The omics approach in measuring the double burden of malnutrition.
In addition to environmental factors, genetic factors are important in determining the risk of disease.
The Human Genome Project has been crucial in developing the technology for genetic analyses.
Single Nucleotide Polymorphisms (SNPs) are the most common type of genetic variation among people.

3 genotypes: Models: Additive Dominant Recessive
Other "omics"

- SNP
- CNV
- LOH
- Genomic rearrangement
- Rare variant
- DNA methylation
- Histone modification
- Chromatin accessibility
- TF binding
- miRNA
- Gene expression
- Alternative splicing
- Long non-coding RNA
- Small RNA
- Protein expression
- Post-translational modification
- Cytokine array
- Metabolite profiling in serum, plasma, urine, CSF, etc.

Phenome
- Cancer
- Metabolic syndrome
- Psychiatric disease
Epigenetics is the study of heritable changes in gene expression that does not involve changes to the underlying DNA sequence.

DNA-methylation

Is the addition of a methyl (CH$_3$) group to DNA (cytosine), often modifying gene expression.

Histone Modifications

Micro-RNA regulation
- **Transcriptomics.** Focuses on RNA expression, including the analysis of the whole transcriptome or differences in the expression of selected genes.

- **Proteomics:** Is the study of the proteome.

- **Lipidomics:** Focuses on the study of the lipidome (comprehensive analysis of the molecular lipid species).

- **Metabolomics:** Focuses 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.
Hypotheses, to explain why certain populations in the modern day are prone to obesity, type 2 diabetes and other chronic diseases

1. The thrifty genotype hypothesis

In 1962, James Neel suggested that exposure to periods of famine during human evolutionary history resulted in selection pressures in favour of a “thrifty genotype”. Individuals carrying thrifty genes would thus better survive times of food scarcity.

However, in an abundance of foods, this thrifty genotype is suggested to lead to metabolically detrimental phenotypes (obesity, type-2 diabetes, etc.) (Am J Hum Genet, 1962)

2. The thrifty phenotype hypothesis

Barker (Diabetologia, 1992) suggested that poor nutrition at certain stages of pregnancy, programs the fetus for more efficient utilization and storage of energy and this is associated with increased risk of obesity and type 2 diabetes later in life.
Can We Escape Our Genes?
Example of a thrifty genotype: The Apolipoprotein A2 (APOA2) genotype

Lipoproteins

APOA-II the second most important apolipoprotein of HDL-C

Cromosome 1

APOA2 GENE

-265 T/C

PROMOTER

Studies With Apolipoprotein A-II Transgenic Mice Indicate a Role for HDLs in Adiposity and Insulin Resistance
Lawrence W. Castellani, Aimie M. Goto, and Aldons J. Lusis

Diabetes, 2001

APOA2 genotypes

TT (Normal)

TC

CC (Thrifty genotype)

Higher obesity risk
Analysis of a gene-diet interaction between the APOA2 genotype and saturated fat

APOA2, Dietary Fat, and Body Mass Index

Replication of a Gene-Diet Interaction in 3 Independent Populations

Dolores Corella, PhD; Gina Peloso, MSc; Donna K. Arnett, PhD, MSPH; Serkalem Demissie, PhD; L. Adrienne Cupples, PhD; Katherine Tucker, PhD; Chao-Qiang Lai, PhD; Laurence D. Parnell, PhD; Oscar Coltell, PhD; Yu-Chi Lee, MSc; Jose M. Ordovas, PhD

First gene-diet interaction study in obesity replicated in 3 different populations

Between the APOA2 gene promoter (-265T>C) and saturated fat

Obesity risk for the CC genotype depending on SATFAT intake
Interaction between the -265T>C APOA2 polymorphism and Saturated fat intake in determining BMI in the Framingham Study

![Graph showing interaction between APOA2 polymorphism and saturated fat intake](image)

Corella et al, Arch Int Med 2009
Replication of the APOA2-saturated fat interaction in three American populations

Corella et al, Arch Int Med 2009
Replication of the APOA2-diet interaction in the Mediterranean population

Association between the APOA2 promoter polymorphism and body weight in Mediterranean and Asian populations: replication of a gene–saturated fat interaction

Identifying new candidate genes and polymorphisms associated with the double burden of malnutrition

To identify these SNPs:
- Traditional candidate gene approach,
- Genome wide association studies” or GWAs

-In these studies high density arrays are used to determine hundreds of thousands of polymorphisms

-and then the statistical significance of the association between the marker and the trait is estimated. The results are represented on Manhattan plots.
- Many GWAs have been carried out focusing on BMI.
- Dozens of new genes and polymorphisms related to obesity have been identified.
- Among which we could mention the FTO locus (Science, 2007). Other genes are NEGR1, TMEM18, MC4R, FAIM2, etc.
FTO is also a thrifty genotype. Gene-diet interactions have been reported.

A High Intake of Saturated Fatty Acids Strengthens the Association between the Fat Mass and Obesity-Associated Gene and BMI$^{1-3}$

Dolores Corella,$^{4-6}$ Donna K. Arnett,$^{7,14}$ Katherine L. Tucker,$^{8,14}$ Edmond K. Kabagambe,$^7$ Michael Tsai,$^9$ Laurence D. Parnell,$^4$ Chao-Qiang Lai,$^4$ Yu-Chi Lee,$^4$ Daruneewan Warodomwichit,$^{10}$ Paul N. Hopkins,$^{11}$ and Jose M. Ordovas$^{4,12,13}$

### Table 1. General characteristics of the study population.$^9$

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>514</td>
<td>564</td>
</tr>
<tr>
<td>Age, years</td>
<td>49.1 (16.1)</td>
<td>48.1 (16.3)</td>
</tr>
<tr>
<td>Weight, kg$^9$</td>
<td>90.5 (16.4)</td>
<td>75.9 (17.1)</td>
</tr>
<tr>
<td>Height, m$^9$</td>
<td>1.78 (0.72)</td>
<td>1.65 (0.68)</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>28.5 (4.9)</td>
<td>28.0 (6.2)</td>
</tr>
</tbody>
</table>

Boston Puerto Rican Health Study
In addition, there is an $\text{FTO}^\text{physical activity}$ interaction

Physical Activity Attenuates the Influence of $\text{FTO}$ Variants on Obesity Risk: A Meta-Analysis of 218,166 Adults and 19,268 Children

- Higher physical activity counteracted the effects of the $\text{FTO}$ risk allele.
From among all the genes discovered, we can see that two of them, the FTO (Fat Mass and Obesity) and the MC4R (Melanocortin 4 Receptor) occupy a central position, currently being the most relevant.
Genetic Risk Score (GRS)

\[
\text{GRS}_{\text{unweighted}} = \sum_{i=1}^{n} \text{SNP}_i = \text{SNP}_1 + \text{SNP}_2 + \text{SNP}_3 + \text{SNP}_4
\]

\[
\text{GRS}_{\text{weighted}} = \sum_{j=1}^{m} E_j \cdot \text{SNP}_j = E_1 \cdot \text{SNP}_1 + E_2 \cdot \text{SNP}_2 + E_3 \cdot \text{SNP}_3 + E_4 \cdot \text{SNP}_4
\]

\[
= 3 \cdot \text{SNP}_1 + 0,7 \cdot \text{SNP}_2 + 2,5 \cdot \text{SNP}_3 + 1,3 \cdot \text{SNP}_4
\]
Association between a GRS of the FTO and MC4R SNPs and BMI

<table>
<thead>
<tr>
<th></th>
<th>FTO rs9939609 (n = 7,052)</th>
<th>MC4R rs17782313 (n = 7,019)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT (n = 2329)</td>
<td>TT (n = 4336)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.0 (6.2)</td>
<td>66.9 (6.2)</td>
</tr>
<tr>
<td>Adherence to the Mediterranean diet (points)</td>
<td>8.6 (1.9)</td>
<td>8.7 (2.0)</td>
</tr>
<tr>
<td>Energy intake (kcal/d)</td>
<td>2288.2 (616.1)</td>
<td>2274.3 (607.1)</td>
</tr>
<tr>
<td>Physical activity** (kcal/d)</td>
<td>228.7 (234.6)</td>
<td>231.4 (239.5)</td>
</tr>
</tbody>
</table>

Figure 1. Association between the aggregate genetic score of the FTO rs9939609 and MC4R rs17782313 and body mass index (BMI). Multivariate adjusted means. Error bars: SE of means. 0 points (non-variant alleles); 1 point (one variant allele either at FTO or MC4R; 2 points (two variant alleles), 3 points (3 variant alleles) and 4 points (4 variant alleles). P¹: unadjusted P-value for the comparison of means; P²: adjusted for sex, age, center, diabetes, energy intake and physical activity.
Statistically significant interaction FTO/MC4R with physical activity (PA) in a Mediterranean population

N>7000

Corella et al, PlosONE, 2012
Gene-environment interaction between the FTO polymorphism and education in determining BMI in a Mediterranean population

Corella et al, NMCD; 2011
**EPIGENOMICS:** DNA methylation of Selected genes or Epigenome-Wide-association studies (EWAS)

**Figure 5:** Methylation (%) between diabetics and non-diabetics in CpG4

**Figure 6:** Methylation (%) according to physical activity in CpG5

**Figure 7:** Methylation (%) according to the adherence to a Mediterranean Diet in CpG4
Epigenome-Wide Study Identifies Novel Methylation Loci Associated with Body Mass Index and Waist Circumference

<table>
<thead>
<tr>
<th>TABLE 1: Demographic and anthropometric characteristics of the study populations</th>
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<tbody>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Sex, % female</td>
</tr>
<tr>
<td>Race, %</td>
</tr>
<tr>
<td>European American, %</td>
</tr>
<tr>
<td>African American, %</td>
</tr>
<tr>
<td>Current smokers, %</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
</tr>
</tbody>
</table>

*Values are shown as mean ± SD or %.

Carnitine palmitoyltransferase 1A (CPT1A):
- This enzyme is essential for fatty acid oxidation, a multistep process that breaks down (metabolizes) fats and converts them into energy.
- Higher methylation status of CPT1A results in decreased expression of the gene, which in turn is negatively correlated with BMI and WC.
- Dietary factors such as intake of long-chain monounsaturated fatty acids have also been shown to regulate CPT1A expression as well as DNA methylation patterns.

Carayol et al, J Proteome Res. 2017
Integration of the different omics is one of the main challenges in biomedical research. There are still huge computational limitations and only partial integration. Studies are been undertaken.
Until now, most medical treatments have been designed for the “average patient.”

As a result of this “one-size-fits-all” approach, treatments can be very successful for some patients but not for others.

**Precision Medicine/Nutrition**, on the other hand, is an innovative approach that takes into account individual differences in people’s genes, environments, and lifestyles.
- **OMICs** technologies may help us to identify the pathways of malnutrition. **GWAs** and **EWAs** could be specifically applied to the phenotype of the double burden of malnutrition, including, as cases, subjects who respond to that definition.

  Similarly, metabolomics and the other Omics can be integrated too in a multi-omics approach.

- However, although the various omics may help us to identify certain forms of malnutrition, their direct application to the prevention and treatment is still not possible, as they are still in a research stage and more work is needed.

- Due to the fact that these techniques are still expensive to use, particular attention must be paid to not increasing inequality of access to them, depending on socio-economic factors.
THANK YOU