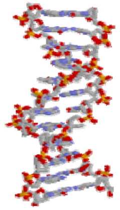
Department of Human Nutrition

The multiple facets of diet-gene and gene-diet interactions

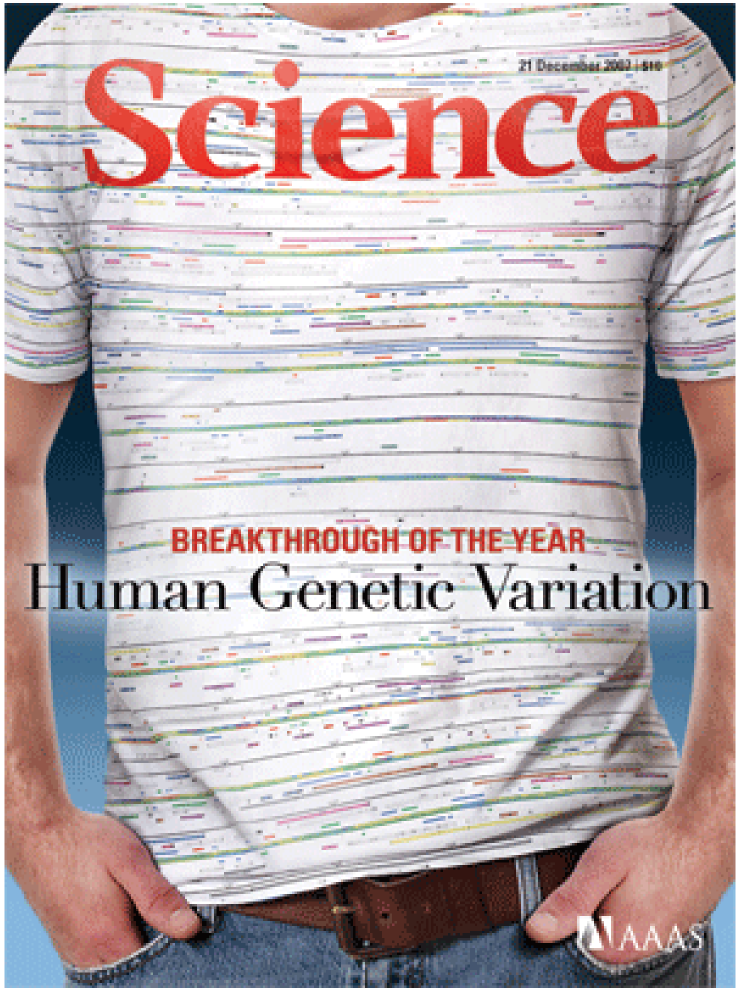
Lars O. Dragsted – Dept. Human Nutrition/ Life Sciences/ University of Copenhagen



The Human Genome

- ~ 30,000 genes
- ~ 3 x 10^9 base pairs (A, C, G, T)
- ~ 3 x 10^6 Single Nucleotide Polymorphisms (SNPs)

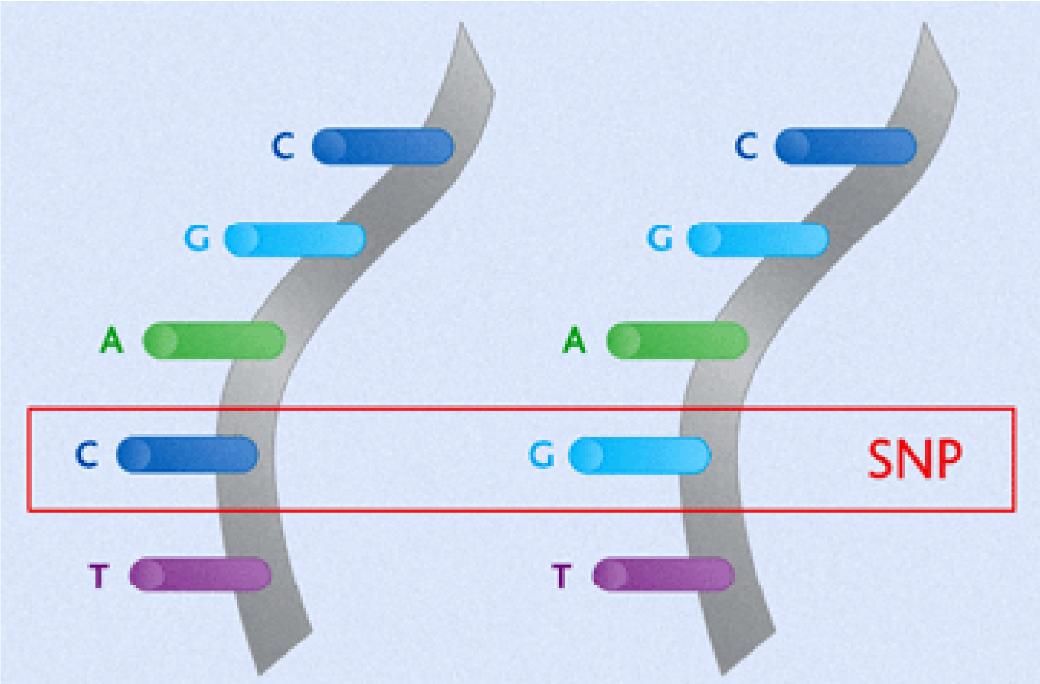
Human Genetic Variation



Human Genetic Variation

- Single Nucleotide Polymorphisms (SNPs)
- Copy Number Variants (CNVs)
- Nucleotide Repeats
- Insertions/Deletions

Single Nucleotide Polymorphism (SNP)



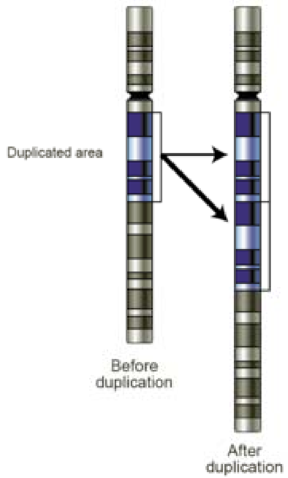
CC

CG

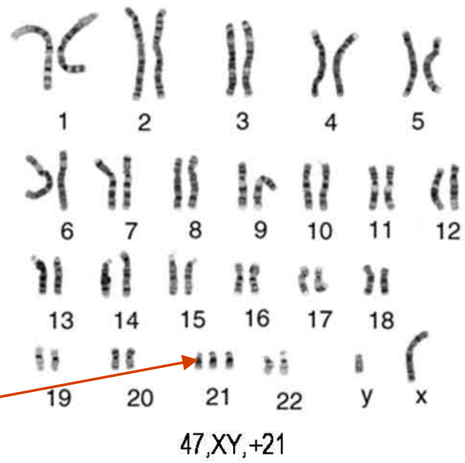
GG

Individual genetic code changes

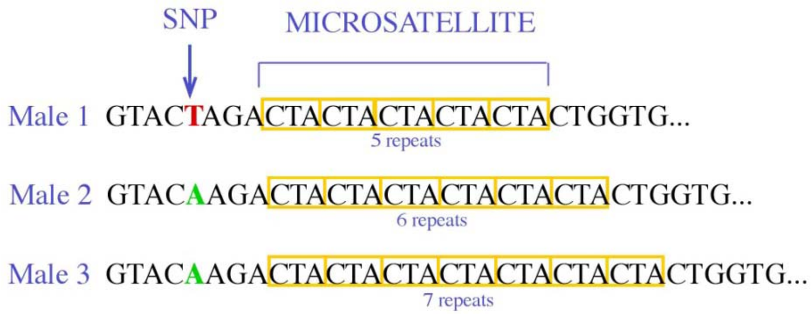
Copy number variant (gene duplication)



Trisomy (triple chromosome variants)

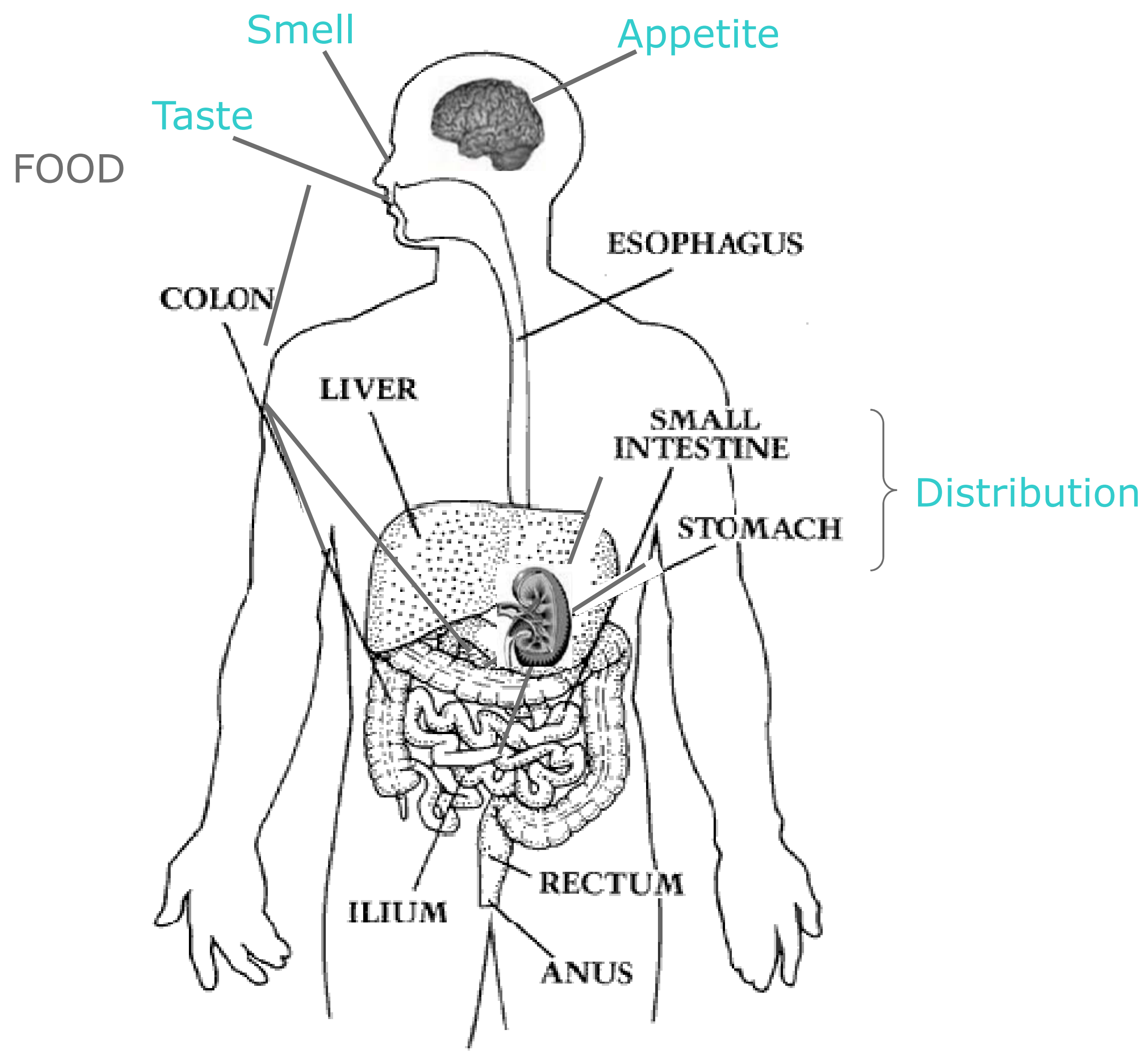


Microsatellite repeats



http://www.le.ac.uk/ge/maj4/SNP_STR.jpg

Genetic variation can affect....



Types of diet - gene interactions

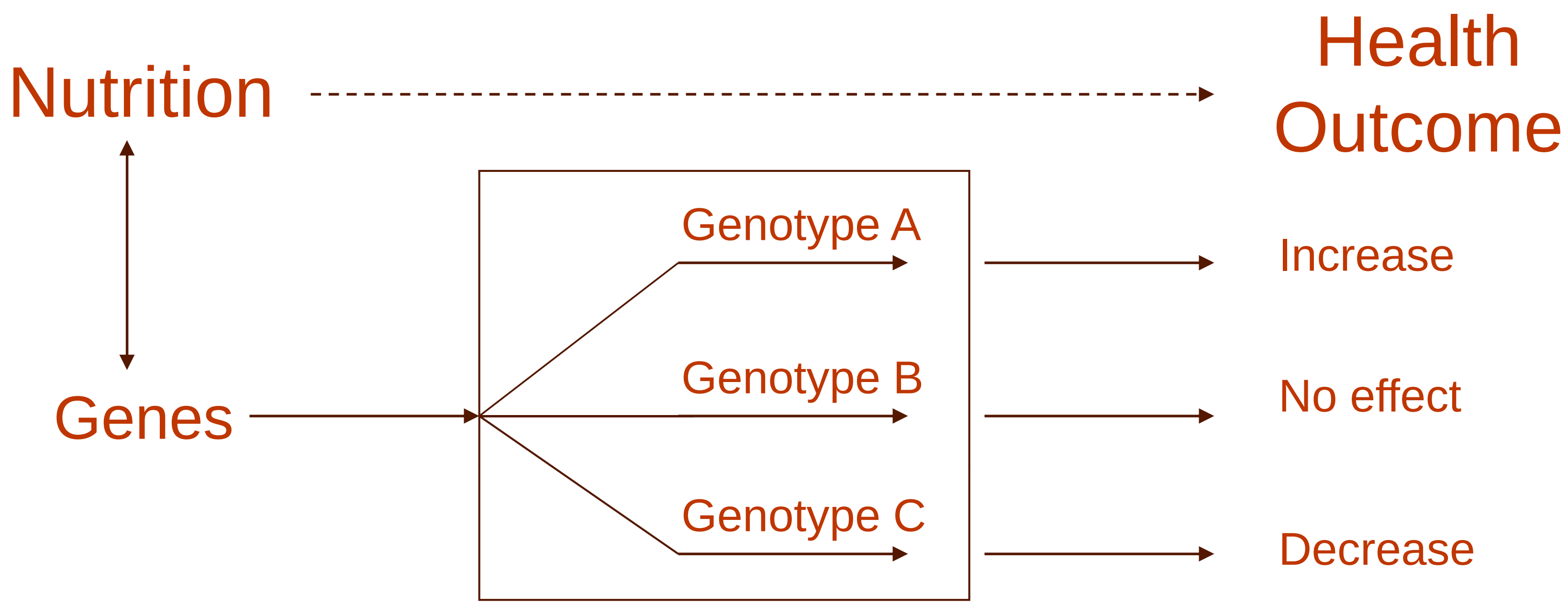
1. Dietary factors causing somatic or germline mutations
2. Interactions between dietary factors and genetic polymorphisms (including SNP's)
3. Dietary factors interacting with gene expression (induction / repression)

Gene variant-disease studies are often disappointing…

Polymorphic gene	Function / coding for	Meta-analysis outcome
c-Ha-ras and *L-myc*	Proto-oncogenes	Not consistent (all cancers, 1991)
ACE	Angiotensin-converting enzyme	Not consistent (diabetic neuropathy, 1998)
apo (var epsilon)	Apo E variants	Not consistent (CVD, 2002)
p53 (Arg72Pro)	Tumor suppressor gene	Not consistent (cervical caner, 2004)
CYP1B1 (Val432Leu)	Estrogen oxidative metabolism	Not consistent (breast cancer, 2007)
HMTFR (677 C>T)	Folate metabolism	Not consistent (Congenital heart defects, 2007)
COMT (Val158Met)	Catechol metabolism	Not consistent (mental disorders, 2007)

And many dietary factors also show variable relationships with disease

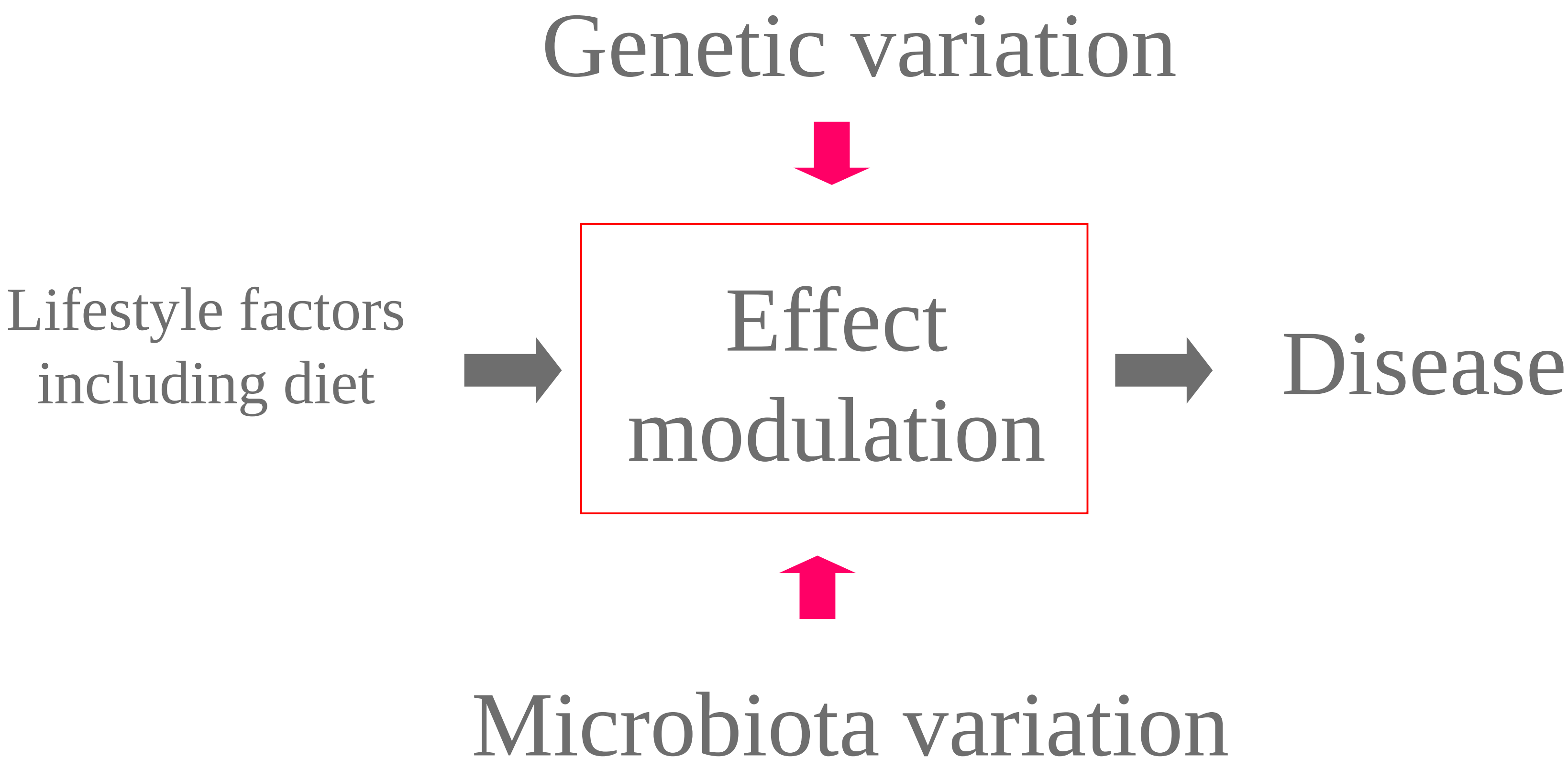
- (FRIED/CURED) MEAT: associates with colon cancer risk
- FRUIT and VEGETABLES : weak association with cancer, stronger with CVD
- CRUCIFERS / BROCCOLI: Association with CRC possibly stronger than for F&V
- FATS, SUGARS, ENERGY: Inconsistent associations with cancers and CVD
- FOLATE: controversial effects on colon cancer risk and CVD risk
- COFFEE: controversial CVD effects of coffee/caffeine consumption
- ALCOHOL: mostly consistent with increased breast cancer risk

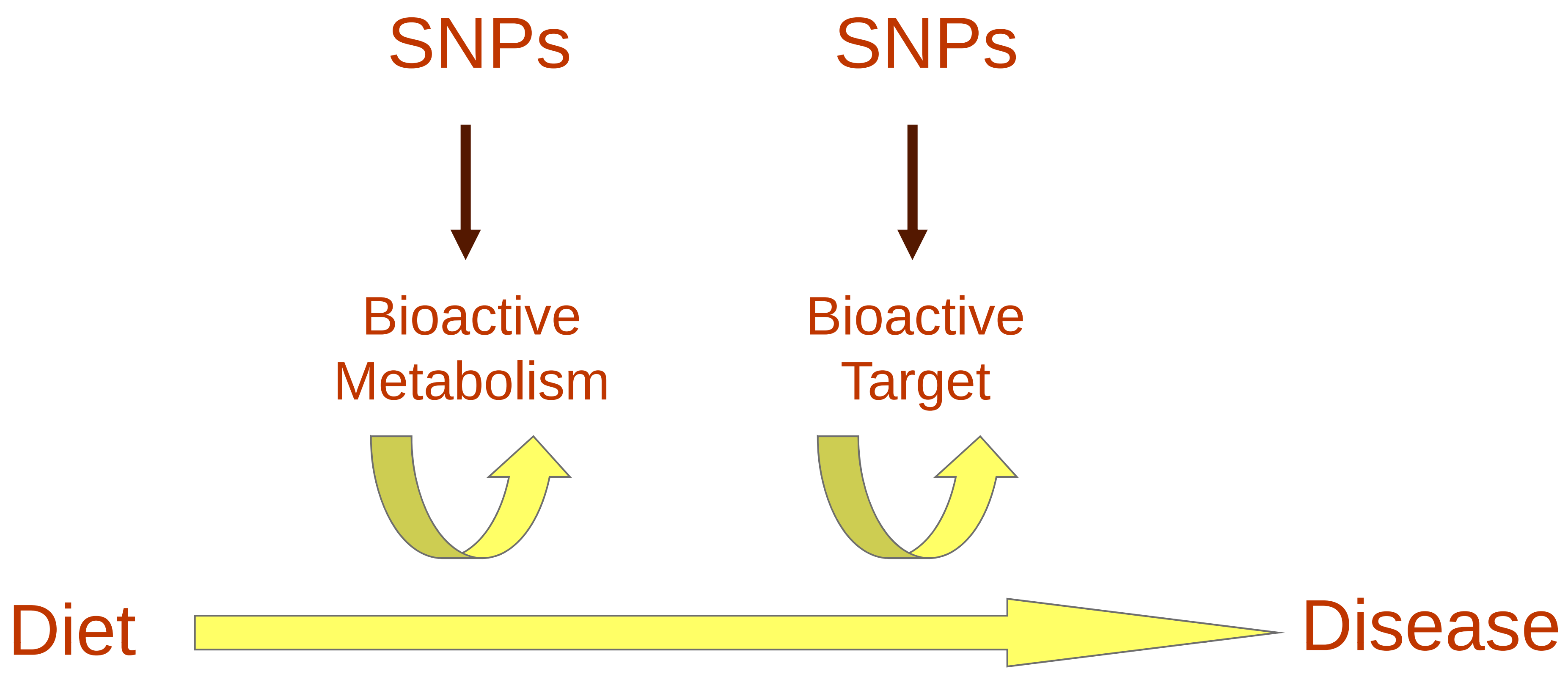

Health
Outcome
Nutrition
Genotype A
Increase
Genes
Genotype B
No effect
Genotype C
Decrease

But gene-diet studies may be more promising

- COFFEE: CYP1A2 fast/slow predicts CVD effects of coffee/caffeine consumption
- FOLATE: HMTFR 677 C>T predicts colon cancer risk and CVD risk in low folate diets (low fruit and vegetables, high alcohol)
- FRIED MEAT: CYP1A2, NAT2, and GSTA may predict colon cancer risk in high fried meat consumers
- OXIDATIVE STRESS: Gpx Pro198Leu may predict breast cancer in individuals with high alcohol, low fruit&vegetable consumption
- BROCCOLI: GSTM1+T1 null may increase the cancer preventive action of broccoli
- TOBACCO: GSTP1 Ile105Val may increase tobacco-induced bladder cancer
- ALCOHOL: PPARγ Pro12Ala may predict alcohol-induced breast cancer risk

Hypothesis: Few foods or gene variants are risk factors per se, risks emerge as interactions




SNPs
SNPs
Bioactive Metabolism
Bioactive Target
Diet
Disease

Is Coffee associated with heart disease?

↑ Risk

No Effect

↓ Risk

Bioactives in coffee

aliphatic acids

magnesium

potassium

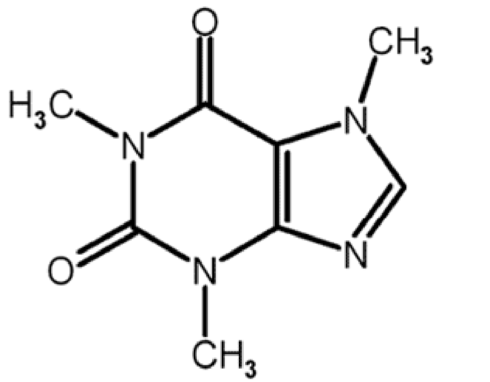
caffeine

melanoidins

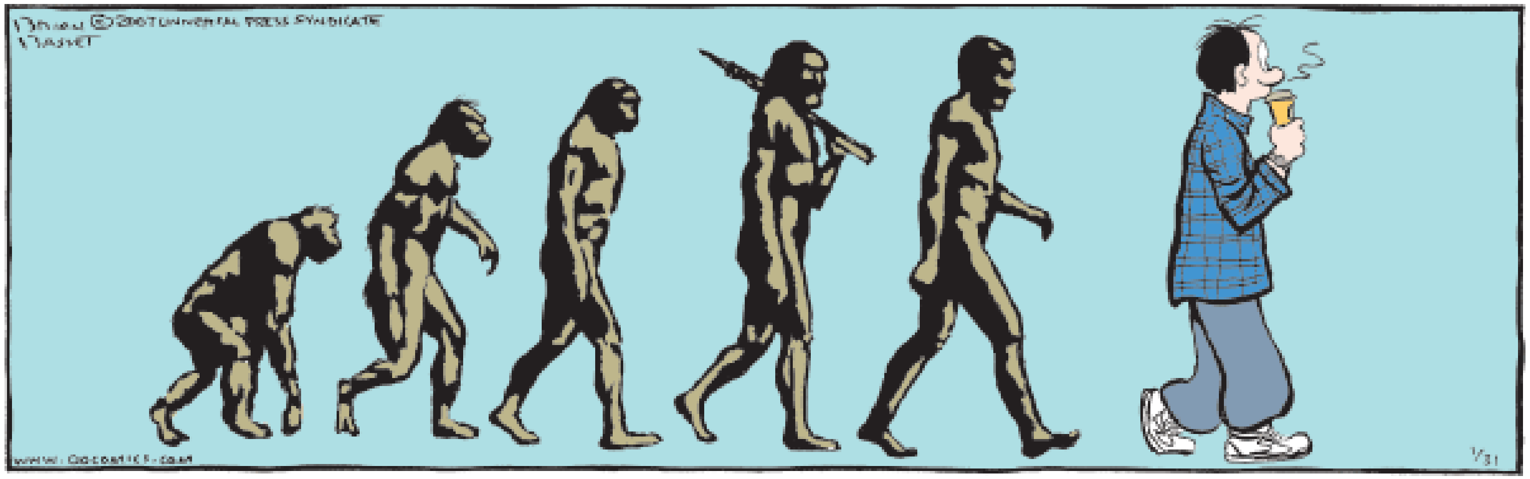
diterpenoids

polyphenols

Caffeine (1,3,7-trimethylxanthine)



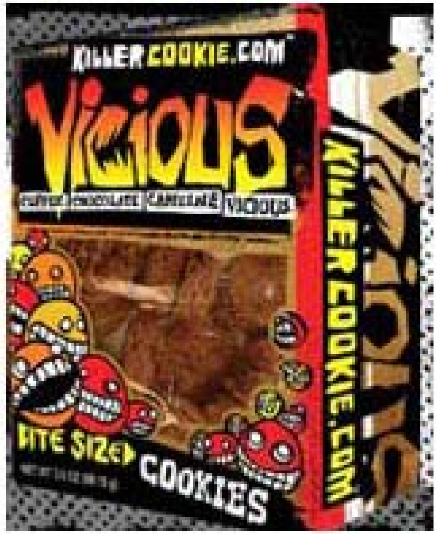
Caffeine ($C_8H_{10}N_4O_2$)
Image by Erowid, © 2001 Erowid.org




hi★ball
ENERGY
LEMON★LIME BOOM


SHOCK
HYPER-CAFFEINATED
COFFEE


PENGUIN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VICIOUS
BITE SIZED COOKIES
KILLERCOOKIE.COM


BUZZ BITES
CHOCOLATE ENERGY CHEWS
SERIOUSLY CAFFEINATED
FOOSH
ENERGY MINTS
SERIOUSLY CAFFEINATED

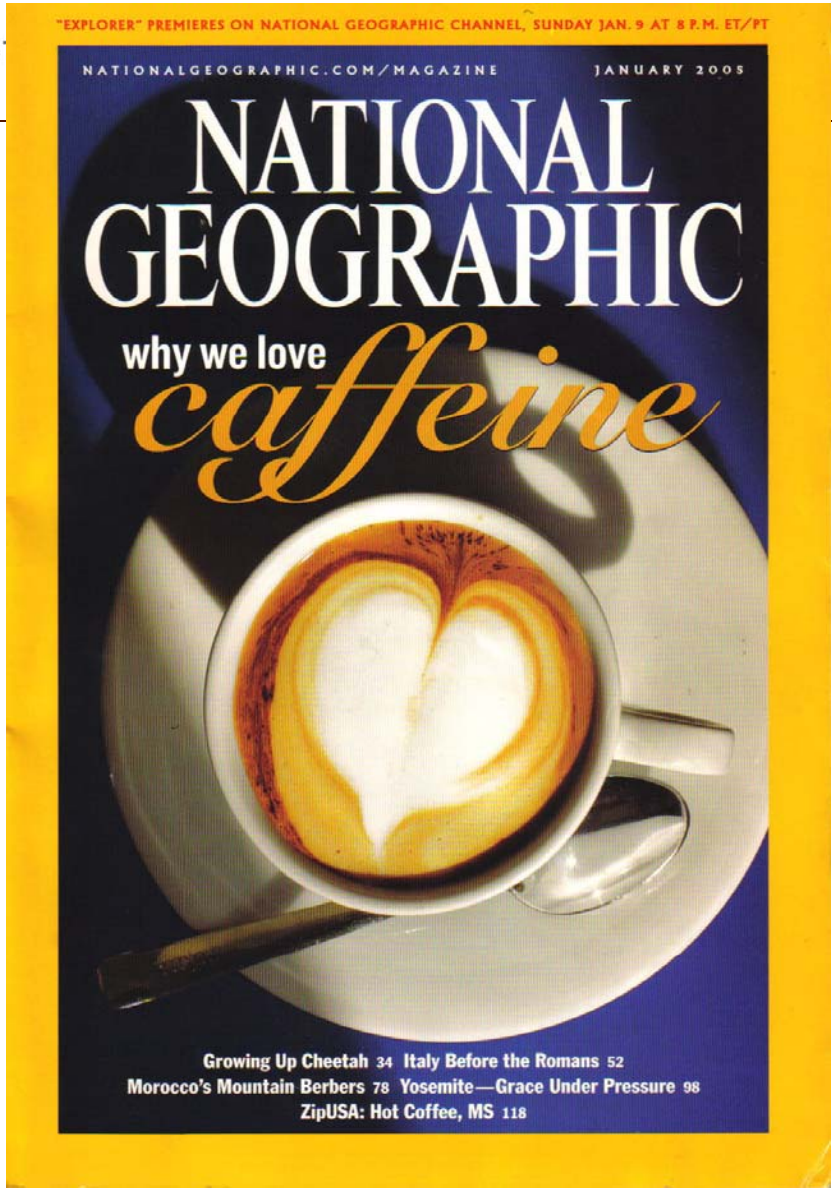
.0

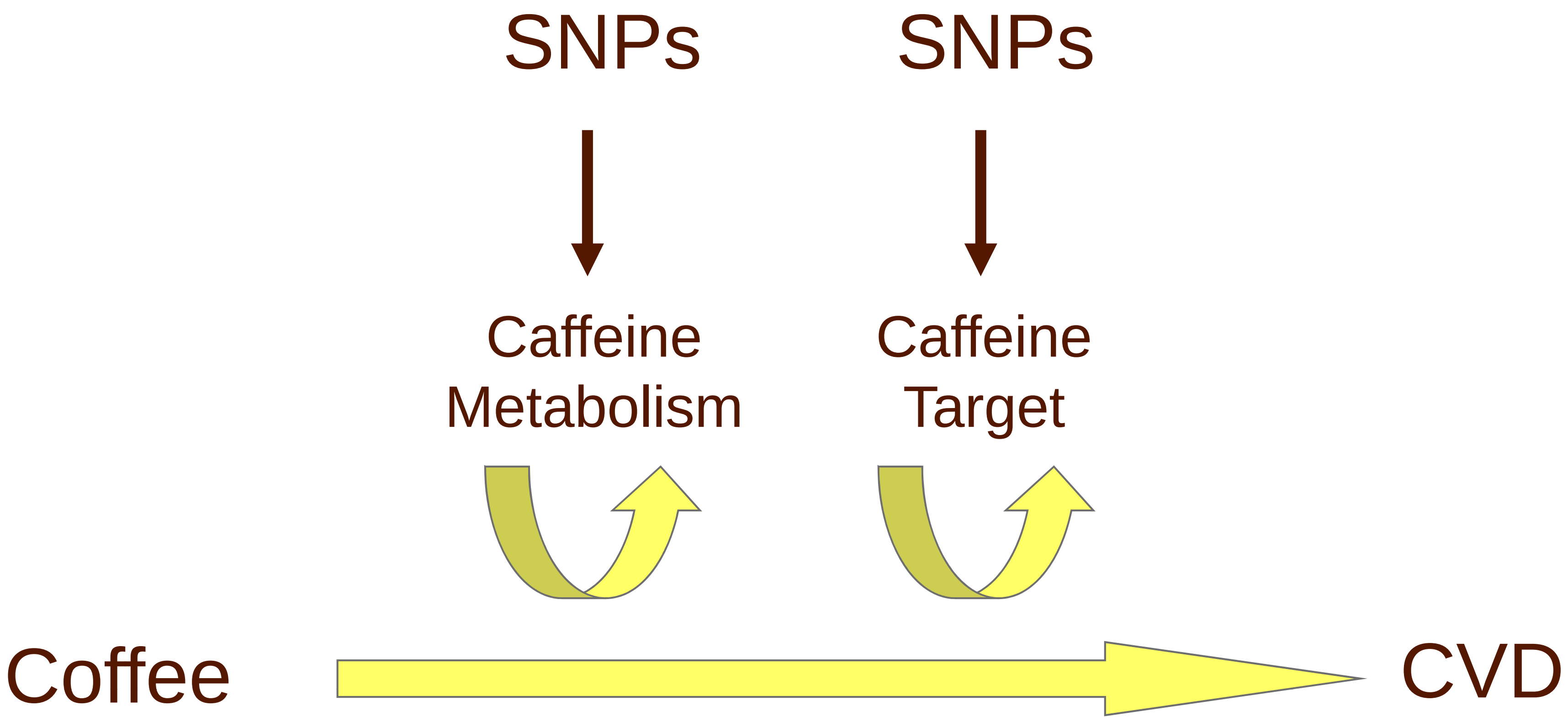

TAURINE CAFFEINE B-VITAMINS
NRG
POTATO CHIPS
PHOENIX FURY
NET WT. 1.75 OZ. (49.6G)

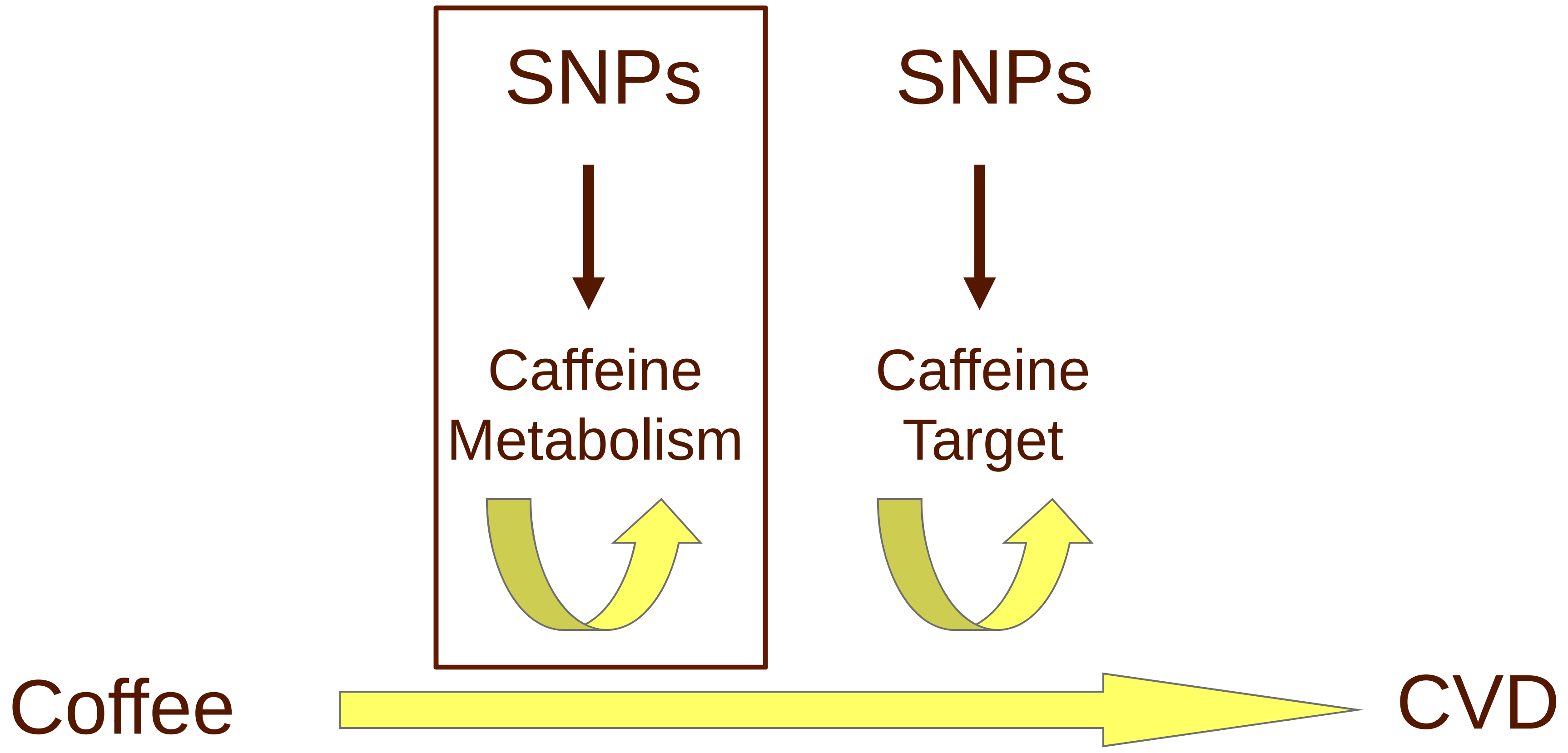

220mg of VITAMIN C
NO-CRASH ENERGY
made in U.S.A.
LOUD TRUCK
ENERGY FUELED GUMMI
Energy Gummies
citrus blast
B Vitamins FOR ENERGY
NATURAL & ARTIFICIAL FLAVORS
NET WT. 1 oz (28.3g)
Tastes Great

"The Legal Alternative"

Department o




SNPs
SNPs
Caffeine Metabolism
Caffeine Target
Coffee
CVD


SNPs
Caffeine Metabolism
SNPs
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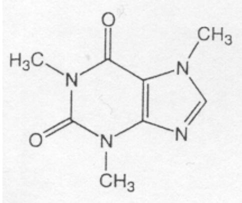
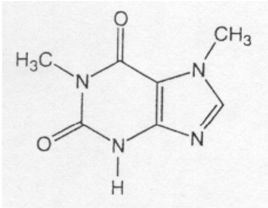
Coffee
CVD

Caffeine



CYP1A2



Paraxanthine

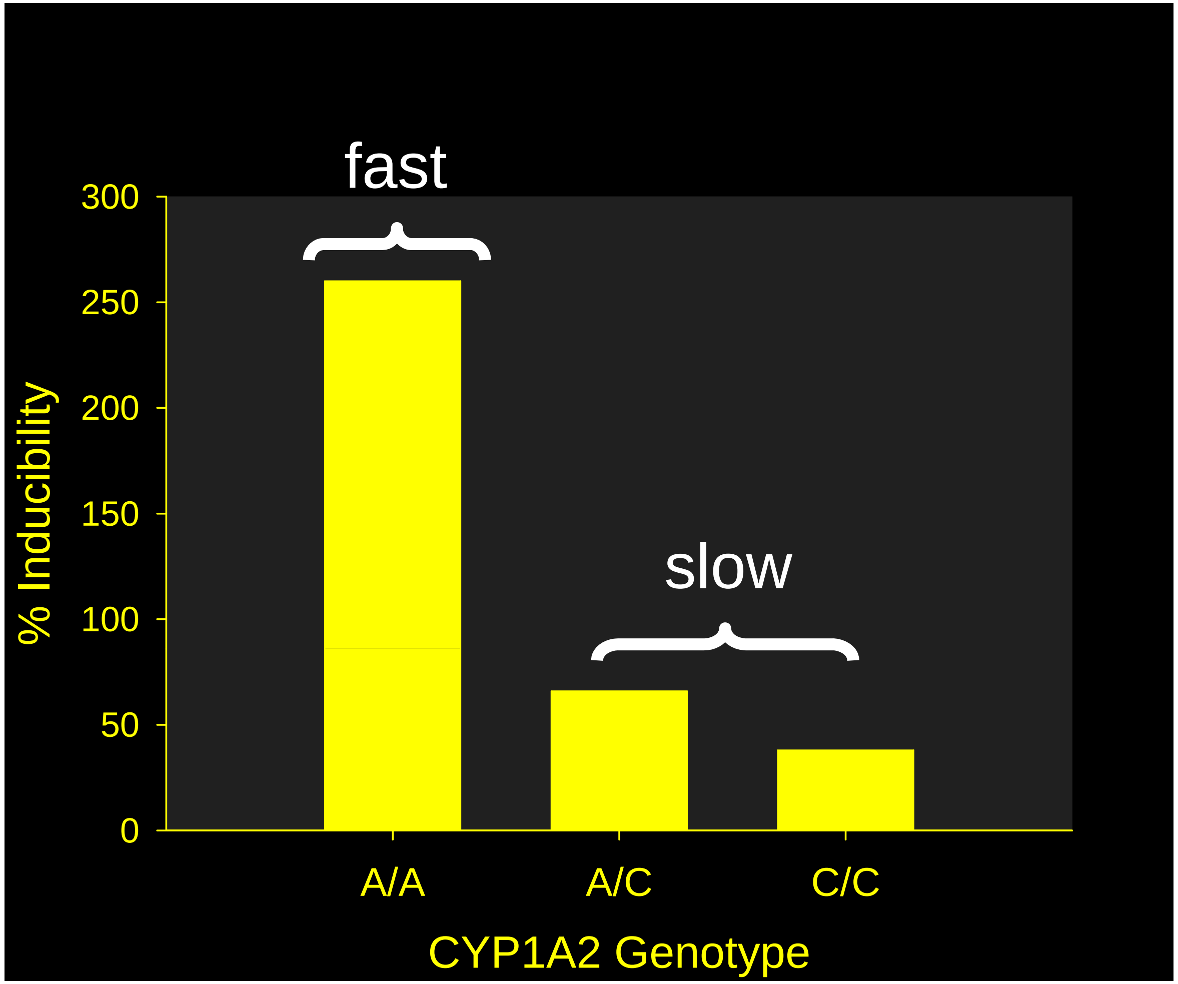
1,7-dimethyluric acid

1-methylxanthine

5-acetylamino-6-formylamino-3-methyluracil

1-methyluric acid

Genetic Variation in CYP1A2 -163 A→C



ORIGINAL CONTRIBUTION

Coffee, CYP1A2 Genotype, and Risk of Myocardial Infarction

Marilyn C. Cornelis, BSc
Ahmed El-Sohemy, PhD
Edmond K. Kabagambe, PhD
Hannia Campos, PhD

Context The association between coffee intake and risk of myocardial infarction (MI) remains controversial. Coffee is a major source of caffeine, which is metabolized by the polymorphic cytochrome P450 1A2 (CYP1A2) enzyme. Individuals who are homozygous for the *CYP1A2*1A* allele are "rapid" caffeine metabolizers, whereas carriers of the variant *CYP1A2*1F* are "slow" caffeine metabolizers.

Objective To determine whether CYP1A2 genotype modifies the association between coffee consumption and risk of acute nonfatal MI.

Design, Setting, and Participants Cases (n=2014) with a first acute nonfatal MI and population-based controls (n=2014) living in Costa Rica between 1994 and 2004, matched for age, sex, and area of residence, were genotyped by restriction fragment–length polymorphism polymerase chain reaction. A food frequency questionnaire was used to assess the intake of caffeinated coffee.

Main Outcome Measure Relative risk of nonfatal MI associated with coffee intake, calculated using unconditional logistic regression.

Results Fifty-five percent of cases (n=1114) and 54% of controls (n=1082) were carriers of the slow *1F* allele. For carriers of the slow *1F* allele, the multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of nonfatal MI associated with consuming less than 1, 1, 2 to 3, and 4 or more cups of coffee per day were 1.00 (reference), 0.99 (0.69-1.44), 1.36 (1.01-1.83), and 1.64 (1.14-2.34), respectively. Corresponding ORs (95% CIs) for individuals with the rapid *1A/*1A genotype were 1.00,

EPIDEMIOLOGIC STUDIES EXAMINing the association between coffee consumption and risk of myocardial infarction (MI) have been inconclusive.[1-14] Coffee is a major source of caffeine (1,3,7-trimethylxanthine), which is the most widely consumed stimulant in the world and has been implicated in the development of cardiovascular diseases such as acute MI.[15-17] However, coffee contains a number of other chemicals that have variable effects on the cardiovascular system.[18] Because of the strong

2013 cases (myocardial infarction)

2013 population-based controls

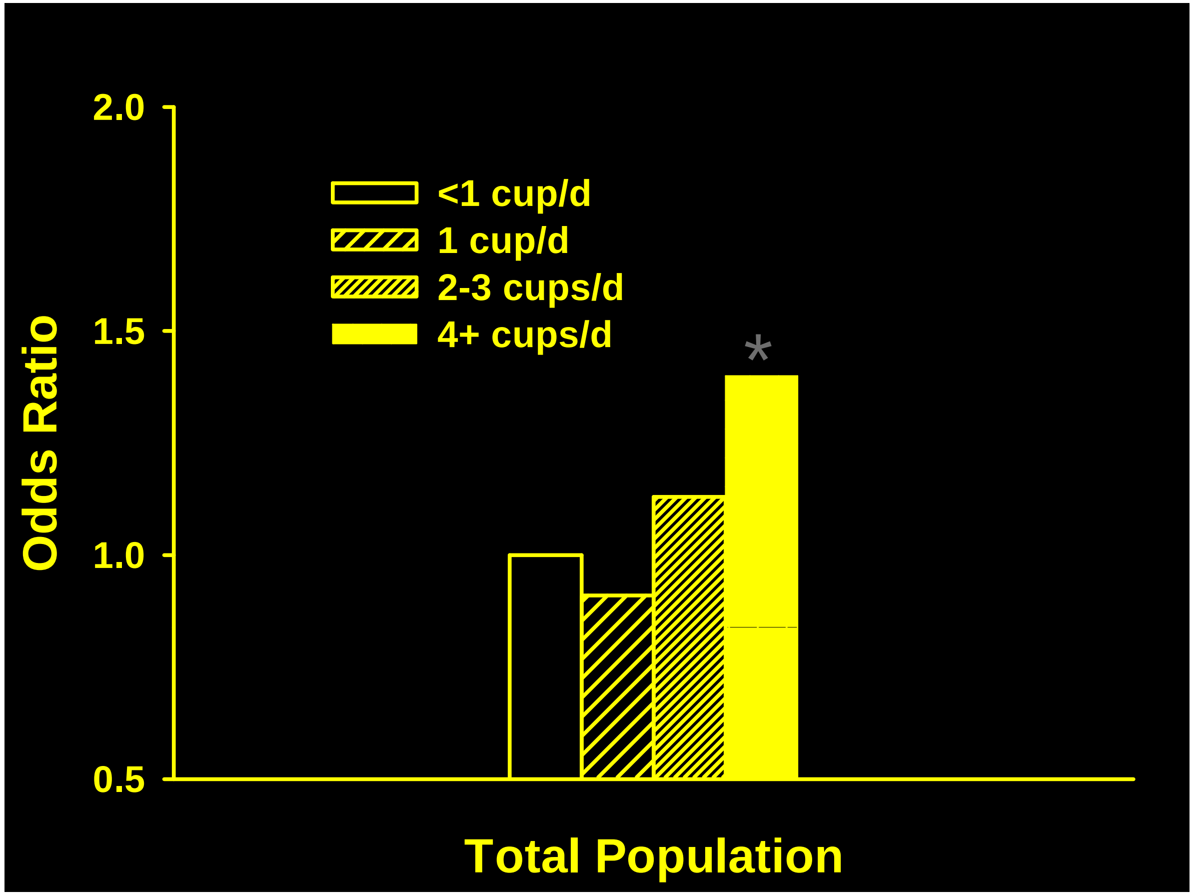
- matched (age, sex, area of residence)

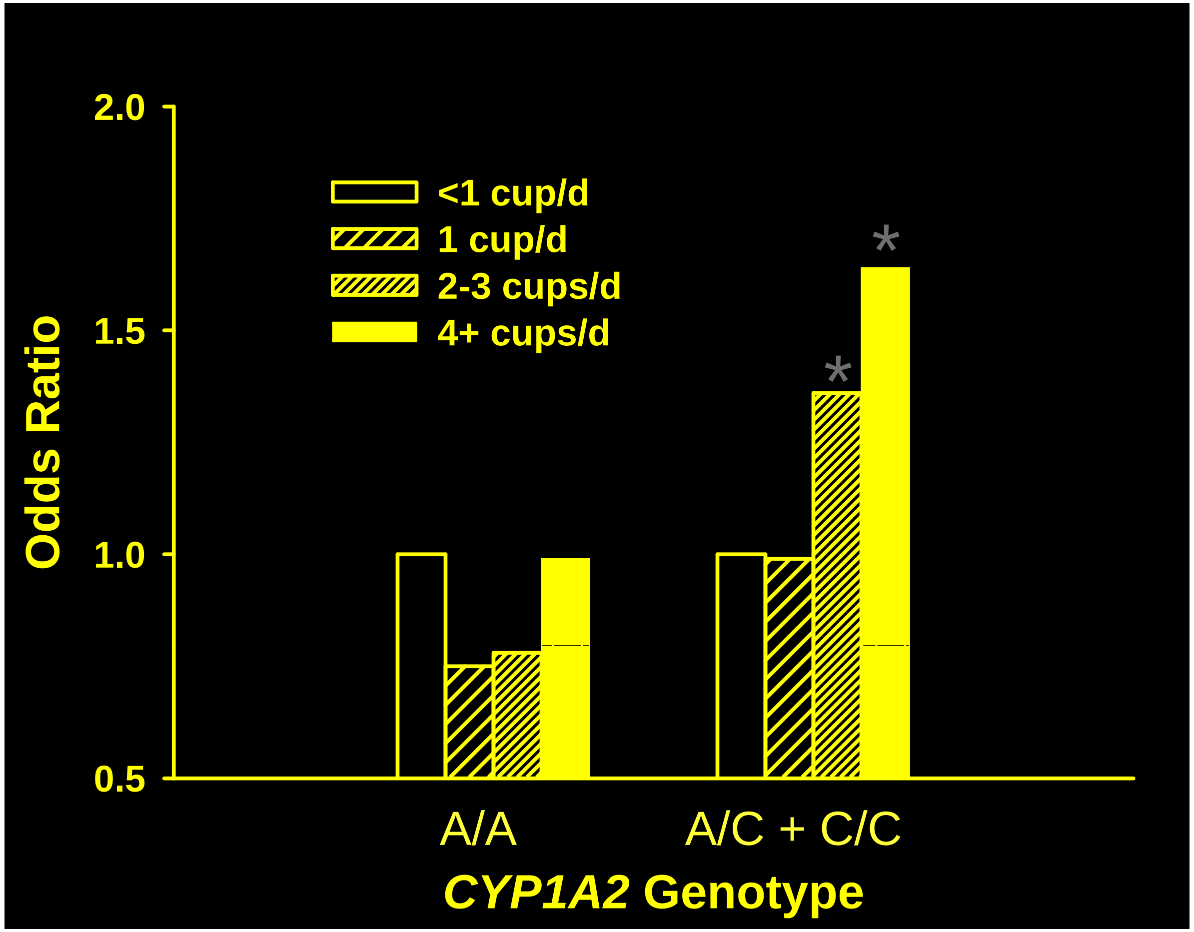
Data collection:

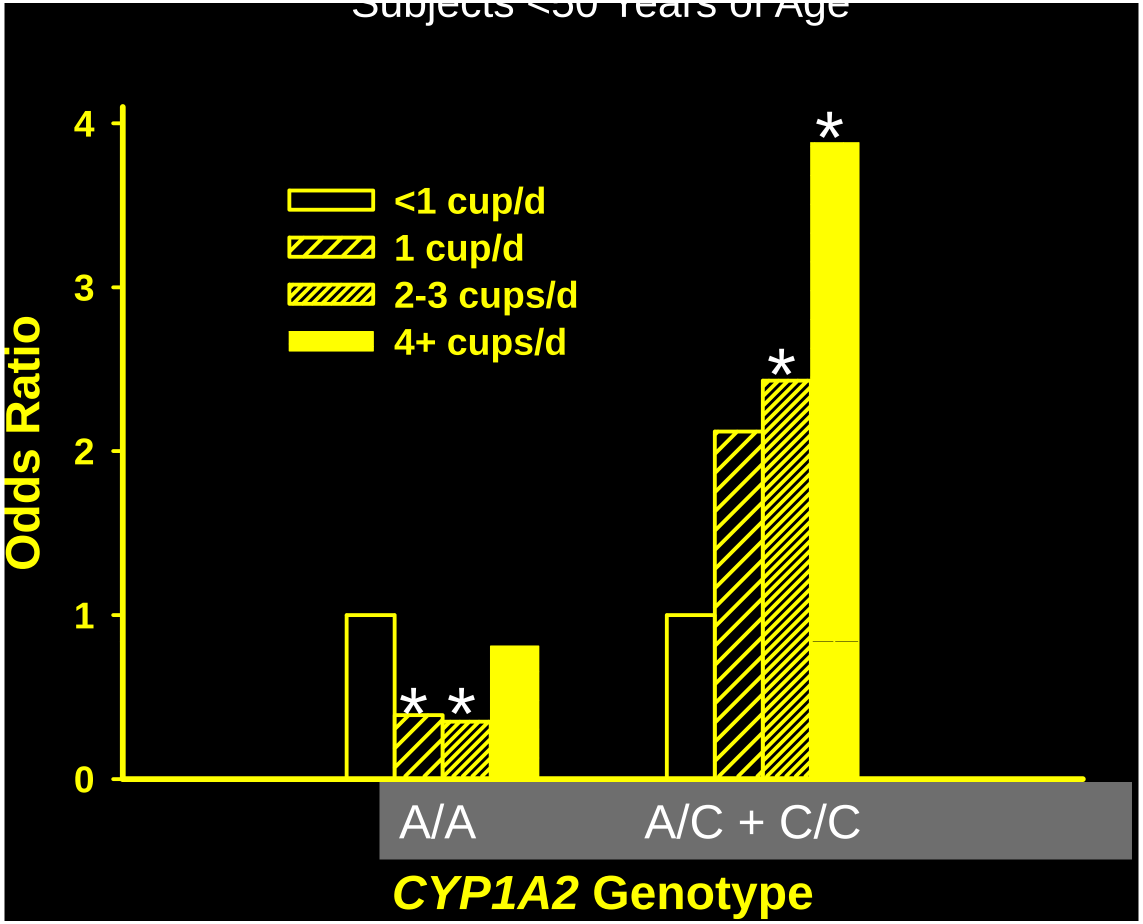
- food frequency questionnaire
- health and lifestyle questionnaire
- fasting blood sample (DNA)

CYP1A2 Genotype Distribution

CYP1A2 Genotype	Controls %	Cases %
A/A	46	45
A/C	43	44
C/C	10	11


2.0
1.5
1.0
0.5
Odds Ratio
<1 cup/d
1 cup/d
2-3 cups/d
4+ cups/d
*
Total Population


2.0
1.5
1.0
0.5
Odds Ratio
<1 cup/d
1 cup/d
2-3 cups/d
4+ cups/d
*
*
A/A
A/C + C/C
CYP1A2 Genotype


Odds Ratio
0
1
2
3
4
<1 cup/d
1 cup/d
2-3 cups/d
4+ cups/d
A/A
A/C + C/C
CYP1A2 Genotype

THE TIMES 60p
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THE TIMES WEDNESDAY MARCH 8 2006 NEWS 11

Gene that could make your next coffee your last

New research suggests that some people cannot process caffeine as quickly as others and may therefore be more vulnerable to a heart attack, **Sam Lister** reports

HELEN ATKINSON

High amounts of caffeine can be dangerous, but some doctors suggest coffee also has benefits

COFFEE drinkers who have more than three cups a day could significantly increase their chances of suffering a heart attack.

New research suggests that people who carry a particular variation of a gene cannot process caffeine as quickly as other people. Such individuals could be up to 64 per cent more likely to have a heart attack if they drink large amounts of coffee.

long be a source of controversy, with high amounts of caffeine long blamed for over-stimulating the nervous system. It contains ditrepenes, said to be responsible for raising levels of a stress hormone called homocystine, which can lead to strokes.

Pregnant women have been urged not to drink more than three cups of coffee a day in case it increases the chances of

CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension

Paolo Palatini[a], Giulio Ceolotto[a], Fabio Ragazzo[a], Francesca Dorigatti[a], Francesca Saladini[a], Italia Papparella[a], Lucio Mos[b], Giuseppe Zanata[c] and Massimo Santonastaso[d]

Journal of Hypertension 2009, 27:000–000

Fig. 1

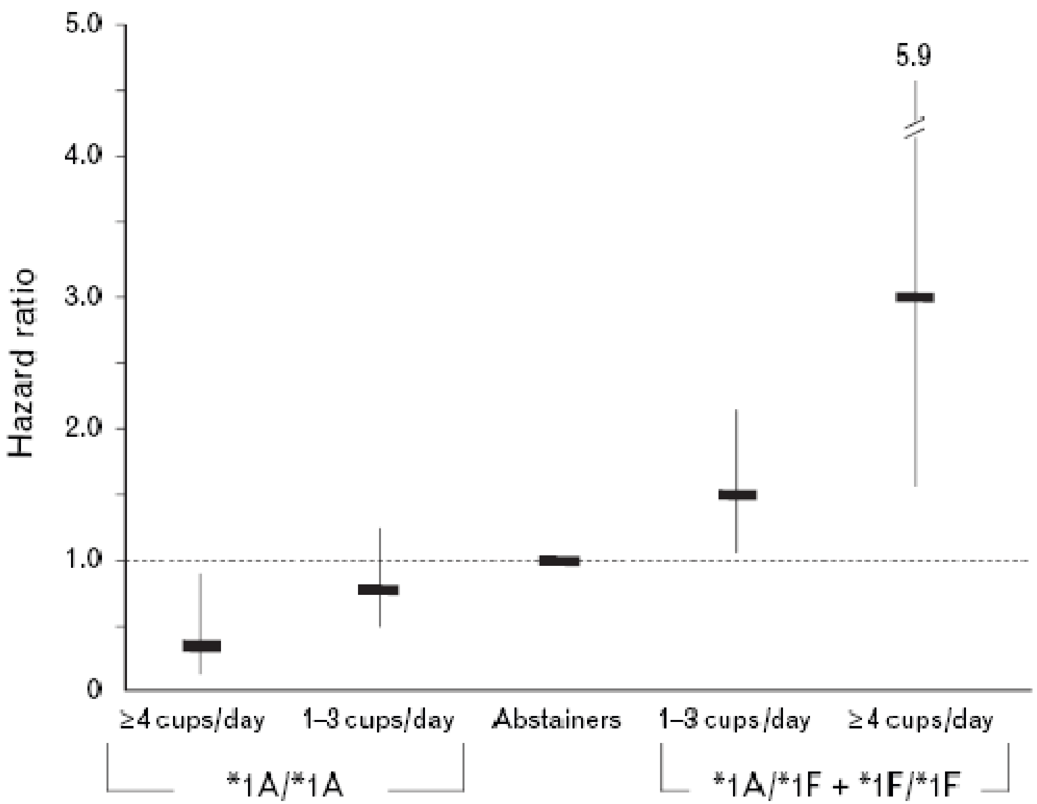

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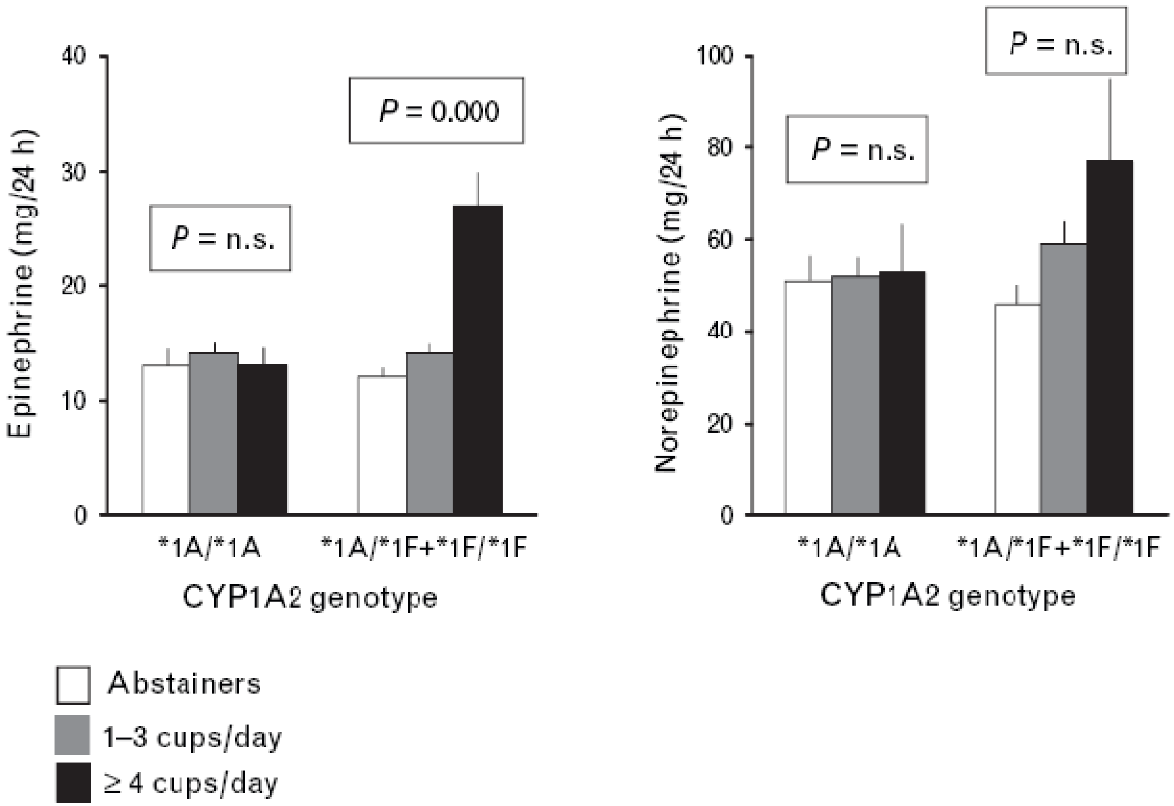
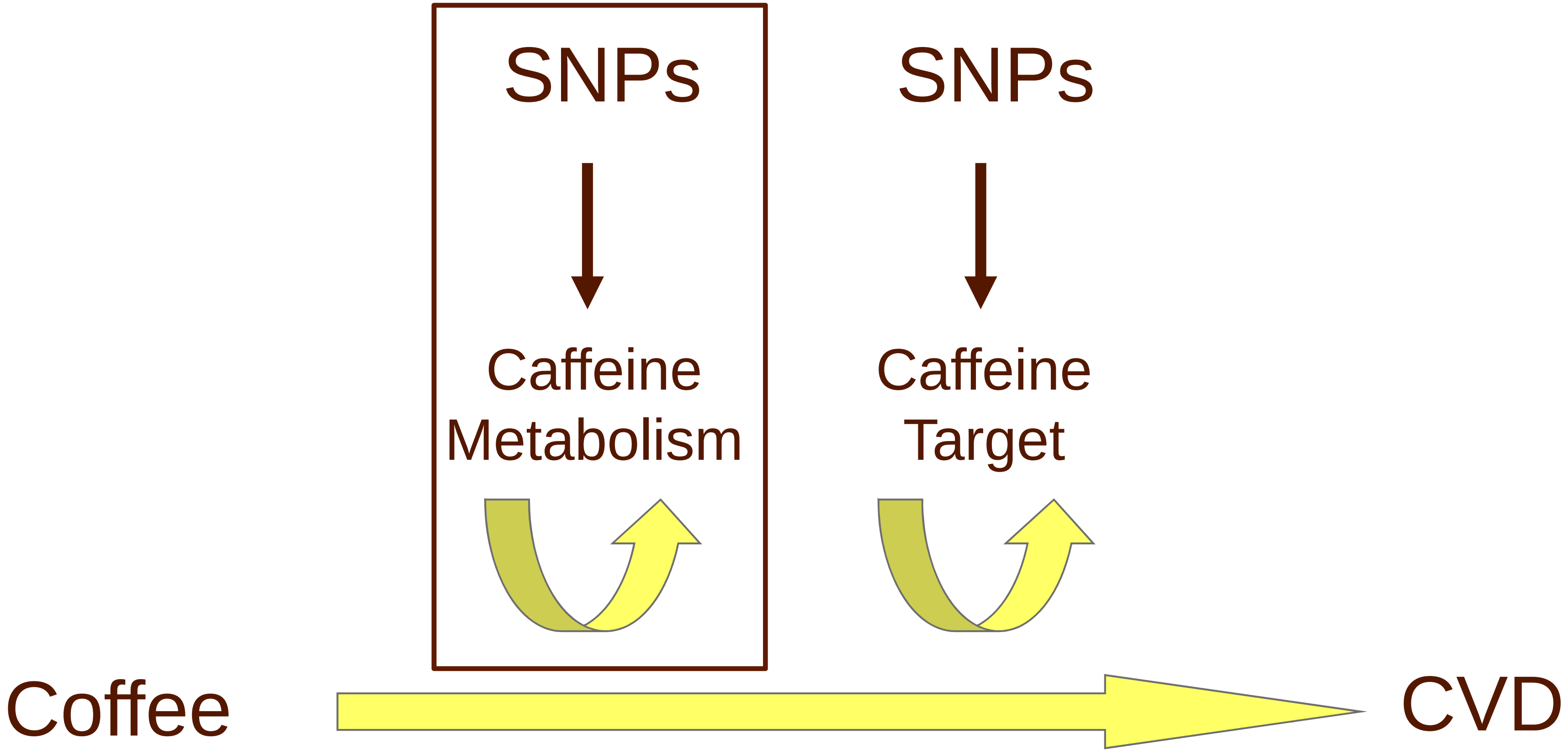
Fig. 2




SNPs
Caffeine Metabolism
SNPs
Caffeine Target
Coffee
CVD

Genetic polymorphism of the adenosine A_{2A} receptor is associated with habitual caffeine consumption[1–3]

Marilyn C Cornelis, Ahmed El-Sohemy, and Hannia Campos

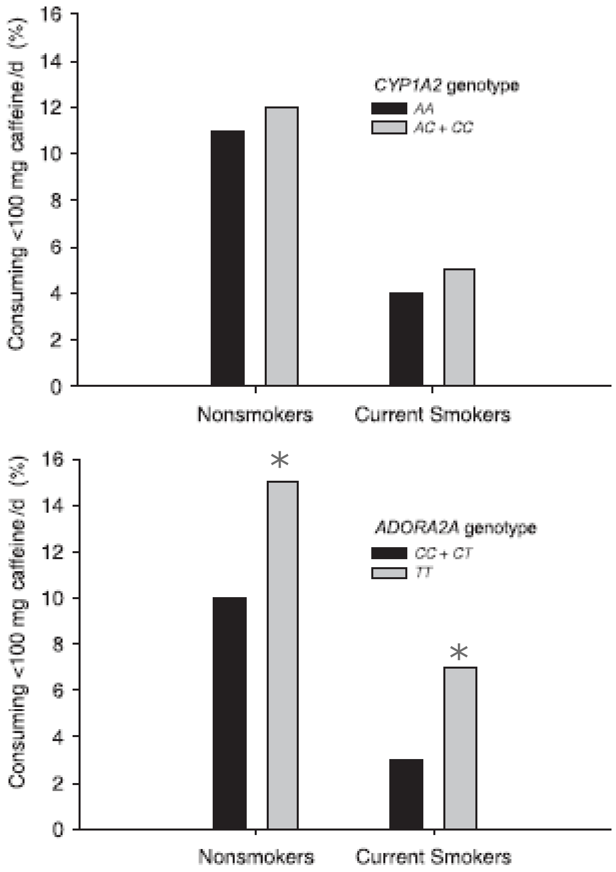
ABSTRACT

Background: Caffeine is the most widely consumed stimulant in the world, and individual differences in response to its stimulating effects may explain some of the variability in caffeine consumption within a population.

Objective: We examined whether genetic variability in caffeine metabolism [cytochrome P450 1A2 (*CYP1A2*) −163A→C] or the main target of caffeine action in the nervous system [adenosine A_{2A} receptor (*ADORA2A*) 1083C→T] is associated with habitual caffeine consumption.

(1, 4, 5). However, some persons experience anxiety, tachycardia, nervousness, or other adverse effects with low-to-moderate intakes of caffeine (4). These differences in response to caffeine may explain some of the variability in caffeine intake within a population (1, 6, 7). Although demographic, psychosocial, health-related, and environmental factors such as smoking have been linked to habitual caffeine consumption (8–11), there is some evidence that genetic factors are also important (12–15). Twin studies report heritability estimates of up to 77% for caffeine use, toxicity, tolerance, and withdrawal symptoms (12–15).

Genetic polymorphism of the adenosine A_{2A} receptor is associated with habitual caffeine consumption[1–3]

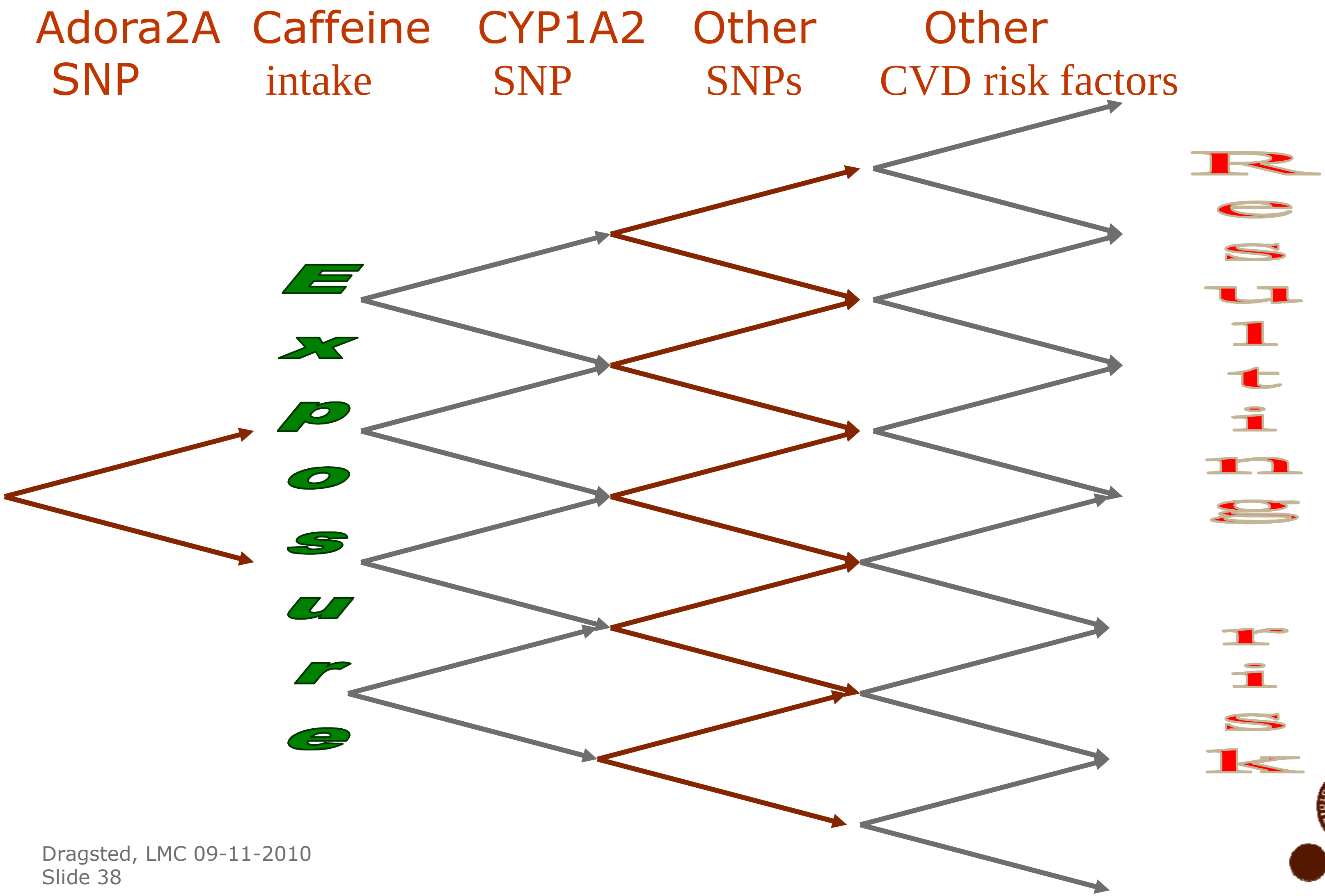


	Genetic modifiers of exposure	Genetic modifiers of biological effect
Caffeine →	CYP1A2 FMO CYP2A6 NAT2 CYP2E1	ADR ADORA HTT GRK HTR COMT
Diterpenes →	UGT SULT	CETP PLTP LDLR ACAT SREBP GST
Flavonoids →	CYP1A2 CYP3A4 CYP2D6 CYP1A1 UGT SULT CYP2C9 CYP2E1	ACE TNF NFκB VCAM1 PKC PPARG PDE CREB GLUT PKA
Polyphenols →	UGT GST SULT	GLP1R GLUT FAS1 ACE NOX G6PT1

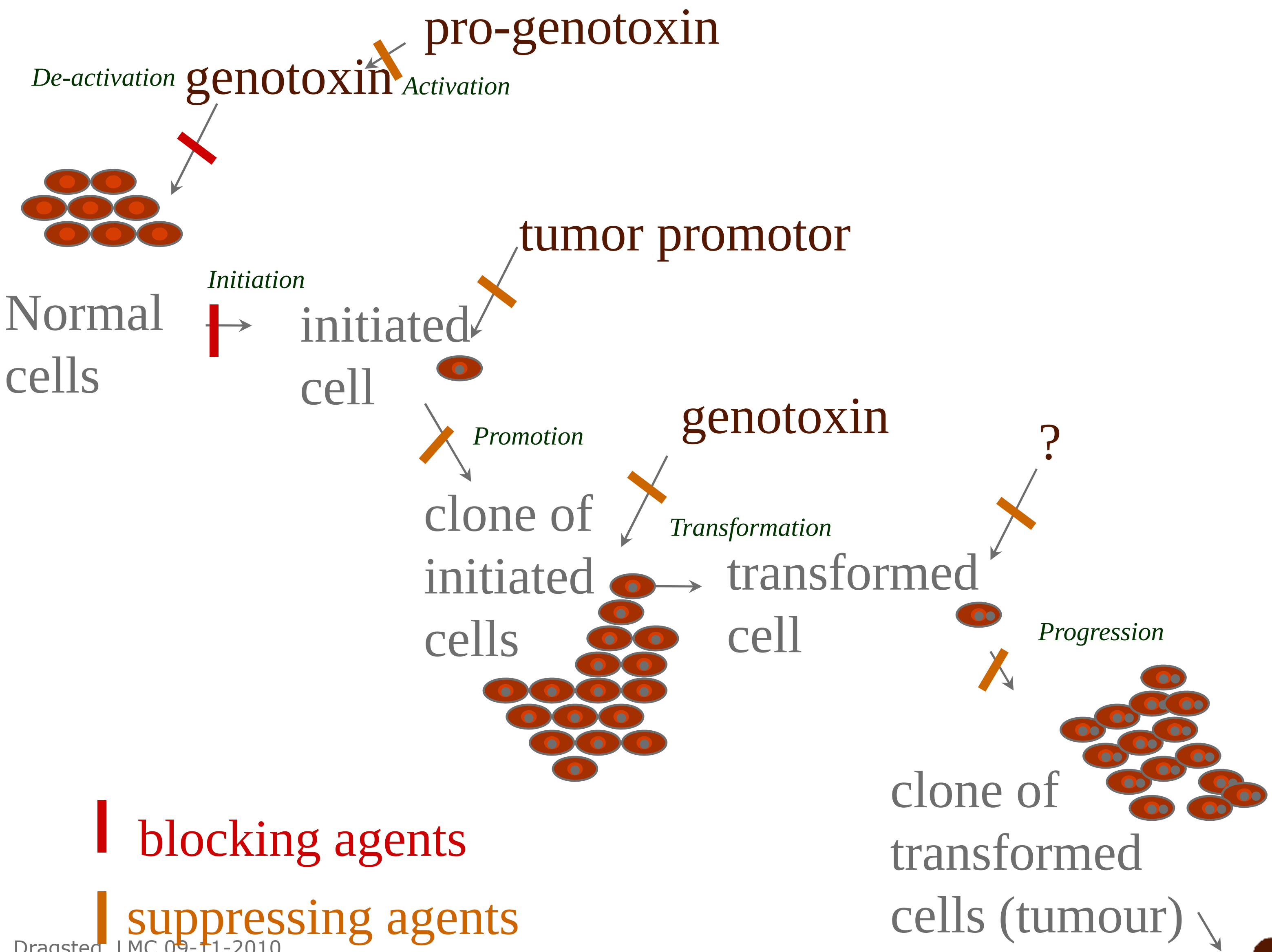
→ ↕ CHD Risk

Curr. Opin. Lipidol, 18: 13-19, 2007

Exposure, genetics and CVD risk

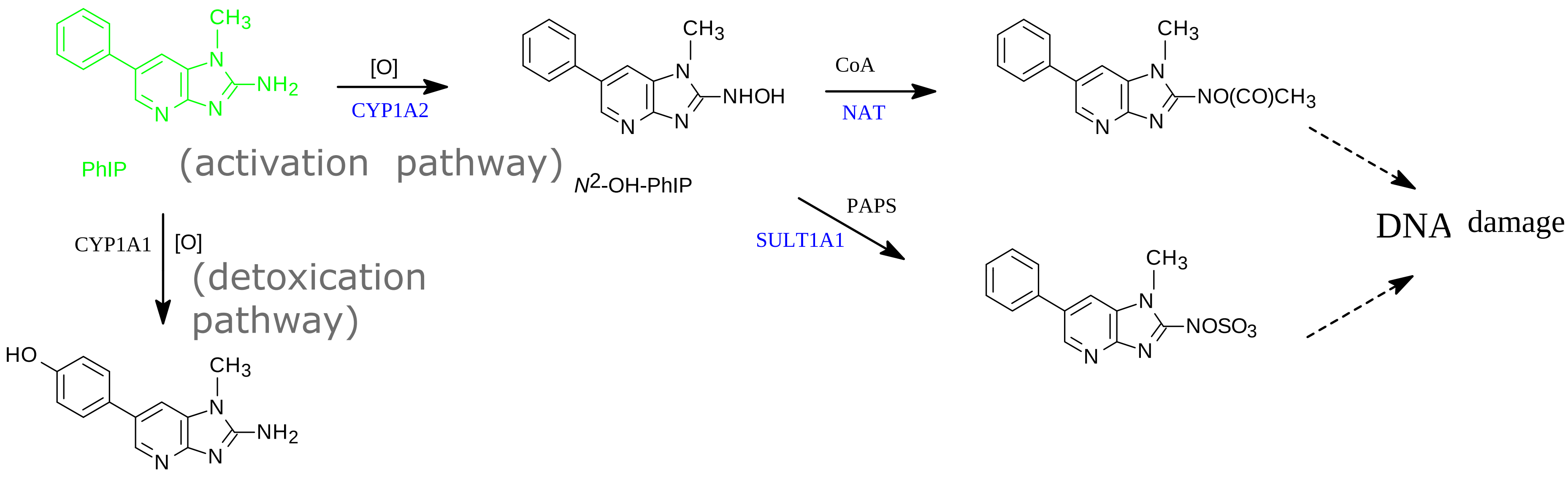


A simple carcinogenesis / anti-carcinogenesis model

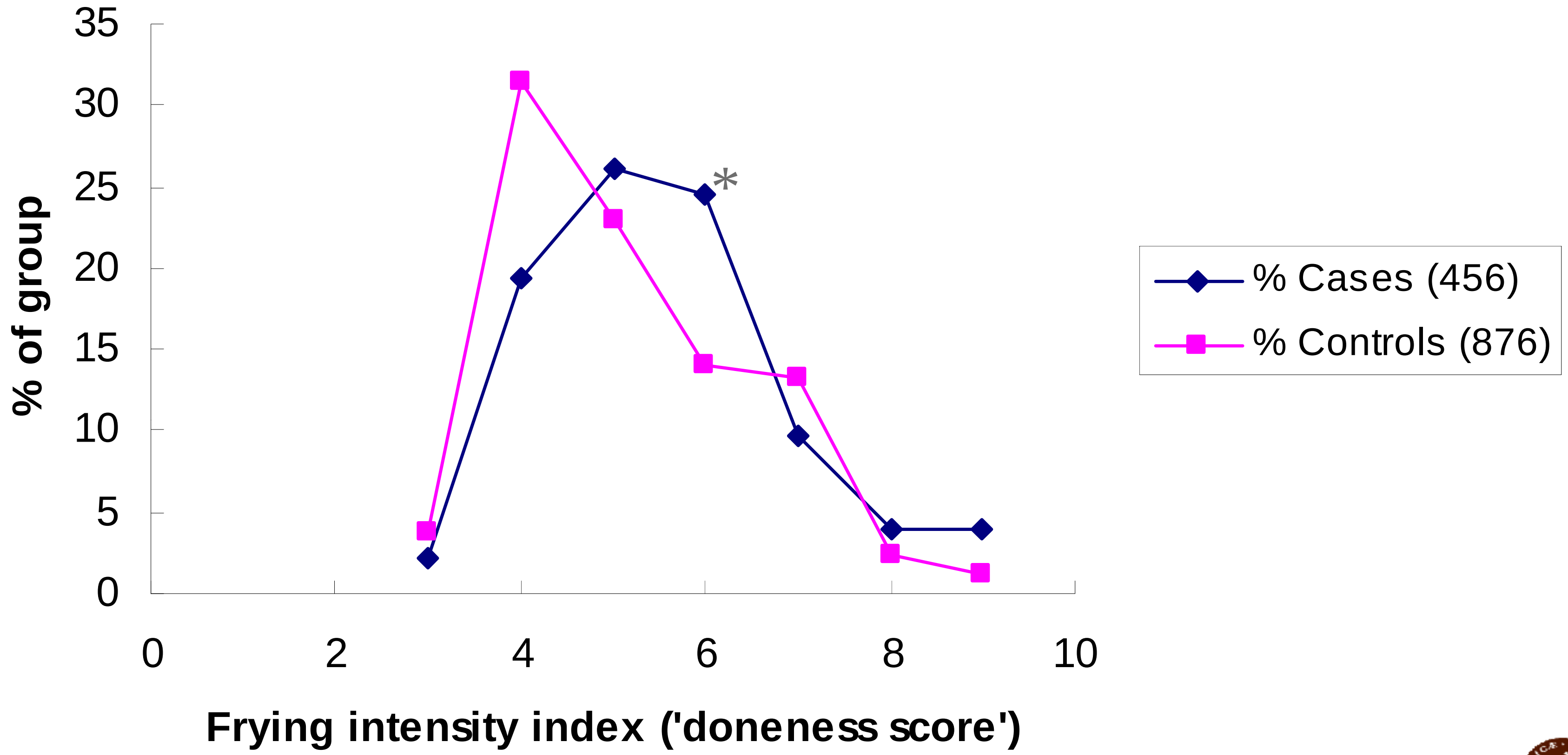


Example: The carcinogen, PhIP, is formed when meat is fried – *activation of PhiP involves several genes*

Phase I Phase II

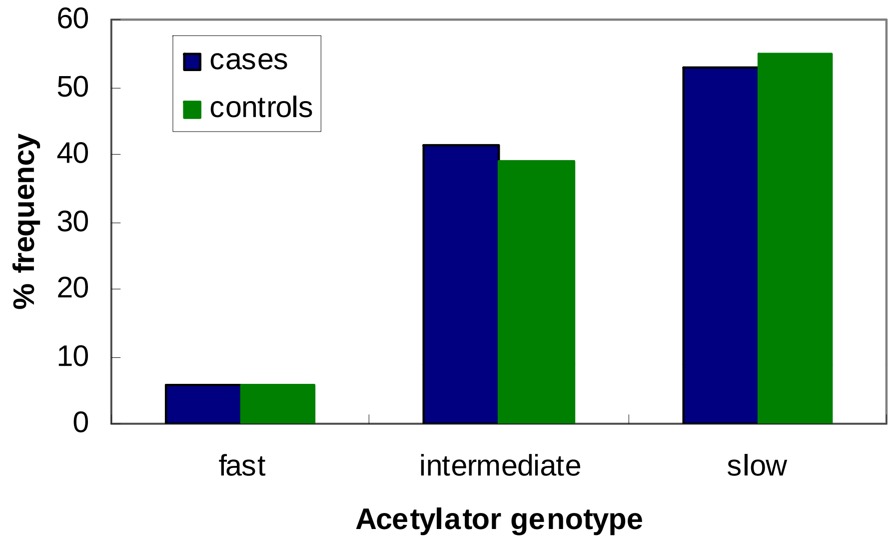


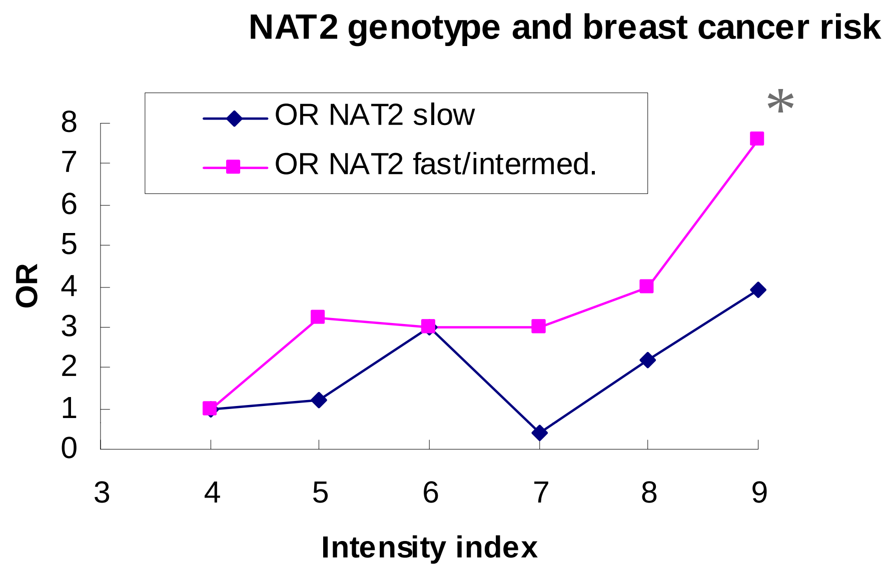
Frying and breast cancer in the Iowa womens health study



Deitz et al., Cancer Epidemiol, Biomark Prev. 9 (2000) 905-910

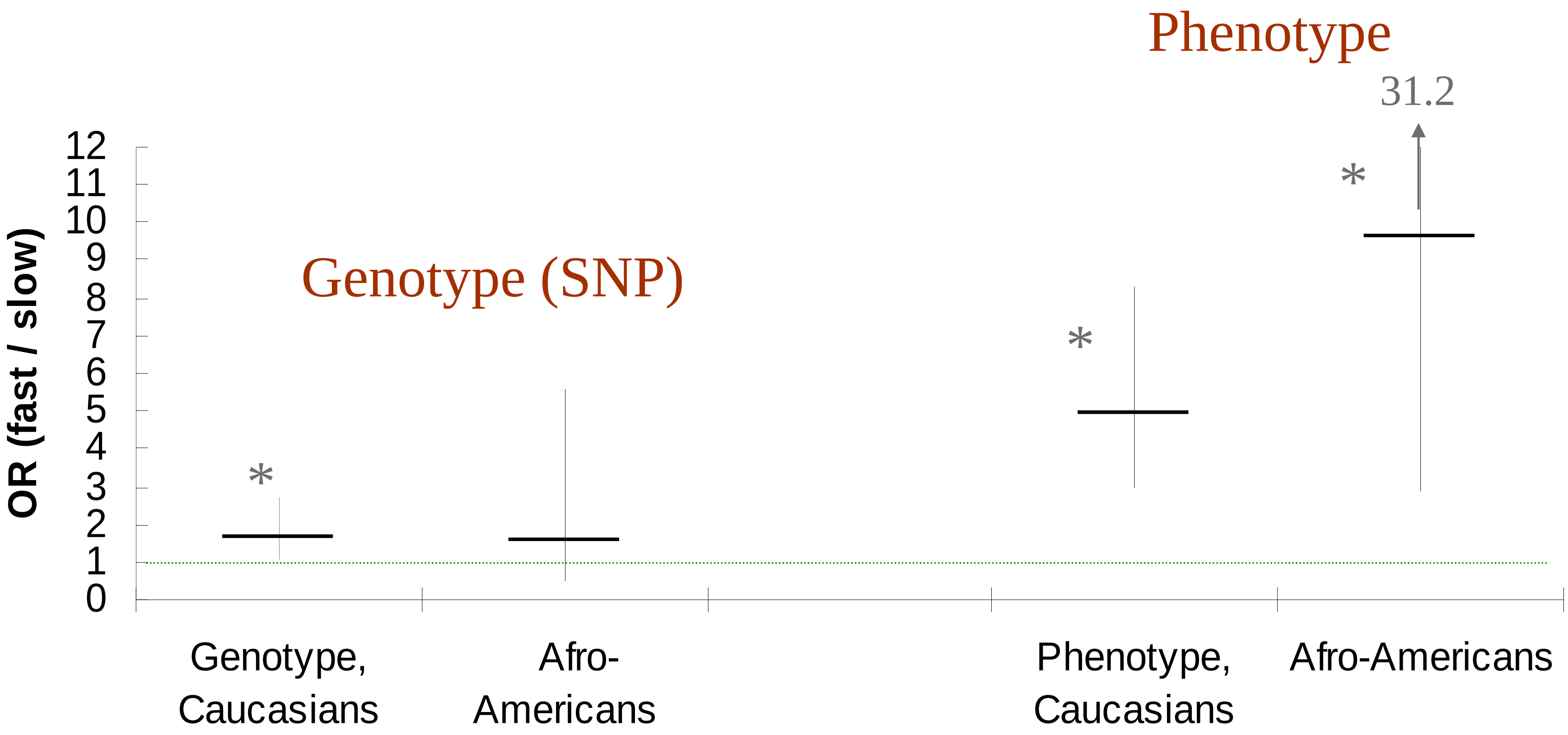
NAT2 genotype and breast cancer risk
- interaction with frying intensity index





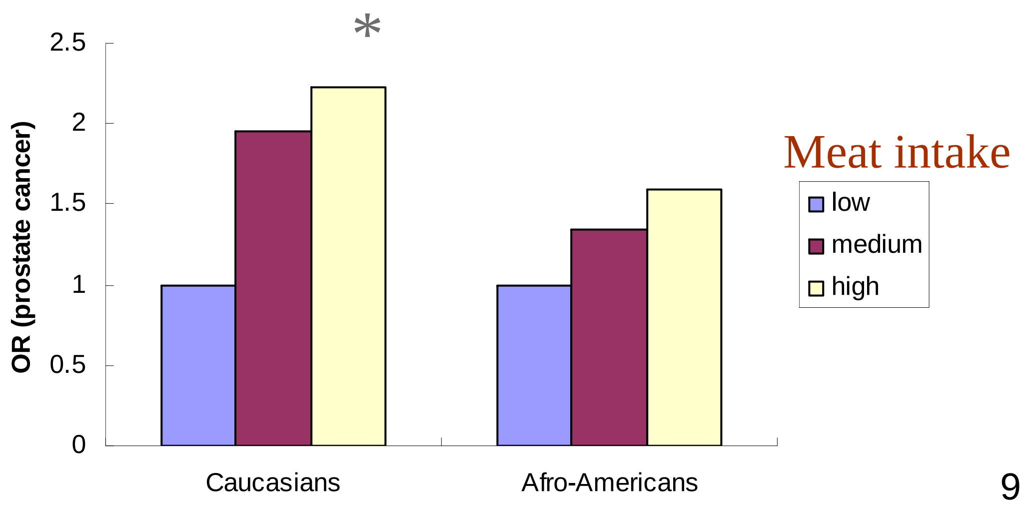
Deitz et al., Cancer Epidemiol, Biomark Prev. 9 (2000) 905-910

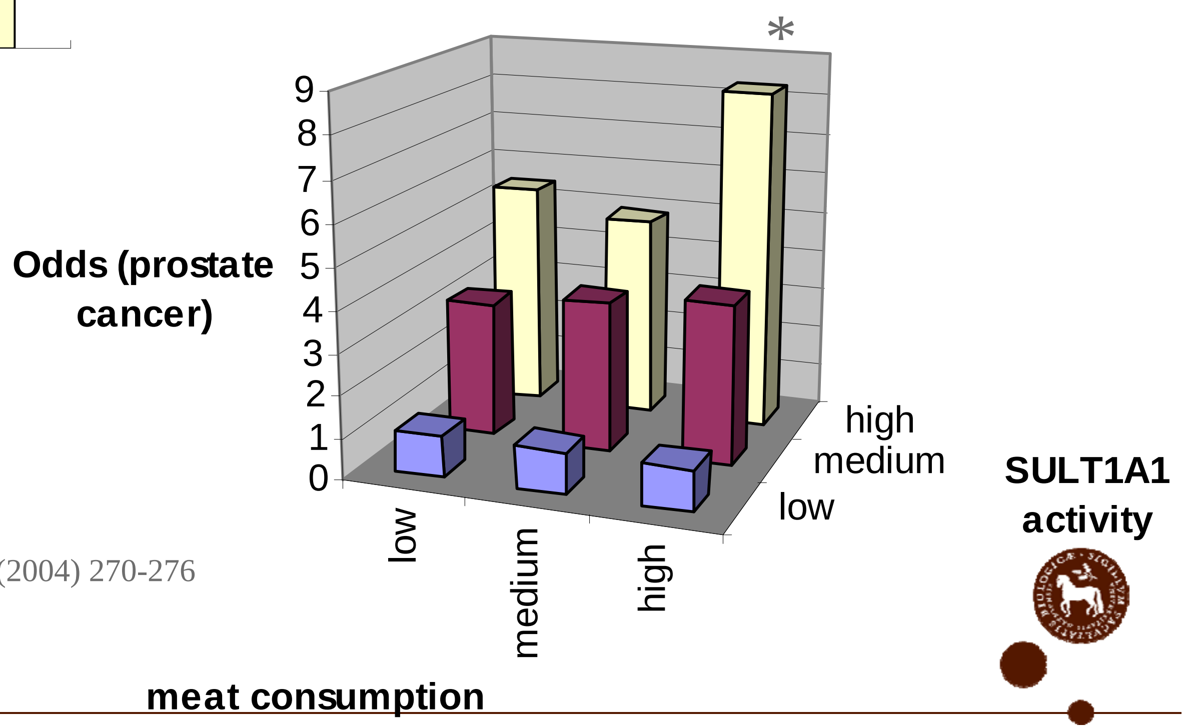
SULT1A1 in prostate cancer cases (454) and controls (459)



Nowell et al., Cancer Epidemiol, Biomark Prev. 13 (2004) 270-276

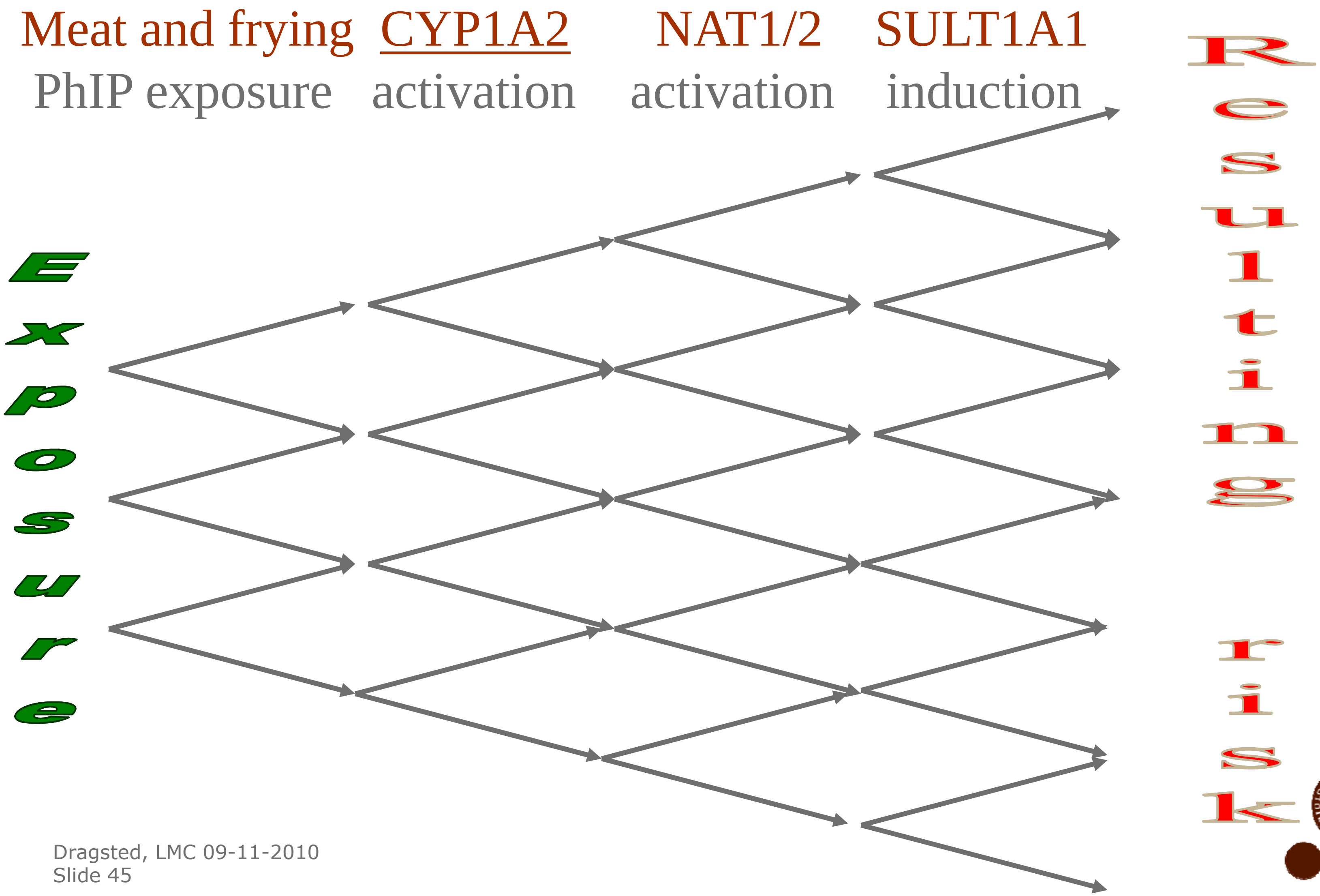
SULT1A1, meat indtake and prostate cancer risk case-control study



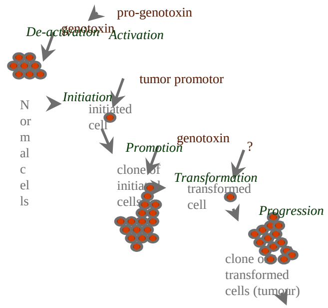


Nowell et al., Cancer Epidemiol, Biomark Prev. 13 (2004) 270-276

Relation between exposure, genetics and risk



Oxidative damage and risk of cancer



Initiation:

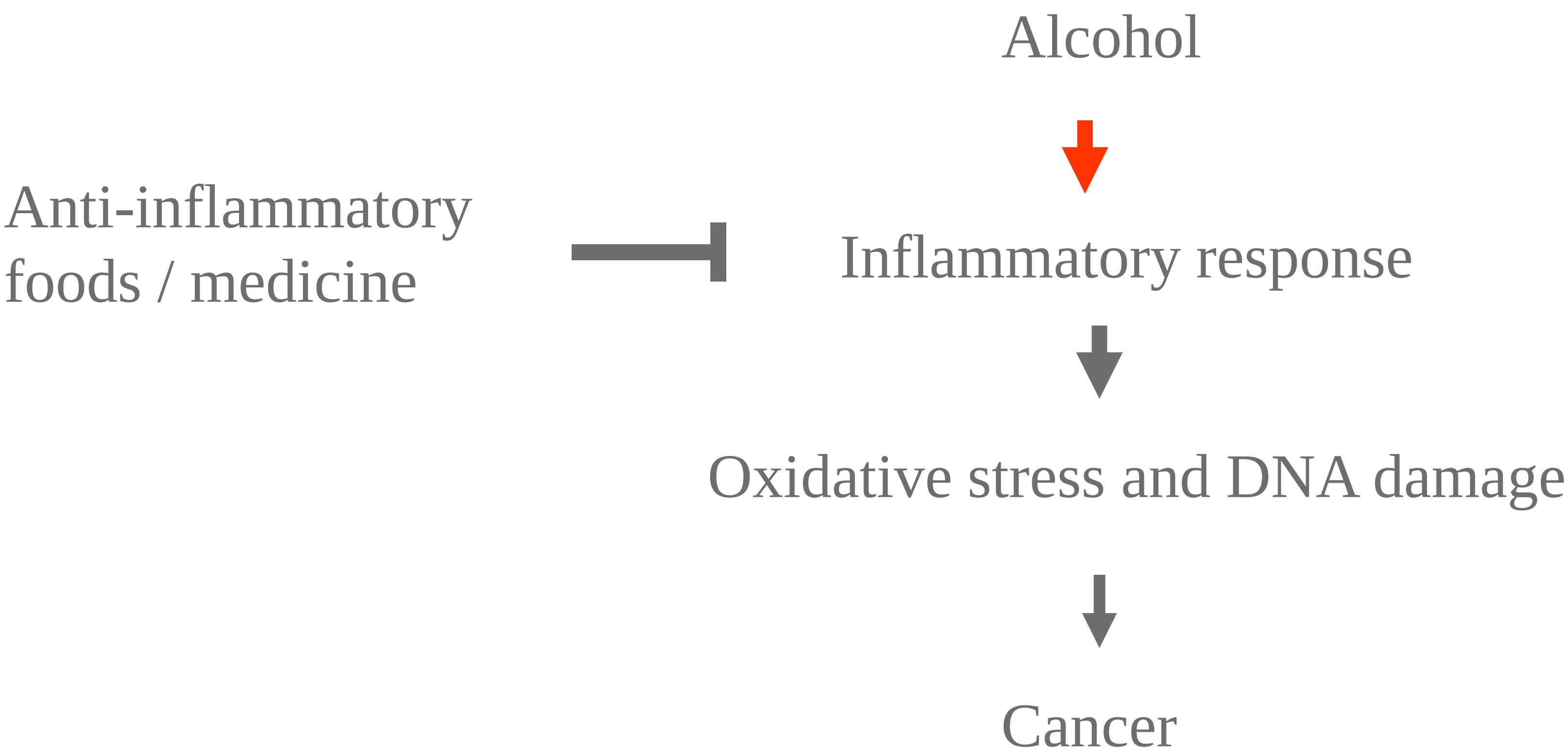
- Reactive oxygen species may modify DNA leading to mutation

- Reactive lipid oxidation products may also damage DNA

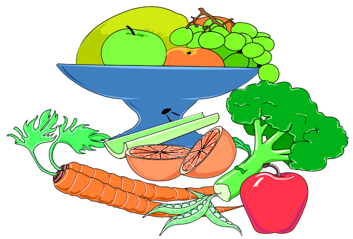
Tumour promotion

- Prolonged oxidative stress may cause inflammatory reactions

Pathways: Inflammation and DNA repair



Fruit and vegetables – 6-a-Day study: Design



Run-in	Intervention period	Follow-up
(3 days)	(25 days), 3 groups	(28 days)
habitual diet	Controlled diet	habitual diet

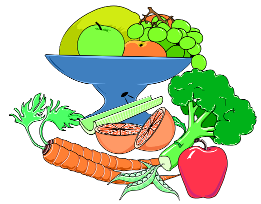
600g Fruit & Veg.

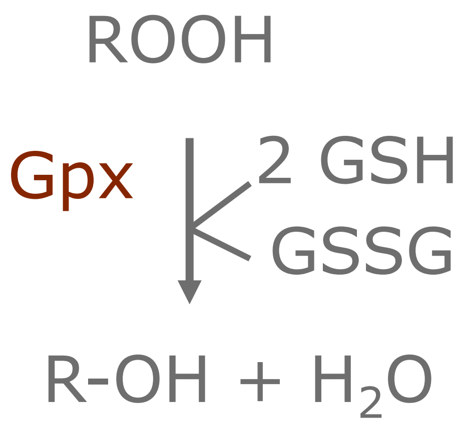
vitamins & minerals

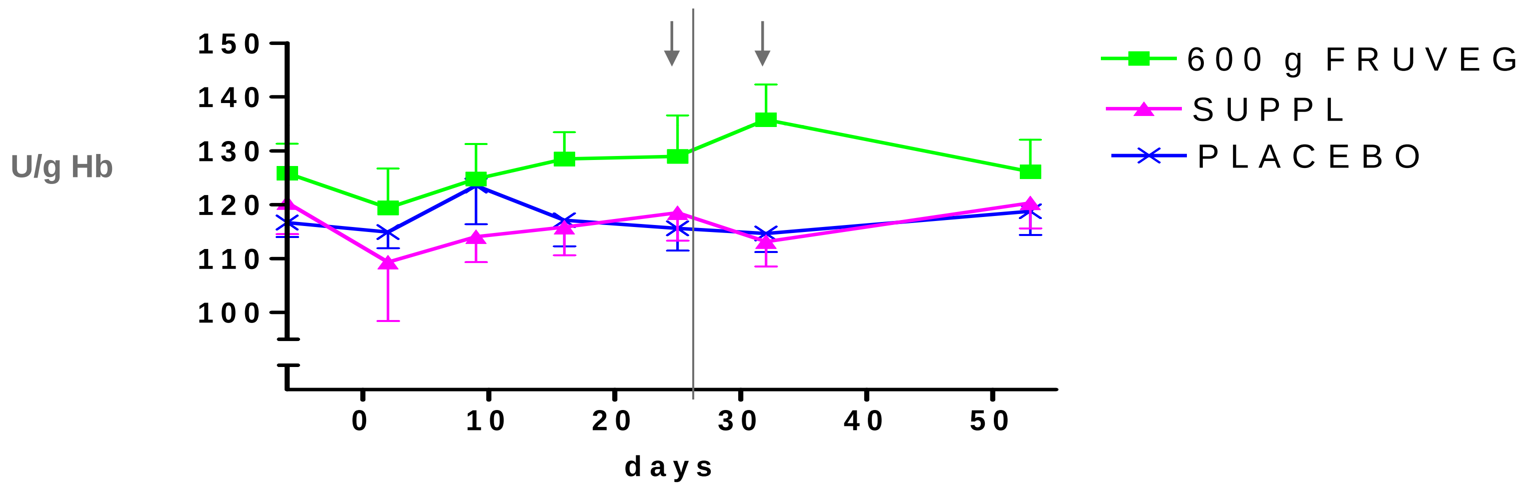
placebo

samples	X	X	X	X	X	XX	X	X
day	-3	0	2	9	16	24-25	32	53

6-a-day study – glutathion peroxidase

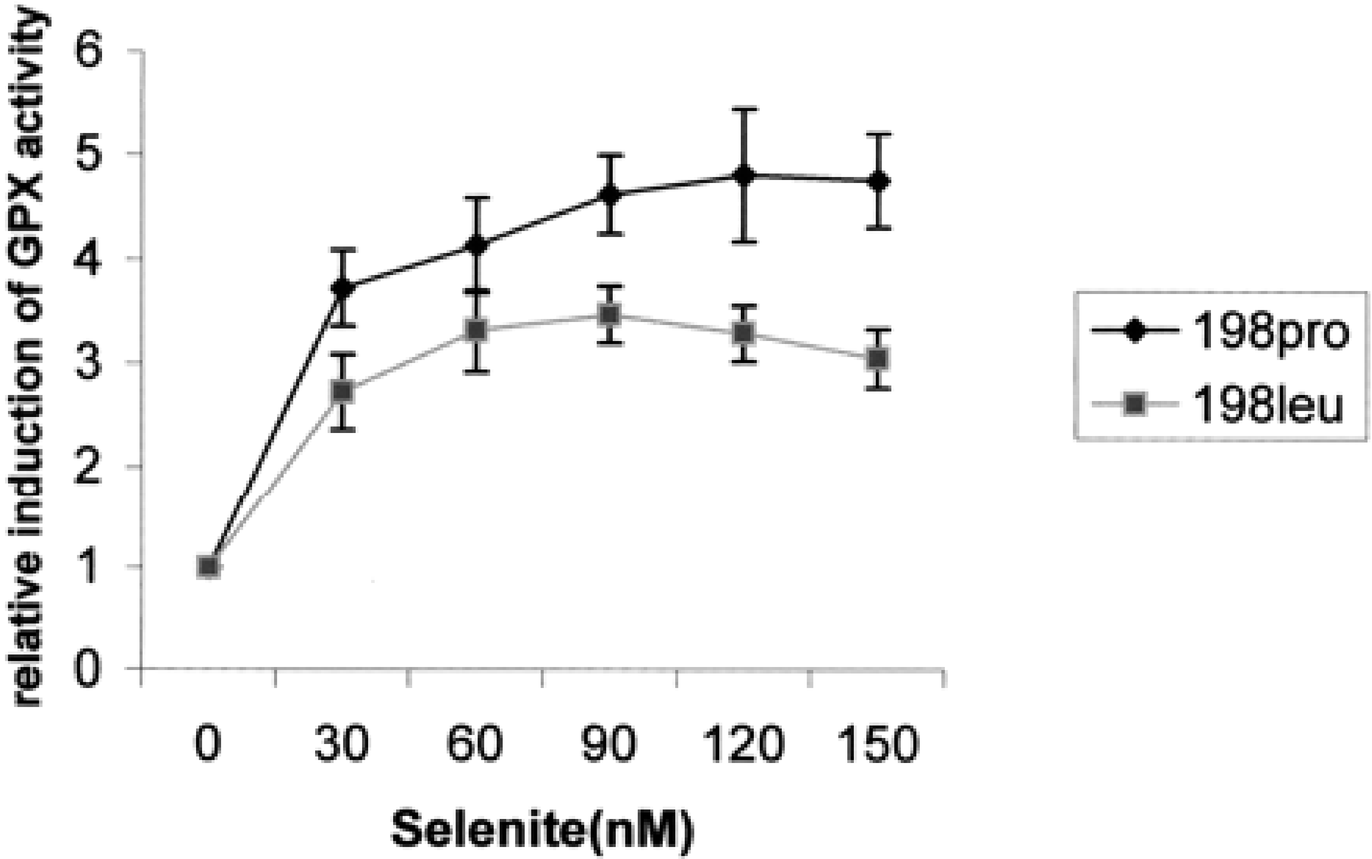






Dragsted et al., AJCN (2004)

Lower enzyme activity of GPX ^{198}Leu *in vitro*



Hu & Diamond, Cancer Res 63; 3347-3351, 2003

The Diet, Cancer and Health Cohort

Collected by the Danish Cancer Society:

57,053 Danes, aged 50-65

Collected 1993-1997

Questionaire, blood, urine, fat, nails

DNA, RNA can be purified from frozen lymphocytes

Prospective!

Some validation (weight, height, food frequency)

GPX Pro198Leu is weakly associated with breast cancer risk

GPX $Pro^{198}Leu$	$N_{cases}/N_{control}$	IRR	IRR[a]
CC	176/205	1.00 (ref)	1.00 (ref)
CT	168/136	1.43 (1.06-1.92)	1.48 (1.09-2.01)
TT	33/36	1.15 (0.68-1.96)	1.22 (0.70-2.12)

a) Adjusted for parity (parous/nulliparous, number of births and age at first birth), education, duration of hormone replacement therapy (HRT), body mass index (BMI) and alcohol.

Ravn-Haren et al, 2006, Carcinogenesis

Predictors for GPX activity in red blood cells of controls

Dietary and lifestyle factors	**GPX activity (U/g Hb)**	**P**
Fruits and vegetables, per 100 g/day	+0.3	0.35
Alcohol, per 10 g/day	+2.0	<0.0001
Present smokers	-2.9	0.05
Selenium ≤40 μg, per 10 μg/day	+3.4	0.03
Selenium >40 μg, per 10 μg/day	-0.7	0.20
GPX1 Pro198Leu, per allele	-4.2	<0.0001

GPX1 Pro198Leu and breast cancer risk - interaction with alcohol consumption

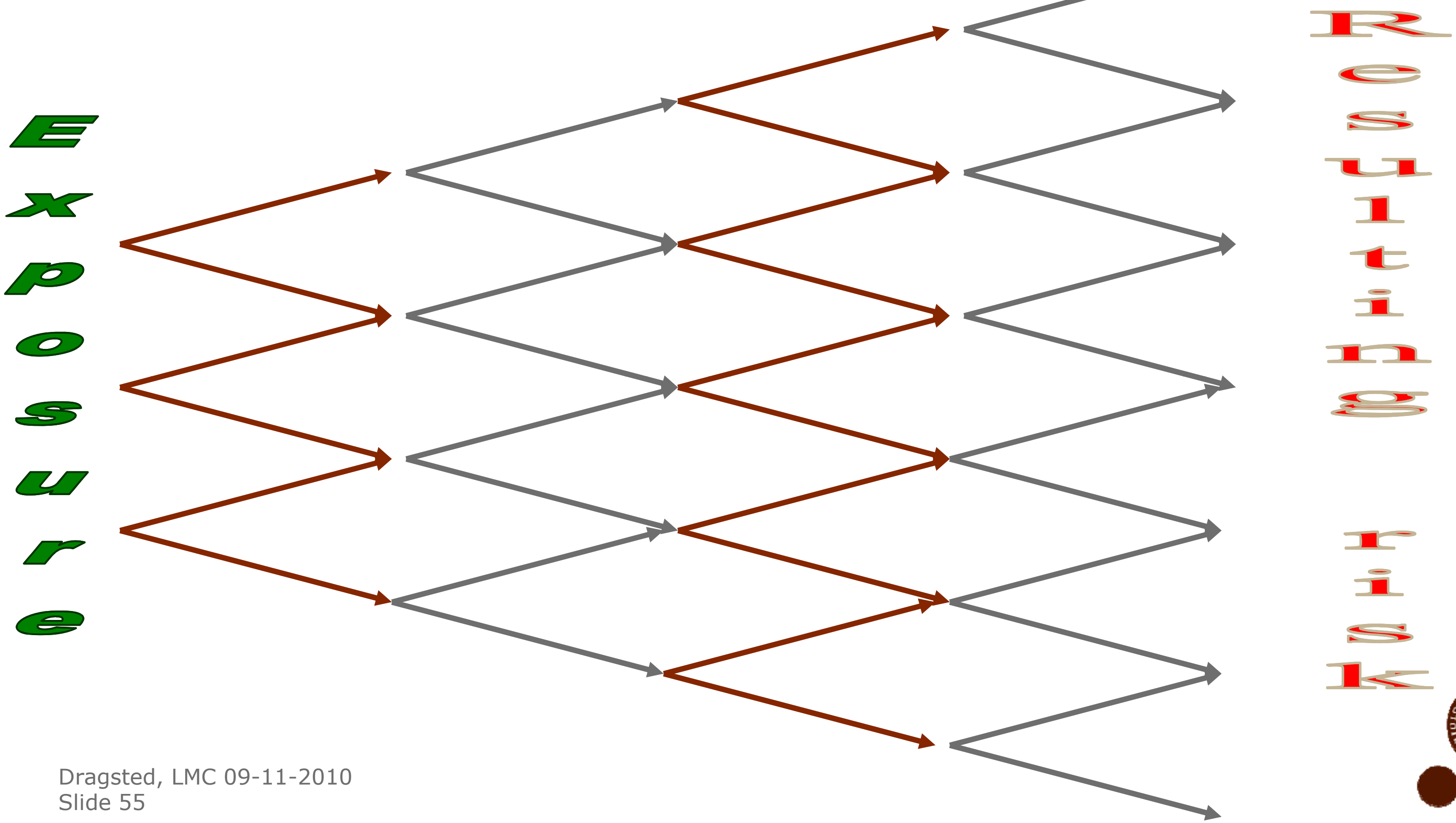
***GPX1* Pro198Leu**	**Alcohol intake (g/day)**			
	≤ 3 g/day		**> 3 g/day**	
	N	RR (95% CI)	N	RR (95% CI)
CC	118	1	308	1.63 (1.04-2.53)
CT+TT	96	1.69 (0.97-2.93)	322	1.95 (1.26-3.00)[a]

a) P interaction=0.30

Ravn-Haren et al., Carcinogenesis (2006) 27 820-5

Exposure, genetics and breast cancer risk

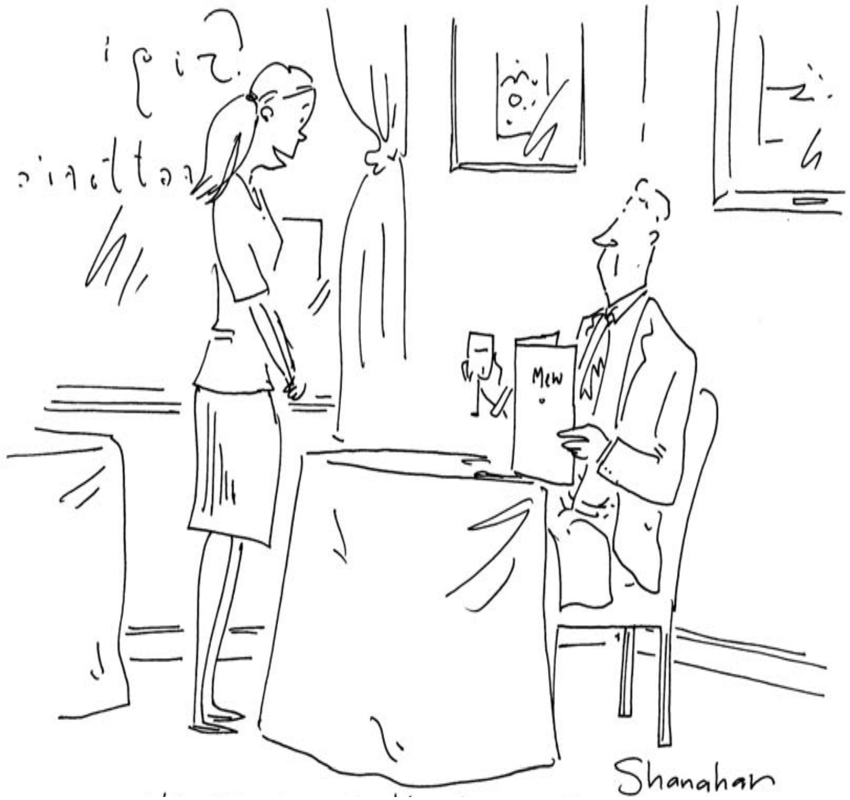
alcohol (ox stress) ±fruit&veg (Gpx1 ↑) genotype ($Gpx1^{Pro198Leu}$) others (Se status, smoking etc.)



What can we learn from this ?

Diet and genetic constitution interact in multiple ways to affect taste, preferences, reactions and diaseaserisk factors

Gene variant studies and studies on variations in our microbiota will specify a range of high-risk groups, depending on diet and life-style factors



"Hi, my name is Krystyn, and I will be the diet-gene liaison to your waiter tonight"