HARVARD
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Genetic determinants of caffeine intake: instrumental variables or effect modifiers?

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Background & Significance

- Caffeine is the most widely consumed stimulant in the world
- Widely available and socially acceptable
- In North American and European countries >75% of caffeine consumed by adults daily comes from coffee

heterocyclic amines

pyrols

furans

caffeine

melanoidins

cafestol &
kahweol

chlorogenic acid

Background & Significance

Coffee, caffeine and health

- Very strong evidence
  - ↓ risk of Parkinson's: caffeine
- Strong evidence
  - ↓ risk of type 2 diabetes
  - ↓ risk of Alzheimer's
- *Pending*

CHD	stroke	bone health
hypertension	cancers	suicide
depression	obesity	reproductive health

Factors associated with coffee / caffeine intake

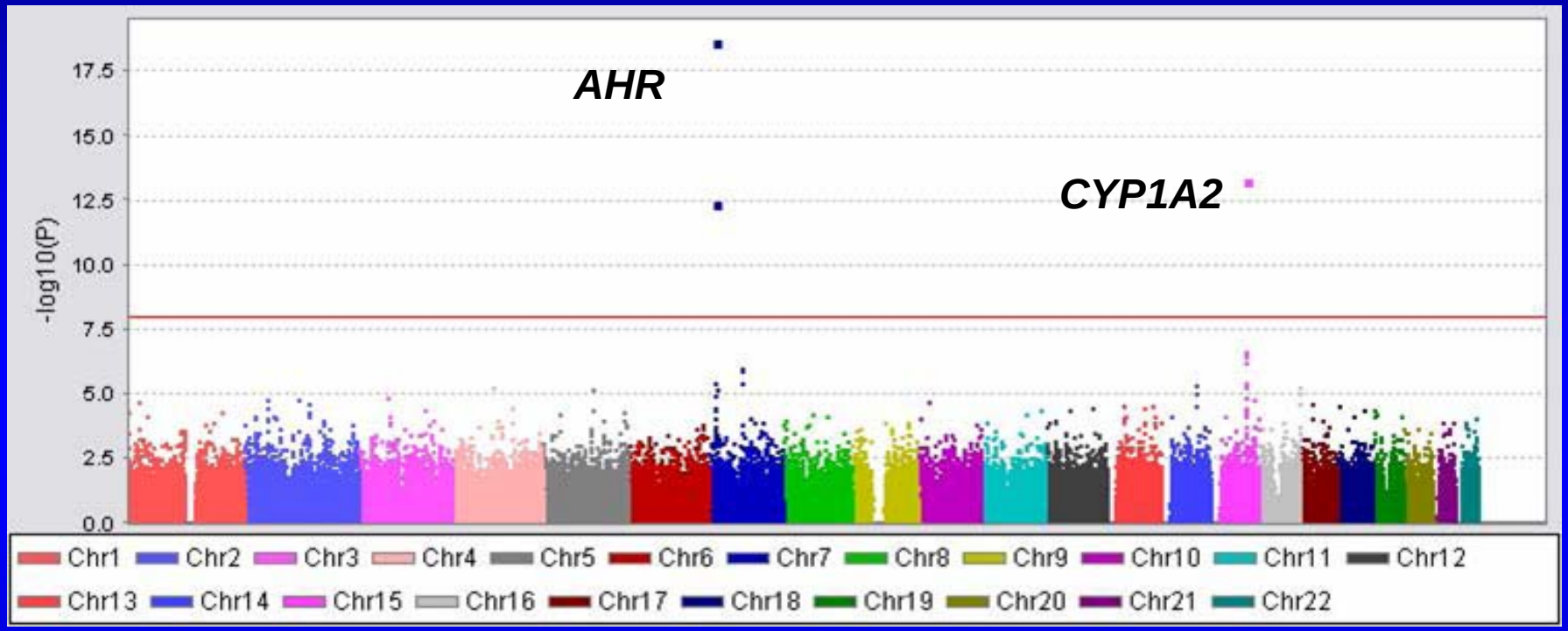
- **psychological effects (+ / -)**
- smoking
- taste preferences
- personality
- demographics
- current health
- medication
- pregnancy
- other lifestyle factors

Heritability for caffeine use: 43-58%

Cornelis, Coffee Intake. In: Nutrigenetics and Nutrigenomics. Prog Mol Biol Transl Sci, *in press*

Caffeine GWAS: Meta-analysis

semi-quantitative food frequency questionnaires



Total N: 47, 341

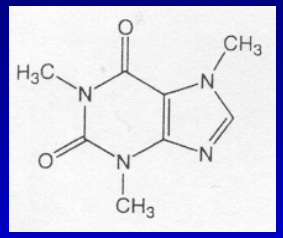
Men and Women

50-60 years

European Ancestry

Cornelis *et al*, PLoS Genet, 2011

Caffeine

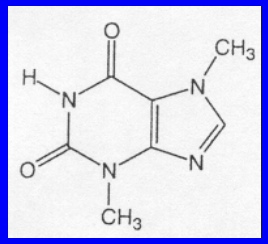


rs2470893 *TT* : ~38 mg more than *CC*

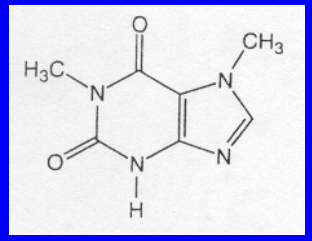
CYP1A2

CYP1A2

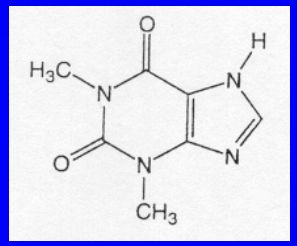
CYP1A2



Theobromine



Paraxanthine



Theophylline

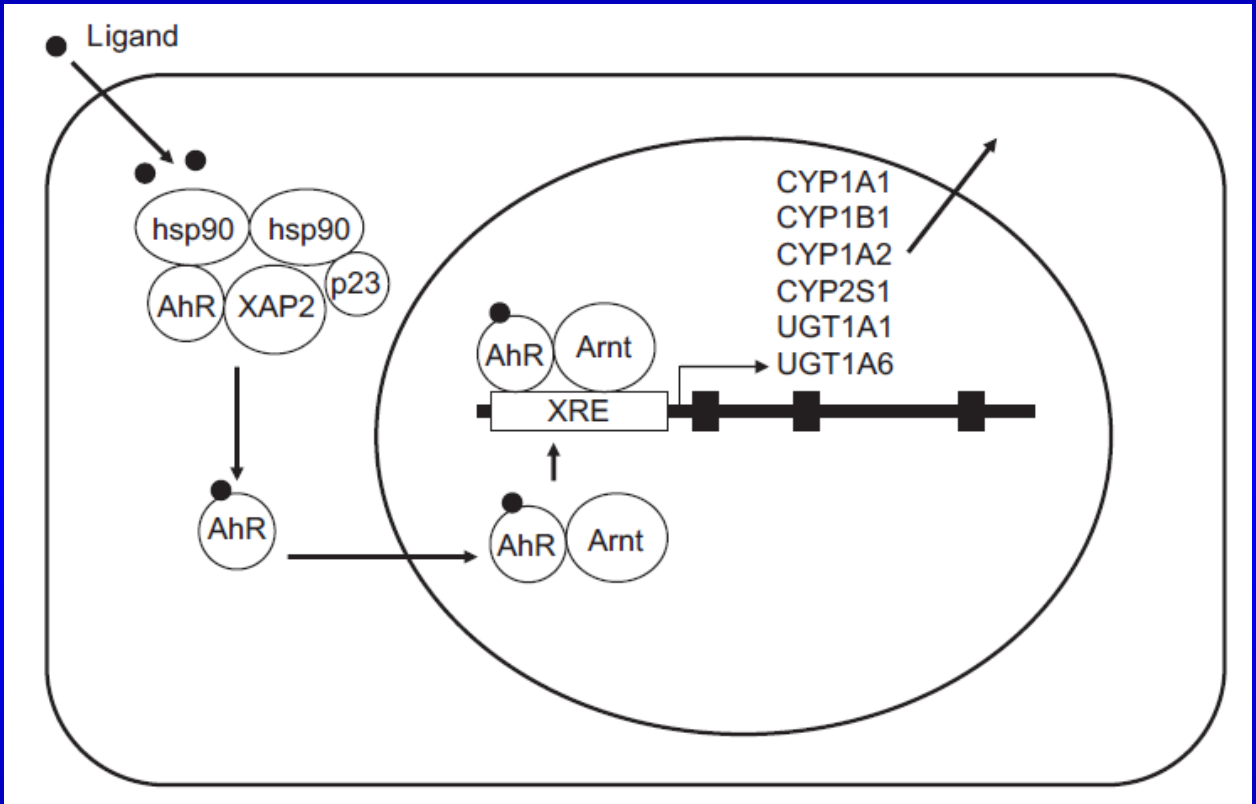
1,7-dimethyluric acid

1-methylxanthine

5-acetylamino-6-formylamino-3-methyluracil

1-methyluric acid

AHR



rs4410790 *: CC* consumes ~44 mg/d more than *TT*

NEW: GWAS of caffeinated coffee intake Stage 1

WGHS ♦
ARIC
PLCO ♦
NHS ♦
HPFS ♦
Health ABC
CHS
inCHIANTI
THISEAS
TwinGene
DNBC

MESA
FamHS
Framingham ♦
Rotterdam 1
Rotterdam 2
Fenland ♦
EPIC
B58C
HBCS
SHIP

KORA3
KORA4
EGCUT
Colaus
NTR
NFBC66
Good
Busselton
ERF
SORBS

Caffeinated coffee:

cups/d: N ≤ 91,000

extreme: N ≤ 47,000

Stage 1
Caffeinated Coffee (cups/d)

CHR	GENE	EA	EAF	cups/d 'drinkers'		High vs Low
				β	*P*	*P*
7	*AHR*	C	0.63	0.14	1.5e-57	1.8e-37
15	*CYP1A2*	T	0.24	0.15	6.5e-47	1.6e-29
7	***POR***	A	0.29	0.07	9.1e-14	4.4e-09
7	***MLXIPL***	C	0.28	0.05	7.8e-09	7.8e-06
11	***BDNF***	C	0.81	0.05	3.4e-07	4.9e-08

Suhre *et al*

Human metabolic individuality in biomedical and pharmaceutical research

54 | NATURE | VOL 477 | 1 SEPTEMBER 2011

Table 1 | Thirty-seven loci that displayed genome-wide significance

Locus & SNP id	Metabolic trait	*P* value
AHR rs12670403	Caffeine/quinate	4.8×10^{-15}

<u>NOTE</u>: all fasting, no data on habitual caffeine intake

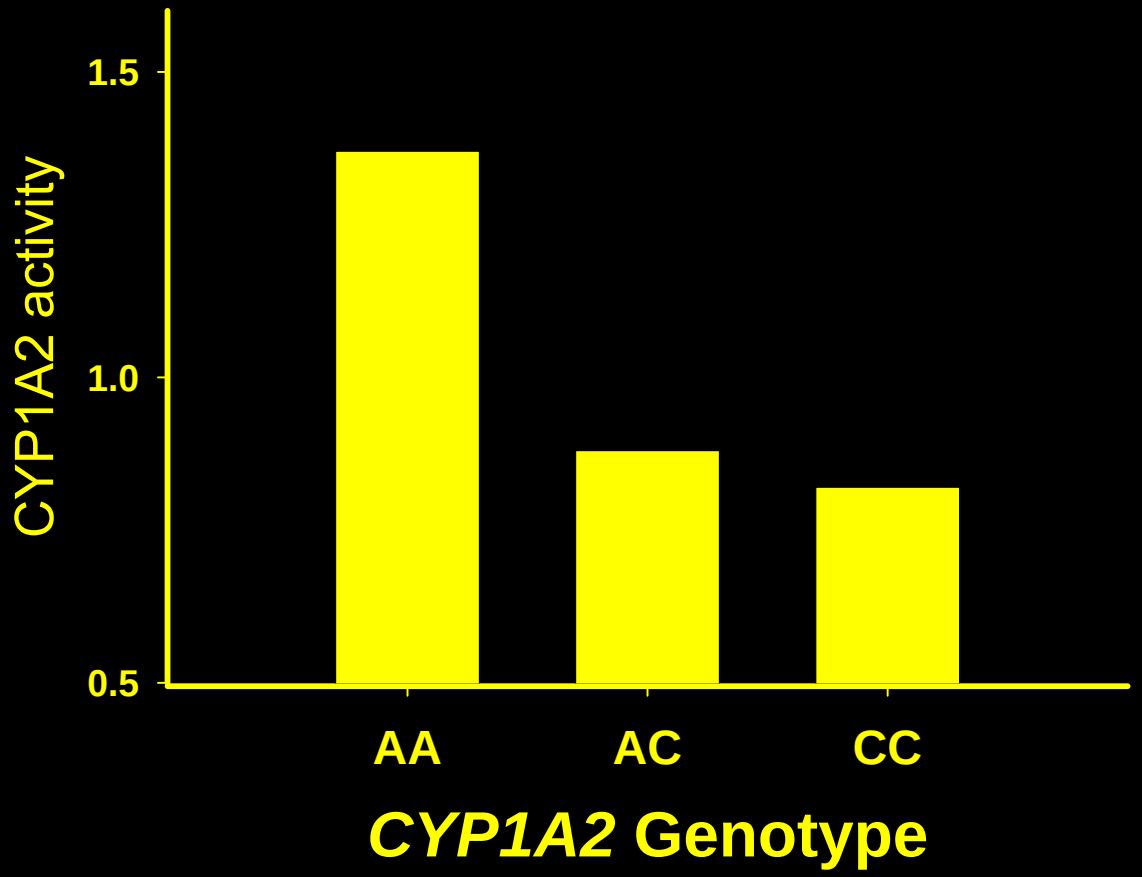
rs12670403 A: ↓ caffeine/quinate plasma levels

rs12670403 & rs4410790: r^2=0.60

GWAS: rs12670403 A ↑ caffeinated coffee intake (*P*=3.3e-43)

CYP1A2, rs762551

Sachse *et al*, Br J Clin Pharmacol, 1999



rs762551 & rs2472297 : r^2=0.09

GWAS: rs762551 A ↑ caffeinated coffee intake (P=5.4e-16)

NHGRI GWAS Catalogue

- *AHR & POR*: no other associated phenotypes
- *CYP1A2*

  r^2=0.09: ↓ blood pressure (4 GWAS)

- *MLXIPL*

  r^2=0.42 to 0.88: ↓ TG (9 GWAS)
  r^2=0.42: ↑ HDL (1 GWAS)
  r^2=0.49 to 0.84: ↓ GGT (2 GWAS)
  r^2=0.58: ↓ Protein C (1 GWAS)
  r^2=0.40: ↓ CRP (1 GWAS)

- *BDNF*

  r^2=1: ↑ risk of smoking initiation (1 GWAS)
  r^2=1: ↑ weight, ↑ BMI (1 GWAS)
  r^2=0.08 to 0.74: ↑ weight, ↑ BMI , ↑ obesity (2 GWAS)

Pleiotropy?

Confounded by caffeine intake?

Support a causal role of coffee/caffeine in these traits?

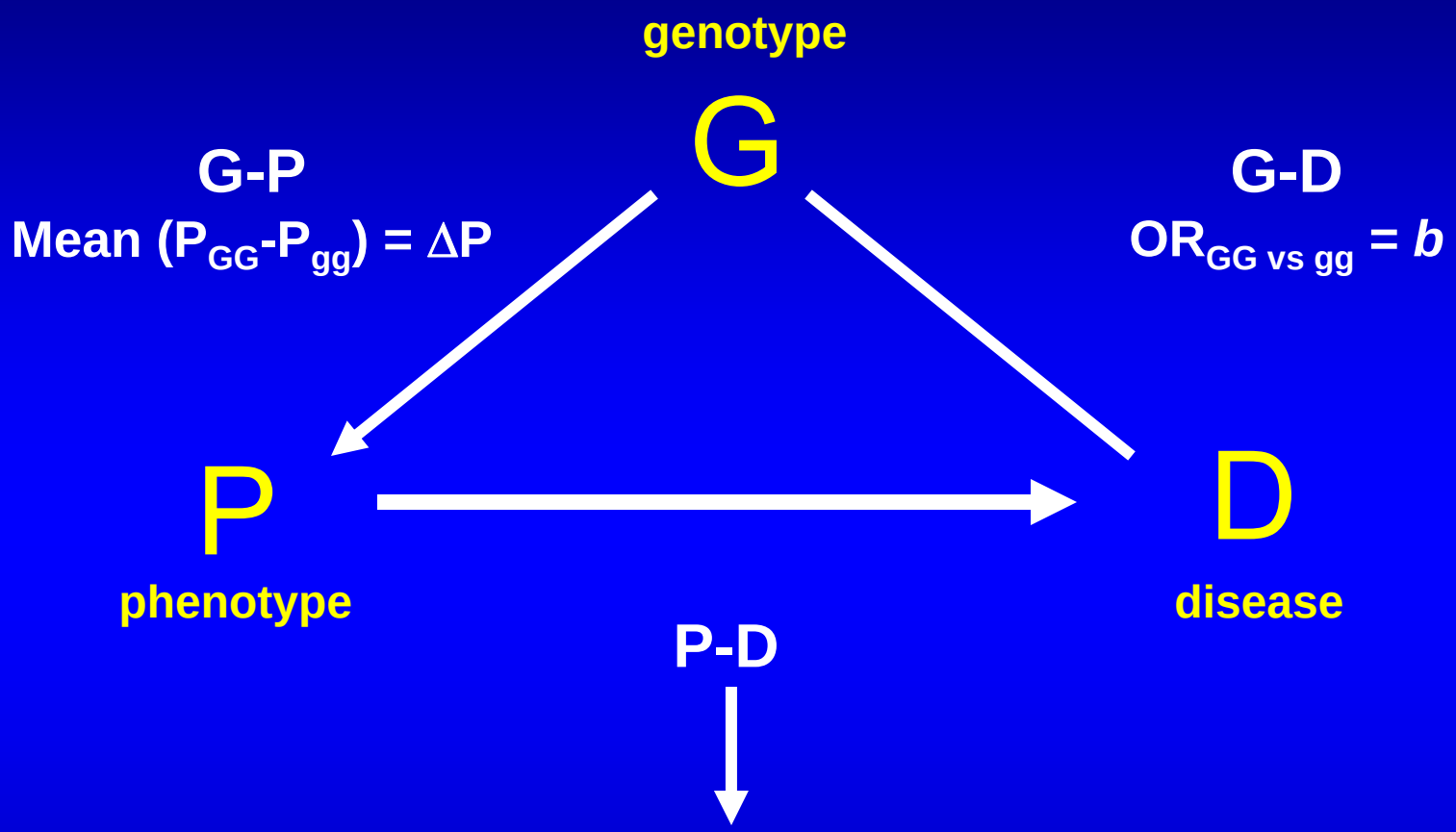
Direction of caffeine- 'consuming' allele

Journal of Alzheimer's Disease 20 (2010) S221–S238
DOI 10.3233/JAD-2010-091525
IOS Press

Caffeine Exposure and the Risk of Parkinson's Disease: A Systematic Review and Meta-Analysis of Observational Studiess

João Costa[a,b,*], Nuno Lunet[c,d], Catarina Santos[c,d], João Santos[a] and António Vaz-Carneiro[a]

~20% ↓ risk for each 300 mg/d


genotype
G
G-P
Mean (P_{GG}-P_{gg}) = ΔP
G-D
$OR_{GG\ vs\ gg}$ = *b*
P
phenotype
D
disease
P-D
OR associated with a K unit change in P
OR_{PD}= *b* $^{k/\Delta P}$

Meta-Analysis of MR studies
ideal scenario

Estimate	Study 1	Study 2	Study 3	Study 4	'Pooled'
genotype-phenotype	×	×	×	×	
genotype-disease	×	×	×	×	
phenotype-disease	×	×	×	×	×

Meta-Analysis of MR studies
realistic scenario

Estimate	Study 1	Study 2	Study 3	Study 4	'Pooled'
genotype-phenotype	×	×			×
genotype-disease			×	×	×
phenotype-disease					×

G-P: includes cases of D?

Minelli *et al*, AJE, 2004

Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies

*International Parkinson Disease Genomics Consortium**

Summary

Background Genome-wide association studies (GWAS) for Parkinson's disease have linked two loci (*MAPT* and *SNCA*) to risk of Parkinson's disease. We aimed to identify novel risk loci for Parkinson's disease.

Lancet 2011; 377: 641–49
Published Online
February 2, 2011

Discovery: 5,333 cases and 12,019 controls

Replication: 7,053 cases and 9,007 controls

Discussion

- We have genetic markers for caffeine intake *behavior*
  genotype A consumes, on average, more caffeine than genotype B

- Genetic markers *likely* play a role in caffeine *metabolism (AHR, CYP1A2)*
- Genetic markers *might* also reflect *biological exposure* to caffeine
  genotype A has, on average, lower plasma levels of caffeine than genotype B

- Are these genetic markers of *caffeine metabolism*?
  IV (for causal effect of caffeine) confounded by caffeine intake behavior.
  G×E studies more appropriate?

CYP1A2 rs762551
A variant: ↑ metabolism, ↑ intake

- Breast Cancer
  - G × E: Coffee ↓ risk only among C carriers only (Kotsopoulos, 2007)
  - G × E: Coffee ↓ AOD ↑ ER- among AA only (Bageman, 2008)
- Ovarian Cancer
  - Caffeine/coffee ↓ risk overall, especially among AA (Goodman, 2003)
- **Parkinson's disease**
  - Caffeine/coffee ↓ risk, *especially* among CC (Popat, 2011)
  - C carriers ↑ risk among women only (Palacios, 2010)
- Cardiovascular Disease
  - G × E : Coffee ↑ risk of MI among C carriers only (Cornelis, 2006)
  - G × E : Coffee ↑ risk of HTN and ↑ BP among C carriers only (Palatini, 2009)
- Recurrent Pregnancy Loss
  - G × E : caffeine ↑ risk among AA only (Sata, 2005)

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- Are these genetic markers of *caffeine metabolism*?
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  G×E studies more appropriate?

- Are these genetic markers of coffee intake/exposure, adjusted for caffeine?
  IV for testing causal effect of non-caffeine components of coffee.
  re: GWAS catalogue

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GENEVA

CHARGE

International Parkinson's Disease Genomics Consortium