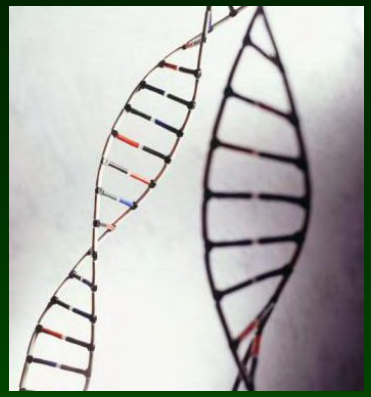


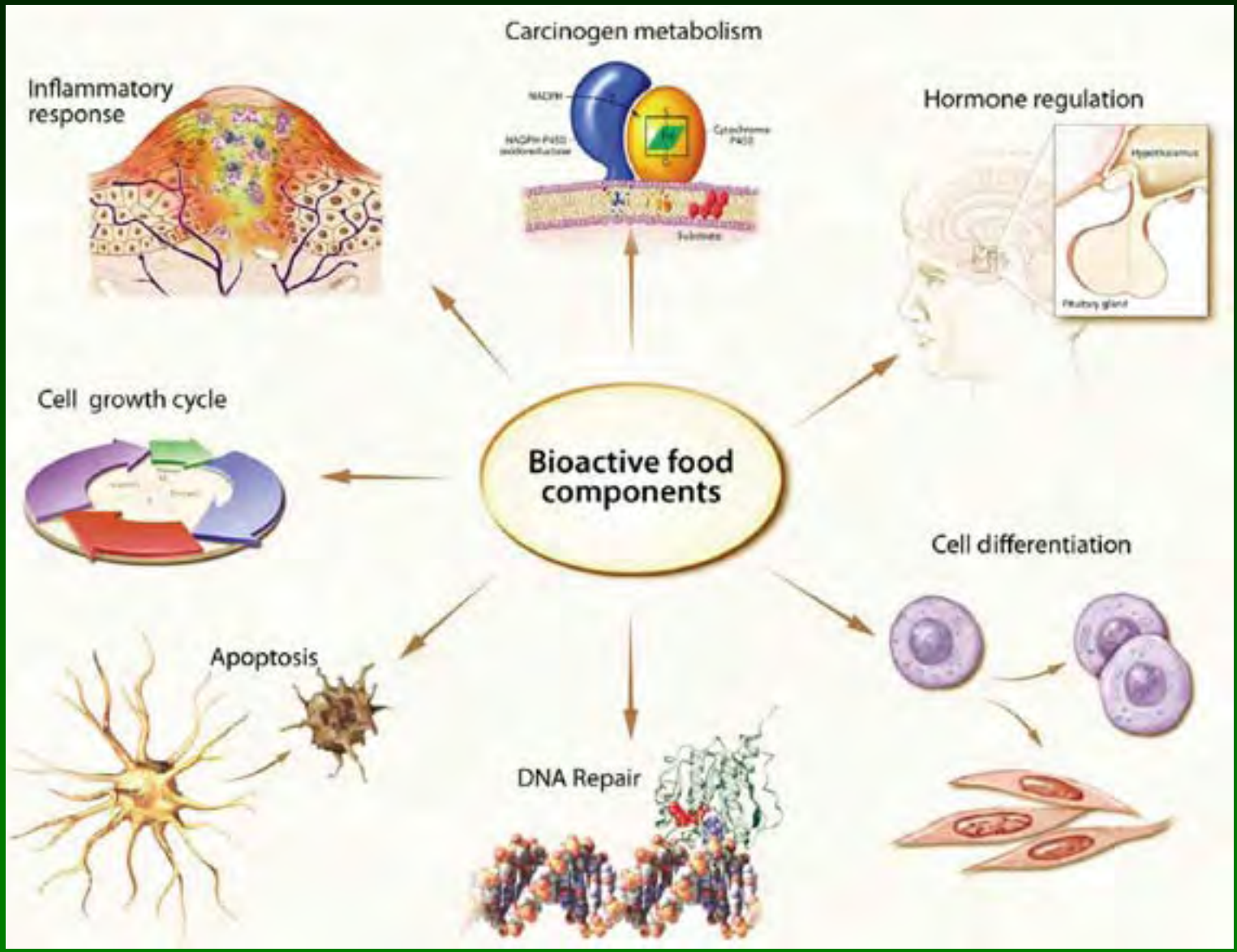
NUTRIGENOMICS, THE NEW FRONTIER IN NUTRITION RESEARCH

Giuditta Perozzi, Chiara Murgia and Carlo Cannella#

INRAN - National Research Institute on Food & Nutrition, Roma, Italy

 # University of Rome La Sapienza, Roma, Italy

Parma, october 4, 2007



SIMULTANEOUS CHANGES IN SEVERAL PATHWAYS DEFINE A RESPONSE PHENOTYPE

MOLECULAR NUTRITION STUDIES

DIET

NUTRIENTS AND BIOACTIVE FOOD COMPONENTS

Metabolism

Signal transduction

GENE EXPRESSION

HOMEOSTASIS

TRANSCRIPTION FACTORS MEDIATING NUTRIENT-GENE INTERACTIONS

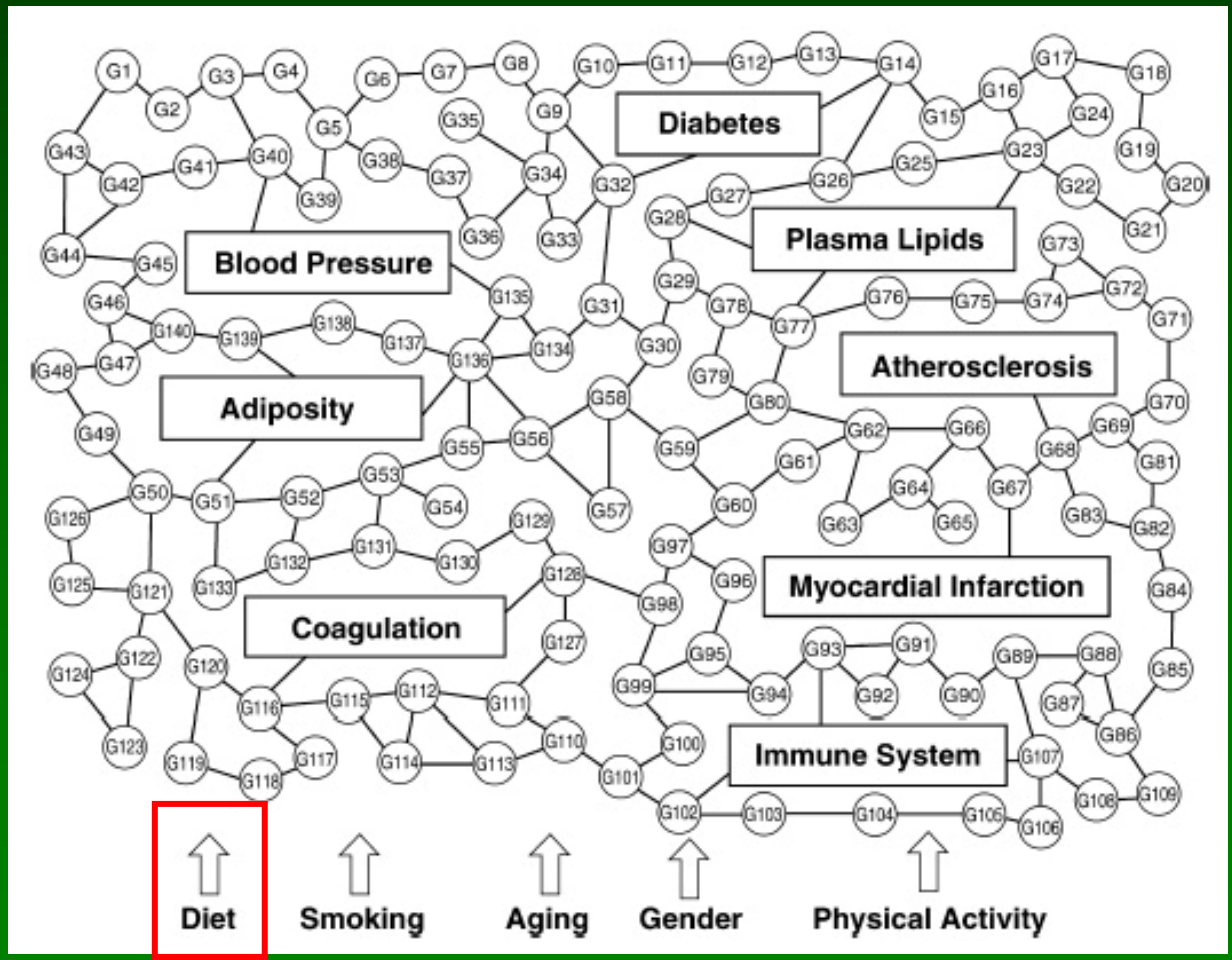
	MOLECULE	TRANSCRIPTION FACTORS
MACRONUTRIENTS		
Lipids	Fatty acids	PPARs, SREBPs, LXR, HNF4, ChREBP
	Cholesterol	SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Aminoacids	C/EBPs
MICRONUTRIENTS		
Vitamins	Vitamin A	RAR, RXR
	Vitamin D	VDR
	Vitamin E	PXR
Minerals	Calcium	Calcineurine/NF-ATs
	Iron	IRP1, IRP2
	Zinc	MTF1
BIOACTIVE MOLECULES		
	Flavonoids	ER, NF-kB, AP1
	Xenobiotics	CAR, PXR

FOOD COMPONENTS AS HEALTH FACTORS

Regular uptake of specific food components was associated with decreased incidence of chronic diseases such as cardiovascular diseases and some types of diabetes and cancer.

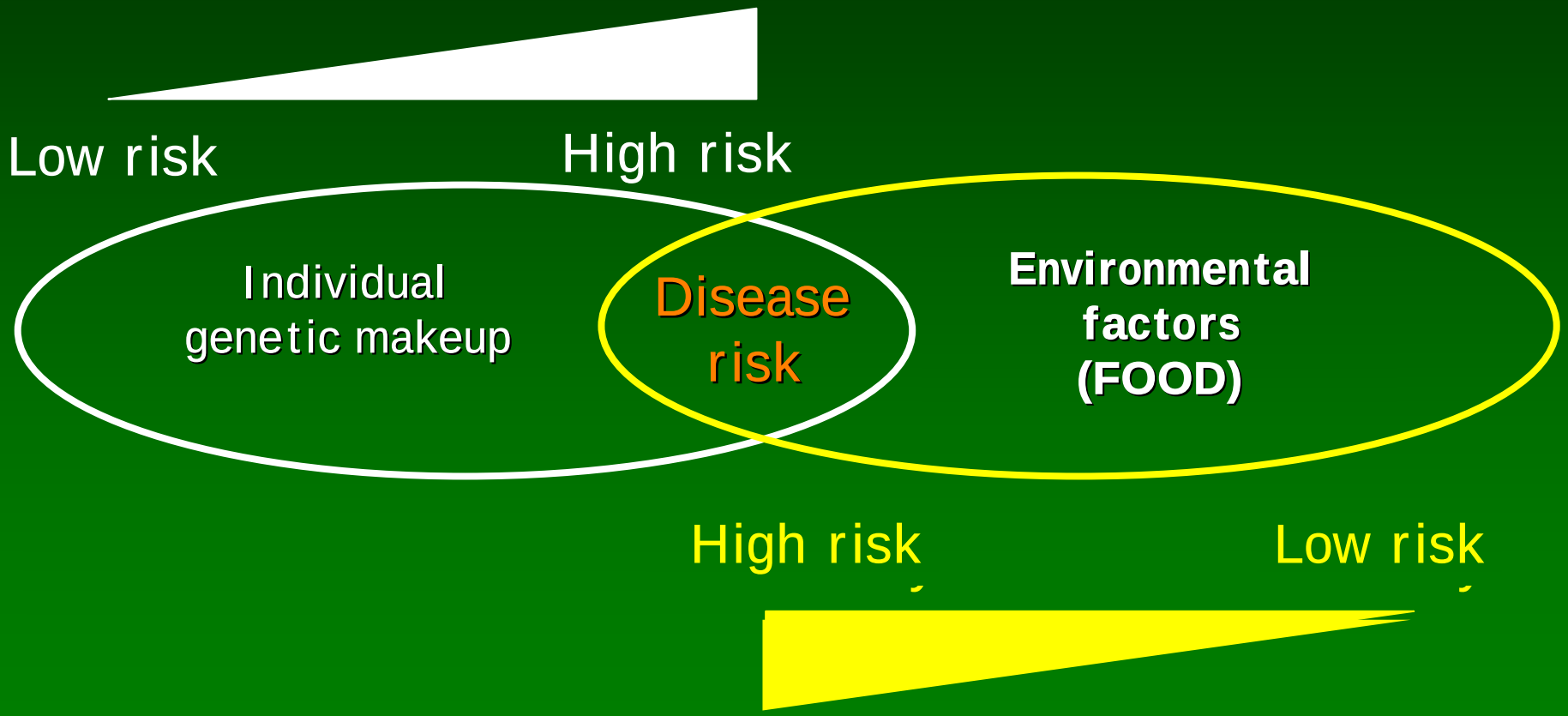
These results have led to the concept of OPTIMAL NUTRITION, which includes not only adequate nutrient uptake to meet physiological needs, but also the presence of food components shown to be capable of dicreasing the risk of chronic diseases

The majority of nutritionally related chronic diseases are **POLYGENIC AND MULTIFACTORIAL**, as their onset and progression are affected by multiple genes (and GENE VARIANTS) as well as by SEVERAL ENVIRONMENTAL FACTORS



Ghazalpour et al., 2004

GENE-NUTRIENT INTERACTION AND DISEASE RISK



INDIVIDUALS CONSUMING THE SAME DIET HAVE DIFFERENT DISEASE RISK DEPENDING ON THEIR GENETIC MAKEUP

INDIVIDUALS CARRYING THE SAME GENOTYPE HAVE DIFFERENT DISEASE RISK DEPENDING ON THEIR DIETARY HABITS

GENETIC MAKEUP AFFECTS PHYSIOLOGICAL RESPONSE TO DIET

PROTECTIVE ALLELES
vs
"RISKY" ALLELES

Park et al., 1997. J. Nutr. 127: 566

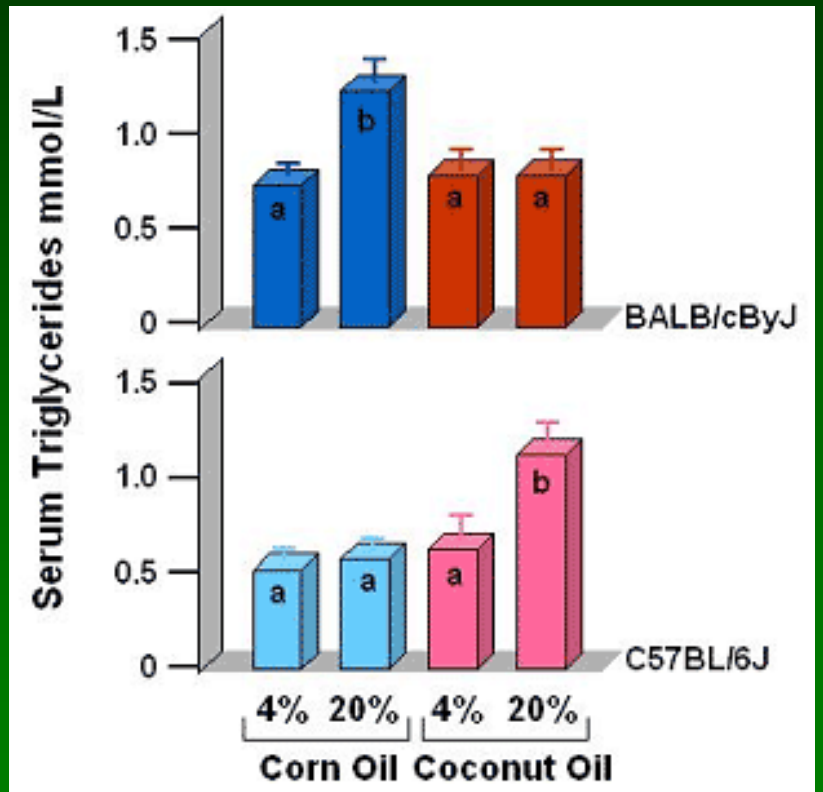


Figure 2: Serum tryiglyceride levels respond differently to different types and levels of corn and coconut oil in BALB/c vx C57BL/6. Strain X oil source interaction p = 0.009, strain X oil source X level interaction = 0.014

NUTRIGENOMICS

Study of nutrient-gene interactions at the genome level (transcriptome, proteome, metabolome) with the aim of lowering the risk of diet-related diseases

But also.....

Study of the individual genetic makeup (genotype) and its effect on nutrient metabolism (NUTRIGENETICS)

Hyppocrates:

Leave medicines in the chemist's pot if you can cure your patients with food

THE LONG-TERM GOAL OF NUTRIGENOMICS IS TO IDENTIFY NUTRITION-RELATED DISEASE GENES AND TO DEVELOP PERSONALIZED DIETS BASED ON GENETIC MAKEUP TO LOWER DISEASE RISK

NUTRIGENOMICS CONCEPTS

Some dietary compounds affect gene expression

Some diet-regulated genes could play a role in the onset, progression, and/or severity of chronic diseases.

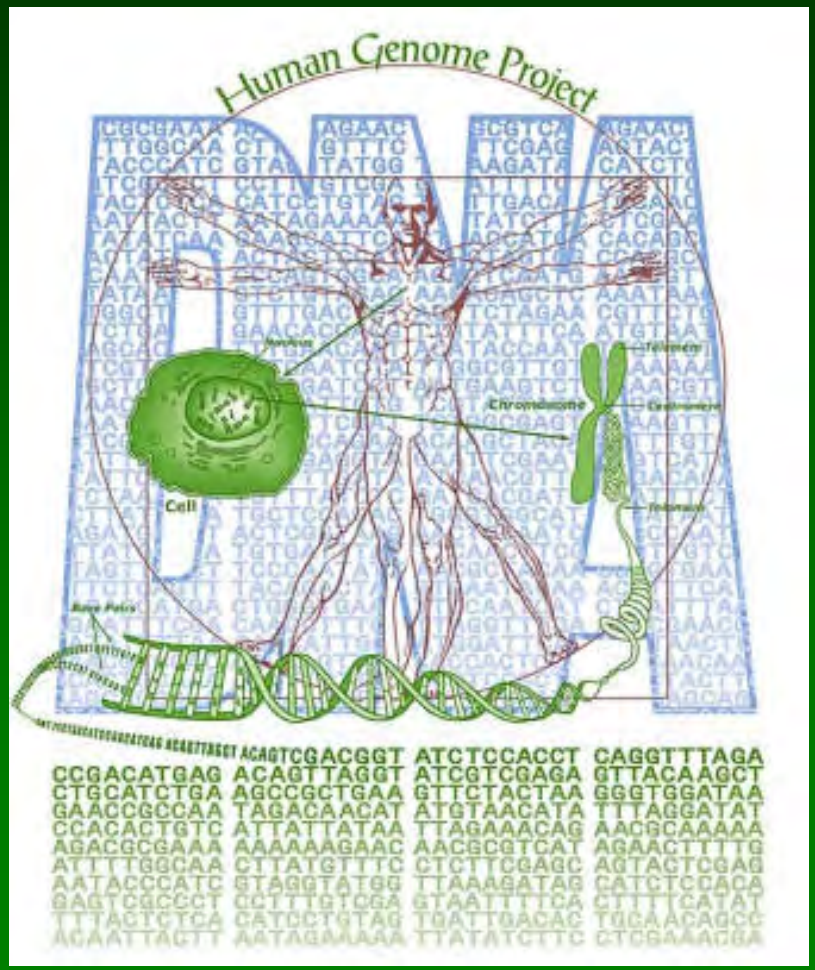
Diet can therefore represent a risk factor for some chronic diseases

Influence of diet on health depends on individual genetic makeup.

"PERSONALIZED DIETS" BASED ON NUTRITIONAL REQUIREMENTS, NUTRITIONAL STATUS, AND GENOTYPE COULD PREVENT, MITIGATE OR CURE CHRONIC DISEASE

COMPLETION OF HUMAN GENOME SEQUENCING IN 2001

(International Human Genome Sequencing Consortium)



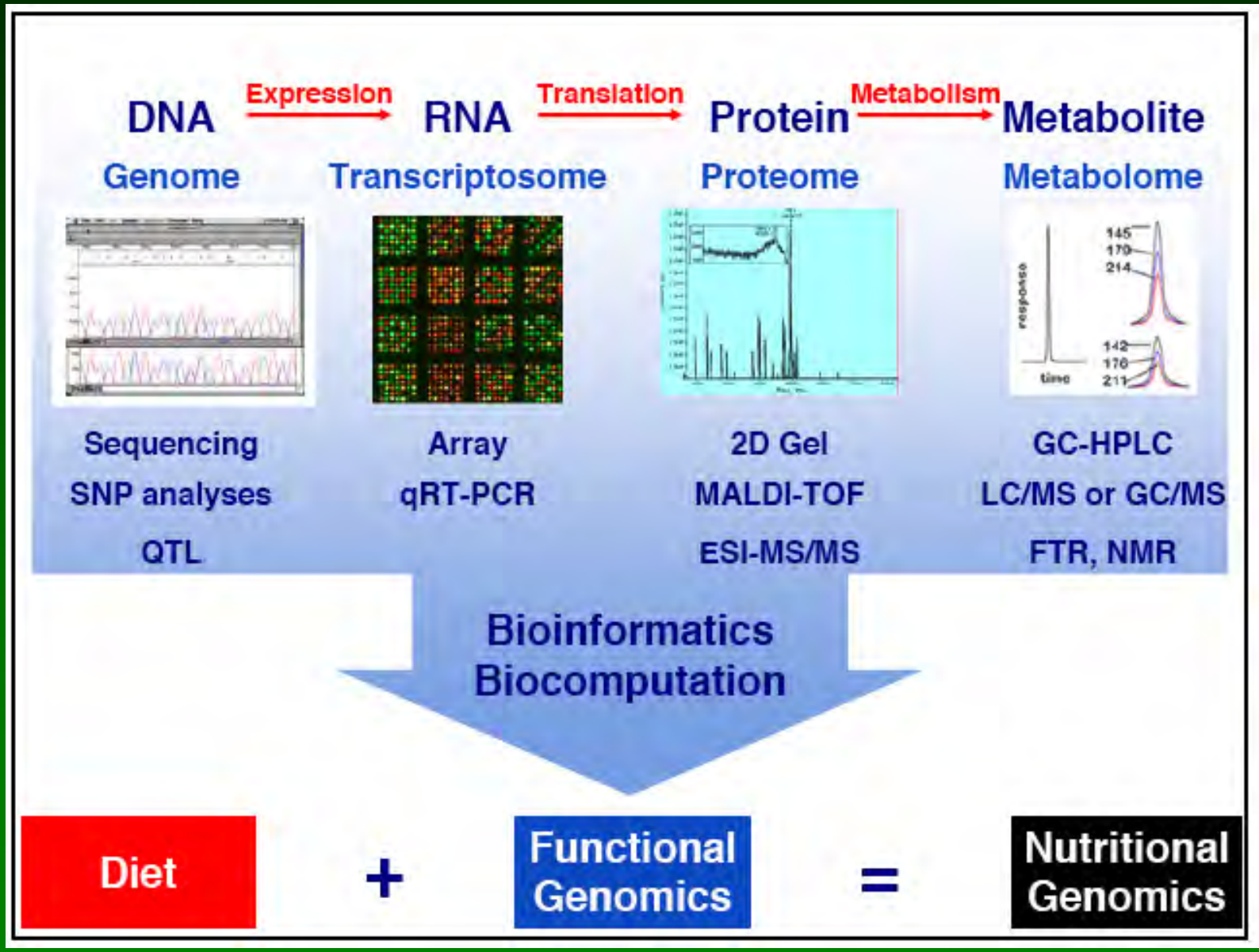
BIOINFORMATICS

(acquisition, management, storage, retrieval of high throughput datasets)

BIOCOMPUTATION

(analysis of high throughput datasets)

HIGH THROUGHPUT NUTRIGENOMICS TECHNOLOGY



NUTRIGENETICS

Identification of genetic polymorphisms associated with increased disease risk and of their modulation with dietary intervention

SNP = Single Nucleotide Polymorphism

Allelic gene variant detected within a population group with higher frequency than expected from independent mutations

APR 1999 - OTT 2005

SNP CONSORTIUM (20 labs in 6 nations)

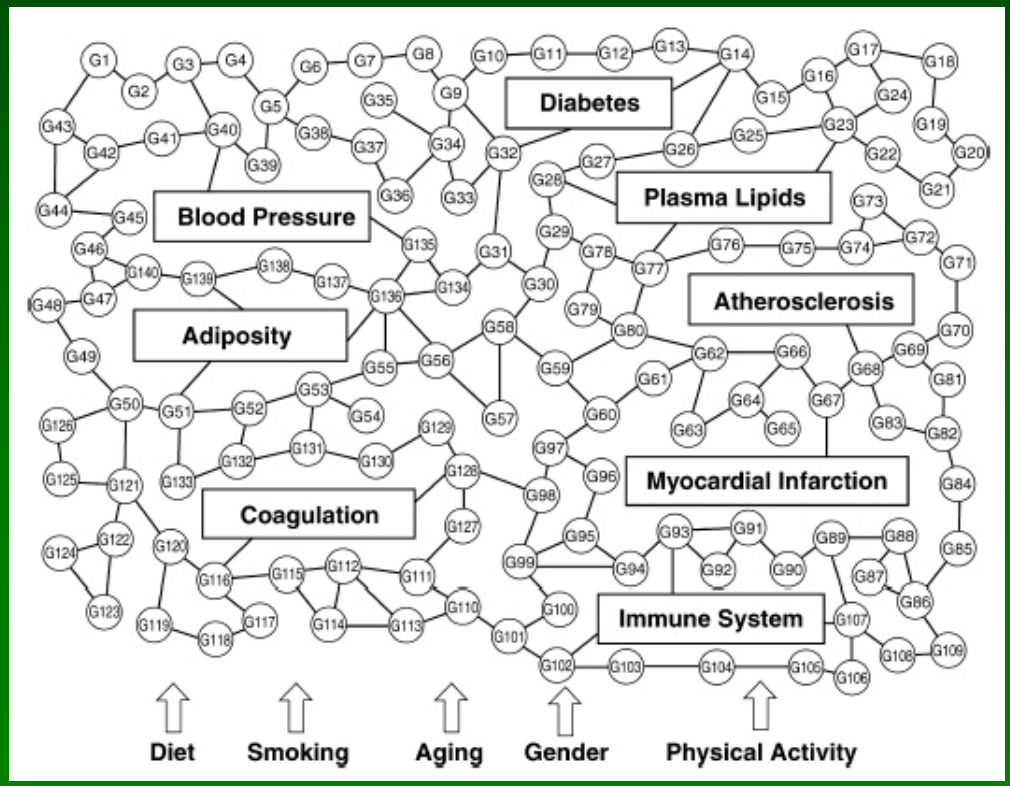
ANALYSIS OF > 1 million SNPs

- **THE GENOMES OF UNRELATED HUMAN BEINGS IS 99.9% IDENTICAL**

- **INDIVIDUAL GENETIC VARIATION IS ACCOUNTED FOR BY THE REMAINING 0.1% INDIVIDUAL VARIATION**

Small changes in gene sequence can cause significant, demonstrated and unequivocal changes in enzyme activity or protein function.

Such changes can have significant health effects.



Dietary and/or lifestyle changes can have a positive effect and overcome the effect of the gene variant

Ghazalpour et al., 2004

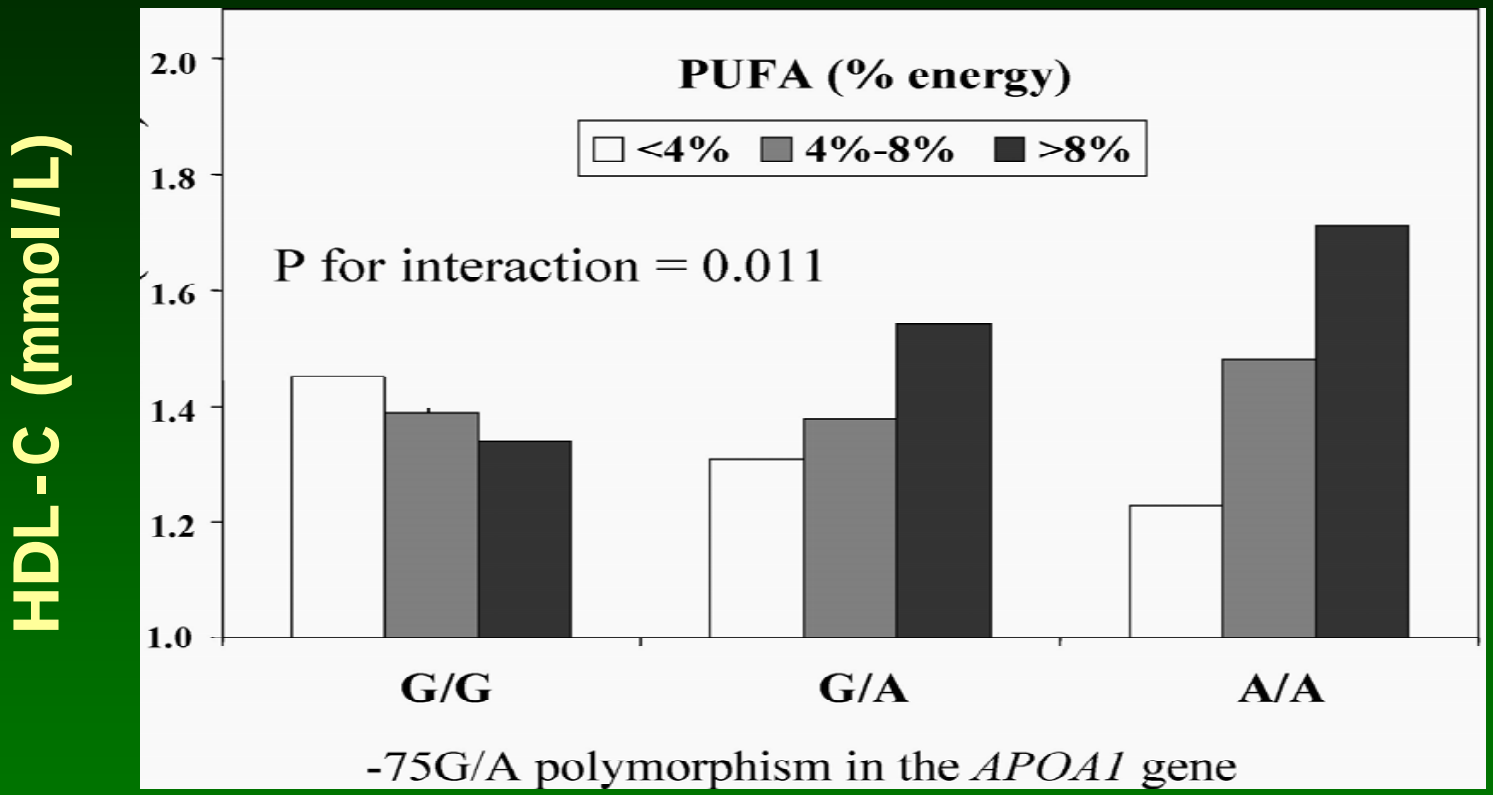
EXAMPLES: 1. SNPs ASSOCIATED WITH DIFFERENTIAL CVD RISK

LIPID TRANSPORT

- Cholesteryl ester transport protein CETP
- Phospholipid transport protein PLTP
- Microsomal tryglyceride transport protein MTP
- Fatty Acid transport protein FATP1
- Apolipoprotein E
- Apolipoprotein A

BLOOD PRESSURE

- eNOS
- Endothelin-1
- Prostacyclin synthase



Effect of APOA1 (SNP -75G/A) on serum concentration of HDL-cholesterol, in response to diets containing different amounts of PUFAs

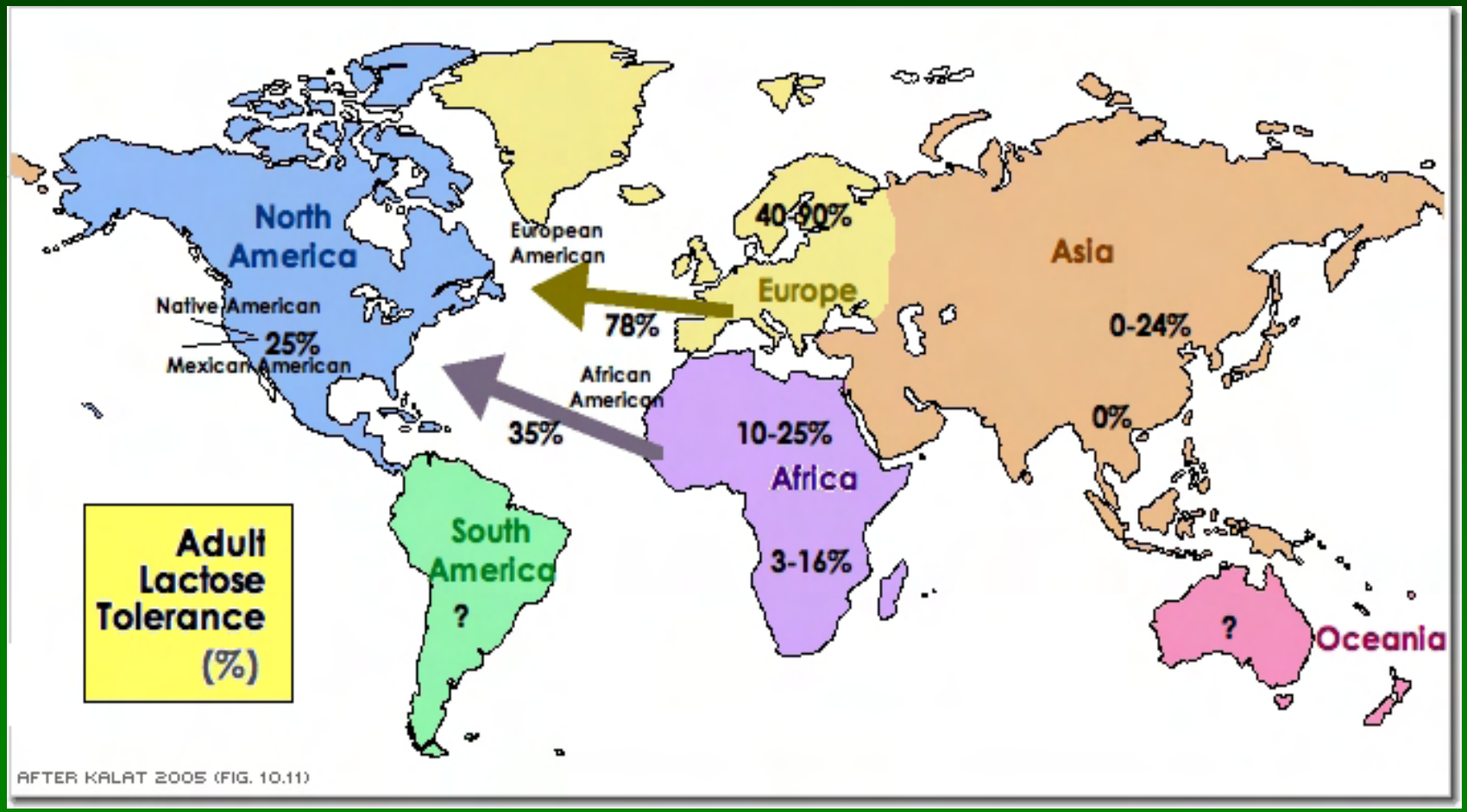
EXAMPLES - 2. LACTOSE INTOLERANCE

70% Afro-Americans

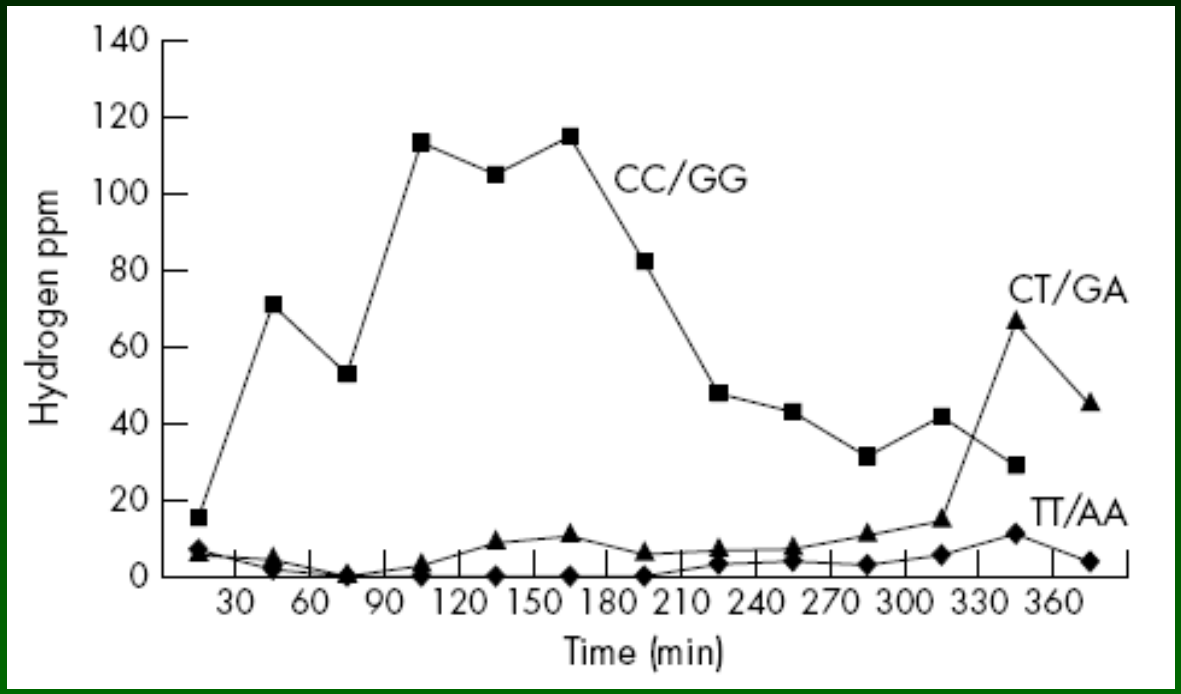
90% Asian Americans

53% Mexican Americans

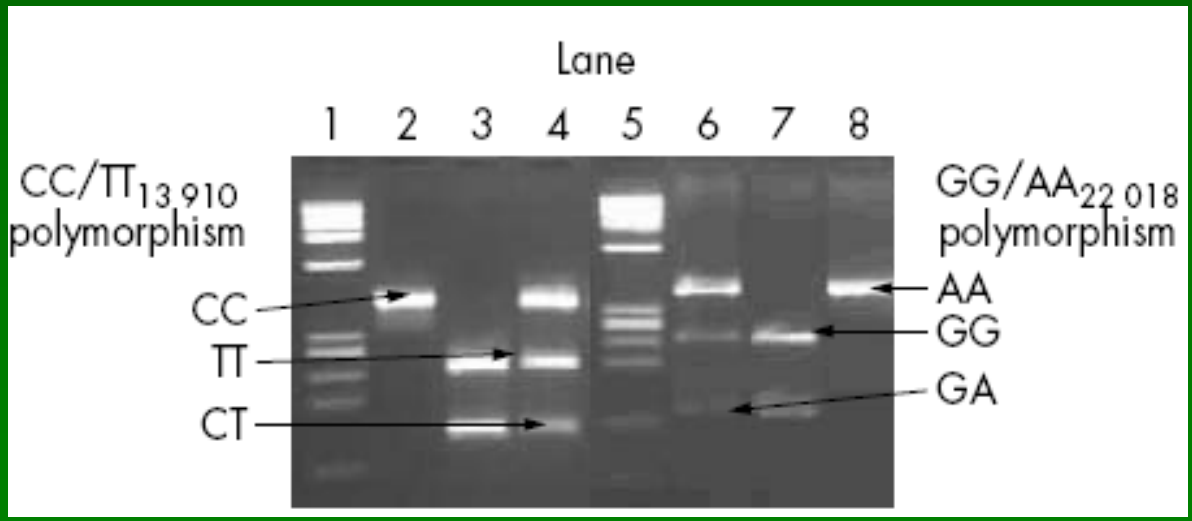
74% American Indians



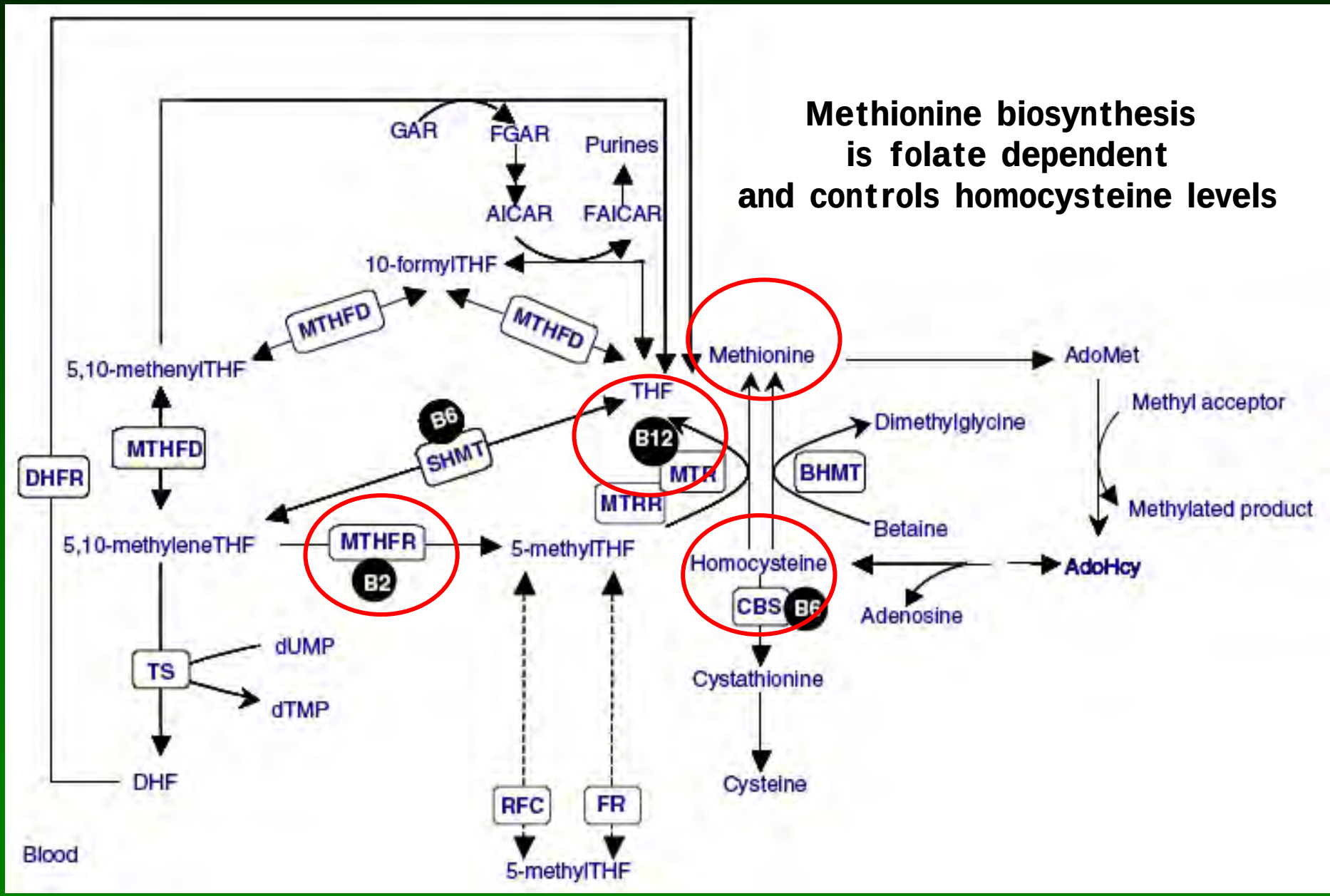
GENOTYPING OF LACTOSE INTOLERANCE



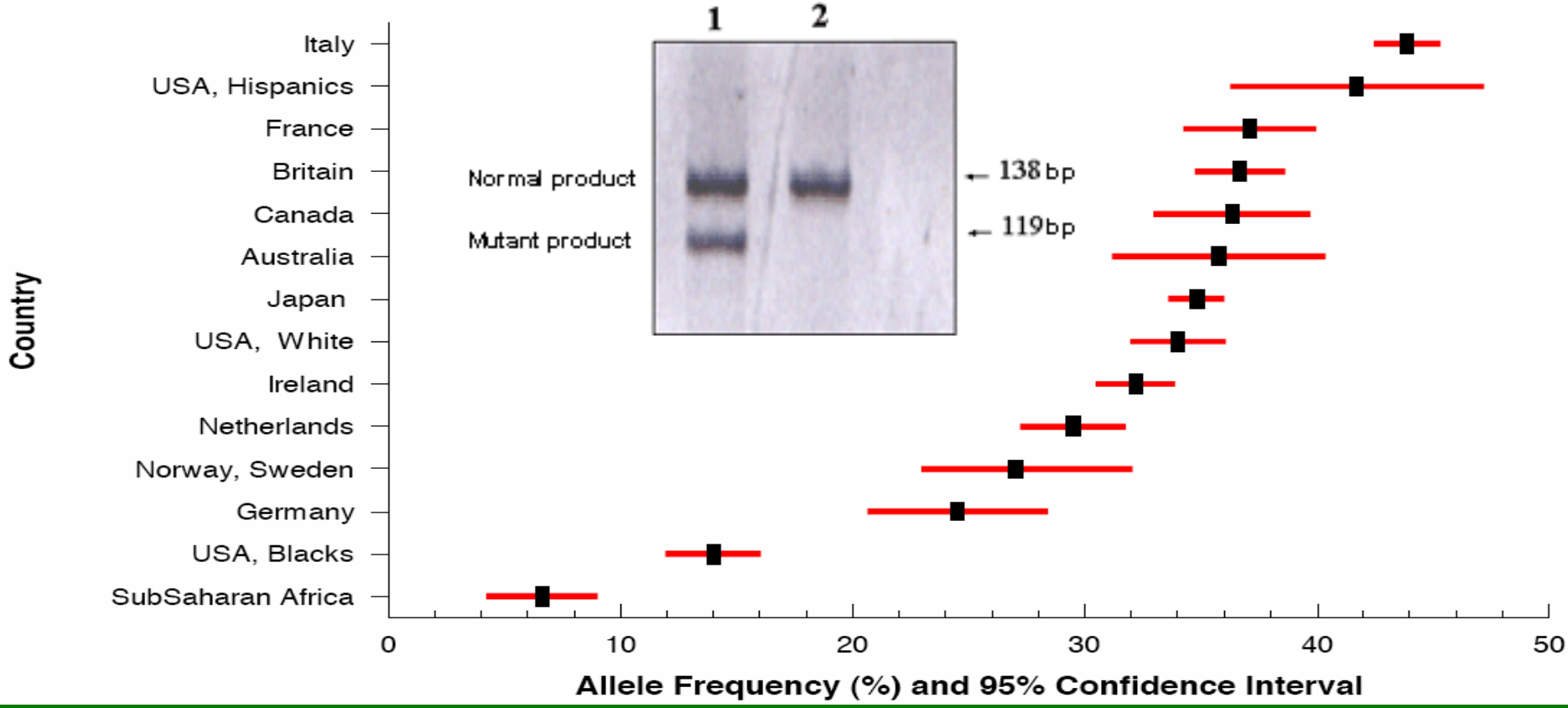
Study of 9 finnish families identified 2 SNPs in the promoter region of the LACTASE GENE responsible for lactose TOLERANCE



EXAMPLES - FOLIC ACID SUPPLEMENTATION



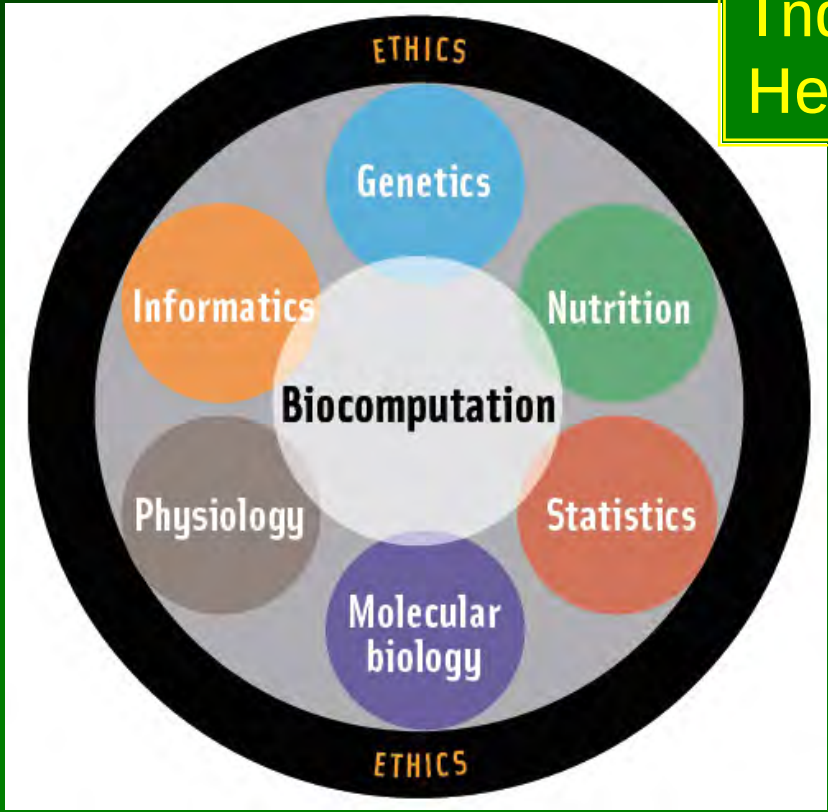
THE PRESENCE OF THE C677T ALLELE OF THE MTHFR GENE LEADS TO INCREASED SERUM LEVELS OF HOMOCYSTEINE WHEN DIET LACKS ADEQATE AMOUNTS OF FOLATE



FOLATE SUPPLEMENTATION CAN COUNTERACT ADVERSE GENOTYPE AND DECREASE RISK OF CVD

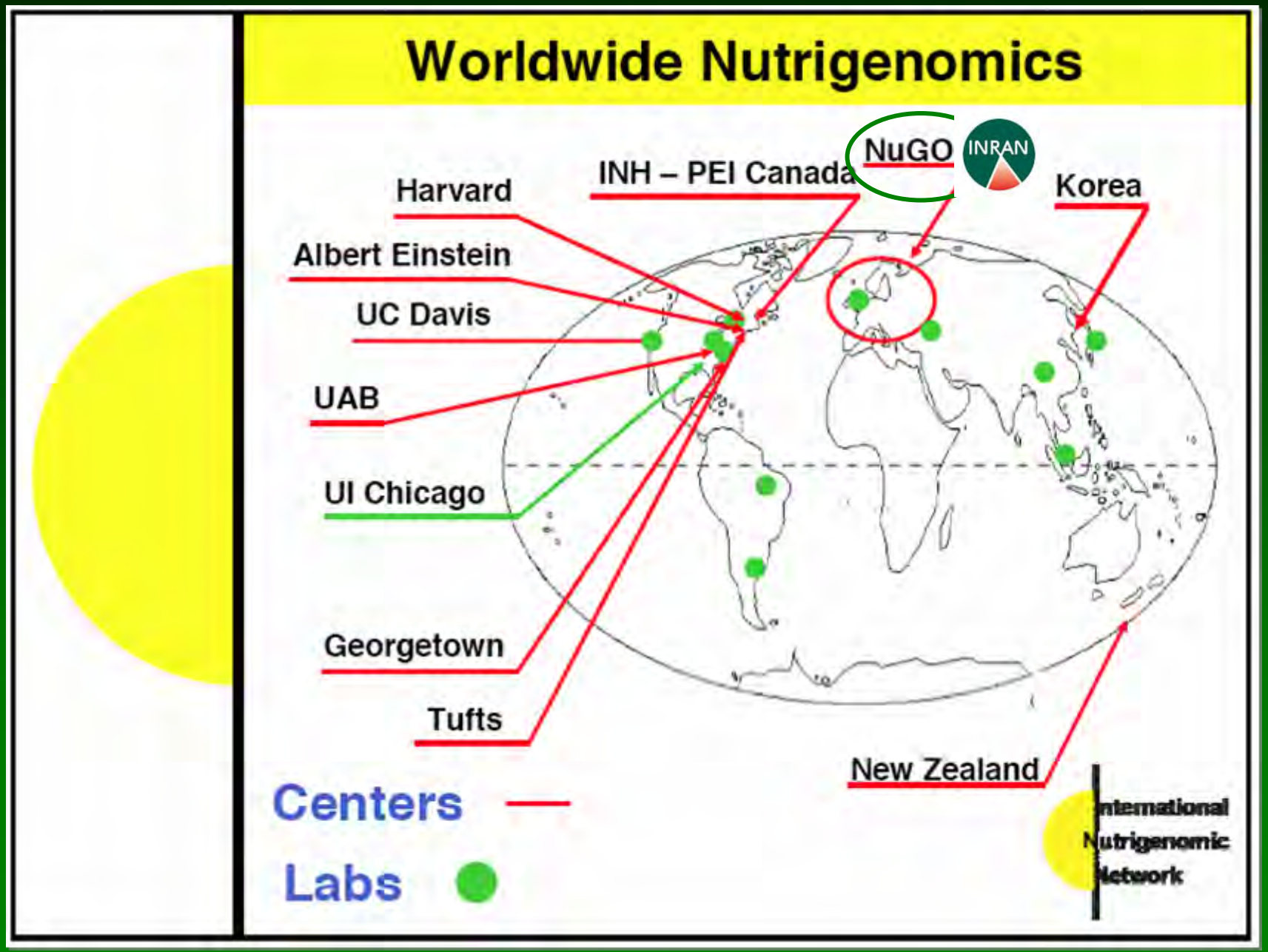
MULTIDISCIPLINARITY OF NUTRIGENOMICS RESEARCH

Diet = *Nutritional Science*
Gene expression = *Molecular Biology*
Individual = *Genetics/Genomics*
Health = *Physiology*



...a science investiganting SYSTEMS BIOLOGY is necessarily MULTIDISCIPLINARY

INTERNATIONAL NETWORKS



NuGO is a European-funded Network of Excellence, linking genomics, nutrition and health researc

NuGO is funded by EC - VI FP - Food Quality and Safety Priority (2004-2009)

Primary aims of NuGO:

- Train European scientists to use post-genomic technologies in nutrition research
- Develop and integrate genomic technologies for the benefit of European nutritional science
- Facilitate the application of these technologies in nutritional research world-wide
- Create the world-leading virtual centre of excellence in nutrigenomics

NUTRIGENOMICS @ INRAN

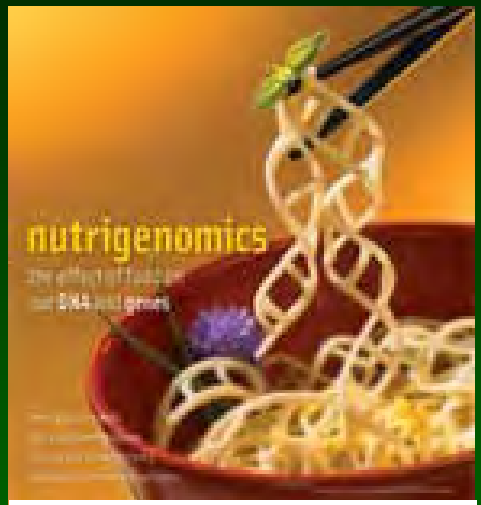
Identification of candidate genes and proteins involved in nutrient modulation of cardiovascular diseases and Type 2 Diabetes (TRANSCRIPTOMICS, PROTEOMICS)

Identification of candidate genes and proteins modulating bioavailability of bioactive food components (TRANSCRIPTOMICS, PROTEOMICS)

Modulation of metabolic disease risk by post-prandial phenomena in relation to meal pattern (METABOLOMICS)

Identification of genotypes associated with differential disease risk in response to diet (BIOCOMPUTATION)

The 2007 path to personalized nutrition……



Eat well

Exercise

Choose ancestors wisely

Jim Kaput, 2005