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
pyrolysis

furans

chlorogenic acid

heterocyclic amines

caffeine

cafestol & kahweol

melanoidins
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%

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

CYP1A2

Caffeine → Theobromine
Caffeine → Paraxanthine
Caffeine → Theophylline

rs2470893 TT : ~38 mg more than CC

1,7-dimethyluric acid
1-methylxanthine
5-acetylamino-6-formylamino-3-methyluracil
1-methyluric acid
rs4410790: CC consumes ~44 mg/d more than TT
### NEW: GWAS of caffeinated coffee intake

**Stage 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage 1</th>
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<th>Stage 1</th>
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<tbody>
<tr>
<td>WGHS</td>
<td>MESA</td>
<td>KORA3</td>
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<td>FamHS</td>
<td>KORA4</td>
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<td>SHIP</td>
<td>SORBS</td>
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**Caffeinated coffee:**

- cups/d: N ≤ 91,000
- extreme: N ≤ 47,000
### Stage 1
Caffeinated Coffee (cups/d)

<table>
<thead>
<tr>
<th>CHR</th>
<th>GENE</th>
<th>EA</th>
<th>EAF</th>
<th>cups/d 'drinkers'</th>
<th>High vs Low</th>
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<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>β</td>
<td>P</td>
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<tr>
<td>7</td>
<td>AHR</td>
<td>C</td>
<td>0.63</td>
<td>0.14</td>
<td>1.5e-57</td>
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<td>15</td>
<td>CYP1A2</td>
<td>T</td>
<td>0.24</td>
<td>0.15</td>
<td>6.5e-47</td>
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<tr>
<td>7</td>
<td>POR</td>
<td>A</td>
<td>0.29</td>
<td>0.07</td>
<td>9.1e-14</td>
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<tr>
<td>7</td>
<td>MLXIPL</td>
<td>C</td>
<td>0.28</td>
<td>0.05</td>
<td>7.8e-09</td>
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<tr>
<td>11</td>
<td>BDNF</td>
<td>C</td>
<td>0.81</td>
<td>0.05</td>
<td>3.4e-07</td>
</tr>
</tbody>
</table>
**Table 1 | Thirty-seven loci that displayed genome-wide significance**

<table>
<thead>
<tr>
<th>Locus &amp; SNP id</th>
<th>Metabolic trait</th>
<th>$P$ value</th>
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</thead>
<tbody>
<tr>
<td>AHR rs12670403</td>
<td>Caffeine/quinate</td>
<td>$4.8 \times 10^{-15}$</td>
</tr>
</tbody>
</table>

**NOTE:** 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

CYP1A2 Genotype

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)

*Direction of caffeine- ‘consuming’ allele*

Pleiotropy?

Confounded by caffeine intake?

Support a causal role of coffee/caffeine in these traits?
Caffeine Exposure and the Risk of Parkinson’s Disease: A Systematic Review and Meta-Analysis of Observational Studiess

João Costa\textsuperscript{a,b,*}, Nuno Lunet\textsuperscript{c,d}, Catarina Santos\textsuperscript{c,d}, João Santos\textsuperscript{a} and António Vaz-Carneiro\textsuperscript{a}

\~20\% \downarrow \text{risk for each 300 mg/d}
Mean (\(P_{GG} - P_{gg}\)) = \(\Delta P\)

\[OR_{GG \text{ vs } gg} = b\]

OR associated with a K unit change in P

\[OR_{PD} = b^{\frac{k}{\Delta P}}\]
## Meta-Analysis of MR studies

*ideal scenario*

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
<th>‘Pooled’</th>
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<td>×</td>
<td>×</td>
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## Meta-Analysis of MR studies

**Realistic scenario**

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<tr>
<td>phenotype-disease</td>
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<td></td>
<td>×</td>
</tr>
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</table>

G-P: includes cases of D?

*Minelli et al, AJE, 2004*
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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• 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?

• 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