NUTRITIONAL GENOMICS:
ESSENTIAL BASICS FOR NUTRITION PROFESSIONALS

Mariëtte Abrahams MBA RD
Course Outline

- Basic Genetics
- Nutrigenomics & Nutrigenetics
- Personalized health era
- Diet-Gene interactions in Chronic diseases
- What does testing involve?
- Limitations, Ethics & regulation of testing
- Nutrigenetics in the marketplace – A global view
- Opportunities for Dietitians
- Resources & Projects
Learning outcomes

☐ Outline the structure and function of DNA and how it is organised in cells to form the human genome
☐ Explain what gene expression is and how environmental factors such as diet can influence gene expression and genome function thereby influencing health and susceptibility to disease
☐ Explain what the fields of nutrigenomics, nutrigenetics and epigenetics are
☐ Demonstrate an understanding of the genetic basis of some chronic diseases
☐ Demonstrate a broad understanding of relevant genetics and genomics principles.
☐ Explain how genetic testing is conducted in practice
☐ Understand and be able to explain the limitations of gene testing
☐ Understand and explain the ethical and legal frameworks surrounding personalised health
☐ Visualise and create future opportunities where chronic disease prevention is concerned
☐ Outline relevant resources for accessing further detailed information
Part 1 – The Foundation
What is DNA??

- DNA is a long chain of building blocks (A,T,G,C)
- A gene is a unit of information
- Genes are located on chromosomes
- Every human has 46 chromosomes
- All 25,000 genes in every cell
Human Genome project

- 13 year project
- Completed April 2003
- Mapped entire human genome sequence
- Identified all genes in human DNA
- Cost $3 billion
The outcome

- 25 000 genes
- 3 Billion base pairs
- 99.9% of DNA is identical
- 0.1% variance has no functional significance
- Approx Only 1-5% of DNA code for genes
Monogenetic vs Polygenetic diseases

- Monogenetic disorders eg PKU
- Polymorphisms are common in the population >1%
Gene Variations

- Everyone has them!

- Changes in genetic information
  - Single Nucleotide (base change, insert, deletion)
  - Groups of nucleotides (repeats)
  - Whole chromosomes (insert, delete, rearranged)

- Impact can be positive, negative or non-existent
Single Nucleotide Polymorphism (SNP)

- Change in Single Nucleotide pair
- Most have no direct effect on health
- [Link](http://www.youtube.com/watch?v=9rPDa2ACtog)
- 3-5% are functional and influence phenotypic differences (Yamada et al 2008)
Reading the literature

- Gene name C275T
- MTHFR 677C>T
- ADRB3 Trp64Arg
- Rs 123456
# Must know nomenclature

<table>
<thead>
<tr>
<th><strong>Description</strong></th>
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<tbody>
<tr>
<td><strong>Allele</strong></td>
<td>A variation of a gene</td>
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<tr>
<td><strong>Wild type, homo/heterozygote</strong></td>
<td>Most common version, two copies, 1 copy of each</td>
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<tr>
<td><strong>Locus/loci</strong></td>
<td>An arbitrary region of the genome that can have mutations /polymorphisms</td>
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<tr>
<td><strong>Genotype vs Phenotype</strong></td>
<td>Inherited DNA vs measureable characteristics</td>
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<tr>
<td><strong>Polymorphism</strong></td>
<td>Differences in DNA sequence found commonly in &gt;1% of population</td>
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<tr>
<td><strong>SNP vs Genome</strong></td>
<td>A change in a single nucleotide/ your total sum of DNA</td>
</tr>
<tr>
<td><strong>Rs numbers</strong></td>
<td>All SNP’s are assigned a unique rs number eg rs 9939609</td>
</tr>
<tr>
<td><strong>Mutations</strong></td>
<td>Differences in DNA sequence in an individual that are rare (&lt;1% of population) and may be unique to the individual</td>
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Nutritional Genomics

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“Studies the silencing and activation of DNA without changing the nucleotide sequence”
What is Gene Expression?

The conversion of the information encoded in a gene into mRNA and then to protein.”
Gene expression

- DNA codes for RNA
- Moves from cell nucleus to cytoplasm
- Directs protein synthesis
How Diet, Lifestyle & environment impact gene expression?

- Directly affect gene expression by acting as ligands for transcription factor receptors eg PUFA’s on PPAR’s

- Nutrients are metabolized by primary or secondary metabolic pathways thereby altering concentrations of substrates or intermediates eg folic acid

(Fenech M et al., 2011)
Omics technologies

- **Transcriptomics**
  (mRNA, micro RNA, non-coding RNA)

- **Metabolomics**
  (Metabolites eg Cholesterol levels)

- **Proteomics**
  (protein structures and function)
NEW NUTRITION PARADIGM
The age of personalized health

- DNA is not your destiny
- Genotype does not mean phenotype
- Tailoring treatment and recommendations to include genetics eg “Pharmacogenomics”
How genomic technology fits in with Nutrition

- Candidate gene approach
- Genome-wide linkage screen

(Lovegrove JA, Gitau R 2008)
From the old into the New

Old Paradigm

- Population based Recommendations based on RDA from observational studies
- Adjust intake on nutritional assessment from diet, anthro, family hx, clinical, age and sex
- General healthy eating recommendations or prudent guidelines for general population

New Paradigm

- Our unique DNA affects our individual nutrient requirements
- RDA may be based on metabotypes or ethnic groups
- Individual needs for vitamins, minerals and phytochemicals
- Move from single gene-nutrient interaction to a systems biology approach
“One man’s food is another man’s poison”
Quick recap!!

- How it all started
- Basic Genetics
- What Nutritional Genomics is
- How diet and lifestyle impact our Genotype and susceptibility to develop chronic diseases
- Omics Technology
- Type of genetic studies
- How there is a shift towards a personalized health approach
Part 2 – The Genes
GENES AND OBESITY
Genetic contribution to BMI

- 40-90% difference within individuals in a population due to genetics (Atwood et al 2002)

- 32 loci explains <1.5% of variation in BMI

- It is certainly not the holy grail, but only part of the story
Four levels of genetic contribution to Obesity

1. **Genetic obesity** - mutation in a single gene despite environment (1 - 5%)

2. **Strong predisposition** - overweight in non-obesogenic environment and obese in obesogenic environment

3. **Slight predisposition** - normal weight in non-obesogenic environment and overweight in obesogenic environment

4. **Genetically resistant** - normal weight in obesogenic environment.

(Loos and Bouchard 2003)
GWAS identified FTO SNPs as having the most important effects on obesity susceptibility and BMI.

FTO may play a role in eating behaviour, satiety and dietary intake.

Rs9939609 T>A associated with higher body weight, fat mass and higher risk of obesity.

Minor allele carriers have higher intake of total energy and fat.

Association was replicated in several populations.
FTO T>A genotype

- Prevalence 46%-74% Europeans have 1 copy
- 18% have two copies (A allele)
- 51% West Africans
- 28-44% of Asian descent (Kalpelainen TO et al)
- 16% Chinese
- Increases risk of obesity by 30% one copy, 70% two copies (Frayling et al., 2007)
- A-allele carriers are 3kg heavier than non-carriers (Vialeswaran 2012)
Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case–control study of children.
Fig. 2. BMI-standard deviation score (SDS) of children and adolescents according to SFA consumption (percentage of total energy, dichotomised by the median) and the presence of the fat mass and obesity associated (FTO) rs9939609 polymorphism in a dominant model. Values are means, with their standard errors represented by vertical bars. □, TT; ■, A carriers. *Mean values were significantly different (P < 0.05).
Impact of FTO T>A gene variant

- In A allele carriers **high-fat diets** increase obesity susceptibility.
- A allele increased obesity risk when consuming **high SAT FAT**.
- A allele carriers reported to consume more fat and total energy, experience **less satiety**. Especially children.
- **Low physical activity** accentuates the susceptibility to obesity by A allele.
Peroxisome Proliferator activated receptor gamma (PPAR-y)

RISK ALLELE C

- Nuclear Transcription factor
- Plays a role in Adipocyte growth and differentiation
- Role in Lipid and glucose metabolism
- Reduced transcription related to increased regain of weight
- Decreased insulin sensitivity (Masud et al., 2005)
Impact of PPAR-y gene variant Pro12Ala C>G

- CC most common version
- Memisoglu et al., 2003 – Nurses health study
- CC individuals particularly sensitive total amount of fat in the diet with higher BMI
- No difference in Ala carriers
- MUFA intake inversely associated with BMI in Ala carriers
Beta-2 Adrenergic Receptors (ADRB2)

- Gly16Arg G>A, Gln27Glu C>G
- GA 40%, AA 12%, CG 50%, GG 15%
- Involved in energy expenditure regulation through stimulating thermogenesis and lipid metabolism in adipose tissue
- Knockout mouse studies have conclusively shown that the adrenergic receptors are necessary for diet-induced thermogenesis, and play a critical role in the body’s defense against obesity (Bachman et al., 2002)
ADRB2 SNPs associated with obesity, especially central obesity

**Gln27Glu (C>G)**
- Glu27 (G) carriers more resistant to losing weight, lose weight slower, associated with all measures of obesity
- Martinez et al. (2003) found a significant interaction between high consumption of CHO and obesity in Glu27 carriers

**Gly16Arg (G>A)**
- Long term studies showed that weight gain from childhood to adulthood and weight gain during adulthood are higher in Gly16 allele (Ellsworth et al 2002)
- Also Gly16 more resistant to weight loss and more likely to regain body weight after 6 months (Masuo et al., 2005)
dietary intake of CHO >49% E produced an increased obesity risk in women carrying the Glu27 allele

dietary intake of CHO >49% E associated with higher insulin levels in women carrying the Glu27 allele
-265 T/C (TC 47%, 10-15% CC)

Second most abundant protein of HDL particles

SNP results in 30% drop in transcription activity.

CC individuals had higher obesity risk and higher intake of total fat and SAT FAT.

Three populations have shown a mean increase in BMI in CC genotypes with high SAT FAT intake but not low SAT FAT intake (Corella, 2011).
APOA2, Dietary Fat, and Body Mass Index

Replication of a Gene-Diet Interaction in 3 Independent Populations

Dolores Corella, PhD; Gina Peloso, MSc; Donna K. Arnett, PhD, MSPH; Serkalem Demissie, PhD; L. Adrienne Cupples, PhD; Katherine Tucker, PhD; Chao-Qiang Lai, PhD; Laurence D. Parnell, PhD; Oscar Coltell, PhD; Yu-Chi Lee, MSc; Jose M. Ordovas, PhD

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These figures clearly illustrate the benefit of including genetics and diet in research studies.
“Subjects on Diets Appropriate for their Genotype Achieved Statistically significant Average Weight Loss of 6.2% of Body Weight at one year Compared to Individuals not on a Diet Matched to Genotype (2.4%)” - Stanford Univ
Other areas in weight management:

- The Human Obesity gene map
- Taste preference (TAS2R38)
- Reward deficiency syndrome (DA2D)
- Snacking and Binging (MC4R, CLOCK)
- Appetite (LEP-R)
- Obesity and Gut microbiota
- Epigenetics (Barres et al 2013; Hatoum et al 2011)
Motivation and Commitment?

- Personalised genotype advice improved motivation (Arkadianos et al., 2009)

- Personalized advice more understandable and enjoyable to read (Nielsen and El-Sohemy, 2012)

- FTO status does not impact motivation to lose weight (Jrn Gen Couns 2013, Meisel et al 2012)

What will the future be like?

Genomic Knowledge

Dietetic input

SNP’s & other omics data

Nutrients

Drugs

Activity

Behavioural Rx

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GENES AND DIABETES
Identified in 2006

TCF7L2 gene associated with type 2 diabetes, MetS and obesity.

Associated with increased T2D risk possibly due to defective beta-cell functioning and impaired insulin secretion

Operates via impaired glucagon-like peptide 1 (GLP-1) secretion
TCF7L2 rs7903146–macronutrient interaction in obese individuals’ responses to a 10-wk randomized hypoenergetic diet\textsuperscript{1–3}

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**TCF7L2 rs7903146 AND HYPOENERGETIC DIETS**

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<tr>
<th></th>
<th>CC/CT</th>
<th>TT</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>n=293</td>
<td>n=283</td>
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<tr>
<td>n=29</td>
<td>n=17</td>
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<tr>
<td>ΔWC (cm)</td>
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<td></td>
</tr>
<tr>
<td>n=285</td>
<td>n=277</td>
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</tr>
<tr>
<td>n=29</td>
<td>n=17</td>
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\( P \text{ for interaction: } 0.023 \)

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Mean weight loss was -6.81 kg. All subjects no difference between HF and LF.

CC & CT subjects no difference between HF and LF.

TT genotype weight loss was 2.57kg smaller with HF than LF diet.

TT do better on a LF diet.
TCF7L2 C>T

- During lifestyle intervention, T allele carriers displayed lower reduction in BMI and total body fat.
- T allele requires more long term intervention to manage weight and prevent IR and diabetes.
- Need to manage QUALITY of CHO. GL & GI.
- Implement all diet & lifestyle changes that will prevent development of IR.
The absolute high risk associated with obesity at any level of genetic risk highlights the importance of universal rather than targeted approach to lifestyle

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001647
Nutrigenetics and Alzheimer’s disease

- ApoE4 increases risk of CVD by 40% (Lovegrove & Gitau 2008)
- 25% in UK population
- 40% population will develop late onset AD
- Diet & lifestyle intervention
- REVEAL study - Impact of disclosure of APOE4 status
- Genotype status did impact motivation to change (Chao et al., 2008)
Nutrigenetics and CVD

- DNA cascade screening for Familial Hypercholesterolaemia (Scotland & Wales)
- LDL-R, ApoB, PCSK9
- NOS-3 (Ferguson et al., 2010)
- MTHFR C677T (Klerk et al., 2002)
Nutrigenetics, Epigenetics and Cancer

- Cruciferous veg intake improves detoxification function
- Contains Sulphoraphane (Ferguson and Schlothauer, 2012)
- Epigenetics & polyphenols
“Dietitians and doctors can act as a reality check to Nutrigenomics, they know what goes on in the heads of their patients and clients a lot better than scientists and can therefore bridge science and practical application”

Laura Bouwman PhD Wageningen university.
Summary

- Genes play an important role in health homeostasis
- Personalization may lead to improved motivation and outcomes for chronic diseases
- Specific SNP’s have been repeatedly shown to impact health in different populations
- We don’t have all the answers in terms of gene-gene, gene-nutrient interactions, but we certainly have a starting point
- Although it is early days for a nutrigenomics, in the future can be used as a tool as part of a effective personalized nutrition intervention strategy
- New nutrition research needs to integrate genomic data
Part 3 – Nutrigenetic testing
WHAT DOES TESTING INVOLVE?
Nutrigenetic testing in the market

- Weight Loss
- Wellness
- Sports Performance
- Disease risk
- Lactose Intolerance
- Coeliac disease
- Urine metabolites
Nutrigenetics a global view
Part 4 – Limitations, Ethics and Regulation
LIMITATIONS OF GENE-SNP TESTING
Limitation of DNA testing

- Chronic diseases are polygenic
- Contribution of single SNP to overall disease susceptibility usually small
- Interaction between diet-genes and gene-genes (epistasis) not identified
- Chronic diseases are poly-environmental
- Chronic diseases are more prevalent in some ethnic groups
- Limited Biomarkers to measure impact of SNP’s
- Limited standardization of testing and interpretation
- Only looks at part of the genome
ETHICS OF PERSONALISED NUTRITION
Ethical issues

Individual

Privacy

Behaviour change

Psycological stigma

Discrimination

Ready for practice?

Reilly and DeBusk 2008,
Görman et al., 2012
Stewart-Knox et al., 2013
Bloss et al 2013

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REGULATORY ENVIRONMENT
Regulation of Genetic testing

- UK HGC / EU
  MHRA-medical devices

- US (FDA – medical devices)

Hesketh 2013
Part 5 – The Market need
Who do the public trust to provide personalised nutrition?

![Bar chart showing trust in different sources]

- Social Media
- News media
- Friends/Family
- Personal Trainers
- Dieticians/Nutritionists
- Consumer Orgs
- Universities
- On-Line Pers Nutr Comp's
- Food Manufacturers
- Food Retailers
- NHS
- Eu Commission
- Dept of Health
- Family doctor

Indicate extent you trust or do not trust 1-5 (mean score) (N=9381)

Courtesy Barbara Stewart-Knox, UU

Food4me project 2013
Who are Consumers and what do they want?

- Men and older individuals
- Highly educated
- More likely if result is likely to be positive
- Take preventative action
- May have a relative or at risk themselves

(Collins et al 2013)

- HCP endorsed (Wendel et al., 2013)
- Personalized Approach if high risk and symptomatic (Fallaize et al., 2013)
- Actionable Data
- Data to be kept safe
Where are opportunities for Dietitians?

- Lead research
- Genomic educators in Dietetic curriculum
- Evolve public health guidelines
- Lead and contribute to commercial teams
- Educate public
- Integrate into clinical practice
- Development of functional foods
Market trends & Highlights 2014/15

- 23and me banned from selling personal genome test in 2013
- 23andme launched in the UK 2014
- AND position paper on Nutritional Genomics published
- First NGx sessions at both Canadian and ADA conferences
- Biggest investment yet in digital health
- Fitgenes, RevUP launch integrated platform
- 100 000 genome project gets more funding
- Competency on NGx standard for UK RD’s published
- BBC documentary on Personalised Nutrition aired
Resources & Projects

- Food4me project (http://www.food4me.org)
- Human Variome project
- HAPMAP consortium
- Micronutrient project
- DIFM (http://integrativerd.org)
- Toybox study
- Qua-Li-FY
- Competency Framework for Dietitians 2014
- Diogenes
- NuGO (http://www.nugo.org)
- ISNN (http://www.isnn.info)
- NHS Genetics Education centre
- OMIM database
- AND position paper on Nutritional Genomics 2014
- POUNDS-lost TRial

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Books

Nutrigenomics and Nutrigenetics in Functional Foods and Personalized Nutrition

Lynnette R. Ferguson

NUTRITIONAL GENOMICS
Discovering the Path to Personalized Nutrition

Edited by Jim Kaput and Raymond L. Rodriguez

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The real question........

Where is the evidence?

vs

Where should I start?
Key messages

- 1 SNP does not equal chronic disease
- Start Learning your special interest topics
- Digital and Genomic technologies are changing our roles
- The world is moving towards prevention and personalisation
- The Food industry is responding to consumer demands for more healthy and personalised foods
- The field needs expert nutrition practitioners to lead, educate and get involved
THANK YOU!!!
Inspired to learn & Apply?

- **Basic Nutritional Genomics webinar** - April 16th 2015 & June 2015 - Book within next 72hrs for £145 discount

- 5-week online course - starts May 2015

- Practical Nutrigenomics eBook – 2nd Edition

- Individual Coaching

- Want to get tested?
Contact me

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- **Phone**: ++351 964450622
What is next?

- Send final quizz and feedback questionnaire via email to mariette@marietteabrahams.com
- Certificate of completion sent on return of both
- Pick a topic and find literature!
- Ask questions in LinkedIn group
- You will receive our weekly newsletter
- **Share the knowledge and bring a friend** - earn £10
- Give us a “Tweet” about the course
Products and Services

Business Consulting- Contract

- Partnership to provide training
- Spokesperson services
- Provide strategic advice and consumer & HCP insight
- Technical support
- New Product development
- Creativity & innovation (more details on our website)

Business Coaching

- For nutrition professionals

Interested? , Want to get tested?
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Skype: pnutritionconsulting

E-Book available on Smashwords - $8,99
Question time


FRAYLING ,T.M et al 2007. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science, May 11: 316(5826), 889-894


LUAN


Meisel


