Understanding the potential of nutrigenomics/personalised nutrition to treat inflammation / CVD

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• Response to diet is hugely variable

• Genetics and genotype: the basics

• *APOE* genotype and response to dietary fat composition

• *MTHFR* genotype and response to B-vitamins

• Genotype, diet and inflammation

• Translation of research into public health reality and benefit
At a population level, responsiveness to dietary change is hugely variable.
n-3 PUFA nomenclature

Recommended intake of >450mg EPA+DHA per day (UK Department of Health (SACN), 2004)
FINGEN Study

- Response of ~ 40 cardiovascular disease (CVD) risk indicators
- Examine impact of age/ gender/ APOE genotype on response

- n=312
- Cross-over, 8wk intervention arms

- CO- control oil
- 0.7g EPA+DHA per day
- 1.8g EPA+DHA per day

Caslake MJ et al., 2008
Over one third of participants showed increase in TG in response to fish oils.

% change TG on 1.8FO for 8 weeks, n=312

Group average (n=312) -11%

R109: +150%

R245: -250%

n=118/312 ↑ TG
Genetic information

- 99%+ homogenous

<1% variable
- chromosomal disorder
- insertions or deletions: indels
- copy number variation
- repeat sequences
- single nucleotide polymorphisms (SNP)

changes in protein structure
↑↓ expression of gene

metabolic differences
- differences in risk of diseases
- differences in response to environmental factors, including diet/drugs
Two examples of nutrigenetics in action

1. *APOE* genotype and plasma lipid response to altered dietary fat composition

2. *MTHFR* genotype, B-vitamin status and blood pressure
Apolipoprotein E

- Liver (80-90%), brain and macrophages
- Lipid transporter
- most well described E2, E3, E4
  E2: Cys 112, Cys 158
  E3: Cys 112, Arg 158
  E4: Arg 112, Arg 158
APOE4 individuals are particularly sensitive to dietary fat.

Sarkkinen E et al., 1998
Higher lipaemia following fat consumption in \( APOE4 \) carriers

Carvalho-Wells AL et al., 2010
APOE4 males demonstrate the greatest responsiveness to the TG ↓ of fish oils

APOE4 males: 15% and 23% ↓ TG in response to 0.7FO and 1.8FO versus 8% and 11% ↓ in the group as whole

Caslake MJ et al., 2008
Advice re. dietary fat intake and *APOE4* carrier status (25% Caucasians)

- Avoid high fat diets and meals
- Limit intakes of SFA and cholesterol
- Fish oils good TG lowering agent
- Hyperlipidaemics should avoid high dose DHA rich oil 3g DHA/day) as ↑ LDL-cholesterol  
  (Minihane AM et al., 2000; Leigh-Firbank E et al., 2002; Caslake MJ et al., 2008; Olano-Martin et al., 2010)
MTHFR 677C→T genotype:
- MTHFR 677 TC ~ 40% reduced activity and ↑ homocysteine
- MTHFR 677 TT ~ 70% reduced activity & ↑ CVD risk and BLOOD PRESSURE
MTHFR 677C→T genotype, riboflavin (vitB2) and BP

- Premature CVD patients
- TT (n=60), CT (n=85), CC (n=75)
- 1.6g riboflavin or placebo for 16 weeks

- Riboflavin intervention ↓ BP from 144/87 to 131/80mmHg in TT (P<0.05)
- No significant impact in other TC or CC groups

Horigan G et al., 2010
BP response to riboflavin by MTHFR genotype

Riboflavin offers a targeted strategy for managing hypertension in patients with the \textit{MTHFR} 677TT genotype: a 4-y follow-up$^{1-3}$

\textit{Carol P Wilson, Mary Ward, Helene McNulty, J J Strain, Tom G Trouton, Geraldine Horigan, John Purvis, and John M Scott}
Chronic low grade inflammation is a pathological feature of a host of chronic diseases.
Inflammation & atherosclerosis, CVD

Libby P, 2002

Glass & Witzum, 2001
**APOE4 increases macrophage inflammation**

Fig. 2. Cytokine mRNA levels measured using reverse transcription real-time PCR in RAW 264.7-apoE3 and -apoE4 following stimulation with LPS (1 µg/ml) for 6 h or 1 h (TNFα). Results are calculated with the $2^{-\Delta\Delta Ct}$ method and data are expressed as means ± SEM of three independent experiments performed in duplicate. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, comparing E3- vs. E4-cells at each LPS concentration.


Inflammation is a driver of the metabolic dysregulation associated with obesity and excess adipose tissue. Inflammatory status in part differentiates the metabolically healthy but obese (MHO) and the typical metabolically unhealthy obese phenotype.
Anti-inflammatory dietary strategies targeted to those with pro-inflammatory genotype

e.g. n-3 fatty acids, flavonoids, antioxidant vitamins
Nutrigenetics in its relative infancy: Genetic discoveries timeline

<table>
<thead>
<tr>
<th>Discovery of DNA</th>
<th>Sequencing of human genome</th>
<th>Application of genetic information in health management</th>
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<tr>
<td>1953</td>
<td>2001-2004</td>
<td>2004+</td>
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<tr>
<td></td>
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<td>3 billion base pairs</td>
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<td></td>
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<td>20,000-22,000 genes</td>
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- Genetic therapy
- Genetic engineering
- Genetic profiling
- Disease risk prediction
- Understanding of genotype environment-disease/health associations
- Personalised/stratified prevention and therapeutic strategies
Effective personalisation of dietary recommendations will need to be multi-faceted (not just ‘gene-centric’)

<table>
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<tr>
<th>Genes</th>
<th>Habitual diet</th>
<th>Phenotype &amp; other lifestyle factors</th>
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| ![DNA Structure](dna.png) | ![Food Items](food.png) | • Disease/Physiological status  
• Clinical/biochemical measures  
• Gender  
• Medication use  
• Other lifestyle factors |

Gibney and Walsh, 2013
2011 to 2015

n=1200
all internet based
8 centres

**Group 1:** Control group, non-personalised nutrition advice;
**Group 2:** Personalised dietary analysis;
**Group 3:** Personalised dietary advice also based on phenotyping;
**Group 4:** Same as groups 2 and 3 plus personalised advice based on genotype

For all groups, low (0, 3m, 6m) vs. higher frequency contact
Genotyping not likely to be the panacea in public and clinical nutrition, but likely to make a meaningful contribution to the refinement, targeting and efficacy of dietary advice