High Blood Pressure in Irish Adults

Preliminary findings and lessons learned from two JINGO cohorts

Helene McNulty
Northern Ireland Centre for Food and Health (NICHE)
University of Ulster
Mortality due to global risk factors
Attributable Deaths in Thousands

- High Blood Pressure
- Smoking
- High cholesterol
- Child underweight for age
- Unsafe sex
- Low fruit and vegetable intake
- Overweight and obesity
- Physical inactivity
- Alcohol use
- Indoor air pollution from solid fuels
- Unsafe water, sanitation, and hygiene
- Zinc deficiency
- Urban air pollution
- Vitamin A deficiency
- Iron deficiency anaemia
- Contaminated health-care injections
- Illicit drug use
- Unmet contraception need
- Child sexual abuse

East Asia and Pacific
Europe and Central Asia
Latin America and Caribbean
Middle East and North Africa
South Asia
Sub-Saharan Africa
High-income

Lopez et al. 2006 Lancet 367,1747-57
High Blood Pressure in Irish Adults

*This talk will address*

- High blood pressure and genetic risk
- High blood pressure in Irish adults: what the latest analysis shows
- Impact
Homocysteine Metabolism

Trans-sulfuration Pathway

Homocysteine → Cystathionine β-Synthase → Cystathionine → Cysteine → Sulfate + H₂O → Urine

Remethylation pathway

Diet

Methionine → S-Adenosyl-methionine → Methyl Acceptor → Methylated Acceptor → S-Adenosyl-homocysteine

Folate Cycle

Tetrahydrofolate → MTHFR → 5,10 Methylene Tetrahydrofolate → Methionine Synthase → Methionine

B12

B6

NADPH → NADP⁺
Is the $\textit{MTHFR} \ 677C\rightarrow T$ Polymorphism a risk factor for CVD?

- Homozygosity (TT genotype) results in lower MTHFR enzyme activity and increased homocysteine concentrations \textit{in vivo}.

- Meta-analyses\textsuperscript{1-4} estimate that the TT genotype carries an excess risk of CVD by 14-21\%, but large geographical variation in the reported excess risk among countries.

\textsuperscript{1}Wald DS et al. \textit{BMJ} 2002; \textbf{325}: 1202–1206.
\textsuperscript{2}Klerk et al. \textit{JAMA} 2002; \textbf{288}: 2023–2031.
\textsuperscript{3}Lewis et al. \textit{BMJ} 2005; \textbf{331}: 1053–1056.
\textsuperscript{4}Holmes et al. \textit{Lancet} 2011; \textbf{378}: 584-594.
Methylenetetrahydrofolate reductase (MTHFR)

**SUBSTRATE:** 5,10 methylenetetrahydrofolate

**PRODUCT:** 5 methyltetrahydrofolate

**COFACTOR:** Flavin Adenine Dinucleotide (FAD)

**PRECURSOR:** Riboflavin (vitamin B2)

- Polymorphic mutations in MTHFR
  - *MTHFR 677C→T Polymorphism*
    - C to T substitution at base pair 677
    - Alanine/valine change in the amino acid sequence
    - Functionally defective enzyme
# Genotype-specific response to riboflavin

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CC (n = 27)</th>
<th>CT (n = 26)</th>
<th>TT (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.7</td>
<td>12.2</td>
<td>17.6</td>
</tr>
<tr>
<td>After intervention</td>
<td>10.9</td>
<td>11.8</td>
<td>13.0*</td>
</tr>
</tbody>
</table>

Riboflavin 1.6mg/d 12 weeks

*McNulty et al. 2006 Circulation 113(1), 74-80*
**MTHFR 677TT genotype and hypertension**

**ORIGINAL ARTICLE**

Strong association of methylenetetrahydrofolate reductase gene C677T polymorphism with hypertension and hypertension-in-pregnancy in Chinese: a meta-analysis

W-Q Niu¹,²,³,⁶, Y-G You⁴,⁶ and Y Qi⁵

¹State Key Laboratory of Medical Genomics, Shanghai Key Laboratory of Vascular Biology and Department of Hypertension, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ²Laboratory of Vascular Biology, Institute of Health Sciences, Shanghai Institutes for Biological Sciences, Shanghai, China; ³Shanghai Institute of Hypertension, Shanghai, China; ⁴Beijing Tropical Medicine Research Institute, Capital Medical University Affiliated Beijing Friendship Hospital, Beijing, China and ⁵Department of Epidemiology, Capital Medical University Affiliated Beijing Anzhen Hospital, Beijing Institute of Heart, Lung & Blood Vessel Diseases, Beijing, China

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Meta-analysis of 20 studies; 4461 participants

- OR 1.87 (95% CI 1.31-2.68); \( P=0.001 \)

Genome-wide association study identifies eight loci associated with blood pressure

This gene-nutrient interaction may have a novel role in BP

This gene-nutrient interaction has a novel role in BP

Two major changes occurred:

- β-blockers omitted
- Shift from monotherapy to polytherapy
The MTHFR 677TT genotype remained a risk factor for hypertension in this high-risk cohort over the 4-year period.

Riboflavin intervention resulted in an overall decrease of 9mmHg SBP and 6mmHg DBP.

This genotype-specific BP-lowering effect of riboflavin was evident irrespective of current antihypertensive therapy.
Role of this novel gene-nutrient interaction in hypertensive individuals generally (no overt CVD):

**TUDA Participants pre-screened for MTHFR genotype**

- Blood pressure in treated hypertensive individuals with the MTHFR 677TT genotype (recruited to the TUDA Ageing Study) showed a significant BP-lowering response to riboflavin

Genetic risk and a novel gene-nutrient interaction in BP

Some unanswered questions

• What are the determinants of blood pressure in Irish adults at all ages?
  • How important is MTHFR genotype relative to other factors?
  • And what about drugs?

• Can MTHFR genotype increase the risk of developing hypertension?
  • Does diet matter?
Genetic risk and a novel gene-nutrient interaction in BP

Some unanswered questions

- What are the determinants of blood pressure in Irish adults at all ages?
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- Can MTHFR genotype increase the risk of developing hypertension?
  - Does diet matter?

- The JINGO project (through combined analysis of NANS and TUDA cohorts) provided a unique opportunity to address these key questions
Summary of preliminary findings (unpublished)

• Total potential sample (NANS/TUDA): 6706 Irish adults aged 18+ years

• Well known causes of hypertension such as increasing age and overweight/obesity were evident

• Apart from well known causes, more than 1 in 10 Irish adults are genetically at-risk of developing high blood pressure; their higher blood pressure is evident by aged 18 years
  – This risk is evident regardless of whether blood pressure-lowering drugs are being taken
  – A good riboflavin status appears to protect against the development of hypertension in this genetically at-risk group.
In people with TT genotype, MTHFR enzyme less active

\[ \text{higher riboflavin status} \]

MTHFR enzyme more active
(5 methyl THF increased)

\[ \text{Plasma Homocysteine Decreased} \]

\[ \text{Blood Pressure Decreased (Nitric oxide implicated; smooth muscle cell vasodilation)} \]

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Impact
CVD mortality risk increases as BP rises

<table>
<thead>
<tr>
<th>Systolic/Diastolic Blood Pressure (mmHg)</th>
<th>Cardiac Mortality Risk</th>
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<tbody>
<tr>
<td>115/75</td>
<td>1x</td>
</tr>
<tr>
<td>135/85</td>
<td>2x</td>
</tr>
<tr>
<td>155/95</td>
<td>4x</td>
</tr>
<tr>
<td>175/105</td>
<td>8x</td>
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Chobanian AV et al. *JAMA* 2003;*289*:2560-2572
Impact of BP reduction

- Meta-analysis of 61 prospective, observational studies including over 1 million adults\(^1\)

- Potential public health significance of this gene-nutrient interaction on BP

## Lifestyle factors targeted to reduce BP

<table>
<thead>
<tr>
<th>Lifestyle factor</th>
<th>SBP decrease (mmHg)</th>
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<tbody>
<tr>
<td>Weight loss (per 10 kg)</td>
<td>5 - 20</td>
</tr>
<tr>
<td>Riboflavin (genotype-specific)</td>
<td>6 - 13</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4 - 9</td>
</tr>
<tr>
<td>Sodium reduction</td>
<td>2 - 8</td>
</tr>
<tr>
<td>Limit alcohol</td>
<td>2 - 4</td>
</tr>
</tbody>
</table>

Modified from Chobanian *et al.* 2003 JNC 7 report
A novel gene-nutrient-nutrient interaction in BP

Take-home messages

• The **MTHFR 677TT genotype** increases the risk of developing hypertension

• **Riboflavin** can play an important preventative role against hypertension *specifically* in people with the TT genotype
  – Independent of current antihypertensive therapy
  – Increased riboflavin intake in this genetically at-risk group may offer a ‘personalised’ non-drug approach to preventing/treating hypertension.

• **Future work**
  – Targeted randomised trials in individuals pre-screened for MTHFR genotype
  – Confirmation of these results in other populations in the world
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Conal Cunningham
Miriam Casey

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Carol Wilson (2010)
Rosie Reilly (current)
Emma Hughes (current)

Clinical Collaborators
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Tom Trouton
John Purvis

DSM
Bright Science. Brighter Living.