



# Nutrigenetics and Nutrigenomics: Overview

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## **Outline**

**Defining nutrigenetics and nutrigenomics**

**NGx has a long history**

**Responders vs. non-responders**

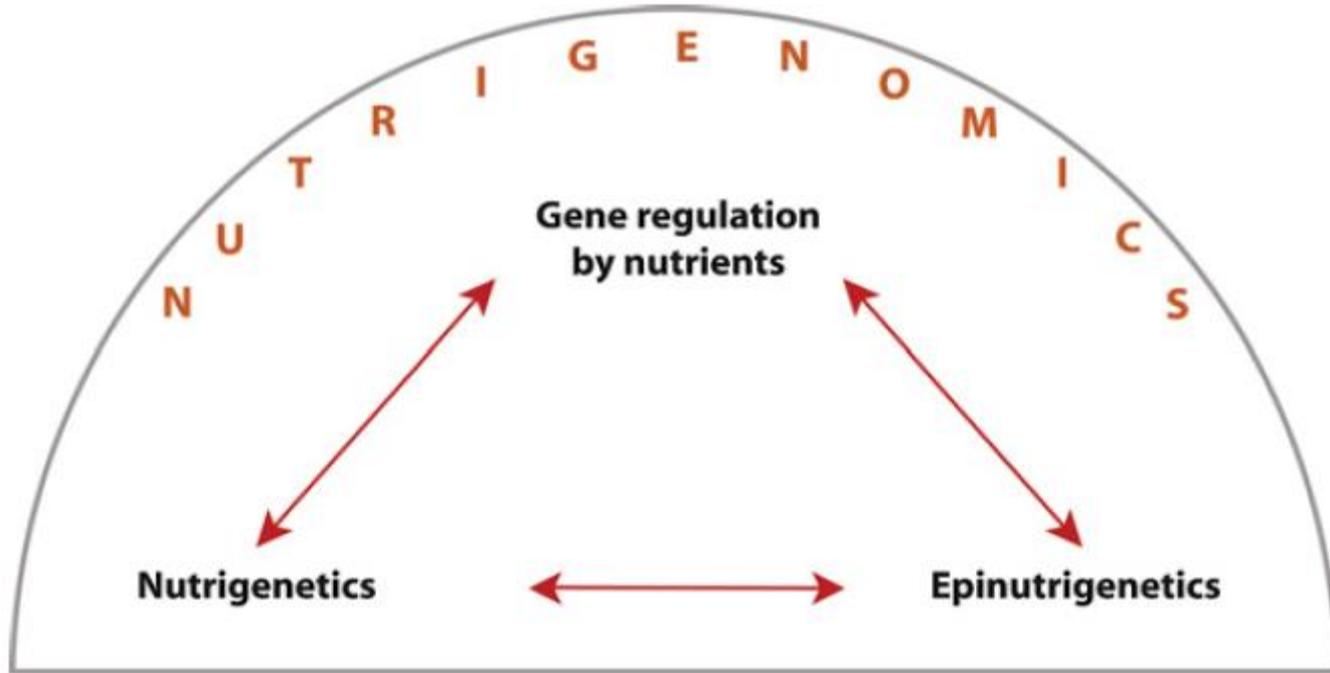
**The evolutionary history of our genetic blueprint**

**Why we need to know about NGx in research**

**What our genetic differences mean**

**Practical applications**

# Scope of nutrigenomics



# Nutrigenomics is not new

## QUOD ALI CIBUS EST ALIIS FUAT ACRE VENENUM

Titus Carus Lucretius, around 60 BC

Even those idiosyncrasies with regard to drugs and articles of food which are summed up in the proverbial saying that what is one man's meat is another man's poison presumably have a chemical basis.

Archibald Garrod, Croonian Lecture, Royal College of Physicians, 1908

# Nutrigenomics is not new

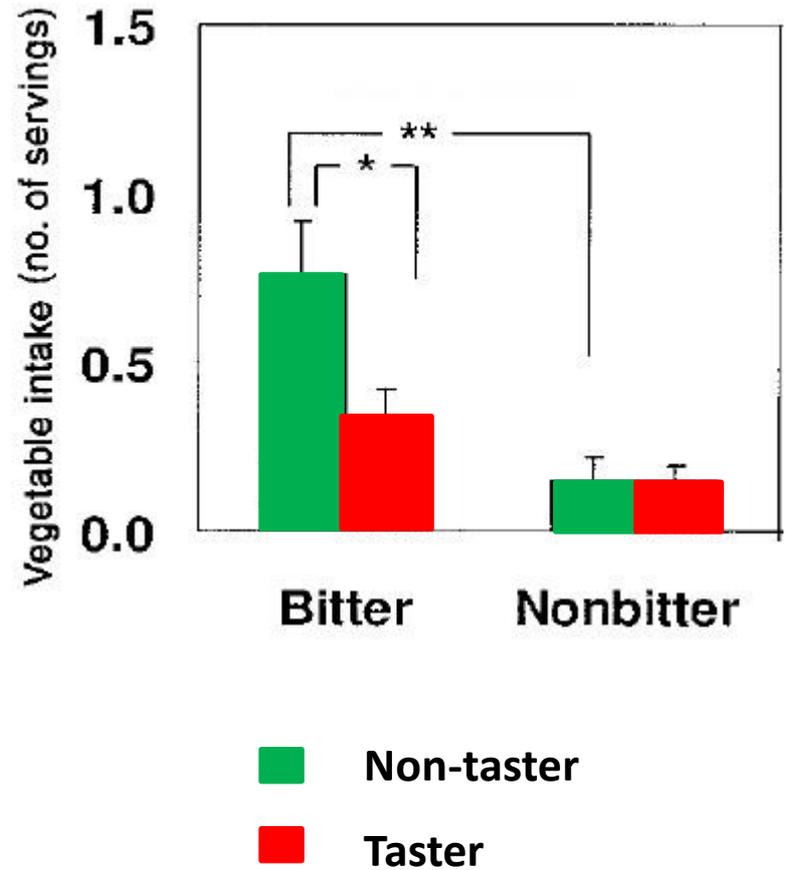
1908	Garrod	<b>Inborn Errors of Metabolism (IEM):</b> cystinuria
1934	Følling	Discovery of phenylketonuria (PKU)
1953	Bickel	Effective dietary therapy of PKU
1994	Calonge et al.	Gene responsible for cystinuria located
2003	HGP, Venter	Human genome sequence decoded
2015	23andMe	1 million customers genotyped
2016	VeritasGenetics	\$1000 personal genome sequence
1942	Waddington	Epigenetics: genetic effects on development
1975	Riggs, Holliday	DNA methylation sets epigenetic markers
2006	Waterland	Maternal feeding alters fetal Agouti gene



**We are all different**

# We are all different

## Carrots or Broccoli?



# Lactase persistence

## Responders vs. Non-responders

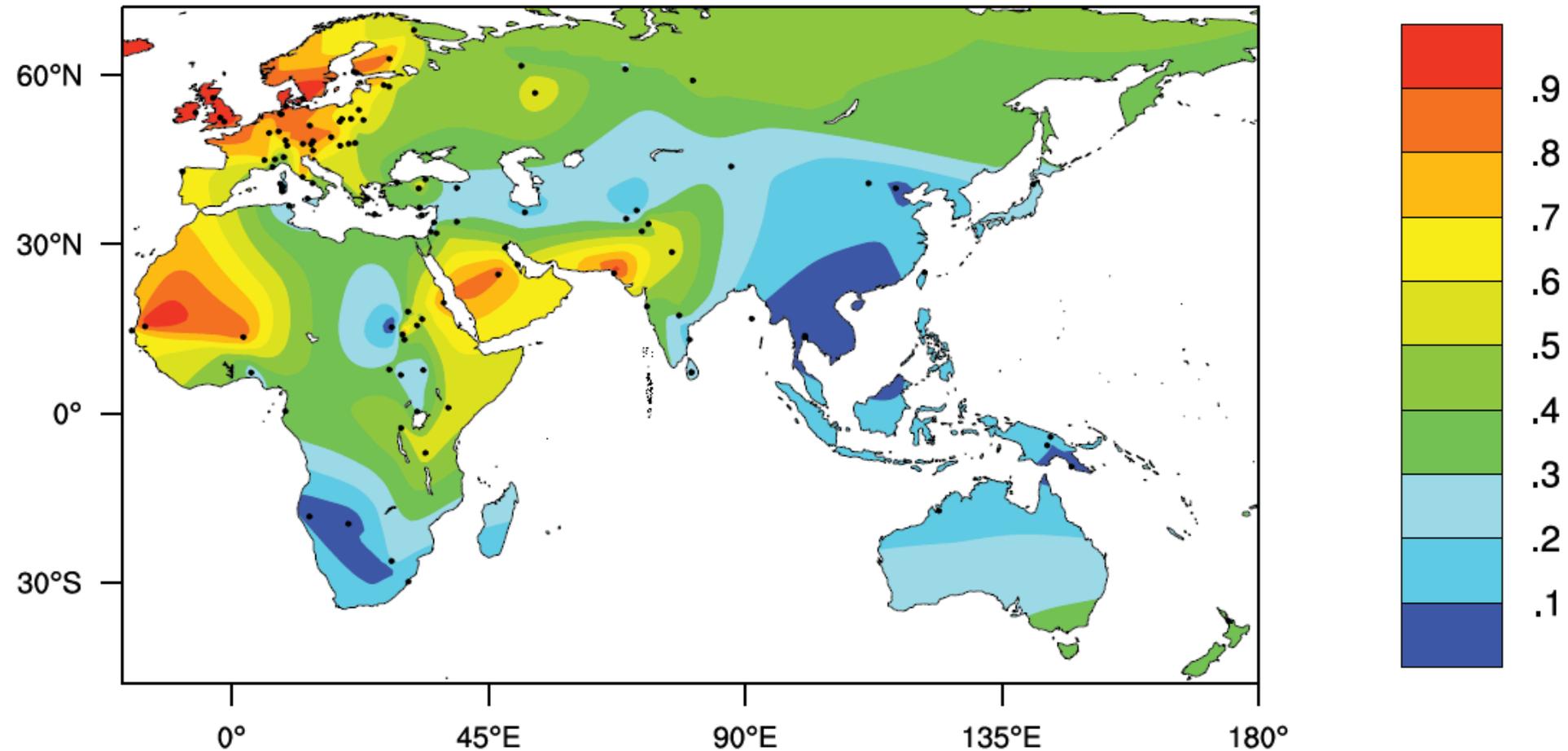
How much lactose can I tolerate?



**11-12 g lactose in a 240 ml glass of milk**

# Lactase persistence

## Frequencies of LP in the Old World



# Lactase persistence

**Where is nutrigenetic heterogeneity coming from?  
Humans have inhabited diverse 'nutritopes' throughout history  
and have adapted to new food patterns.**



**Xhosa in South Africa  
LCT -14,010 C**



**Arabs in Oman  
LCT -13,915 G**



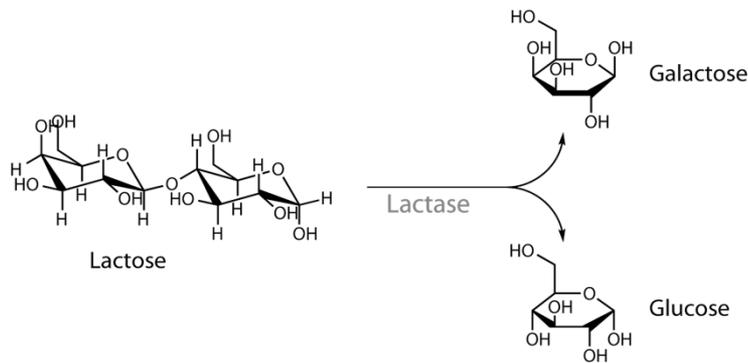
**Vikings on Atlantic Islands  
LCT -13,910 T**

**Small changes in the lactase gene of these people sustain enzyme expression into adulthood. This adaptation helped them to consume lots of milk and survive in environments with otherwise sparse food supplies.**

# Lactase persistence

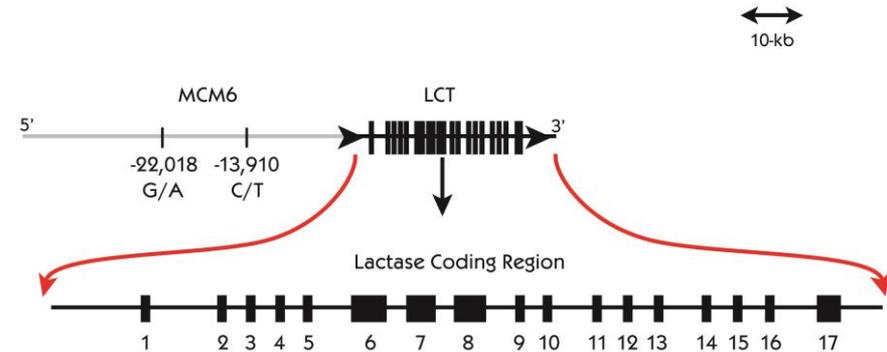
## Why you want to know about this:

Lactose intolerance often mimics the symptoms of inflammatory bowel disease. You can use predictive genetic assessment to improve dietary guidance.



The **normal state** (65-70% world-wide) is **loss of lactase expression after infancy**.

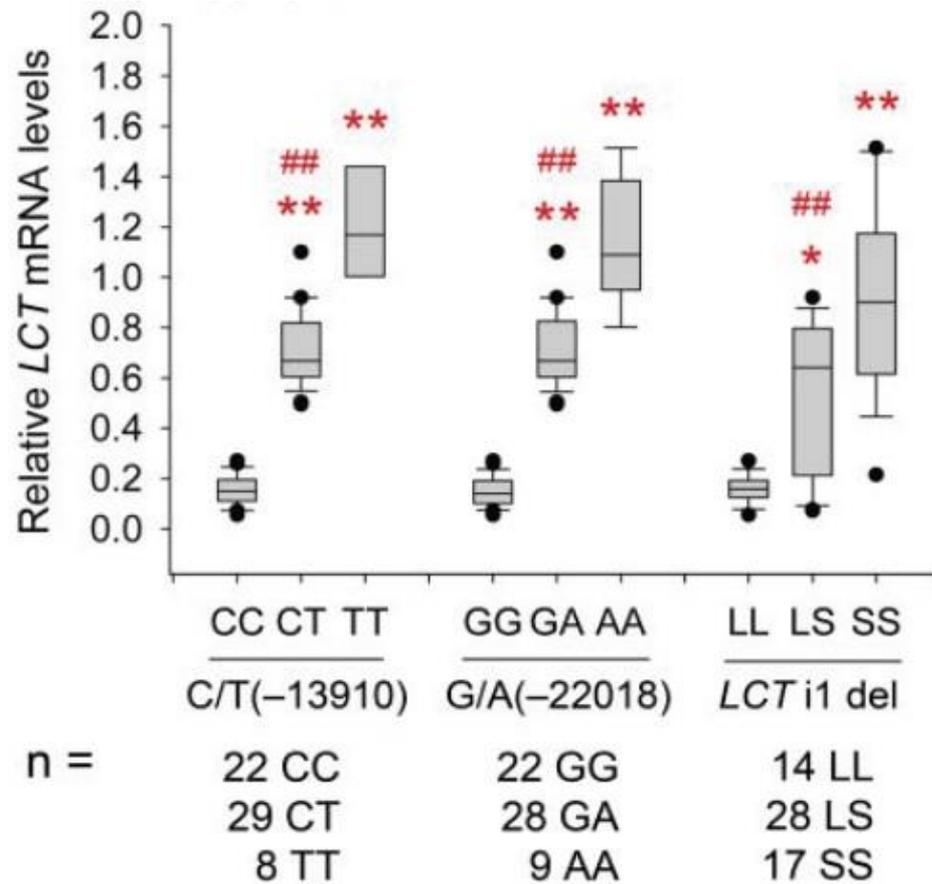
Pastoral populations have evolved variants in the upstream enhancer region causing persistent expression in adulthood.



## The persistence alleles are dominant

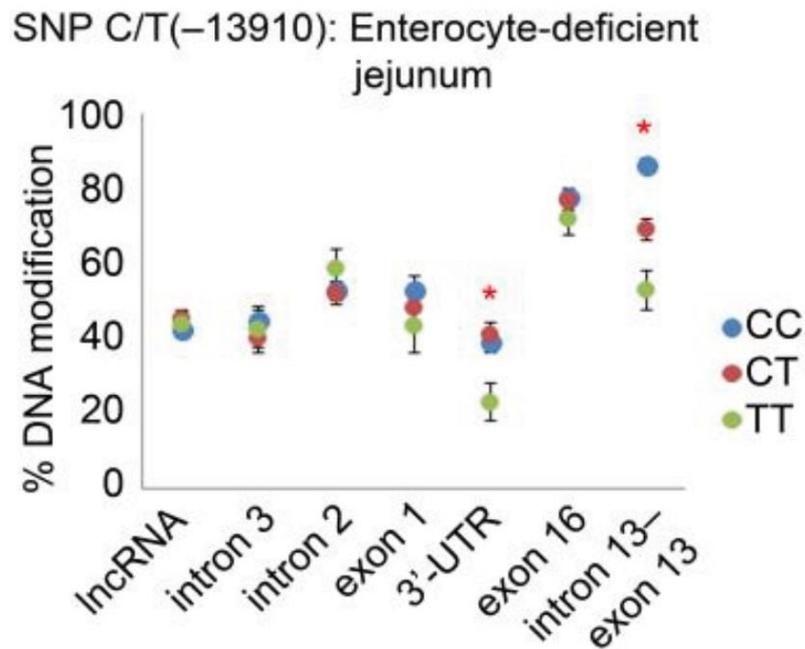
- 13838 A in some Tibetans
- 13907 G in about 5% of East Africans
- 13910 T in more than 80% of Europeans
- 13915 G in many Yemenis, Saudis, Kuwaitis
- 13937 A in Xhosa, Brazilians
- 13965 G in East Africans
- 14009 G in Somalis
- 14010 C in Kenyans, Tanzanians
- 14042 G, -14107 A in East Africans

# Lactase persistence



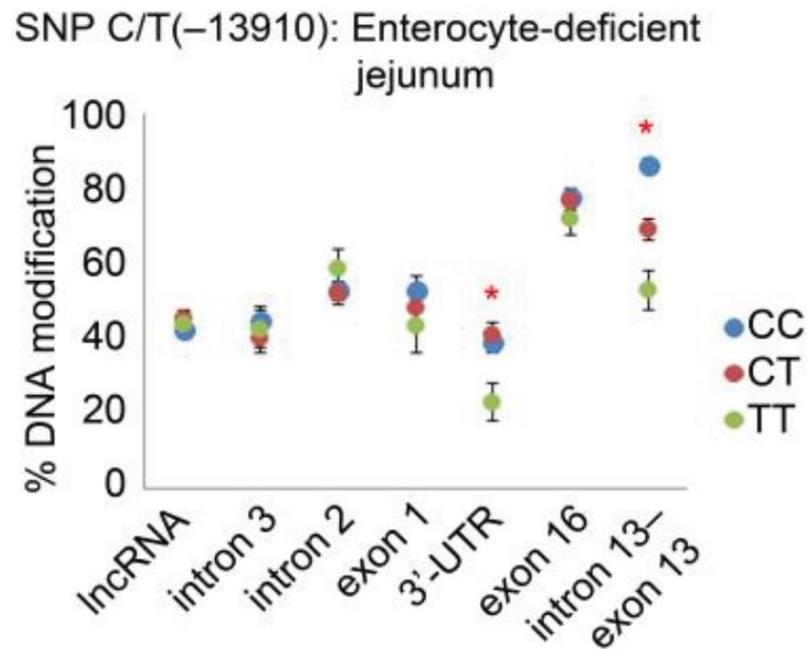
# Lactase persistence

Genotype-specific decline of jejunal lactase expression with age is related to the progressive accumulation of epigenetic changes



# Lactase persistence

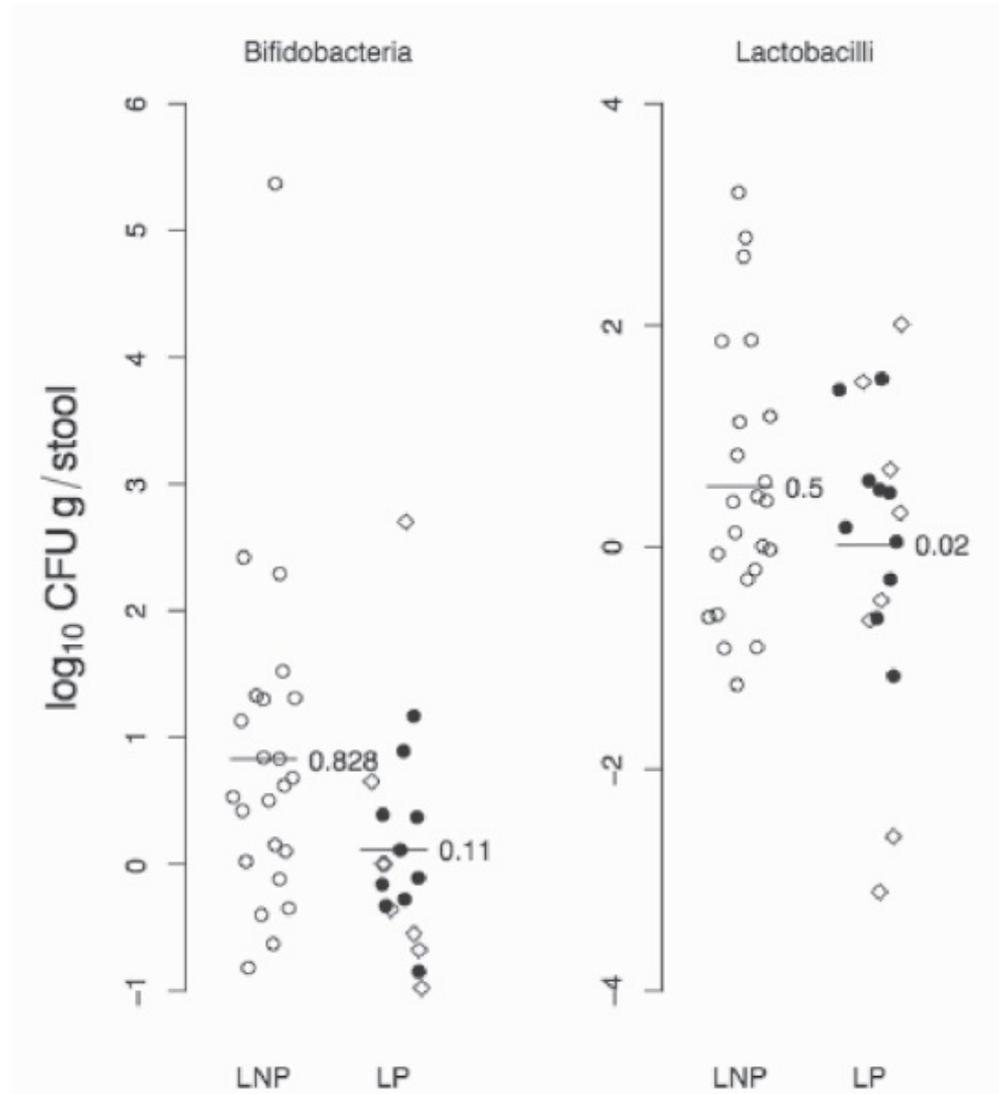
**Genotype-specific decline of jejunal lactase expression with age is related to the progressive accumulation of epigenetic changes**



Advancement of the epigenetic clock appears to depend on the genetic landscape.

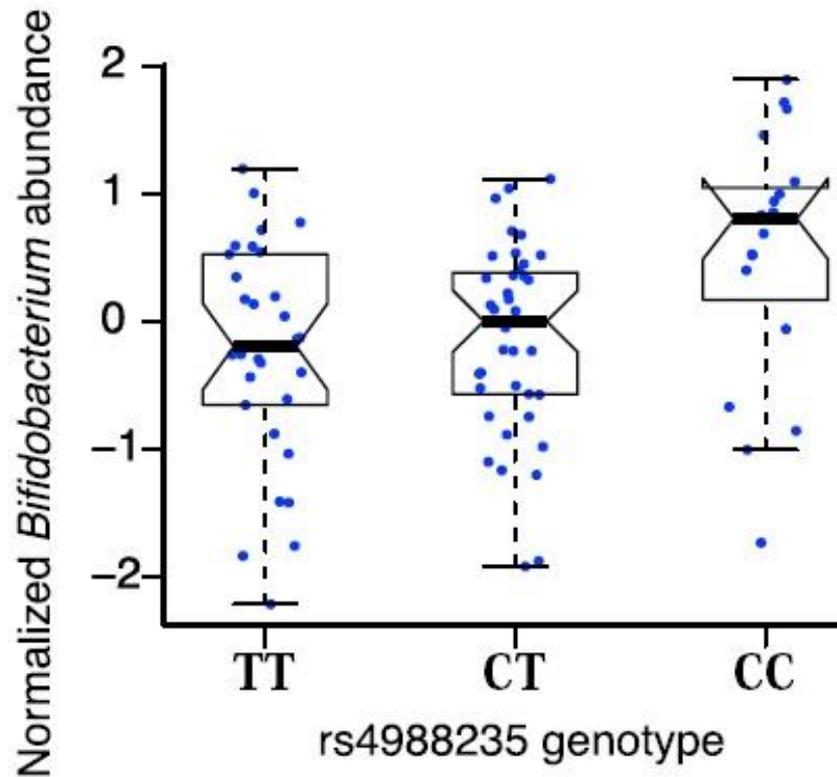
# Lactase persistence

**Persistence (LP)  
decreases abundance  
of *Bifidobacteria* and  
*Lactobacilli* in the  
small intestine**



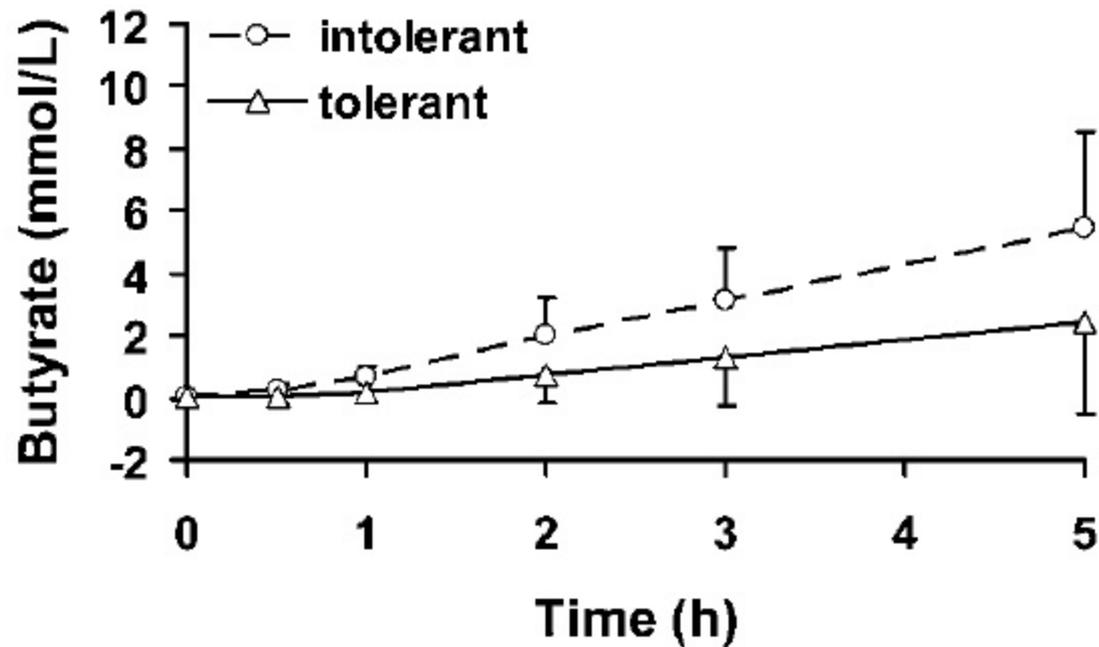
# Lactase persistence

Persistence-linked LCT allele -13910 T decreases abundance of the *Bifidobacterium* genus in the small intestine



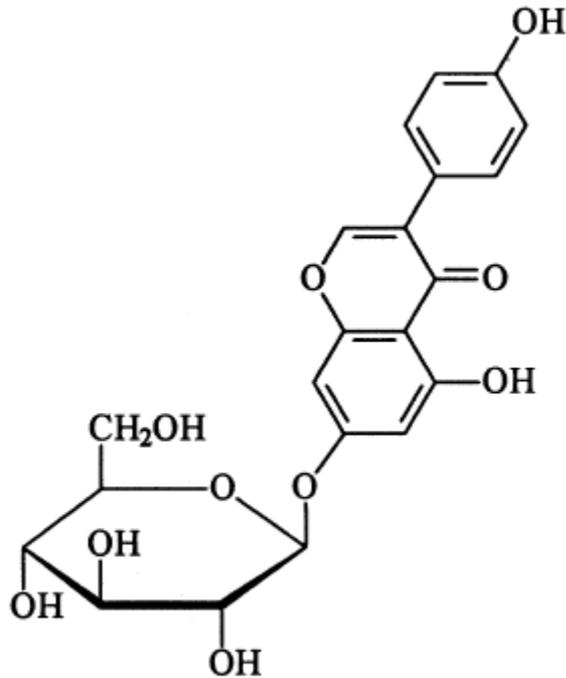
# Lactase persistence

Intolerance associated with metabolite profile in vitro

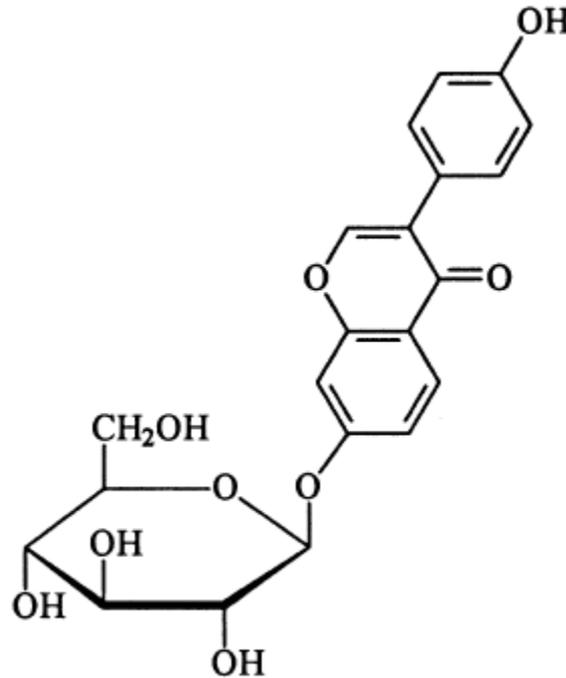


# Lactase persistence

Lactase is the only enzyme in the small intestine that cleaves glucosides of flavonoids and other common phytochemicals, some of which are highly toxic



Genistein-7-glucoside



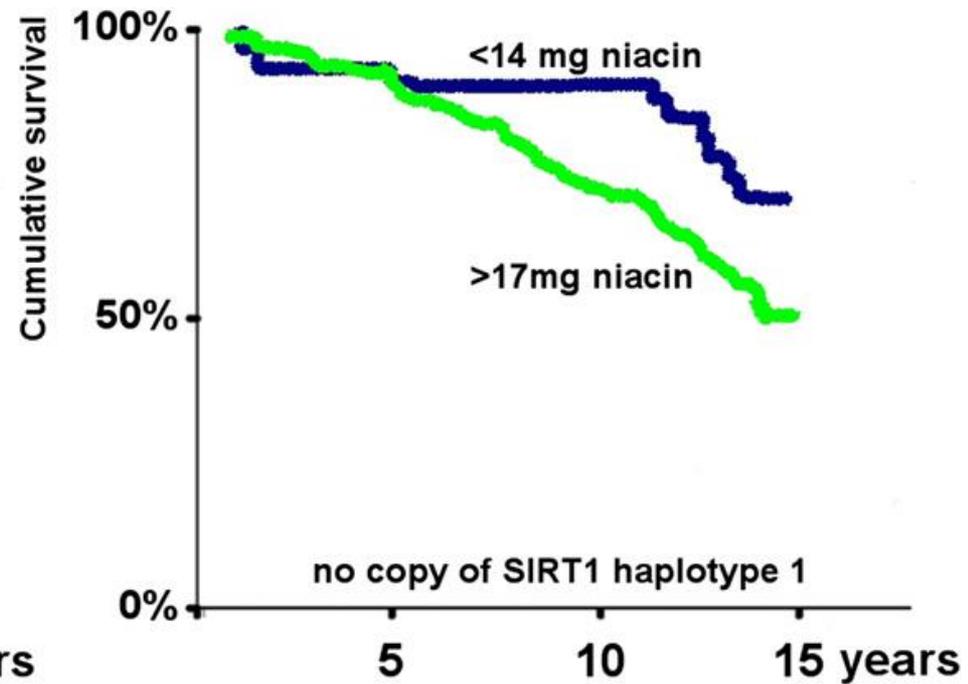
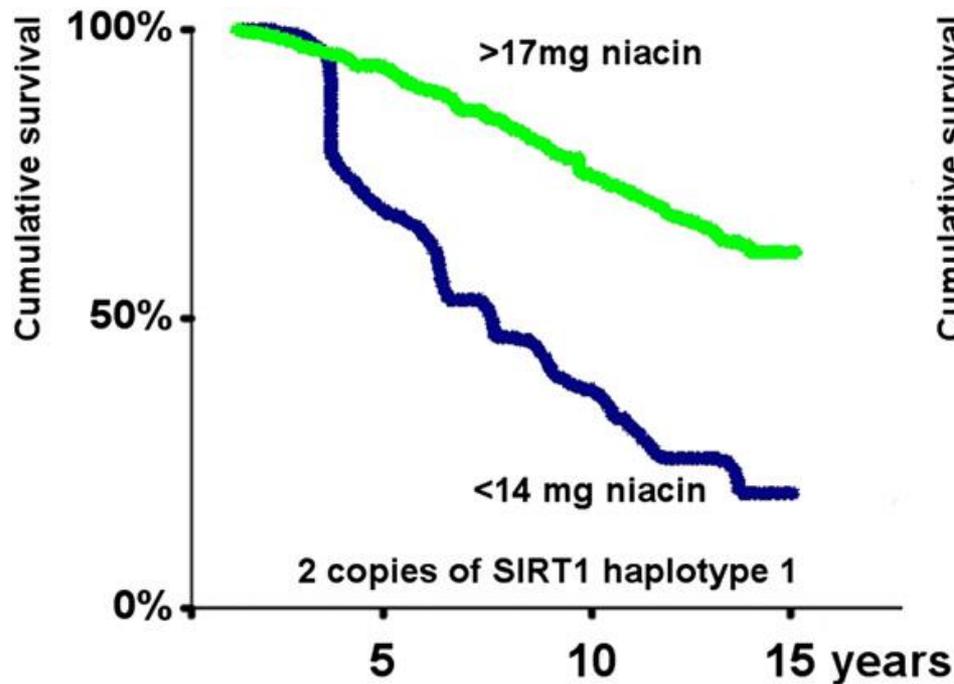
Daidzein-7-glucoside



## **Why we need to know about NGx in research**

# The need to know about NGx

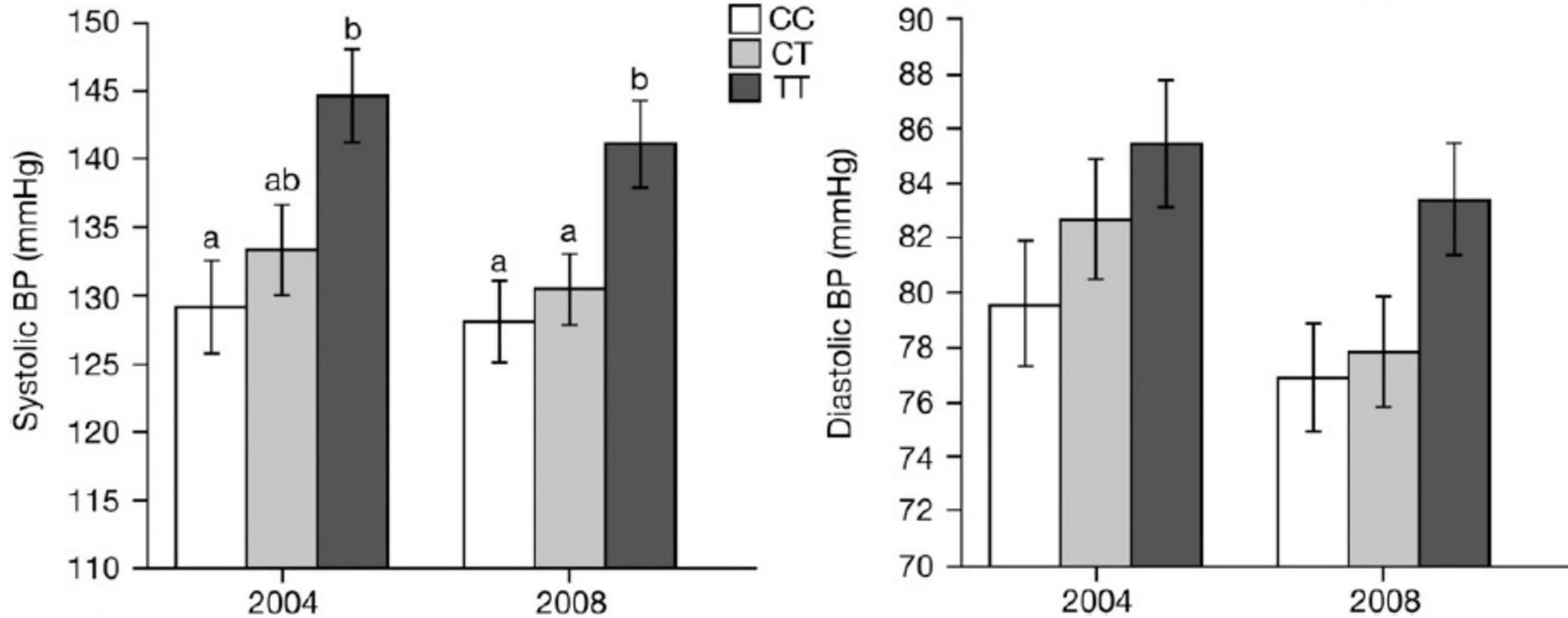
It may be a matter of life and death for some



H1/H1 frequency 1 in 6

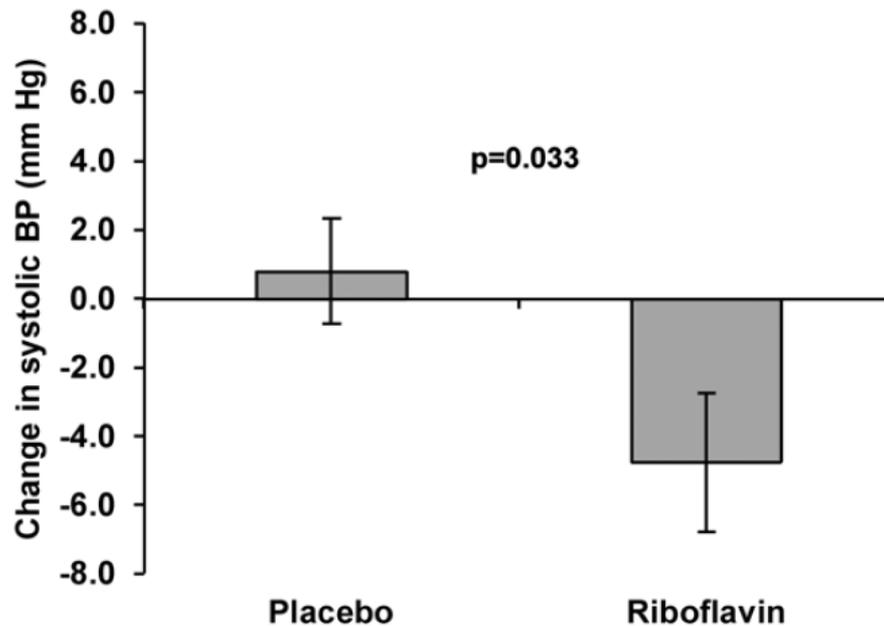
# The need to know about NGx

## MTHFR-related blood pressure differences



# The need to know about NGx

## 16-week riboflavin supplementation lowered BP



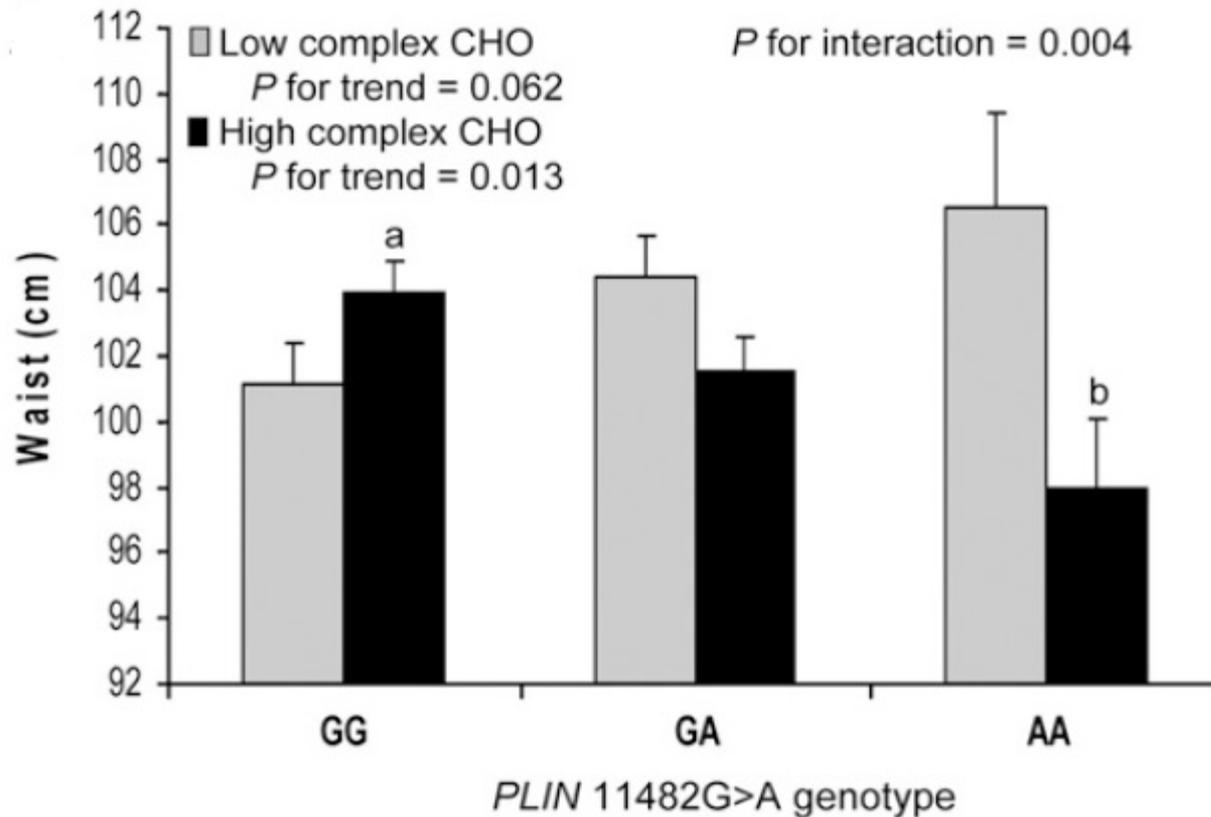
**RCT in Ireland of treated hypertensive adults with MTHFR TT, achieving an average reduction of systolic BP by 5.6 mm Hg**





# The need to know about NGx

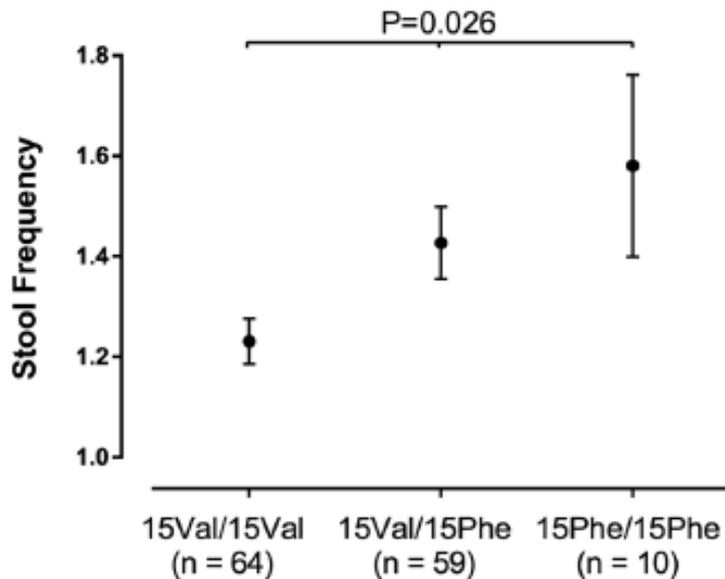
## The response to carbohydrate is genotype-specific



# The need to know about NGx

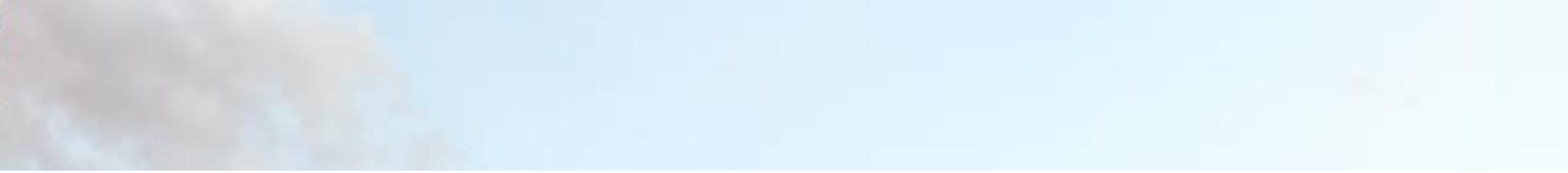
## The capacity to digest sugars differs between individuals

The sucrase (SI) variant rs9290264 is associated with inefficient hydrolysis of sucrose (O- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 2)- $\beta$ -D-fructofuranoside). Carriers with high sugar consumption have increased stool frequency and have higher risk of irritable bowel syndrome (IBS).



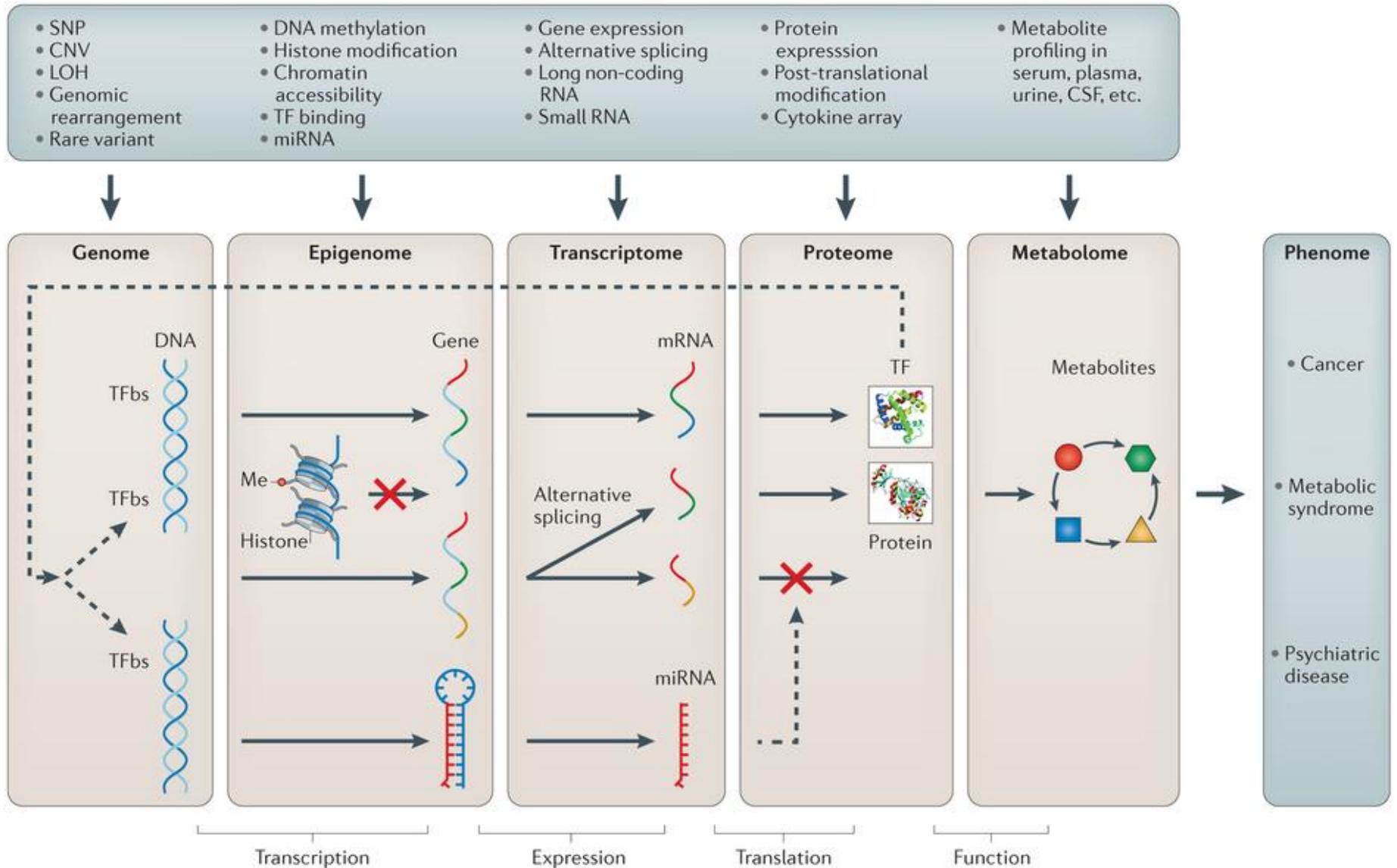
### Association of the 15Phe variant with IBS

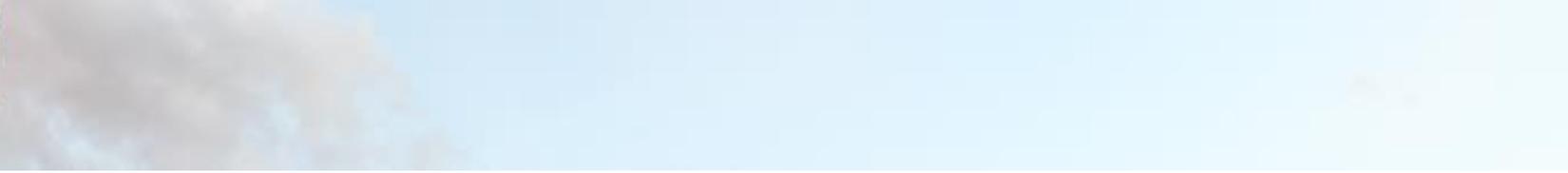
	CTRL	IBS		
	AF	AF	p Value	OR
Case-control	0.264	0.306	<i>0.0030*</i>	<i>1.26</i>
PopCol	0.29	0.417	<i>0.045</i>	<i>1.89</i>
Combined	0.268	0.309	<i>0.0013*</i>	<i>1.27</i>



# **NGx Studies**

# Integration of research data





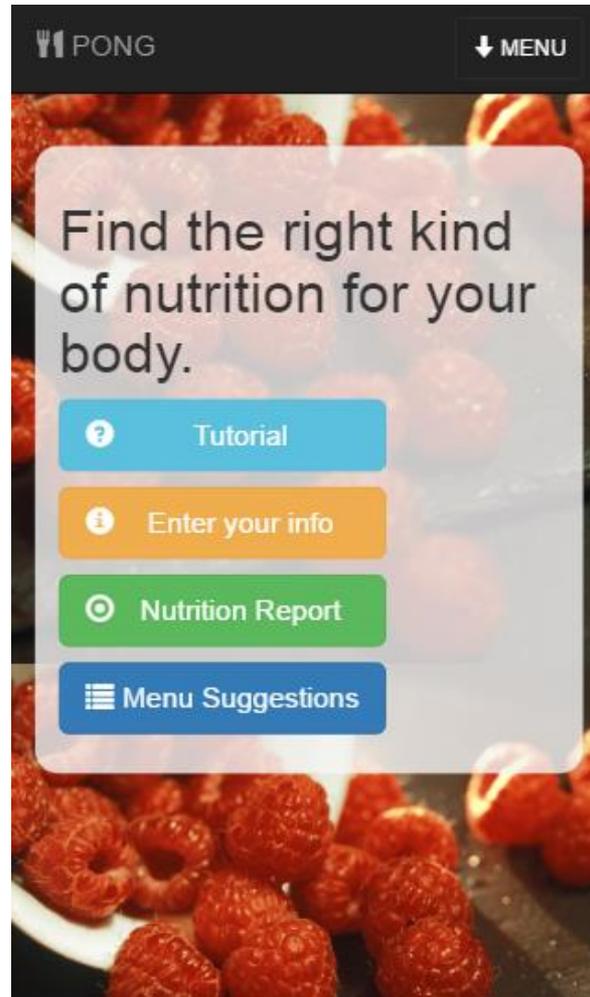
# **Practical Applications**

# Practical applications

## Personalized Online Nutrition Guidance

**Gluten-free**  
**Lactose-free**  
**Genotype-specific**

**Vegetarian**  
**Vegan**  
**Low-Carb**



# Practical applications

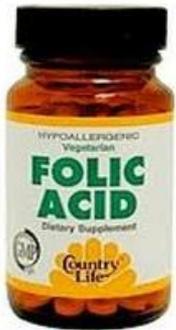
## Product development



# Practical applications

## Regulations and policies

Should high-dosed folate  
require a prescription?



How much should the caffeine content  
be allowed to vary between brews?



Should these fava beans come  
with a safety warning?





## **Final comments**

**Intervention effects in genetic subgroups are easily obscured by the lack of significant response of the majority.**

**Some nutritional interventions are only effective, if they are targeted to genetically susceptible models or individuals.**

**The likely effect size of some genotype-specific interventions is as large as that of medical treatments.**



**Questions?**