascular cell adhesion molecule 1.



https://nutrirejournal.biomedcentral.com/articles/10.1186/s41110-017-0033-2

Nutrigenómica

Ejemplos de nutrientes que modulan la expresión génica

Numerous dietary components can alter genetic and events:

Essential Nutrients - Ca, Zn, Se, Folate, C, E, D, fat, carbohydrates, …

Non-Essential:

- Phytochemicals - Carotenoids, Flavonoids, Indoles, Isothiocyanates, Allyl Sulfur
- Zoochemicals - Conjugated linoleic acid, n-3 fatty acids
- Fungochemicals - Several compounds in mushrooms
- Bacteriochemical - Those formed from food fermentations and those resulting from intestinal flora

Transcription-factor pathways mediating nutrient-gene interaction

Nutrient	Compound	Transcription factor
Macronutrients		
Fats	Fatty acids Cholesterol	PPARs, SREBPs, LXR, HNF4, ChREBP SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Amino acids	C/EBPs
Micronutrients		
Vitamins	Vitamin A Vitamin D Vitamin E	RAR, RXR VDR PXR
Minerals	Calcium Iron Zinc	Calcineurin/NF-ATs IRP1, IRP2 MTF1
Other food components		
	Flavonoids Xenobiotics	ER, NFκB, AP1 CAR, PXR

Muller M & Kersten S. (2003) *Nature Reviews Genetics* 4:315-322
https://www.ncbi.nlm.nih.gov/pubmed/12671662 - https://www.ncbi.nlm.nih.gov/pubmed/15506946

Diet and Gene Expression Profiles

Certain nutrigenomic studies assessing gene expression profiles associated with nutritional interventions

Nutritional interventions	Target genes	Expression changes	Potential health effects	Ref.
Mediterranean diet	*NFKB1, IKBKB, MMP9, IL1B, MAPK8, XBP1*	–	Anti-inflammatory, antiatherogenic	[53]
Mediterranean diet plus olive oil	*NFKB1, MMP9, TNFA*	–	Anti-inflammatory, antiatherogenic	[55]
Mediterranean diet	*NFE2L2, SOD1, SOD2, TXNRD1*	–	Anti-inflammatory, antioxidant	[54]
High MUFA	*APOBR*	–	Antilipidemic, antiatherogenic	[56]
Energy-restricted diet plus EPA	*IL10*	+	Anti-inflammatory	[58]
High PUFA	*POMC, GALP*	+	Antiobesity	[57]
High PUFA	*HCRT, MCH*	–	Antiobesity	[57]
Energy-restricted diet plus EPA and α-lipoic acid	Lipid catabolism genes	+	Antilipidemic	[59]
Energy-restricted diet plus EPA and α-lipoic acid	Lipid storage genes	–	Anti-lipidemic	[59]
High protein	*PPARGC1A, PCK1, GSTA, CPT1A*	+	Antisteatotic	[60, 61]
High protein	*FGF21, SCD1*	–	Antisteatotic	[60, 61]
Curcumin	*MMP-9, MMP-13, EMMPRIN*	–	Antiatherogenic, anticancer	[62, 63]
Resveratrol	*EMMPRIN*	–	Antiatherogenic	[64]
Apple polyphenols	*LEP, SREBF1, PLIN*	–	Antiobesity	[65]
Apple polyphenols	*PPARGC1A, AQP7, AEBP1*	+	Antiobesity	[65]
Flavonoid-fish oil supplement	Phagocytosis-related inflammatory genes	–	Anti-inflammatory	[145]
High n-3/n-6 PUFA ratio	*TLR4, TNFA, IL6, CRP*	–	Anti-inflammatory, antidiabetic	[146]
EGCG	*MMP9, MMP2*	–	Antitumorigenic	[147, 148]
Theaflavin	*MMP2*	–	Antitumorigenic	[149]
Resveratrol	*FASN*	–	Antisteatotic	[150]
Sulforaphane	*EGR1*	+	Anticancer	[151]
Genistein	*P21, P16*	+	Anticancer	[152]
Genistein	*BMI1, c-MYC*	–	Anticancer	[152]

MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; *NFKB1*, nuclear factor kappa B subunit 1; *IKBKB*, inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta; *MMP9*, matrix metallopeptidase 9; *IL1B*, interleukin 1 beta; *MAPK8* (*JNK1*), mitogen-activated protein kinase 8; *XBP1*, X-box binding protein 1; *TNFA*, tumor necrosis factor alpha; *APOBR*, apolipoprotein B receptor; *NFE2L2*, nuclear factor, erythroid 2 like 2; *SOD1*, superoxide dismutase 1; *SOD2*, superoxide dismutase 2; *TXNRD1*, thioredoxin reductase 1; *IL10*, interleukin 10; *POMC*, proopiomelanocortin; *GALP*, galanin like peptide; *HCRT*, hypocretin neuropeptide precursor; *MCH*, melanin-

Ramos-López y col., Guide for Current Nutrigenetic, Nutrigenomic, and Nutriepigenetic Approaches for Precision Nutrition Involving the Prevention and Management of Chronic Diseases Associated with Obesity. J Nutrigenet Nutrigenomics 2017;10:43-62 - https://www.karger.com/Article/FullText/477729

Diet and Gene Expression Profiles

Nutrigenomic examples of interactions between dietary intakes and gene expression profiles involved in disease risk

Dietary factors	Target genes	Expression changes	Putative disease risks	Ref.
Low protein	*NR1H3*	–	T2DM	[47]
Low protein	*HSD11B1, PCK1*	+	T2DM	[47]
Choline and folate deficiency	*PPARGA*	–	NAFLD	[48]
Chromium deficiency	Insulin signaling genes	–	T2DM	[49]
Selenium deficiency	*TLR2, ICAM1*	+	CVD	[50]
Vitamin B_{12} deficiency	*SREBF1, LDLR*	+	Dyslipidemia	[51]
Vitamin A deficiency	*GATA4*	–	CVD	[52]
High fat and high sugar	*LEP, SREBF1, PLIN*	+	Obesity	[65]
High fat	*OPRM1, PENK, DAT*	+	Obesity	[74]
Low protein	*CYP7A1*	–	Dyslipidemia	[75]
Selenium deficiency	*VHL*	–	Cancer	[79]
Vitamin D deficiency	*NFKBIA*	–	T2DM	[80]
High SFA	*TNFA, IL6*	+	CVD	[132]
High SFA	Proinflammatory "obesity-linked" genes	+	Obesity-related inflammation	[133]
High SFA	*PPARGC1A*	–	NAFLD	[134]
High SFA	*ADGRE1*	+	Obesity-related inflammation	[134]
High fat	*LEPR, NPY*	+	Obesity	[135]
High fat	*TH, DRD4*	+	Obesity	[136]
High fat rich in lard	*OPN, ADGRE1, TNFA, NFKB1*	+	Obesity-related inflammation and insulin resistance	[137]
High fat rich in lard	*OPN, TLR2, TLR4, TNFA*	+	Obesity-related inflammation and insulin resistance	[138]
High fat and high sugar	*DRD2*	–	Obesity	[139]
High fat and high sugar	*NPY*	+	Obesity	[140]
High fat and high sugar	*POMC*	–	Obesity	[140]
High carbohydrate	*FGF21*	+	NAFLD	[141]
Low folate and choline	Genes involved in cellular proliferation	+	Liver cancer	[142]
Western diet plus vitamin D deficiency	*TLR2, TLR4, TLR9, IL1B, IL4, IL6, RETN*	+	NAFLD	[143]
Choline and folate deficiency	*APOE, FOXA1, FOXA2*	–	NAFLD	[144]

SFA, saturated fatty acids; *TNFA*, tumor necrosis factor alpha; *IL6*, interleukin-6; *PPARGC1A*, peroxisome proliferative activated receptor, gamma, coactivator 1 alpha; *ADGRE1*, adhesion G protein-coupled receptor E1; *LEPR*, leptin receptor; *NPY*, neuropeptide Y; *TH*, tyrosine hydroxylase; *DRD4*, dopamine receptor D4; *OPRM1*, opioid receptor, mu 1; *PENK*, preproenkephalin; *DAT*, dopamine transporter; *OPN*, osteopontin; *NFKB1*, nuclear factor kappa B subunit 1; *TLR2*, toll-like receptor 2; *TLR4*, toll-like receptor 4; *DRD2*, dopamine receptor D2; *POMC*, proopiomelanocortin; *LEP*, leptin; *SREBF1*, sterol regulatory element binding transcription factor 1; *PLIN*, perilipin;

Ramos-López y col., Guide for Current Nutrigenetic, Nutrigenomic, and Nutriepigenetic Approaches for Precision Nutrition Involving the Prevention and Management of Chronic Diseases Associated with Obesity. J Nutrigenet Nutrigenomics 2017;10:43-62 - https://www.karger.com/Article/FullText/477729

Los genes modulan el efecto de los nutrientes

NUTRIGENÉTICA

- Estudia la influencia de las variaciones genéticas (POLIMORFISMOS) en la respuesta individual a la dieta, a los nutrientes. Por qué la población responde de manera diferente a la misma dieta.

- *Objetivos:*
  - *Identificación y caracterización de estos polimorfismos.*
  - *Marcar recomendaciones dietéticas específicas (individuales) para conseguir la óptima salud:*
    - ✓ *"Nutrición personalizada" según la constitución genética*
    - ✓ *"Dieta a la carta"*

    (modulación de la susceptibilidad genética)

Nutrigenetics

A major contribution of the Human Genome Project was to lay the foundation that led to the discovery of millions of differences in the nucleotide sequence of genes. The variants occurring in at least 1% of any distinct population are called polymorphic variants or polymorphisms. A particularly common type of polymorphism is defined by the replacement of one nucleotide base with another, and therefore called 'single nucleotide polymorphism' (SNP). Some SNPs may affect the synthesis and function of proteins, and may therefore alter nutritional requirements and nutrient metabolism, as well as playing important roles in an individual's risk of developing disease.

A further way in which genetic variations occur is through structural DNA changes that include insertions/deletions, translocations and copy number variations (CNVs). CNVs explain about 1% of the genetic variation between two individuals. Some of them appear to play an important role in human health through association with the risk of disease development and progression.

The discovery of diseases associated with genetic variants has provided a better understanding of nutrient/diet effects on human health and disease, and has helped individuals to achieve customized nutritional treatments. One example of this is **phenylketonuria (PKU)**, an inborn error of metabolism caused by mutations in the gene that encodes the hepatic enzyme phenylalanine hydroxylase. Individuals with PKU need to avoid foods rich in the amino acid phenylalanine. Another example is **lactase persistence**, which evolved a few thousand years ago in response to the development of dairy farming. Carriers of variants associated with lactase persistence have their lactase gene permanently 'turned on' after weaning and can digest lactose even as adults. Lactose (milk sugar) is a disaccharide, made from glucose and galactose. Therefore, the 70% of the global population, who do not have such genetic variants, are better off limiting consumption of milk and other dairy products rich in lactose.

Recent studies investigating genetic variants associated with **obesity risk or with resistance to weight loss** in human populations have helped clarify molecular mechanisms involved in obesity. One such example is the fat mass and obesity-associated (FTO) gene. The minority (16%) of individuals with two copies of the common FTO variant (rs9939609) weigh around 3 kg more than noncarriers and have a 1.67-fold increased risk of obesity. Variants in numerous other obesity candidate genes, such as peroxisome proliferator-activated receptor, uncoupling proteins (UCP1 and UCP3), leptin receptor and melanocortin 4 receptor, can also affect weight gain or loss in genetically predisposed subjects.

Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 - Fields of Precision Nutrition, 2016 - https://www.karger.com/Article/FullText/445350

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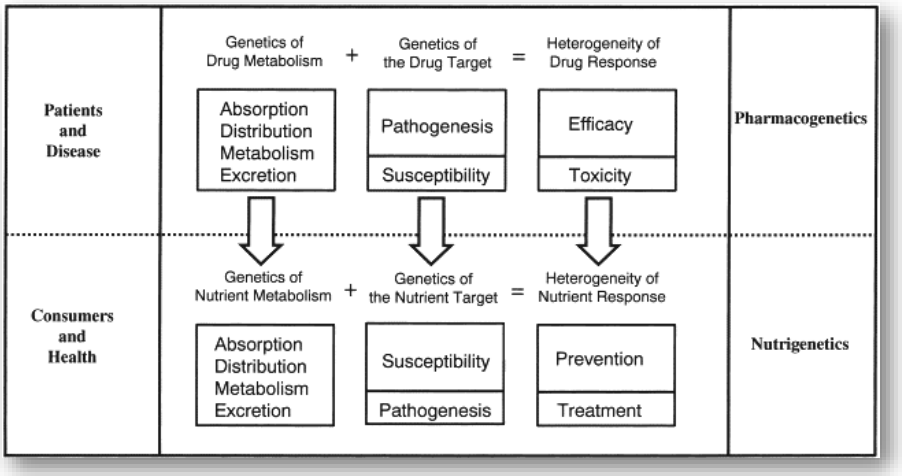
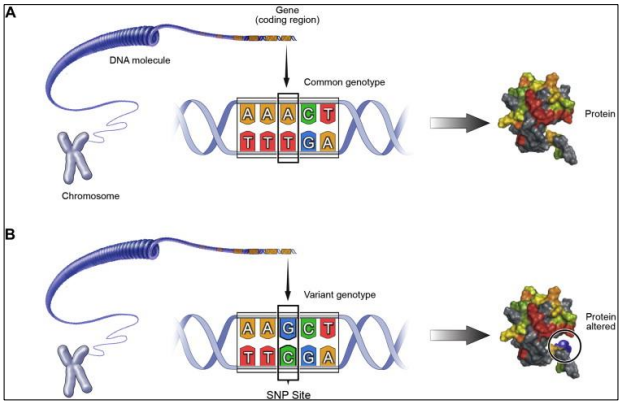
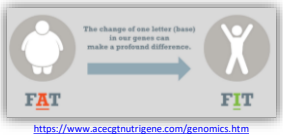
The principles of nutrigenetics follow naturally from those of pharmacogenetics



Gillies, J Am Diet Assoc 2003;102:S50-S55

Los polimorfismos de un solo nucleótico (SNPs) son la principal fuente de variación genética y pueden determinar la respuesta individual a la dieta.
Su estudio puede contribuir a la definición de dietas óptimas
SNPs → 6 millones en genoma humano





https://www.acecgtnutrigene.com/genomics.htm

Single nucleotide polymorphisms (SNPs) are small sequence differences within genes where the DNA sequences of many individuals vary by a single base; not all SNPs result in structural protein changes. For example, some people may have a chromosome with an A at a particular site where others have a chromosome with a G. SNPs occur in about 1% of the population.

Journal of the Academy of Nutrition and Dietetics 2014 114, 299-312DOI: (10.1016/j.jand.2013.12.001)

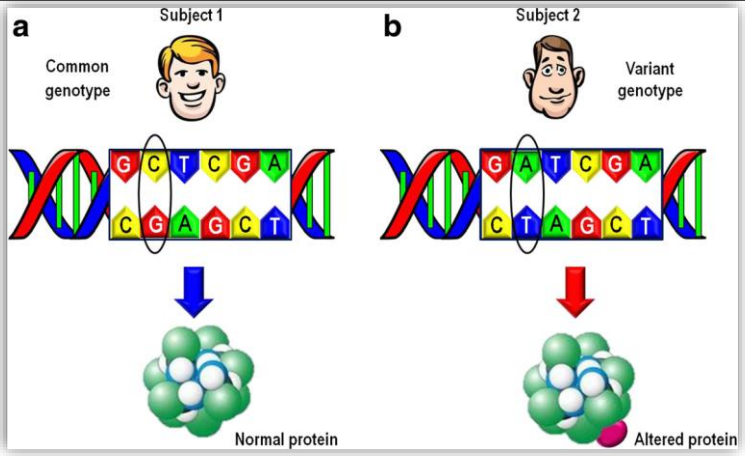


Fig. 1 Single nucleotide polymorphism: variations in nucleotides can occur all along the DNA sequence. Here, two examples of genotypes are illustrated: a in the "*common genotype*" there is a codon GCT, which is transcribed into CGA in mRNA and encodes an arginine. b In the "*variant genotype*," nucleotide C was exchanged for an A. Codon GAT will be transcribed into CUA in mRNA, which encodes a leucine, promoting, therefore, a change in the translated protein.

SNPs are the most common type of variation in the human genome (about 90% of all variations) and refer to the replacement of only one nucleotide in a certain DNA position. When the nucleotide exchange occurs in the coding region, it might promote a change in the structure and/or function of the translated protein. Due to the genetic code degeneracy, when the exchange of nucleotide does not alter the amino acid, the SNP is known as "synonymous" or "silent" because it does not change the translated protein (e.g., GUC → GUA, both encode a valine). When the change gives rise to a codon resulting in the translation of a different amino acid, the SNP is known as "non-synonymous" or "missense" (e.g., UUA → UCA, the first encodes a leucine and the second, a serine). If the nucleotide exchange results in a premature stop codon, the SNP will be known as "nonsense" (e.g., UAU → UAG, wherein the first encodes tyrosine and the second is a stop codon).

https://nutrirejournal.biomedcentral.com/articles/10.1186/s41110-017-0033-2

- **Mutación** cualquier cambio en la secuencia de nucleótidos del ADN
- **Polimorfismo mutación con alelo de frecuencia superior a 1%**

ENFERMEDADES MONOGÉNICAS	ENFERMEDADES POLIGÉNICAS
Celiaquía	Obesidad
Intolerancia a la lactosa	Diabetes tipo 2
Hipercolesterolemia familiar	Hiperlipidemias
Fenilcetonuria	Hipertensión
Galactosemia	Enfermedad cardiovascular
	Osteoporosis
	Enfermedades neurodegenerativas
	Cáncer

Genotipo (gen A, B, C, ...) y ambiente

- **Factores exógenos**: exposición a toxinas o productos químicos, radiación, alérgenos, contaminantes, virus y bacterias....
- **Factores volitivos**: estilo de vida, ejercicio físico, consumo de alcohol o tabaco, ingestión calórica y componentes de la dieta, alteraciones del sueño....

HAPLOTIPO + AMBIENTE → PREDISPOSICIÓN (% contribución)

Alfredo Martínez, NUGO Barcelona, 2015
http://www.nugo.org/wp-content/uploads/2015/10/NUGO-Barcelona-final.pdf
NUGO, http://www.nugo.org/member-organisations/

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Nutrigenetic analysis of SNPs within some CVD-related genes

CVD Risk Factor	Gene	SNPs	Genotype
Lipids	APOAI	-75G→A	GA
Lipids	APOC3	3175C→G	GG
Lipids	APOE	ε2, ε3, ε4	2, 3
Lipids	CETP	279G→A	GG
Blood pressure	ACE	Ins/Del	ID
Blood pressure	AGT	-6C→A	AA
Infammation	IL1B	-511C→T	TT
Inflammation	IL6	-174G→C	GC
Methylation (folate)	MTHFR	677C→T	TT
Methylation (B12)	TCN2	776C→T	CT

M Koziołkiewicz, 2011

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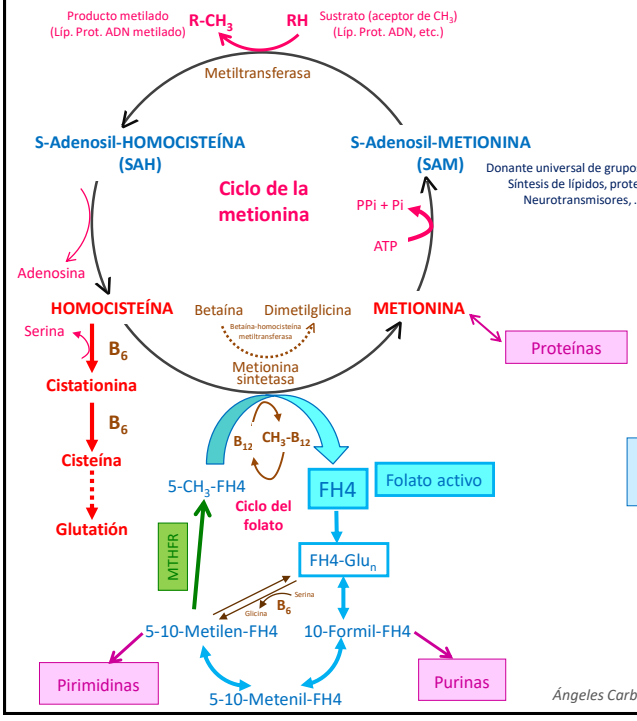

Gen de MTHFR

Deficiencia vit B12:
Deficiencia funcional de folato

Nutrigenética

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Gen de MTHFR 677C→T

Prototipo

Cromosoma 1 (11 exones)

Exón 4, posición 677 → polimorfismo de un solo nucleótido: cambio de C por T →

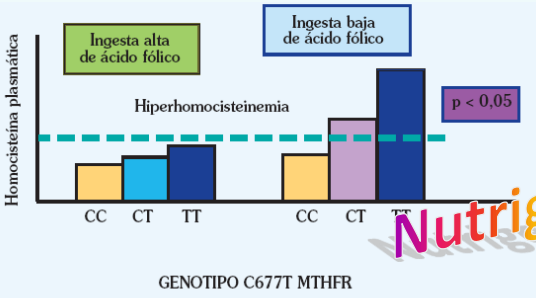
Cambio alanina por valina en posición 222 de **MTHFR → termolábil, inestable → 70% menos activa**

Forma homocigótica:
5% población general
17% pacientes con enf. Coronaria

↑ Homocisteína
↑ ECV
↑ Defectos de cierre del tubo neural

Meta-analyses (2003) reported about **20% higher risk for degenerative vascular disorders** for the homozygous genotype (Herrmann y col., 2007)

La ingesta de folato puede modular el riesgo genético de HHCY Se compensa con dietas ricas en folato



Nutrigenética

(Corella, 2007)

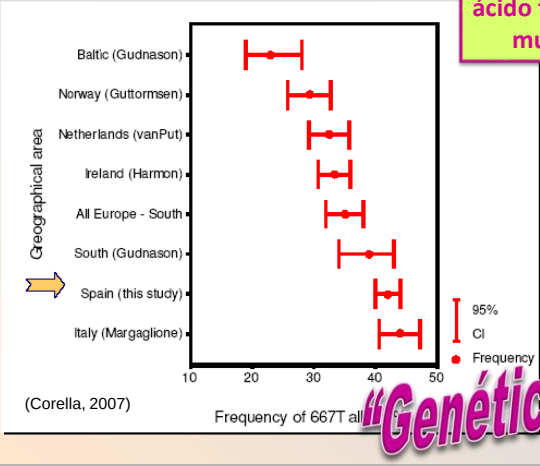
Guillén et al.

Prevalence of the methylenetetrahydrofolate reductase 677C > T mutation in the Mediterranean Spanish population. Association with cardiovascular risk factors.

Eur J Epidemiol. 2001

Nutrigenética

Recomendar mayor consumo de ácido fólico a las personas con la mutación (sur de Europa)

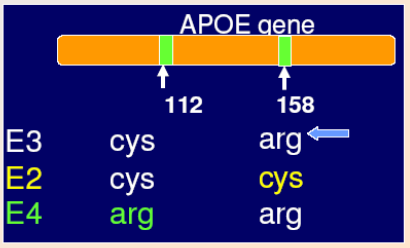


(Corella, 2007)

"Genética mediterránea"

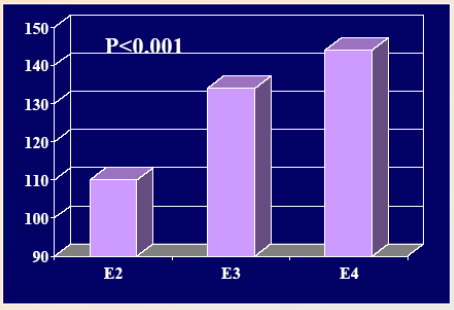
(Grasa Ullrich y col., 2002)

Algunos ejemplos de interacciones gen-dieta



(Corella, 2007)

Gen APOE y c-LDL



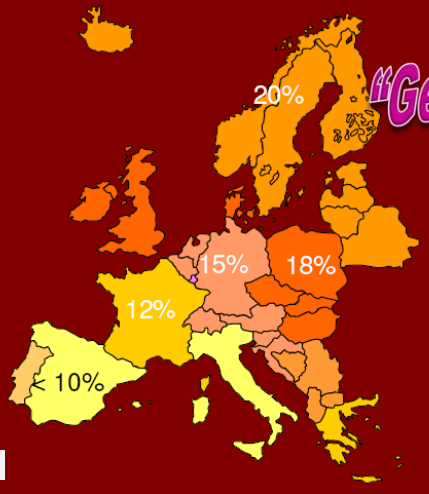
LDL-C (mg/dL)

El alelo E4 se ha asociado consistentemente con mayores concentraciones de c-LDL

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4921111/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5102878/

Apolipoproteína E

Gradiente Norte-Sur en la frecuencia del alelo E4



(Corella, 2007)

El alelo E4 se ha asociado consistentemente con mayores concentraciones de c-LDL

"Genética mediterránea"

(Grasa Ullrich y col., 2002)

Las recomendaciones dietéticas (grasa) tendrán que ser diferentes en el norte y en el sur de Europa

Dieta Mediterránea

Patrimonio Cultural Inmaterial

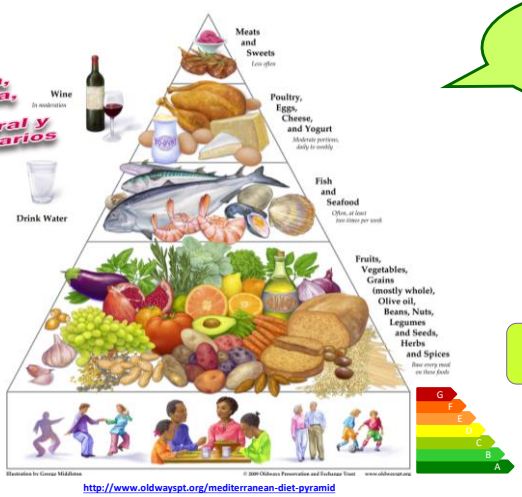
UNESCO

16-nov-2010

Excelente ejemplo de fusión:

Gastronomía + Cultura + Nutrición + Salud + Sostenibilidad

Estilo de vida, actividad física, sociabilidad, intercambio cultural y de hábitos alimentarios



http://www.oldwayspt.org/mediterranean-diet-pyramid

Modelo de dieta prudente, saludable y sostenible. "nutrición óptima"

Programados genéticamente para ella

Menor morbi-mortalidad
Mayor esperanza de vida

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Genetic Background and Nutritional Prescriptions

Nutrigenetic examples of SNPs-diet interactions involved in disease risk

Genes	Polymorphisms	Alleles	Diet interactions	Putative disease risks	Ref.
TAS1R2	rs35874116	G	High carbohydrate	Hypertriglyceridemia	[16]
CD36	rs1761667	A	High fat, SFA	Hypercholesterolemia	[17]
MTHFR	rs1801133	T	Low folate, vitamin B_6, and vitamin B_{12}	Breast cancer	[18]
MTR	rs1805087	G	Low folate, vitamin B_6, and vitamin B_{12}	Breast cancer	[18]
VDR	rs1544410	A	Low calcium	Osteoporosis	[22]
APOC3	rs5128	C	Western dietary pattern	Metabolic syndrome	[23]
APOA1	rs670, rs5069	A, T	Western dietary pattern	Metabolic syndrome	[24]
CYP1A2	rs762551	C	Moderate and heavy coffee drink	Hypertension, CVD	[25, 26]
FTO	rs9939609	T	Low adherence to Mediterranean diet	T2DM	[106]
MC4R	rs17782313	T	Low adherence to Mediterranean diet	T2DM	[106]
FTO	rs9939609	A	High fat	Obesity	[107, 108]
FTO	rs8050136	A	High carbohydrate	Obesity	[109]
MC4R	rs12970134	A	Western dietary pattern and high SFA	Metabolic syndrome	[110]
APOB	rs512535	G	High fat	Metabolic syndrome	[111]
TCF7L2	rs7903146	T	High dessert and milk	T2DM	[112]
TCF7L2	rs7903146	T	High SFA	Metabolic syndrome	[113]
LCT	rs4988235	T	High dairy products	Obesity	[114]
PPARG	rs1801282	G	High fat	Obesity	[115]
PNPLA3	rs739409	G	High carbohydrate	NAFLD	[116]
TXN	rs2301241	T	Low vitamin E	Abdominal obesity	[117]

MTHFR, methylenetetrahydrofolate reductase; *MTR*, methionine synthase; *FTO*, fat mass and obesity associated; *MC4R*, melanocortin 4 receptor; *APOC3*, apolipoprotein C3; *APOA1*, apolipoprotein A1; *APOB*, apolipoprotein B; *CD36*, cluster of differentiation 36; *TCF7L2*, transcription factor 7 like 2; *LCT*, lactase; *PPARG*, peroxisome proliferator activated receptor gamma; *PNPLA3*, patatin like phospholipase domain containing 3; *TAS1R2*, taste 1 receptor member 2; *VDR*, vitamin D receptor; *CYP1A2*, cytochrome P450 family 1 subfamily A member 2; *TXN*, thioredoxin; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease.

Ramos-López y col., Guide for Current Nutrigenetic, Nutrigenomic, and Nutriepigenetic Approaches for Precision Nutrition Involving the Prevention and Management of Chronic Diseases Associated with Obesity. J Nutrigenet Nutrigenomics 2017;10:43-62 - https://www.karger.com/Article/FullText/477729

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Genetic Background and Nutritional Prescriptions

Certain nutrigenetic trials analyzing SNPs-diet interactions involved in the differential responses to nutritional interventions

Genes	Polymorphisms	Alleles	Diet interactions	Dietary responses	Ref.
FTO	rs1558902	A	High protein	Greater weight loss	[118]
FTO	rs1558902	A	Low fat	Less reductions in insulin and HOMA-IR	[119]
TCF7L2	rs7903146	T	High fat	Smaller weight loss and HOMA-IR	[120]
APOA5	rs964184	G	Low fat	Greater reduction in TC and LDL-c	[121]
GIPR	rs2287019	T	Low fat	Greater weight loss and greater decreases in glucose, insulin and HOMA-IR	[122]
CETP	rs3764261	C	High fat	Larger increases in HDL-c and decreases in triglycerides	[123]
DHCR7	rs12785878	T	High protein	Greater decreases in insulin and HOMA-IR	[124]
LIPC	rs2070895	A	Low fat	Higher decreases in TC and LDL-c and a lower increase in HDL-c	[125]
PPM1K	rs1440581	C	High fat	Less weight loss and smaller decreases in insulin and HOMA-IR	[126]
TFAP2B	rs987237	G	High protein	Higher weight regains	[127]
IRS1	rs2943641	C	High carbohydrate	Greater decreases in insulin, HOMA-IR and weight loss	[128]
PCSK7	rs236918	G	High carbohydrate	Higher decreases in insulin and HOMA-IR	[129]
MTNR1B	rs10830963	G	High protein	Lower weight loss in women	[130]
IL6	rs2069827	C	Mediterranean diet	Lower weight gains	[131]

FTO, fat mass and obesity associated; *TCF7L2*, transcription factor 7 like 2; *APOA5*, apolipoprotein A5; *GIPR*, gastric inhibitory polypeptide receptor; *CETP*, cholesteryl ester transfer protein; *DHCR7*, 7-dehydrocholesterol reductase; *LIPC*, lipase C, hepatic type; *PPM1K*, protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1K; *TFAP2B*, transcription factor AP-2 beta; *IRS1*, insulin receptor substrate 1; *PCSK7*, proprotein convertase subtilisin/kexin type 7; *MTNR1B*, melatonin receptor 1B; *IL6*, interleukin-6; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance.

Ramos-López y col., Guide for Current Nutrigenetic, Nutrigenomic, and Nutriepigenetic Approaches for Precision Nutrition Involving the Prevention and Management of Chronic Diseases Associated with Obesity. J Nutrigenet Nutrigenomics 2017;10:43-62 - https://www.karger.com/Article/FullText/477729

"Diálogo entre el genoma y medio ambiente"

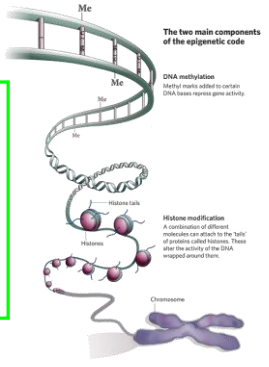
"The missing link between genetics, the environment and the outcome phenotypes"

EPIGENÉTICA

- Cambios heredables (potencialmente reversibles) en la expresión génica (fenotipo) que no van acompañados de cambios en la secuencia de ADN.
- Modificación por el entorno: edad, dieta, tabaco,…

La composición de la dieta puede alterar la **estructura del ADN**: afecta a la expresión génica y al fenotipo (cambios epigenéticos). No cambia la secuencia del ADN.

Modificaciones epigenéticas
- Metilación de ADN
- Modificación de histonas:
  - Acetilación
  - Metilación
- Expresión de ARNs reguladores



Modifican el fenotipo sin alterar el genotipo

https://www.karger.com/Article/FullText/358883 - https://www.sciencedirect.com/science/article/pii/S0370410615003265 - http://www.mdpi.com/1422-0067/17/9/1469/htm

Epigenetics/Epigenomics

Epigenetic processes bring about reversible modifications in chromatin structure and DNA modification without altering the underlying sequence. Epigenetic changes include DNA methylation and histone modification. Different classes of small noncoding RNAs (such as microRNAs) or long noncoding RNAs have been proposed as key regulators of gene expression, chromatin remodeling and epigenetic changes through multiple mechanism, showing a potential as biomarkers of human diseases. Additionally, external effects (including diet) on the epigenome alter the expression of genes, providing a link between environment, nutrition and disease.
DNA methylation is the most widely studied form of epigenetic modification. One of numerous specific methyltransferases adds a methyl group to the cytosine in the carbon 5′ position of a CpG dinucleotide (cytosine followed by a guanine). The added methyl group often silences the gene by blocking the binding of transcription factors. In recent years, development of new technologies such as NGS has allowed the detection of site-specific methylation patterns with great accuracy and led to the discovery of new types of epigenetic modifications.
Histone modifications, consisting of acetylation, methylation, phosphorylation and ubiquitination, affect transcription through compacting DNA. This process can activate or repress gene expression by controlling accessibility of genes to transcriptional regulators.
Epigenetics depends on the presence of enzymes and dietary nutrients, and can occur in a gene-specific or in a global manner. S-adenosylmethionine (SAM) is the universal methyl donor for all methyltransferases that methylate DNA and histones. The availability of SAM can be diminished under some circumstances by insufficient availability of folic acid, vitamin B12, vitamin B6, vitamin B2, choline, betaine and methionine, both due to low intake and individual genetic vulnerabilities.

Some studies have shown a relationship between nutritional intake during pregnancy and changes in methylation patterns in rats. Nutritional interventions in pregnancy and lactation such as energy restriction and excessive dietary fat can alter epigenetic modifications. Other studies have shown that epigenetic modifications change the risk of inflammation, obesity and chronic diseases. A study of obese men on a hypocaloric diet to lose weight found distinct differences in DNA methylation patterns between individuals with high weight loss compared to those with little weight loss. Studies in diabetic individuals found associations between the secretion of insulin and the DNA methylation pattern in the promoter region of the PCG-1A gene of pancreatic β-cells.

Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 - Fields of Precision Nutrition, 2016 - https://www.karger.com/Article/FullText/445350

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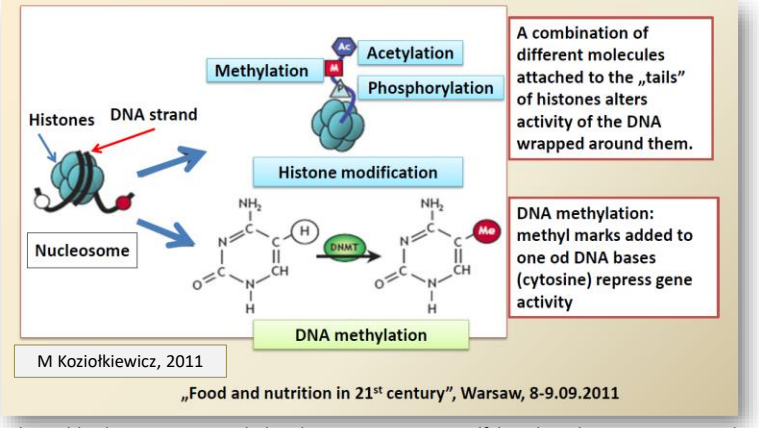
The two main components of the epigenetic labeling



Epigenetics are the heritable changes not encoded in the DNA sequence itself, but that play an important role in the control of gene expression. Epigenetics is the process that regulates how and when genes are silenced and activated; epigenomics refers to the analysis of epigenetic changes in a cell. Diet can cause epigenetic changes that may turn certain genes on or off, ultimately affecting cellular function and metabolism. One epigenetic mechanism is DNA methylation, which refers to the degree to which methyl groups are present or absent from certain regions of genes. **Generally, hypomethylation allows gene expression to be activated; hypermethylation interferes with gene expression**. Both hypomethylation or hypermethylation describe an aberrant scenario and the influence on a gene will depend on the specific genes, the time point, and the tissues. https://jandonline.org/article/S2212-2672(13)01783-8/fulltext#sec3.4

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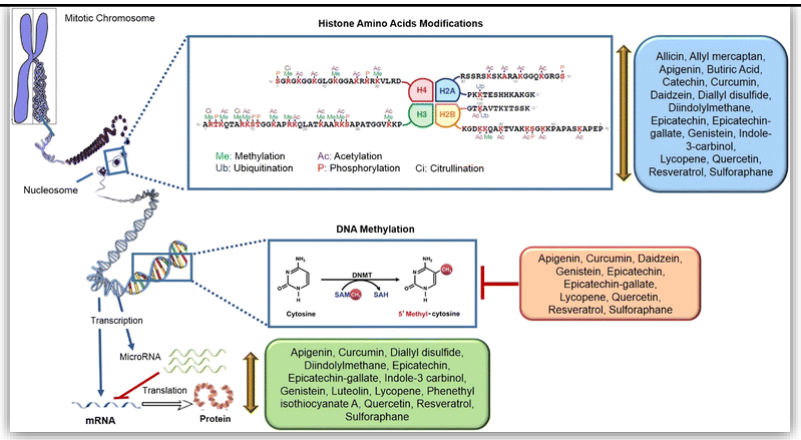
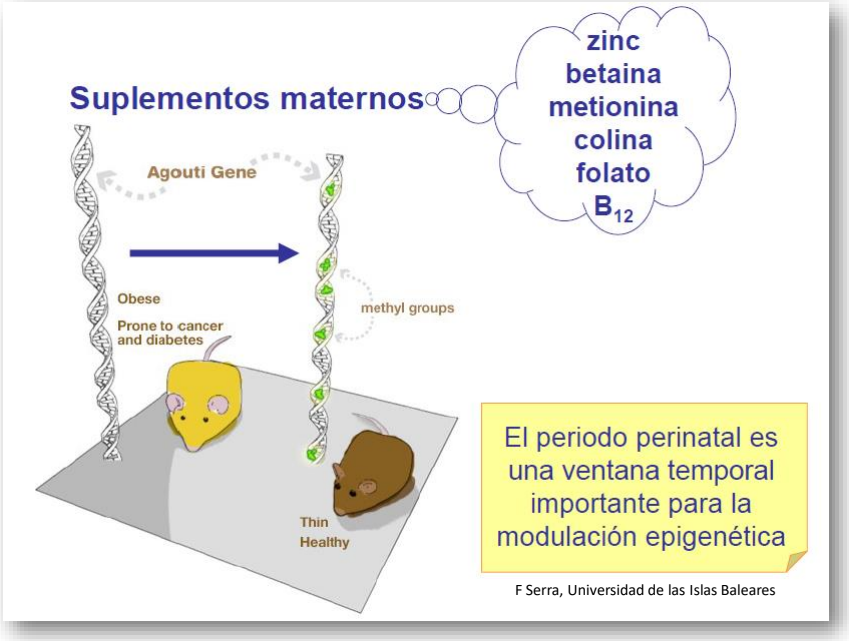


Fig. 4 Overview of epigenetic mechanisms regulating gene expression. Dietary phytochemicals involved in DNA methylation patterns, histone modifications, and changes in microRNA expression.

The status of folic acid, vitamin B12, methionine, choline, and betaine appear to be the most important factor for the DNA methylation pattern, especially because these nutrients play a critical role in methyl groups' availability and collectively regulate the one-carbon metabolism.

Another interesting example is **calorie restriction**, which if not accompanied by nutritional deficiencies, appears to be related to longevity. This effect may be partly mediated by modulation of epigenetic events, as it causes activation of the histone deacetylase sirtuin 1 (SIRT1). SIRT1 also induces deacetylation of histone associated to the FOXO1, FOXO3, and FOXO4 genes, which results in modulation of cell cycle, increased defenses against reactive oxygen species, and reduced apoptosis.

https://nutrirejournal.biomedcentral.com/articles/10.1186/s41110-017-0033-2



Ante la evidencia del papel que juegan los factores ambientales en el desarrollo de estas patologías, en los últimos anos se ha acuñado un nuevo termino, la **nutriepigenómica**, que permite ampliar los conceptos de *nutrigenómica* (cómo los nutrientes influyen en la expresión de los genes) y *nutrigenética* (cómo la secuencia genética condiciona la respuesta individual a determinados nutrientes) y que **estudia los efectos de los nutrientes y los alimentos sobre la salud humana a través de las modificaciones epigenéticas**. Estas modificaciones epigenéticas son cambios heredables en la función y expresión de los genes, que se producen sin alterar la secuencia primaria del ADN, es decir, sin asociarse a polimorfismos.

Esta aproximación ha demostrado que, si se producen desequilibrios nutricionales y alteraciones metabólicas durante determinados momentos críticos del desarrollo, las alteraciones epigenéticas resultantes pueden dar lugar a cambios permanentes en la expresión de determinados genes que afecten a la estructura o función los tejidos y órganos, predisponiendo así a la enfermedad.

Aunque esos cambios epigenéticos pueden ser heredables, hay tres conceptos que hacen muy interesante el estudio de la epigenética:

1) El primero es que los fenómenos epigenéticos parecen representar uno de los mecanismos principales por el que los factores dietéticos y ambientales pueden alterar la expresión de los genes y el metabolismo a largo plazo, explicando así algunos problemas desarrollados en la edad adulta, cuyo origen procede de edades más tempranas o incluso en comportamientos atribuibles a los padres o abuelos.

2) El segundo es que las modificaciones epigenéticas son potencialmente reversibles, lo que abre la puerta a nuevas terapias dietéticas o farmacológicas enfocadas a su modificación, tanto en la infancia como en la edad adulta.

3) El tercero es que la detección precoz de esas marcas epigenéticas alteradas puede ayudar a un diagnóstico precoz de la enfermedad o, aun mejor, a una temprana actuación preventiva previa a su desarrollo. Esto último se representa en la Figura 1, junto con los demás tipos de biomarcadores que se están abordando en nutrición.

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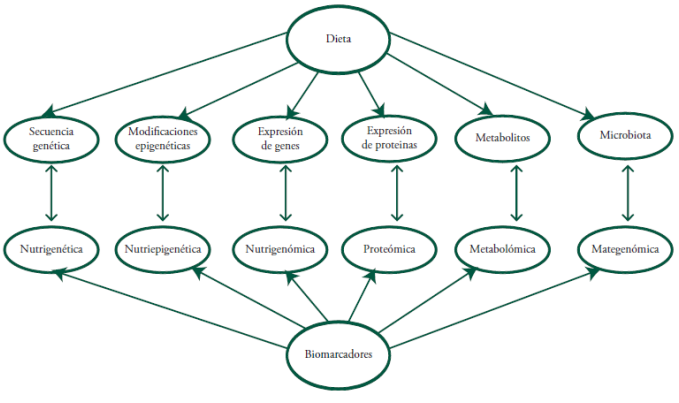
http://www.publicacionescajamar.es/publicaciones-periodicas/mediterraneo-economico/mediterraneo-economico-27-nutricion-y-salud/740/

Figura 1. La dieta interactua con numerosos procesos moleculares a la hora de determinar el riesgo a sufrir una patología, y eso determina también el tipo de biomarcadores y aproximaciones que se pueden abordar para la detección precoz de los individuos en riesgo



Fuente: basado en Nordheim (2012).

La nutrición personalizada a través de la epigenómica, Milagro y Martínez, 2015
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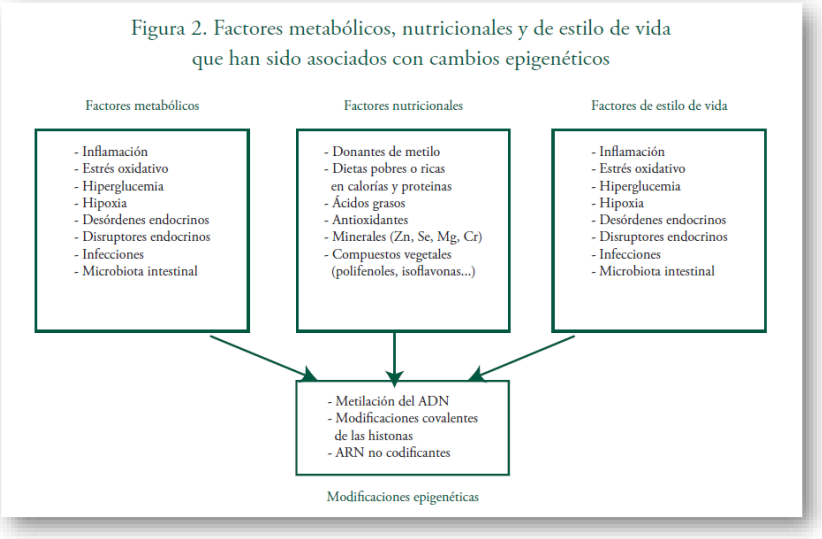


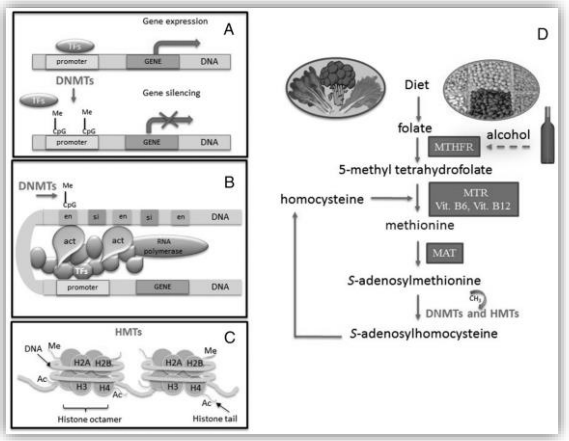
La nutrición personalizada a través de la epigenómica, Milagro y Martínez, 2015
http://www.publicacionescajamar.es/publicaciones-periodicas/mediterraneo-economico/mediterraneo-economico-27-nutricion-y-salud/740/

Table 1. Main nutritional factors influencing the immune system through an epigenetic mechanism.

Nutritional Factors	Epigenetic Mechanism
Folic acid	DNA methylation [25,29,30,31,32,33,34,35,36]
Choline and betaine	DNA methylation [38,39,40]
Vitamins	DNA methylation [2,32] microRNAs [48]
Dietary fibers (butyrate production by gut microbiota) [12]	DNA methylation [21] Histone modifications [10,53]
Fat feeding, protein, hormones	microRNAs [42,43,44,45]
Ethanol	DNA methylation [41] microRNAs [42,43,44,45,49]
Carbohydrates	DNA methylation [50,51,52]

http://www.mdpi.com/2072-6643/6/11/4706/htm

Fig. 1. Simplified folate pathway and connection with DNA/histone methylation. (A) Cytosine methylation hampers gene expression by limiting binding of TFs and RNA polymerases. (B) Gene expression controlled by methylation of regulatory regions. (C) Methyl groups from the folate pathway are used by histone methyltransferases (HMTs) for modifying chromatin structure and finally regulating gene expression. (D) Simplified folate pathway leading to methyl groups useful for DNA and histone methylation. TFs: transcription factors; MTHFR: methylenetetrahydrofolate reductase; MTR: 5-methyltetrahydrofolate-homocysteine methyltransferase; MAT: methionine adenosyltransferase; en: enhancer; act: activator; si: silencer.



The methylation process is strongly dependent on the availability of methyl group donors during pregnancy and through life via the one-carbon metabolism (folate) pathway (Fig. 1D). **The availability of methyl groups is associated with a folate-rich diet (i.e., green leaves, asparagus, beans, lentils, peas, liver, etc.) and to supplementation of folic acid during pregnancy, together with the availability of B6 and B12 vitamins**. Methylenetetrahydrofolate reductase (MTHFR) catalyzes the transfer of a methyl group to folate, leading to 5-methyl tetrahydrofolate and finally to homocysteine which is then converted into methionine by 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR). For this step, the presence of B12 is necessary, and because it is present only in animal food (i.e., meat, fish, eggs), in vegans, a synthetic one can be taken orally through sublingual treatment to avoid its hydrolysis by the liver. Methionine adenosyltransferase (MAT) catalyzes the synthesis of ***S*-adenosylmethionine (SAM), which is the key factor for methylation**, because DNMTs employ its methyl groups to methylate DNA. Alcohol intake, for example, can interfere with SAM synthesis and for this reason should be avoided during pregnancy and breast-feeding, likewise deficits of folic acid and folate from food (Fig. 1D).

https://www.sciencedirect.com/science/article/pii/S0955286317309373?sf186401414=1

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Raíces transgeneracionales de la enfermedad crónica
- Epigenética
- Programación fetal
- Crecimiento compensatorio
- Nutrición materna
- Nutrición fetal
- Thrifty genotype
- Thrifty phenotype
- Thrifty epigenotype.
- Hipótesis de Barker y Lucas

Hambrunas Epigenética

Por qué la dieta de la madre durante el embarazo puede afectar a la salud del hijo

Children wait to be fed during the Dutch Hongerwinter of 1944–1945

Ahmed F. Epigenetics: Tales of adversity. Nature. 468 (Supplement 1):S20, 2010.
https://www.nature.com/articles/468S20a

The Great Chinese Famine, 1958-1961
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049720

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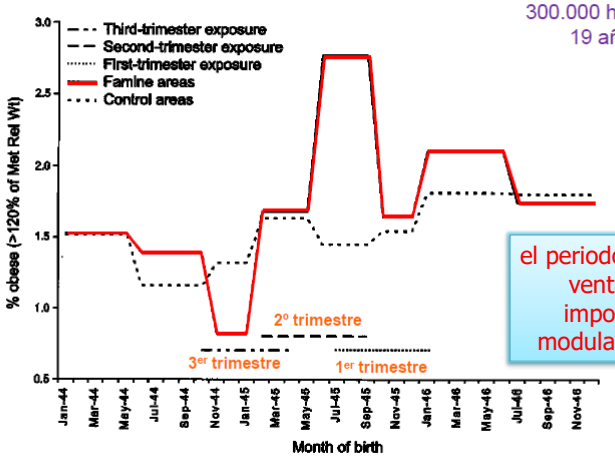
Hongerwinter 1944

- German's blocked food to the Dutch in the winter of 1944.
- Calorie consumption dropped from 2,000 to 500 per day for 4.5 million.
- Children born or raised in this time were small, short in stature and had many diseases including, edema, anemia, diabetes and depression.
- The Dutch Famine Birth Cohort study showed that women living during this time had children 20-30 years later with the same problems despite being conceived and born during a normal dietary state.

https://academic.oup.com/ije/article/36/6/1196/814573
https://www.atherosclerosis-journal.com/article/S0021-9150(17)31270-4/fulltext
http://www.pitt.edu/~super7/45011-46001/45931.ppt
https://es.coursera.org/learn/epigenetics/lecture/GKOzq/5-4-the-dutch-famine-human-epidemiological-studies-and-the-developmental-origins

Estudios de la hambruna holandesa durante la 2ª guerra mundial



el periodo perinatal es una ventana temporal importante para la modulación epigenética

Ravelli et al (1976), NEJM

F Serra, Universidad de las Islas Baleares

http://www.project-earlynutrition.eu/eneu/

Herencia epigenética

Hasta no hace mucho, se estimaba que las marcas epigenómicas se suprimen en el periodo embrionario y se reconstruyen desde cero. Sin embargo ahora se admite que algunas marcas epigenéticas permanecen en su lugar y pasan a la siguiente generación, como la información genética, en un proceso llamado herencia epigenética. Por ejemplo, algunas de las conclusiones obtenidas en el estudio epidemiológico Överkalix, el nombre de una localidad del norte de Suecia de la que hay registro de la mayor o menor disponibilidad de alimentos durante el siglo XIX, solo se pueden explicar a partir de la herencia epigenética transgeneracional (Bygren, 2014). Así, cuando la abuela paterna vivió, hasta la pubertad, varios cambios bruscos (de un año para otro) en el suministro de alimentos, las hijas de sus hijos tenían un riesgo mucho mayor de mortalidad cardiovascular.

Otros resultados proceden del Invierno del Hambre holandés (Hongerwinter) de 1944-45. En este estudio, como era esperable, los hijos de las mujeres que estaban embarazadas durante la hambruna eran más pequeños. Sin embargo, cuando estos niños crecían y tenían sus propios hijos, esos niños también eran, sorprendentemente, más pequeños que la media (Painter, 2008). Estos datos sugieren que la hambruna experimentada por las madres causaba algún tipo de cambio epigenético que se transmitía a la siguiente generación. Este estudio sugiere que algunas marcas epigenéticas se mantienen mucho tiempo después y pueden estar implicadas directamente en el aumento del riesgo a desarrollar enfermedad. Así, los individuos que resultaron expuestos a la hambruna en su época fetal presentaban, seis décadas más tarde, menor metilación en el gen (imprinted) IGF2 (factor de crecimiento insulínico tipo 2) que sus hermanos del mismo sexo no expuestos a la hambruna (Heijmans, 2008). Y los efectos fueron más claros cuando la hambruna ocurrió en la época periconcepcional y los tres primeros meses de gestación.

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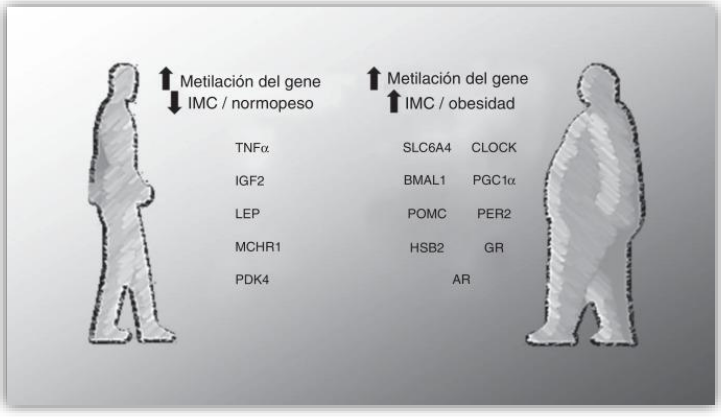
Hipermetilación del ADN y su asociación con la obesidad.

Genes cuyo nivel de metilación se relaciona de manera negativa (panel izquierdo) o positiva (panel derecho) con el IMC o la presencia de obesidad.



https://www.sciencedirect.com/science/article/pii/S037041061630122X

Diet and Epigenetic Signatures

Nutriepigenetic examples of interactions between dietary intakes and epigenetic modifications involved in disease risk

Dietary factors	Epigenetic signatures	Modification types	Putative disease risks	Ref.
Low protein	*NR1H3* acetylation	–	T2DM	[47]
Chromium deficiency	Methylation of insulin signaling genes	+	T2DM	[49]
Selenium deficiency	*TLR2*, *ICAM1* methylation	–	CVD	[50]
Vitamin B_{12} deficiency	*SREBF1*, *LDLR* methylation	–	Dyslipidemia	[51]
Vitamin A deficiency	*GATA4* methylation	+	CVD	[52]
High fat and high sugar	*LEP* methylation	+	Obesity	[65]
High fat	*OPRM1*, *PENK*, and *DAT* methylation	–	Obesity	[74]
Low protein	*CYP7A1* acetylation	–	Dyslipidemia	[75]
Choline and folate deficiencies	miR-134, miR-409-3p, miR-410 and miR-495 expressions	+	NAFLD	[76]
Choline and folate deficiencies	miR-34a, miR-122, miR-181a, miR-192, and miR-200b expressions	+	NAFLD	[77]
Low folate, vitamin A, vitamin B_1, potassium, iron	*P16*, *P14*, and *hMLH1* methylation	+	Cancer	[78]
Selenium deficiency	*VHL* methylation	+	Cancer	[79]
Vitamin D deficiency	*NFKBIA* methylation	+	T2DM	[80]
Calcium deficiency	*HSD11B1* methylation	–	T2DM	[81]
Magnesium deficiency	*HSD11B2* methylation	+	T2DM	[82]
High fat and high sugar	*FASN* methylation	–	Obesity, NAFLD	[88]
Choline and folate deficiencies	*APOE*, *FOXA1*, and *FOXA2* methylation	+	NAFLD	[144]
High fat and high sugar	*FASN* methylation	–	Obesity, NAFLD	[153]
Low fruit consumption and folate deficiency	*LINE-1* methylation	–	Cancer	[154]

LEP, leptin; *FASN*, fatty acid synthase; *OPRM1*, opioid receptor, mu 1; *PENK*, preproenkephalin; *DAT*, dopamine transporter; *CYP7A1*, cytochrome P450 family 7 subfamily A member 1; *NR1H3*, nuclear receptor subfamily 1 group H member 3; *LINE-1*, long interspersed element-1; *MLH1 (HMLH1)*, mutL homolog 1; *APOE*, apolipoprotein E; *FOXA1*, forkhead box A1; *FOXA2*, forkhead box A2; *SREBF1*, sterol regulatory element binding transcription factor 1; *LDLR*, low-density lipoprotein receptor; *NFKBIA*, NFKB inhibitor alpha; *GATA4*, GATA binding protein 4; *TLR2*, toll-like receptor 2; *ICAM1*, intercellular adhesion molecule 1; *VHL*, von Hippel-Lindau; *HSD11B1*, hydroxysteroid 11-beta dehydrogenase 1; *HSD11B2*, hydroxysteroid 11-beta dehydrogenase 2; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease.

Ramos-López y col., Guide for Current Nutrigenetic, Nutrigenomic, and Nutriepigenetic Approaches for Precision Nutrition Involving the Prevention and Management of Chronic Diseases Associated with Obesity. J Nutrigenet Nutrigenomics 2017;10:43-62 - https://www.karger.com/Article/FullText/477729

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Diet and Epigenetic Signatures

Certain nutriepigenetic studies evaluating epigenetic modifications related to diverse nutritional interventions

Nutritional interventions	Epigenetic signatures	Modification types	Potential health effects	Ref.
Apple polyphenols	*SREBF1* methylation	–	Antiobesity	[65]
Apple polyphenols	*PPARGC1A* methylation	+	Antiobesity	[65]
Mediterranean diet	*EEF2*, *IL4I1* methylation	–	Anti-inflammatory	[84]
Mediterranean diet	*MAPKAPK2* methylation	+	Anti-inflammatory	[84]
Mediterranean diet	*IL6* methylation	+	Anti-inflammatory	[85]
Fish oil and pectin	miR-19b, miR-26b, miR-203 expressions	+	Anticancer	[86]
DHA	miR-192, miR-30c expressions	+	Antilipidemic	[87]
Pterostilbene	*FASN* methylation	+	Antiobesity	[88]
Curcumin	p300 HAT activity	–	CVD prevention	[89]
Curcumin	*FGFR3*, *FZD10*, *GPX4*, *HOXD3* methylation	–	Antifibrotic	[90]
Resveratrol	miR-129, miR-328-5p, miR-539-5p		Antilipidemic	[149]
Genistein	P21, P16 chromatin activators	+	Anticancer	[151]
Genistein	P21, P16 chromatin repressors	–	Anticancer	[151]
Methyl donor supplementation	*FASN* methylation	+	Antisteatotic	[155]
Extra-virgin olive oil	CNR1 (CB1) methylation	–	Anticancer	[156]
PUFA	Global DNA methylation	+	Anticancer	[157]
Resveratrol	*BRCA-1* methylation	–	Anticancer	[158]
Resveratrol	miR-101b, miR-455 expressions	+	Anti-inflammatory, anticancer	[159]
Resveratrol	Sirt1 activation	+	Anti-inflammatory, anticancer	[160, 161]
EGCG	*RXRA* methylation	–	Anticancer	[162]
EGCG	miR-16 expression	+	Anticancer	[163]
Green tea polyphenols and EGCG	EZH2, class I HDAC activity	–	Anticancer	[164]
Green tea polyphenols and EGCG	P53 acetylation	+	Anticancer	[165]
Curcumin	miR-22 expression	+	Anticancer	[166]
Sulforaphane	HDAC activity	–	Anticancer	[167, 168]
Sulforaphane	P21 acetylation	+	Anticancer	[168]
Genistein	P21, P16 acetylation	+	Anticancer	[169]

DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid; EGCG, epigallocatechin-3-gallate; *EEF2*, eu-

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Table 1. A summary of the epigenetic and anti-cancer effects of food components.

Food Component	Source	Epigenetic or Cellular Effect	Cancer Effect	Reference
Polyphenols: Genistein	Soybeans	Suppress expression of the androgen receptor (ER-β); inhibition of DMNT; demethylation of *RARβ, p16* and *MGMT* promoters; demethylation of promoters of miR-29a and miR-1256	Inhibition of PCa cell proliferation and invasion; decreased risk of PCa and breast cancer	[2,66,71,72,73,74]
Polyphenols: Resveratrol	Grapes, peanuts	DNMT 3b inhibitor; decrease in *RASSF-1a* methylation with increasing circulating resveratrol; Suppress expression of the androgen receptor	Decreased risk of PCa and breast cancer	[36,70,75]
Polyphenols: Epigallocatechin-3-gallate	Green tea	Demethylation and/or suppressed methylation of TSG promoters (*p15* and *p16*); inhibits HDAC activity.	Antioxidant activity; inhibition of angiogenesis; induction of apoptosis; inhibited invasive metastasis in a human pancreatic adenocarcinoma cell line.	[4,76,77,78,79]
Isothiocyanates	Cruciferous vegetables	Interaction with xenobiotic compounds, smoking and consumption of cruciferous vegetables	Anti-cancer effect: induced apoptosis and suppressed metastatic potential in lung cells.	[80,81,82]
Folate	Periconceptional folic acid supplementation; dark green leafy vegetables	Higher *IGF2* methylation in offspring; higher *hMLH1* promoter methylation	Lower birth weight; association with CRC risk.	[83,84]
Zinc	Seafood, beef, lamb	Zinc deficiency may induce protein kinase B and thus inhibit *PTEN* activity or inhibit alternative cancer associated inflammatory pathways.	Inhibition of cell proliferation in human prostatic carcinoma cell lines; evidence from cell line and mouse model studies (respectively): deficiency may contribute to prostate and oesophageal carcinomer risk and/or progression	[85,86,87]
α linoleic acid	Flaxseed	Decreased expression of COX 1 and COX 2 when fed to male Fischer rats; Decreased COX 2 expression when fed to hens; Changed expression of genes associated with brain	Tumour incidence, multiplicity and size decreased; reduction in ovarian cancer incidence and severity; influence on brain development.	[88,89,90,91]
		development, memory and learning in mice—no correlation between gene expression and methylation status; In mice, maternal supplementation induced hypomethylation of the *FADS2* promoter.		
Omega 3—EPA and DHA	Fish oils	Methylation of the COX 2 promoter in numerous cancer cell lines is linked to COX 2 silencing; Maternal intake of PUFA influences epigenetic regulation of FADS 2 in the offspring.	Fish oils increase apoptosis during tumour initiation and act through the COX 2 pathway; lower levels of COX 2 expression.	[92,93,94]
trans fatty acids	Industrially processed foods and low levels in meat.	DNA hypomethylation in the brains of offspring; histone modifications; hypomethylation at the SacII site in the *ER* gene in response to a diet high in omega 6 PUFA	during seven years of follow-up serum trans MUFA levels were associated with risk of invasive breast cancer.	[95]

COX 2: cyclooxygenase-2; CRC: colorectal cancer; DHA: docosahexaenoic acid; DMNT: DNA methyl transferase; EPA: eicosapentaenoic acid; *ER: Estrogen receptor*; FADS2: fatty acid desaturase 2; HDAC: histone deacetylase activity; *hMLH1: human mutL homolog 1; IGF2: insulin like growth factor 2; MGMT: O-6-methylguanine-DNA* methyltransferase; MUFA: monounsaturated fatty acids; PCa: prostate cancer; *PTEN: Phosphatase and tensin homolog*; PUFA: polyunsaturated fatty acids; *RARβ: Retinoic acid receptor beta; RASSF-1a: Ras association domain family 1 isoform a; TSG: tumour suppressor gene.*

http://www.mdpi.com/2072-6643/7/2/922/htm

Major challenges of personalized nutrition

Limitaciones actuales:
- Falta de resultados robustos y reproducibles,
- Alto coste de tecnologías ómicas y aspectos metodológicos en el diseño,
- Análisis e interpretación de datos (Big-data)

1. Strengthening the science
   - a Creation of risk map
   - b Creation of a reliable 'bank' of polymorphisms
   - c Tests of epigenetic assessment
   - d Identification of valid biomarkers
   - e Microbiome and lipidomics studies
   - f Implementation into public health policies
   - g Metagenomics view
   - h Development of new technologies (bioinformatics) for analyzing data
   - i Applicability to clinical practice
   - j Tools for evaluating diet in nutrigenomic studies
   - k Regulation of ethical and legal aspects
   - l Cost reduction
2. Training personnel and improving knowledge delivery
   - a Increasing availability of trained allied health professionals capable of interpreting genetic data
   - b Greater involvement of dietetic professionals in dietary recommendations
   - c Promoting introduction of nutrigenomic education into the curricula of allied health professionals
   - d Promoting introduction of nutrigenomic education into medical curricula
3. Public education
   - a Communication with and involvement of science writers
   - b Dissemination of 'lay' information via mainstream media in the form of print, screen and social media

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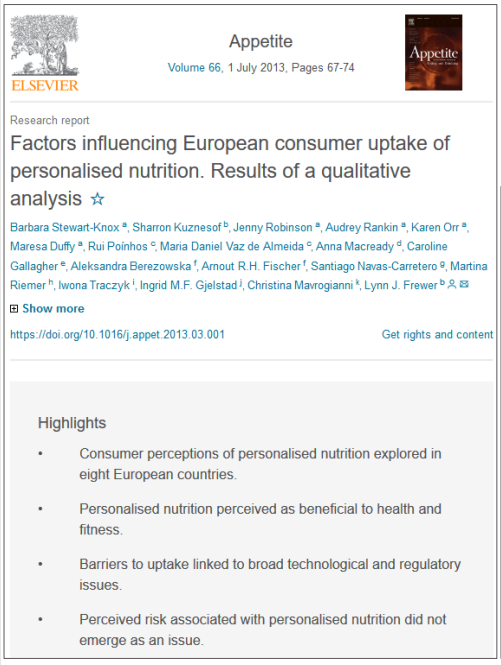
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Appetite

Volume 66, 1 July 2013, Pages 67-74

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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Highlights

- Consumer perceptions of personalised nutrition explored in eight European countries.
- Personalised nutrition perceived as beneficial to health and fitness.
- Barriers to uptake linked to broad technological and regulatory issues.
- Perceived risk associated with personalised nutrition did not emerge as an issue.

Consideraciones éticas

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.

Bueno o malo?

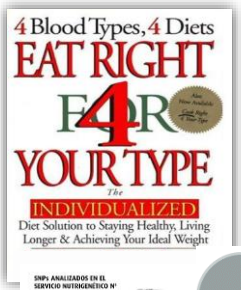
- Bueno …
  - Prevenir y tratar enfermedades
  - Podemos cuidar mejor de la salud.
  - Puede ser un marcador temprano de enfermedad.
- Algunos suplementos y alimentos especiales pueden contribuir a mejorar la salud.

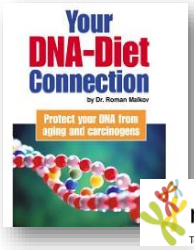
- Ethical, Legal, and Social Issues
  - Coste
  - Interpretación, ..
- Malo …
  - Podemos despreocuparnos de cambiar.
  - Puede crear una sensación de fatalismo.
- Sólo la población con recursos podrá acceder a ello. Creará desigualdad.
- Compañías de seguros!!
- (Etiquetado, ej. "susceptible a enfermedad").
- Riesgo de estafa.

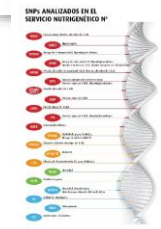
Diabetes Care 2013 May; 36(5): 1413-1421. https://doi.org/10.2337/dc12-2211
http://care.diabetesjournals.org/content/36/5/1413

https://jandonline.org/article/S2212-2672(13)01783-8/fulltext
https://www.karger.com/Article/FullText/446347

El Mercado …





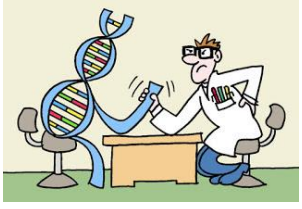


https://www.gao.gov/products/GAO-06-977T

Era post-genómica

Genómica nutricional

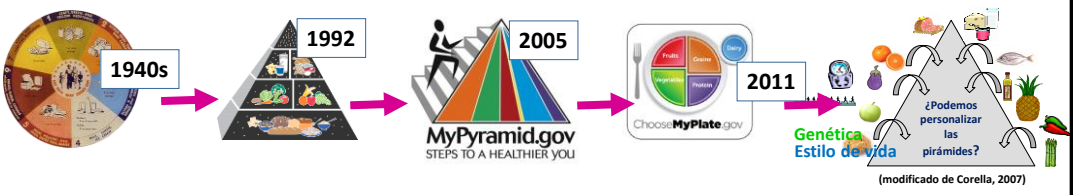
- No nos dejemos engañar por los productos del mercado que prometen milagros.
- Todavía una ciencia muy joven.



El riesgo genético se hereda, pero puede modularse

Las interacciones entre genotipo, fenotipo metabólico, dieta, estilo de vida y ambiente

→ Dieta personalizada, Nutrición de precisión



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"Our challenge is to persuade children to tell their parents to eat as Mediterraneans do"
(Keys, 1995)

"Deja que sea tu alimento tu mejor medicina"
Aforismos Hipocráticos (460-377aC)

https://ich.unesco.org/es/rl/la-dieta-mediterranea-00884

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