



SNP Interpretation Guide



Contents

Introduction	3
DNA Basics	5
DNA Health	6
Introduction	6
LIPID METABOLISM	7
LPL 1595 C>G	7
CETP 279 G>A	8
APOC3 3175 C>G	8
APOE E2/E3/E4	9
PON1 -192 Gln>Arg (A>G)	10
DNA METHYLATION	11
MTHFR 677 C>T and MTHFR 1298 A>C	12
MTR 2756 A>G	12
MTRR 66 A>G	13
CBS 699 C>T	13
COMT Val158Met (472 G>A)	14
DETOXIFICATION	15
CYP1A1 Msp1 T>C and CYP1A1 Ile462Val A>G	15
GSTP1 313 A>G	16
GSTM1 Insertion/Deletion	16
GLUTATHIONE S-TRANSFERASE T1	17
NQO1 609 C>T	17
INFLAMMATION	18
TNFA -308 G>A	18
IL-1A 4845 G>T or -889 C>T, IL-1B 3954 C>T & -511 A>G, & IL-1RN 2018 C>T	19
IL-6 -174 G>C	20
OXIDATIVE STRESS	20
eNOS 894 G>T	21
SOD2 -28 C>T	21
GPX1 Pro198Leu (C>T)	22
CAT -262 C>T	22
BONE HEALTH	23
VDR Fok1 T>C	23
VDR Bsm1 G>A	24
VDR Taq1 C>T	24
COL1A1 1546 G>T	25
INSULIN SENSITIVITY	25
PPARG Pro12Ala C>G	26
TCF7L2 rs7903146 C>T	26
FTO T>A	27
GLUT2 coded by SLC2A2 Thr110Ile (C>T)	27
FOOD RESPONSIVENESS	28
Lactose Intolerance	28
HFE Cys282Tyr (C282Y) HFE His63Asp (H63D)	29
TAS2R38 145 C>G (Pro49Ala), 785 C>T (Ala262Val) & 886 G>A (Val296Ile)	30
ALDH2 rs671 G>A	31
PUFA Metabolism	32
Caffeine Sensitivity	33
Salt Sensitivity	33
DNA Diet	35
Introduction	35
FABP2 Ala54Thr G>A	35

PPARG Pro12Ala C>G	36
ADRB2 Arg16Gly G>A	36
ADRB2 Gln27Glu C>G	37
ADRB3 Trp64Arg T>C	37
APOA2 -265 T>C	38
TCF7L2 rs7903146 C>T	38
FTO rs9939609 T>A	39
CLOCK 3111 T>C	39
APOA5 -1131 T>C	40
PLIN 11482 G>A	40
MC4R T>C	41
TNFA -308 G>A	41
DRD2 (Taq1A)	42
TAS1R2 Ile191Val	42
GLUT2 coded by SLC2A2 Thr110Ile	43
ADIPOQ -11391 G>A	43
UCP1 -3826 A>G, UCP2 -866 G>A, UCP3 -55 C>T	44
DNA Oestrogen	45
Introduction	45
CYP1A1 Ile462Val A>G and CYP1A1 Msp1 6235 T>C	45
CYP17A 34 T>C	46
CYP1B1 1294 C>G	46
COMT 472 G>A	47
SULT1A1 638 G>A	47
Factor V 1691 G>A	48
DNA Sport	49
Introduction	49
COL1A1 Sp1 G>T	49
COL5A1 BstUI RFLP C>T	50
GDF5 5' UTR C>T	50
IL-6 -174 G>C	51
IL-6R Asp358Ala A>C	51
CRP 219 G>A	52
TNFA -308 G>A	52
SOD2 Val16Ala -28 C>T	53
eNOS Asp298Glu 984 G>T	53
AGT Met238Thr T>C	54
ACE Insertion/Deletion	54
BDKRB2 Rpt sequence exon 1 C>T	55
VEGF -634 C>G	56
NRF2 A>G	56
PPARGC1A Gly482Ser G>A	57
PPARA Intron7 G>C	57
ADRB2	58
TRHR T>G	59
CYP1A2 -163 C>A	59
ACTN3 577 R/X	60
VDR Taq1 T>C	60
DNA Single SNPs	61
Introduction	61
DIO2 Rs225014 T>C	61
NAT2 rs1495741 G>A	62
Gluten Intolerance / Coeliac disease risk HLA DQ2/DQ8	62
Factor V 1691 G>A	63
Appendix	64

Introduction

DNA Health

DNA Diet

DNA Oestrogen

DNA Sport

Single SNPs

Appendix

Introduction



About dnalife®

dnalife was formed when Nordic Laboratories and DNALysis teamed together to provide practitioner education about DNA testing, and to offer support in the interpretation of DNA test results. The company has since expanded its offering to include a number of specialist testing services and products for practitioners in the functional medicine industry

Nordic | **DNALysis**
Laboratories | Biotechnology

About Nordic Laboratories

Nordic Laboratories places the advancement of functional medicine at the core of everything it does. The company is highly committed to education in this field, and has its own extensive practitioner-training program, to support the most clinically appropriate use of laboratory testing.

A commitment to deliver the highest quality laboratory evaluations allows it to serve clients from Scandinavia to Spain, the US to the UK, Hong Kong, the Middle East, and South Africa. No matter the locale, Nordic clients receive their tests promptly and have consistent access to the highly qualified members of the Nordic team who can assist them with their order.

About DNALysis

DNALysis provides medical practitioners and their patients with actionable and accurate genetic information to improve and maintain health and wellness. The company is renowned for its dedication to innovation and commitment to medical responsibility, making it a leader in the commercial genetic testing industry. DNALysis experts are available to provide support and assistance to DNALife practitioners as they begin working with nutrigenomics tests.

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DNA Basics

DNA

Deoxyribonucleic acid (DNA) is our hereditary template. Most DNA is located in the cell nucleus (nDNA) within chromosomes, but a small amount is found in the mitochondria (mtDNA).

Bases

The information in DNA is stored as a code made up of four chemical bases:

- adenine (A)
- guanine (G)
- cytosine (C)
- thymine (T)

Base pairs

Two DNA base pairs join to make a unit:

- adenine (A) pairs with thymine (T)
- cytosine (C) pairs with guanine (G)

Nucleotide

One base + one sugar + phosphate = nucleotide

Nucleotides join together and are arranged in two long strands that form a spiral called a double helix.

Replication

Replication takes place when cells divide. It is the process by which DNA copies itself so that the new cell contains the same DNA as the old cell.

Genes

Genes are made up of DNA, they are a template to make proteins. In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases. We have two copies of each gene, one inherited from each parent.

SNP (single nucleotide polymorphism)

A SNP is a difference in a nucleotide, where one nucleotide is replaced with another – they are not mutations. Human DNA consists of about 3 billion bases, 99% of which are the same in all people. SNPs occur on average once in every 300 nucleotides. They can act as biological markers indicating a predisposition towards a behaviour, physical or physiological attribute.

Alleles

Allele is a shortened form of the word allelomorph ('other form'). Alleles are part of the SNP – there are two inherited alleles at a given SNP position, one inherited from each parent. SNPs tell us the position of the changed bases while the allele refers to a single base within a base pair, at that position. It could be a T allele, which tells us that the base being referred to (within the changed base pair) is thymine.

Genotype

The two alleles inherited (one from each parent) at a given SNP position

Chromosomes

Chromosomes are microscopic finger like structures that contain tightly packed DNA. Humans normally contain 23 pairs of chromosomes.

DNA Health

Introduction

DNA Health is concerned with optimising energy, well-being and health by making better lifestyle and diet choices, and using supplements tailored to offset any particular nutritional deficit or genetic shortcoming. The DNA Health approach establishes the optimal nutrition necessary for good health, energy, and longevity.

DNA Health tests 36 gene variations involved in eight key biological processes, which are all key factors in the on set of chronic disease:

- Cholesterol metabolism
- Methylation
- Detoxification
- Oxidative stress
- Inflammation
- Insulin resistance
- Bone health
- Iron metabolism
- Food responsiveness

Many diseases are preventable through the correct diet and lifestyle choices. DNA Health is designed to help healthcare practitioners support their patients to make the best diet and lifestyle choices based on their patients' unique DNA.

LIPID METABOLISM

Atherosclerotic and thrombotic diseases of the cardiovascular system are major causes of death and morbidity. Dramatic strides in unravelling the environmental influences on classic complex cardiovascular disease have translated into major public health efforts to alter lifestyle and diet.

Nutrition has been largely recognized as an important factor in the prevention of cardiovascular disease. Among dietary factors, total dietary fat and the different types of fat have been mostly studied.

The different types of fatty acids have different influences on lipid metabolism, metabolic risk factors and the risk of cardiovascular disease. However, these influences are potentially modulated by genes variations that play a role in fatty acid metabolism.

Single-gene defects affect a relatively small subset (5-10%) of patients at high risk of premature coronary heart disease, while multiple gene variations with minor effects contribute to CVD risk in the vast majority of individuals. Such multigenic effects depend predominantly on environmental influences, which suggests that most premature cardiovascular deaths can be prevented if action is taken to avoid, or modify, external factors that may influence a genetic predisposition to become clinically relevant.

If a number of gene variants in this panel convey moderate to high risk impacts, it may be prudent to assess an individual's cholesterol profile (liposcan) – paying special attention to cholesterol subfractions.

LPL 1595 C>G

LIPOPROTEIN LIPASE

Background

LPL is found in many tissue types, and is a key enzyme in the metabolism of triglyceride-rich lipoproteins. It is anchored to the vascular endothelium and removes lipids from the circulation to place in a target tissue. It does this by hydrolysing the triglycerides in VLDL into free fatty acids. The 1595 C>G variant is a strong indicator of body fat, fat distribution, plasma lipids and insulin concentrations. The beneficial C1595G polymorphism results in a slightly shortened form of the protein due to the insertion of a premature stop codon, which leads to increased functionality of lipoprotein lipase, and therefore a decrease in triglycerides, and increase in HDL cholesterol.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	No Impact
CG	Heterozygote	Beneficial
GG	Homozygote	Beneficial

Absence of the SNP does not mean that CVD risk is increased, but rather, the individual does not have the protection conferred by the G allele.

In individuals with the CC genotype, plasma VLDL-C and triglyceride levels tend to be higher, and HDL-C levels lower, compared to individuals with the G allele. G allele individuals also tend to have lower blood pressure.

Recommendation: CC genotype

Avoid all refined carbohydrates and rather include whole-grain, and complex carbohydrate choices. Limit saturated fat and trans-fat intake.

Ranganathan, G. et al. 2012. & Rip, J., 2006.

CETP 279 G>A

CHOLESTEROL ESTER TRANSFER PROTEIN

Background

CETP plays a key role in the metabolism of high-density lipoproteins (HDL), and mediates the exchange of lipids between lipoproteins, resulting in the eventual uptake of cholesterol by hepatocytes (reverse cholesterol transport). A high plasma CETP concentration is associated with reduced HDL concentrations. CETP is a strong and independent risk factor for CAD.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	Moderate
GA	Heterozygote	Mild
AA	Homozygote	Beneficial

The G allele is associated with increased plasma CETP and higher CETP activity, lower HDL-C and increased cardiovascular disease (CVD) risk. The 279 A allele is associated with reduced plasma CETP levels, increased HDL-C levels and reduced risk of CVD.

Recommendation: G allele

Decrease saturated fat sources in the diet and replace with mono-unsaturated fats, as well as foods rich in omega 3 FA. Avoid all trans-fat foods and moderate alcohol intake.

Li, C., 2013. & Wallace, A. J., 2000.

APOC3 3175 C>G

APOLIPOPROTEIN C3

Background

Apolipoprotein C3 plays an important role in lipid and triglyceride metabolism, and is regulated by insulin. It inhibits lipoprotein lipase and hepatic lipase, delaying catabolism of triglyceride-rich particles - slowing hepatic VLDL uptake, and promotes VLDL production. Raised APOC3 levels are associated with raised triglycerides.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	No Impact
CG	Heterozygote	Mild
GG	Homozygote	Moderate

The G allele is associated with elevated plasma triacylglycerol, cholesterol, and Apoc3 and ApoB concentrations. Carriers of the G variant have an approximate 4-fold increased risk of hypertriglyceridemia. The C allele appears to be more responsive to dietary intervention compared to the G allele.

Recommendation: C allele

Decrease saturated fat and increase MUFA intake. If triglycerides are raised, also modify carbohydrate intake. It is important to avoid modern Western dietary patterns.

G allele

G allele carriers may show enhanced benefit to cholesterol-lowering medication.

Rudkowska, I. et al., 2013. & Song, Y. et al., 2015.

APOE E2/E3/E4

APOLIPOPROTEIN E

Background

Apolipoprotein E has a multi-functional role in lipoprotein metabolism and is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. Two SNPs result in three allelic isoforms, affecting the protein conformation and thus the receptor binding activity and lipoprotein preference of the APOE protein.

Gene impact and information

Genotype	E3	E4	E2
Diet Impact	No Impact	High	Moderate

E3 is the neutral isoform.

The E4 isoform contributes toward a 40 to 50% increased risk of CVD, which is due, in part, to higher levels of total- and LDL cholesterol, as well as an increased oxidative capacity. E4 carriers are hyper-responsive to toxins such as alcohol and smoking. E4 individuals are also more sensitive to the type of fatty acid intake in modulating cholesterol levels.

Recommendation: E4 isoform

Reduce saturated fat and trans fat intake, and replace with mono-unsaturated fat sources. E4 individuals may also benefit from increased intake of omega 3 fatty acids to improve cholesterol levels. It is essential for these individuals to achieve a healthy weight and fat percentage. Increase anti-oxidant intake from vegetables and other food sources, and reduce oxidative stress by decreasing/avoiding alcohol intake, and cessation of smoking. Regular physical activity may show enhanced benefit in E4 carriers.

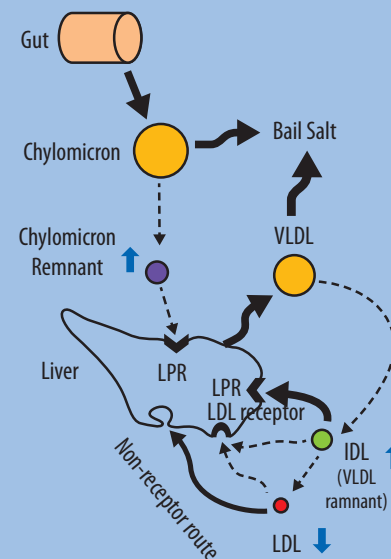
In general, E2 carriers have lower total cholesterol levels and improved anti-oxidant capacity. There is some suggestion that the APOE E2 allele may have a slight protective effect against CVD, however, despite lower cholesterol levels, E2 carriers are not immune to dyslipidaemia and raised triglycerides.

Recommendation: E2 isoform

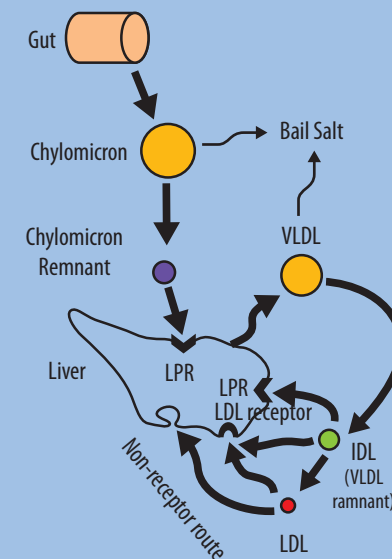
E2 carriers appear to respond less to dietary intervention, but appear to be more responsive to certain cholesterol lowering medications.

Minihane, A. et al., 2007. & Thifault, E. et al., 2013.

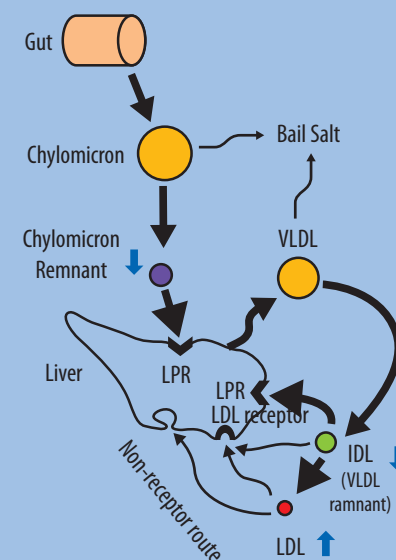
E2/E2 Phenotype



E3/E3 Phenotype



E4/E4 Phenotype



PON1 -192 Gln>Arg (A>G)

PARAOXONASE 1

Background

PON1 encodes the glycoprotein enzyme paraoxonase, which has broad substrate specificity and is able to catalyse the hydrolysis of lipid peroxides, lactones, and organophosphate pesticides. This enzyme is partly responsible for the inhibitory and cardioprotective effect of HDL cholesterol on lipid peroxidation by attaching to HDL particles in serum, and inhibiting LDL oxidation, thus protecting against atherogenesis. Paraoxonase also functions as an anti-oxidant and plays an important role in preserving the integrity of cell membranes. Low serum PON activity has been associated with metabolic syndrome and coronary artery disease risk.

Gene impact and information

Genotype		Impact
AA	Wild type	No impact
AG	Heterozygote	Mild
GG	Homozygote	Moderate

The G allele, specifically the GG genotype, is associated with lower concentrations of PON1 and decreased PON1 activity. This SNP has therefore been linked to increased risk for atherosclerosis, ischaemic stroke, metabolic syndrome, and certain cancers. Studies have shown that mono-unsaturated fatty acids (MUFAS) including oleic acid, present in extra virgin olive oil, has a favourable effect on increasing PON1 activity, so too did phytonutrients and polyphenols from a variety of fruit and vegetables. The Mediterranean diet, which can be described as a diet rich in fruit and vegetables, low in saturated fat and the main source of added fat coming from olive oil, has also been associated with improved PON1 activity and a decreased risk of atherosclerosis.

Recommendation: G allele

Decrease saturated fat intake and increase dietary intake of MUFAs. Sources include olive oil, olives, and avocado. Encourage a high intake of a variety of vegetables and fruit. Also encourage regular physical activity as this has been shown to improve HDL levels, especially in G allele carriers.

Lou-Bonafonte, J. et al., 2015. & Tomas, M. et al., 2001.

DNA METHYLATION

Methylation uses the process of donating 'methyl groups' to a substrate. A methyl group consists of one carbon bound to three hydrogen atoms (CH₃).

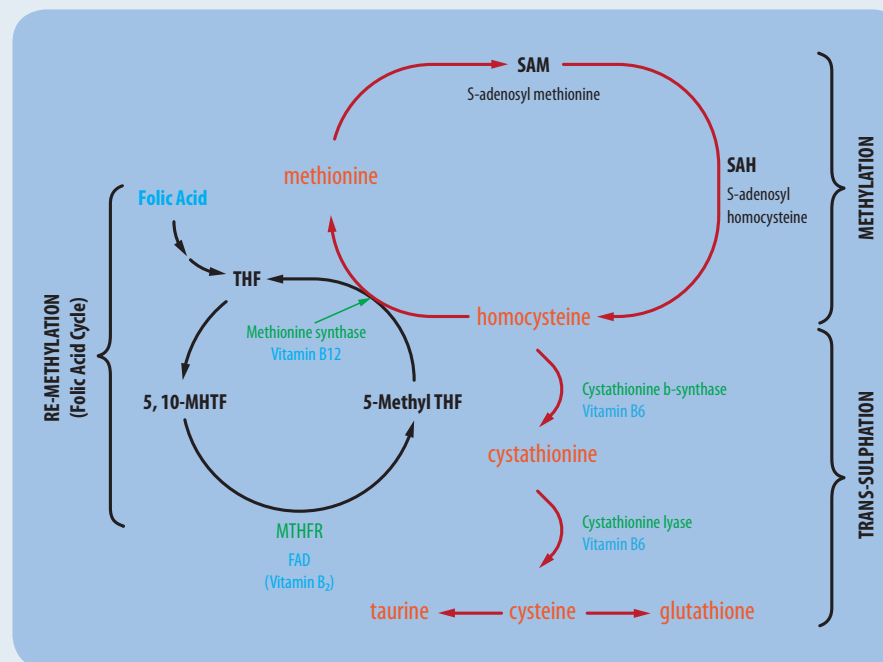
Methyl groups' substrates include DNA and RNA, chemicals, neurotransmitters and hormones and immune cells etc. Methylation serves several functions such as gene regulation, biotransformation (or the processing of chemicals and toxins), myelination (the production of the protective coating on nerves), building of neurotransmitters and immune cells, processing of hormones, and DNA and RNA synthesis. Methylation is regulated by enzymes and substrate (end product), and many enzymes require cofactors, often derived from vitamins and minerals, to be activated.

B vitamins provide building blocks for growing cells, which are constantly being renewed, and play an important role in many physiological processes. B vitamins also supply some of the chemicals necessary for protecting our genes, so that our DNA doesn't accumulate damage from the wear and tear in the daily lives of our cells. These vitamins – including folate, vitamins B6 and B12 – help make new DNA for cells that are constantly growing and renewing themselves. Folate is also involved in turning many genes on and off, and also helps repair DNA. The process of DNA repair is called methylation. Although B vitamins are only required in small amounts, they are crucial for methylation and in producing new DNA.

Folate is a water-soluble vitamin classified as part of the B group of vitamins. Being water soluble, its content is significantly reduced when cooked; the processing of whole grain wheat into flour, for example, removes 68% of the folate content. It has been estimated that only about 20-25% of the folate content of food is biologically available.

Low folate levels, and SNPs involved in the process of methylation, are associated with an increased risk for hyperhomocysteinemia, and a decreased ability to synthesize and replicate DNA properly, and with risk for cardiovascular disease, some forms of cancer and neural tube defects.

If a number of gene variants in this panel convey moderate to high risk impacts, it may be prudent to assess an individual's methylation profile at the biochemical level. This offers insight into actual metabolites in the methylation pathway. Methionine, S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), Homocysteine as well as Cysteine and Cystathionine, metabolites in the trans-sulfuration pathway and precursors of Glutathione.



MTHFR 677 C>T and MTHFR 1298 A>C

METHYLENETETRAHYDROFOLATE REDUCTASE

Background

Methylenetetrahydrofolate reductase is a riboflavin-dependent (FAD) enzyme that catalyzes the NADPH-dependent reduction of 5,10-methylene-tetrahydrofolate (THF) to 5-methyl-THF, and is a key enzyme in the folate metabolism pathway – directing folate from the diet either to DNA synthesis or homocysteine remethylation, a process by which homocysteine is converted back to Methionine. The two polymorphisms described occur at relatively high frequencies in the population, approximately 10-30%, and lower the activity of the MTHFR enzyme.

Gene impact and information

677 C>T polymorphism			1298 A>C polymorphism		
Genotype		Diet Impact	Genotype		Diet Impact
CC	Wild type	No Impact	AA	Wild type	No Impact
CT	Heterozygote	Moderate	AC	Heterozygote	Mild
TT	Homozygote	High	CC	Homozygote	Moderate

MTHFR 677C>T polymorphism

The T allele reduces the stability and lowers activity of the MTHFR enzyme, which results in an increase in homocysteine levels, a decrease in DNA methylation, and thus an increase in DNA adducts. T allele carriers have increased folate, vitamin B2, B6 and B12 requirements. Enzyme function is only 70% of optimal in CT individuals and 30-40% of optimal in TT in individuals.

Recommendation: T allele

Incorporate a folate and B vitamin rich diet. Decrease alcohol intake and cessation of smoking is recommended. Also consider supplementation of active folate (5-methyltetrahydrofolate/5-MTHF) and vitamins B2, B6 and B12.

MTHFR 1298 A>C polymorphism

The C allele affects enzyme regulation by S-adenosylmethionine (SAdMe), and is associated with decreased enzyme function.

Recommendation: C allele

Incorporate a folate and B vitamin rich diet. Decrease alcohol intake and cessation of smoking is recommended. Also consider supplementation of active folate (5-methyltetrahydrofolate/5-MTHF) and vitamins B2, B6 and B12.

Hustad, S. et al., 2007., Miyaki, K., 2010. & Stover, P.J., 2011.

MTR 2756 A>G

METHIONINE SYNTHASE

Background

The methionine synthase (MS) enzyme, encoded by MTR, catalyses the re-methylation of homocysteine to methionine. This reaction is vitamin B-12 dependent, and activity is essential to supply methionine for SAM synthesis and to prevent accumulation of homocysteine and SAH. There is a common polymorphism which affects the functional site of the protein and hence the levels of circulating folate and homocysteine.

Gene impact and information

Genotype		Diet Impact
AA	Wild type	No Impact
AG	Heterozygote	Beneficial
GG	Homozygote	Beneficial

The G allele is associated with decreased levels of homocysteine – the SNP increases activity of the MTR enzyme that converts homocysteine to methionine. There is a dose-dependent decline across AA, AG and GG genotypes. It appears that the polymorphism increases the activity of the enzyme, enhancing the conversion of homocysteine to methionine, and reducing homocysteine levels. Thus, it is a beneficial variant.

Recommendation: Ensure adequate vitamin B12 intake to support enzyme activity.

Chen, J., et al., 2000. & Stover, P.J., 2011.

MTRR 66 A>G

METHIONINE SYNTHASE REDUCTASE

Background

Methionine Synthase Reductase is involved in the reductive regeneration of cob(I) alamin (vitamin B12) cofactor required for the maintenance of methionine synthase in a functional state – it catalyses methylcobalamin, an essential co-factor of methionine synthase (MS), which is essential for maintaining adequate intracellular pools of methionine and is also responsible for maintaining homocysteine concentrations at non-toxic levels.

Gene impact and information

Genotype		Diet Impact
AA	Wild type	No Impact
AG	Heterozygote	Mild
GG	Homozygote	Moderate

The G allele is associated with increased risk for premature coronary artery disease (CAD) and the GG genotype is a significant risk factor for the development of premature CAD and Neural Tube Defects (NTDs) when cobalamin (Vitamin B12) status is low.

Recommendation: G allele

Ensure adequate intake of active folate (5-methyltetrahydrofolate/5-MTHF), vitamins B2, B12 and vitamin B6, especially during pregnancy.

Brown, C. A. et al., 2000. & Lakshmi, V. et al., 2011.

CBS 699 C>T

CYSTATHIONINE β SYNTHASE

Background

CBS is a vitamin B6 dependent enzyme, which catalyses the irreversible conversion of homocysteine to cystathionine and is directly involved in the removal of homocysteine from the methionine cycle, thus any alterations in its activity could affect homocysteine levels. Cystathionine is then converted to cysteine. Together with glutamate and glycine, glutathione can then be produced.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	No Impact
CT	Heterozygote	Mild
TT	Homozygote	Moderate

The variant 699T allele is associated with decreased risk of CAD and an increased responsiveness to the homocysteine lowering effects of folate.

Recommendation: T allele

Check dietary folate intake and homocysteine levels and supplement if necessary.

Kruger, W. D., et al., 2000.

COMT Val158Met (472 G>A)

CATECHOL-O-METHYLTRANSFERASE

Background

COMT catalyses the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. This O-methylation results in one of the major degradative pathways of the catecholamine transmitters. In addition to its role in the metabolism of endogenous substances, COMT is important in the metabolism of catechol drugs used in the treatment of hypertension, asthma, and Parkinson disease.

Soluble catechol-O-methyltransferase (S-COMT) helps control the levels of certain hormones and is also involved in methylation and inactivation of catechol oestrogens. A genetic variant of the COMT gene reduces the activity of the enzyme and has been associated with breast and ovarian cancer; substance use disorder, and mental disorders such as schizophrenia, anxiety, bipolar and depression.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GA	Heterozygote	Moderate
AA	Homozygote	High

The A allele is associated with a 3-4 fold reduction in the methylation activity of the COMT enzyme and so is associated with higher dopamine (stress) levels, a lower pain threshold, and enhanced vulnerability to stress. Individuals carrying the GA and AA genotype have increased risk for breast and ovarian cancer. The G allele is associated with higher COMT activity and therefore lower dopamine levels, and a higher pain threshold, and better stress resiliency.

Recommendation: A allele

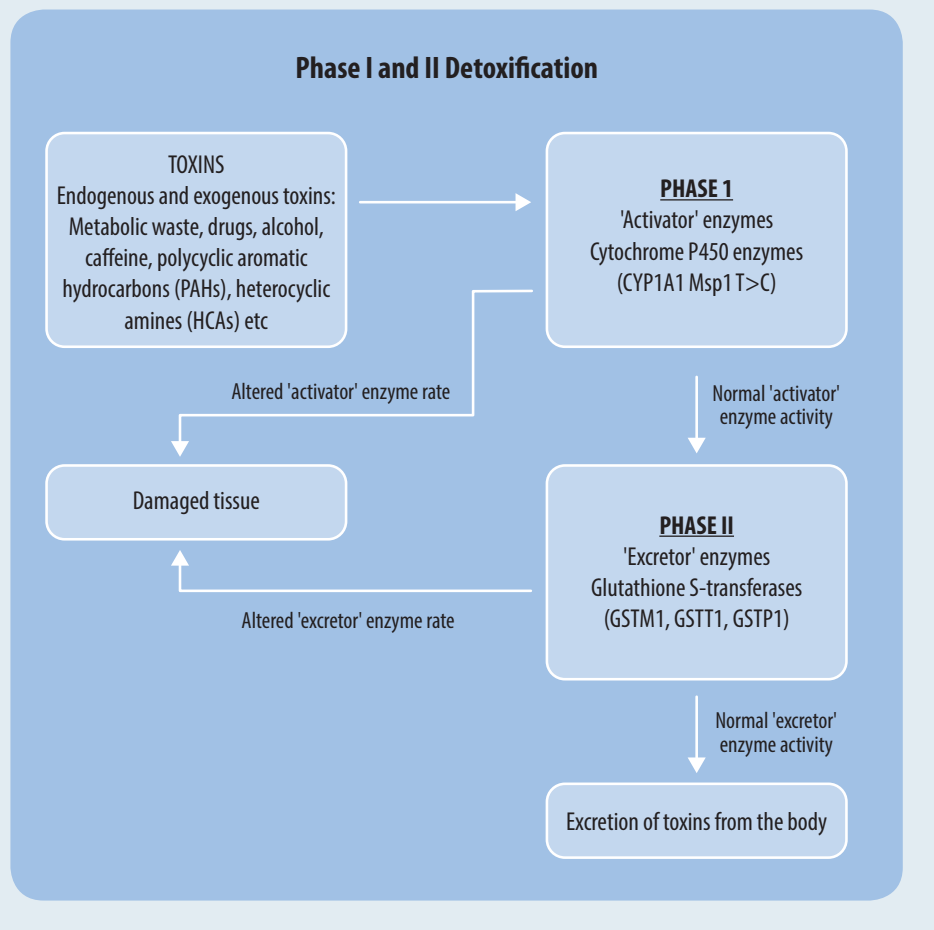
Ensure adequate availability of methylating agents, which may include Vitamin B12, folate and S-adenosyl methionine. Avoid alcohol and a high caffeine intake. Focus on upregulating activity of other phase two detoxification enzymes, by increasing intake of foods such as cruciferous and allium vegetables. Consider supplementation with sulforaphane and/or diindolylmethane (DIM) – both agents that are known to increase expression of phase two enzymes. Ensure adequate magnesium intake.

Happonen, P. et al., 2006. & Zahid, M. et al., 2014.

DETOXIFICATION

The detoxification process in the body has two phases. The enzymes involved in phase one detoxification are known as 'activators'; they activate the substance that needs to be removed, allowing the next phase to proceed. Phase I enzymes must exhibit just the right amount of activity for the detoxification process to be effective. Activated compounds in phase I are potentially harmful.

The enzymes that take over from phase I are called 'excretors' because they catalyze reactions leading to the excretion of toxins from the body. These enzymes bind the chemical compound glutathione to the 'active' toxins from phase I, making them water soluble so they can be excreted through sweat or urine. Decreased activity or deletion of these genes has been associated with cancer and other diseases.



CYP1A1 Msp1 T>C and CYP1A1 Ile462Val A>G

CYTOCHROME P450 1A1

Background

The CYP1A1 gene encodes a phase I cytochrome P450 enzyme, which is one of the main extra-hepatic enzymes that has the ability to metabolize both exogenous and endogenous compounds into their carcinogenic derivatives. It converts environmental pro-carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and aromatic amines to reactive intermediates having carcinogenic effects. In addition, CYP1A1 is involved in the oxidative metabolism of oestrogen, melatonin and inflammatory mediators.

Gene impact and information

Ile462Val A>G polymorphism			Msp 1 T>C polymorphism		
Genotype		Diet Impact	Genotype		Diet Impact
AA	Wild type	No Impact	TT	Wild type	No Impact
AG	Heterozygote	Moderate	TC	Heterozygote	Moderate
GG	Homozygote	High	CC	Homozygote	High

CYP1A1 Ile462Val (A>G) & CYP1A1 Msp T>C

The CYP1A1 Ile462Val snp change from A to G leads to an amino acid substitution (ile>val) of its protein and increased enzymatic activity. The association between this SNP and cancer has been well documented.

The CYP1A1 Msp T>C is a functional polymorphism of which the C allele has been associated with increased transcript half-life and an increase in enzyme activity, leading to elevated levels of activated metabolites such as PAHs, and subsequently, DNA damage. Many association studies have reported that this SNP increases the development of several types of cancer, especially amongst smokers.

Recommendation: CYP1A1 Ile462Val G allele & CYP1A1 Msp T>C C allele

The variant G allele of the CYP1A1 Ile462Val SNP, and the C allele of the CYP1A1 Msp T>C SNP increases enzyme activity resulting in increased rates of carcinogen activation and subsequently DNA damage. In the presence of the G allele, it is important to reduce exposure to all diet and environmental pro-carcinogens such as PAHs, aromatic amines, smoked and chargrilled foods, and smoking of any kind. Encourage a dietary intake that is rich in phytonutrients. Food sources containing resveratrol, green tea, quercetin and curcumin have been shown to be beneficial. In addition, attention should be paid to optimising phase 2 detoxification.

Badal, S. et al., 2014. & Zanger, U. M. et al., 2013.

GSTP1 313 A>G

GLUTATHIONE S-TRANSFERASE P1

Background

Oxidative stress is a risk factor shared by most disorders, and it appears that the efficiency of the GSTP1 enzyme may have an impact on the development and prognosis of diseases influenced by oxidative stress. GSTP1 is the most abundant glutathione-s-transferase subtype in the lungs and is known to metabolise many carcinogenic compounds.

Gene impact and information

Genotype		Diet Impact
AA	Wild type	No Impact
AG	Heterozygote	Mild
GG	Homozygote	Moderate

The **G allele** decreases activity of the enzyme. Conjugation activity is 82% for carriers of one G allele, and 70% for the GG genotype individuals.

Recommendation: G allele

GST enzyme activities are induced in part by the products of cruciferous and allium vegetables. These should be increased significantly in the diet to increase activity of other GST enzymes. Daily intake is recommended. When dietary intake is inadequate a high quality supplement containing DIM or sulforaphane may be required.

Lee, et al., 2008.

GSTM1 Insertion/Deletion

GLUTATHIONE S-TRANSFERASE M1

Background

Glutathione S-transferase M1 is the most biologically active member of the GST super-family and is involved in Phase II detoxification in the liver. It is responsible for the removal of xenobiotics, carcinogens, and products of oxidative stress by conjugating reactive intermediates with glutathione to produce less reactive, water-soluble metabolite that can be readily excreted.

Gene impact and information

Genotype		Diet Impact
PRESENT	Wild type	No Impact
ABSENT		High

A deletion results in an absence of the enzyme, leading to reduced capacity for hepatic detoxification and increases the likelihood that mutagenic DNA adducts will be produced. The GSTM1 null genotype is associated with increased risk of various cancers, chemical sensitivity, coronary artery disease in smokers, atopic asthma, and deficits in lung function.

Recommendation: Deletion

Minimise exposure to toxins and pollutants such as cigarette smoke, pesticides, PAHs, aryl amines etc. Ensure the diet is rich in antioxidants and substantially increase intake of cruciferous and allium vegetables to increase activity of other GST enzymes. When dietary intake is inadequate a high quality supplement containing DIM or sulforaphane may be required.

Garte, S. et al. 2001.& Tse, G., et al. (2014).

GLUTATHIONE S-TRANSFERASE T1

GSTT1 INSERTION/DELETION

Background

Glutathione S-transferase T1 is a member of a super family of proteins that catalyse the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds.

Gene impact and information

Genotype		Diet Impact
PRESENT	Wild type	No Impact
ABSENT		High

The **deletion** is associated with an increased risk of lung, larynx and bladder cancers, as well as skin basal carcinomas.

Glutathione-s-transferase (GST) activities are induced in part by the products of cruciferous and allium vegetables.

Recommendation: Deletion

Minimise exposure to toxins and pollutants such as cigarette smoke, pesticides, PAHs, aryl amines etc. Substantially increase intake of cruciferous and allium vegetables to increase activity of other GST enzymes. When dietary intake is inadequate a high quality supplement containing DIM or sulforaphane may be required.

Moy, et al. 2009. & Tse, et al. 2014.

NQO1 609 C>T

NADP(H:) QUINONE OXIDOREDUCTASE 1

Background

NADP(H:) quinone oxidoreductase 1 (NQO1), often referred to as Quinone Reductase, is an Nrf2 target gene that encodes a cytoplasmic reductase enzyme which reduces reactive quinones to less reactive and less toxic hydroquinones along the Phase II detoxification pathway. It is primarily involved in the detoxification of potentially mutagenic and carcinogenic quinones derived from tobacco smoke, diet and oestrogen metabolism. NQO1 also protects cells from oxidative stress by maintaining the antioxidant forms of ubiquinone and vitamin E. Its single cofactor is riboflavin-derived FAD.

Gene impact and information

Genotype		Diet Impact
CC	Wildtype	No Impact
CT	Heterozygote	Moderate
TT	Homozygote	High

The variant T allele results in reduced enzymatic activity. Compared with the wildtype CC genotype, the heterozygote variant (CT) has a three-fold decrease in enzyme activity and the TT genotype has only 2%–4% of the quinone reductase activity. Individuals with the CT and TT genotype have been associated with an increased risk for developing certain cancers including breast, colorectal and gastrointestinal cancers, especially when there is exposure to cigarette smoke. The polymorphism has also been linked to benzene toxicity.

Recommendation: T Allele

Cessation of smoking and avoidance of polycyclic aromatic hydrocarbons (PAHs) found in smoked foods and chargrilled meats. Increase intake of cruciferous vegetables and possible supplementation with Sulphorofane (a compound found in broccoli) may be recommended.

Ambrosone, C. B. et al. 2009 & Lajin, B. et al. 2013.

INFLAMMATION

Chronic inflammation is a low-grade inflammatory response of prolonged duration whose extended time course is provoked by persistence of the causative stimulus to inflammation in the tissue. The inflammatory process inevitably causes tissue damage and is accompanied by simultaneous attempts at healing and repair.

The exact nature, extent and time course of chronic inflammation is variable, and depends on the balance between the causative agent and attempts by the body to remove it. Important environmental components that can affect the healing process include age (healing slows with age), nutritional deficiencies (specifically vitamin C, protein, zinc, fatty acids), metabolic diseases and some drugs.

Polymorphisms have been identified in several genes that result in higher basal levels of proinflammatory agents. Nutritional and lifestyle interventions aim to either directly affect the gene expression to reduce cytokine levels, or to address the secondary features of the inflammatory response.

TNFA -308 G>A

TUMOUR NECROSIS FACTOR- α

Background

Tumour necrosis factor- α (TNF α), a proinflammatory cytokine secreted by both macrophages and adipocytes, has been shown to alter whole body glucose homeostasis, and has been implicated in the development of obesity, obesity-related insulin resistance and dyslipidaemia.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GA	Heterozygote	Moderate
AA	Homozygote	High

The **A allele** results in a two-fold increase in TNF α transcription, which leads to elevated levels of the circulating TNF α protein. The A allele is also associated with increased risk for obesity, adiposity, dyslipidaemia and insulin resistance, especially when dietary fat intake is high.

Recommendation: A allele

Achieve and maintain a healthy weight and fat percentage, and avoid smoking. Increase intake of n-3 fatty acids, reduce saturated fatty acids and trans fat intake. If the dietary intake of n-3 fatty acids is inadequate, supplementation may be required. Engage in regular, moderate physical activity.

A high sensitivity CRP blood test may give further insight in at risk individuals.

Grimble, R. F. 2001. & Joffe, Y.T. 2010.

IL-1A 4845 G>T or -889 C>T, IL-1B 3954 C>T & -511 A>G, & IL-1RN 2018 C>T

INTERLEUKIN 1

Background

Among the first genes activated by any initiating factor (any challenge to a tissue) are the genes IL-1 and TNF-alpha. Both these molecules are capable of activating each other and are critical components of the inflammatory process. IL-1 has been increasingly implicated as an important leverage point in the inflammatory cascade and so IL-1 expression is key in the pathogenesis of several chronic diseases. The biological activity of IL-1 involves the two agonists – IL-1alpha, which is cell-bound, and IL-1beta, a secreted cytokine, (encoded by IL-1A and IL-1B, respectively), specific IL-1 receptors, and an IL-1 receptor antagonist (encoded by IL-1 RN), which is a negative regulator of the pro-inflammatory response. Certain genetic variations in IL-1A and IL-1B and IL-1 RN lead to a more active inflammatory response, and have been associated with increased risk for a number of chronic diseases.

Gene impact and information

Genotype	Impact
IL-1 positive	High
IL-1 negative	No impact

The combination of IL-1 SNPs of an individual have been linked to differing clinical trajectories of certain diseases, of course also depending on the assaulting stimulus present. IL-1 SNPs, in various combinations, are used in a complex algorithm to determine IL1 status; either being IL-1 positive, or IL-1 negative. In general, individuals with genotypes that match an IL-1 positive result have been associated with increased IL-1 plasma concentrations, as well as increased levels of IL-1 alpha and beta in gingival fluid. IL-1 positive genotypes have been linked with a number of pro-inflammatory chronic diseases, including periodontitis, coronary artery disease, certain autoimmune diseases and cancers.

Recommendation: IL-1 positive

Strategies that have been shown to act directly on IL-1 gene expression, include the intake of curcumin and ginger as well as phytonutrient rich foods such as blueberries and blackberries that contain compounds such as resveratrol, anthocyanins and dehydro-ascorbate. Another nutrient known to inhibit secretion of pro-inflammatory markers is omega 3 fatty acids. Avoiding a high intake of omega 6 fatty acids and eating a diet rich in omega 3 fatty acids, from appropriately-sourced oily fish, is recommended.

Evidence-based recommendations targeting more general anti-inflammatory strategies include weight management, engaging in moderate exercise, and cessation of smoking. Also, following a Mediterranean style diet, has been associated with an improved inflammatory profile.

Kornman, K.S. 2006. & Tsimikas S. et al. 2014.

II-6 -174 G>C

INTERLEUKIN 6

Background

Interleukin 6 is a pro-inflammatory cytokine that plays a crucial role in inflammation and regulates expression of c-reactive-protein (CRP). Low-grade chronic inflammation is associated with obesity and visceral fat deposition, insulin resistance, dyslipidaemia and increased risk for cardiovascular disease.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GC	Heterozygote	Moderate
CC	Homozygote	High

The **C allele** of this functional SNP has been associated with raised IL-6 and CRP concentrations and has been associated with inflammation, obesity, insulin resistance, dyslipidaemia and raised systolic blood pressure. All of these are pronounced in smokers.

Recommendation: C allele

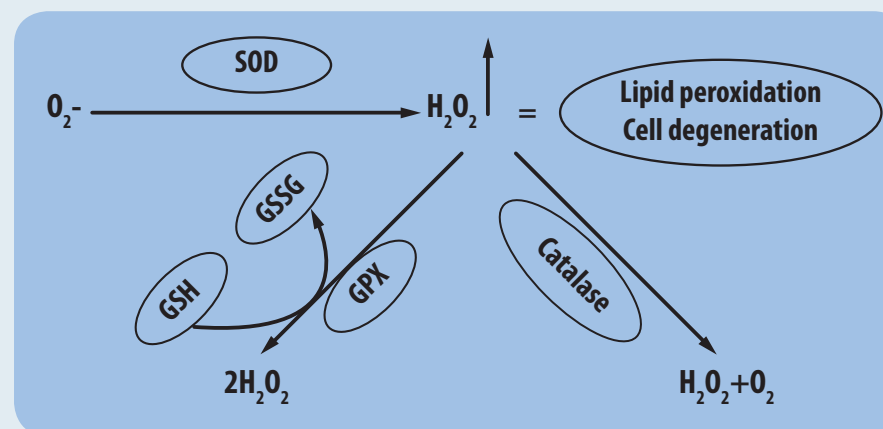
Individuals with the GC and CC genotype should follow a diet to reduce inflammation that includes increasing n-3 fatty acids, decreasing sources saturated fat and trans fat and replacing them with mon-unsaturated fats, moderating omega 6 FA intake, and increasing intake of vegetables and anti-oxidant-rich foods. If dietary intake of n-3 fatty acids is inadequate, supplementation may be required. A healthy weight and avoidance of all smoking is also imperative in managing inflammation.

A high sensitivity CRP blood test may give further insight for at risk individuals.

Joffe, Y.T. et al. 2014. & Razquin C. et al. 2010.

OXIDATIVE STRESS

Free radicals are a normal by-product of the body's energy-generating biochemical processes. They are highly reactive with other molecules, and can damage DNA, proteins and cellular membranes. The balance between oxidation and anti-oxidation is believed to be critical in maintaining healthy biological systems. Dietary anti-oxidants such as vitamin C, vitamin E, carotenoids and polyphenols are free radical scavengers that interact with the free radical to ensure it is no longer a reactive molecule, and play an essential role in many antioxidant mechanisms in living organisms. However, the major role in anti-oxidant defence is fulfilled by the body's own anti-oxidant enzymes.



KEY: superoxide dismutase (SOD), reduced glutathione (GSH), oxidized glutathione (GSSG), glutathione peroxidase (GPX)

eNOS 894 G>T

ENDOTHELIAL NITRIC OXIDE SYNTHASE

Background

eNOS encodes the endothelium-derived nitric oxide synthase enzyme, which catalyzes (or uncouples) nitric oxide, and plays a key role in the regulation of vascular tone and peripheral resistance. It also has vasoprotective effects by suppressing platelet aggregation, leukocyte adhesion and smooth muscle cell proliferation.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GT	Heterozygote	Moderate
TT	Homozygote	High

The **T allele** affects proteolytic cleavage of the enzyme, thereby reducing nitric oxide bio-availability in the blood vessel wall. As a result, it is associated with atherosclerosis, essential hypertension, end stage renal disease and preeclampsia.

Recommendation: T allele

Increase intake of n-3 fatty acids and dietary antioxidant sources. Increase intake of foods such as spinach and beetroot that contain nitrates and are converted naturally in the body to nitric oxide. Avoid all forms of smoke and engage in regular, moderate intensity, physical activity.

Ferguson, J. F. et al. 2010. & Lee, C.R. 2006.

SOD2 -28 C>T

MANGANESE SUPEROXIDE DISMUTASE

Background

The SOD2 enzyme destroys the free radicals that are normally produced within cells and which are damaging to biological systems. Thus the enzyme has important anti-oxidant activity within the cell, especially within the mitochondria.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	High
CT	Heterozygote	Moderate
TT	Homozygote	No Impact

The **T allele** is protective.

There is evidence that people without the variant, i.e. those with the **C allele**, and with a lower consumption of fruits and vegetables, are at increased risk of developing disease, including the risk of developing certain cancers.

Recommendation: C allele

Increase dietary intake of vegetables and fruit, and ensure adequate antioxidant intake from food. Regular, Low to moderate intensity exercise increases expression of this gene. Ensure adequate intake of manganese, the cofactor for SOD2.

Ambrosone, et al. 1999. & Mocchegiani, E. 2014.

GPX1 Pro198Leu (C>T)

GLUTATHIONE PEROXIDASE 1

Background

Glutathione peroxidase 1 (GPx1) is the most abundant of the selenoperoxidases, and one of the most important selenium-dependant antioxidant enzymes. It is ubiquitously expressed in almost all tissues in the body, and is responsible for catalysing the conversion of hydrogen peroxide (H₂O₂) into water (H₂O), as well as reducing fatty acid hydroperoxides and peroxynitrite using glutathione as a substrate, and thus helps to maintain redox balance.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	No impact
CT	Heterozygote	Moderate impact
TT	Homozygote	High impact

The T allele leads to decreased enzyme function, and has been linked to a disturbed anti-oxidative balance. T allele carriers are associated with increased risk for chronic disease, including certain cancers and coronary artery disease especially in the presence of a low fruit and vegetable intake, smoking and high alcohol consumption. There is also evidence that T allele carriers have increased risk of breast cancer with HRT use. Regular brazil nut intake, a rich source of selenium, has been shown to significantly increase the activity of the GPx1 enzyme in C allele carriers. One brazil nut contains approximately 70 mcg of selenium, (providing over 100% RDA). The C allele is therefore more responsive to dietary Se intake.

Recommendation: T allele

Ensure a polyphenol-rich diet with a high intake of vegetables. Include brazil nuts in the diet and other food-rich sources of selenium, such as sardines and turkey. If selenium intake from food is poor, consider supplementation. It is important to moderate alcohol consumption, and to rather drink red wine (due to higher resveratrol levels) as the alcohol of choice. Avoidance of toxin exposure, from heavy metals and pesticides as well as nitrates used as a food preservative, and cessation of smoking should be strongly encouraged. Women carrying the T allele should also be cautious of using HRT. Also, provide adequate intake of glutathione precursors to support glutathione production.

Karunasinghe, et al. 2012. & Meplan et al. 2013.

CAT -262 C>T

CATALASE

Background

The catalase gene encodes the antioxidant enzyme Catalase (CAT), which is most highly expressed in the liver, kidney and erythrocytes. The enzyme is responsible for the rapid conversion of hydrogen peroxide to water and oxygen. It therefore plays a crucial role in redox balance, and decreased CAT activity leads to increased concentrations of hydrogen peroxide, hence increased oxidative stress.

Gene impact and information

Genotype		Diet Impact
TT	Wild type	Moderate
CT	Heterozygote	Mild impact
CC	Homozygote	Beneficial

Decreased CAT activity is associated with diseases related to oxidative stress, including cancer, diabetes and neurodegenerative diseases. The CC genotype has been linked to higher CAT activity, and therefore offers some protection against a redox imbalance.

Recommendation: T allele

Ensure a polyphenol-rich diet with a high intake of vegetables. Decrease dietary and environmental toxin exposure, from pollution, pesticides smoked foods and nitrates used as a food preservative. Cessation of smoking should be strongly encouraged. Women carrying the TT genotype should be cautious, and well informed, before commencing HRT – especially if long-term – in order to avoid the risk of developing breast cancer.

C allele:

Individuals carrying the C allele, especially those with the CC genotype have been associated with a decreased risk of cancer (breast cancer in particular) and better anti-oxidative balance. The protection offered by the C allele is further pronounced in individuals who have a high dietary intake of anti-oxidant and polyphenol rich foods. It is interesting to note that this association was not observed with anti-oxidant supplement intake.

Ahn et al. 2005 & Goth et al. 2012.

BONE HEALTH

Osteoporosis is a complex disease characterized by decreased bone mass, deterioration of bone tissue and increased risk of fractures. Family and twin studies have established a strong genetic contribution to the aetiology of osteoporosis, and 60-70% of the variability in bone mineral mass or bone mineral density (BMD) can be accounted for by genetic variation and variations in diet.

The following categories of contributing genes have been identified: calcium homeostasis, hormonal dysfunction, osteoblast and osteoclast development and regulation, cartilage matrix metabolism and lipoprotein metabolism. Polymorphisms of the Vitamin D receptor have been associated with bone mass in several studies, and there is evidence that this association may be modified by dietary calcium and vitamin D intake.

VDR FokI T>C

VITAMIN D RECEPTOR

Background

Peak bone mass is, to a great extent, genetically determined. The vitamin D receptor (VDR) gene accounts for around 70% of the entire genetic influence on bone density, playing an important role in calcium homeostasis, bone cell growth and differentiation, and intestinal calcium absorption.

Gene impact and information

Genotype		Diet Impact
TT	Wild type	High
TC	Heterozygote	Mild
CC	Homozygote	No Impact

The **T allele** has poorer calcium absorption compared to the C allele. The TT genotype has higher bone turnover and increased bone loss and is associated with a lower BMD and osteoporosis in the lumbar spine.

Recommendation: T allele

Ensure adequate calcium and vitamin D intake and reduce caffeine to less than 300 mg (2-3 cups of coffee) per day. Incorporate load-bearing exercises into the training routine. Increase vigilance for BMD screening. Test for vitamin D status.

Rapuri, P.B. 2001. & Valdivielso, J.M. 2006.

VDR Bsm1 G>A

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
AG	Heterozygote	Mild
AA	Homozygote	High

The **A allele** is associated with reduced BMD in a dose-dependent manner, and predisposes to osteoporosis, especially when calcium intake is low. There is also lower phosphorus re-absorption in the AA genotype when dietary calcium is low, which results in lower calcium absorption and higher rates of hip fracture. Women with the AA genotype have high bone loss when their caffeine intake is more than 300mg/day.

Recommendation: A allele

Ensure adequate calcium and vitamin D intake and reduce caffeine to less than 300 mg (2-3 cups of coffee) per day. Incorporate load-bearing exercises into the training routine. Increase vigilance for BMD screening. Test for vitamin D status.

Rapuri, P.B. 2001. & Valdivielso, J.M. 2006.

VDR Taq1 C>T

Gene impact and information

Genotype		Diet Impact
CC	Wild type	High
CT	Heterozygote	Mild
TT	Homozygote	No Impact

Individuals with the **CC genotype** have higher bone turnover and increased bone loss. This is highest when there is a low calcium intake. Individuals with the CC genotype have higher bone loss when caffeine intake is > 300 mg/d.

Recommendation: CC genotype

Ensure adequate calcium and vitamin D intake and reduce caffeine to less than 300 mg (2-3 cups of coffee) per day. Incorporate load-bearing exercises into the training routine. Increase vigilance for BMD screening. Test for vitamin D status.

Rapuri, P.B. 2001. & Valdivielso, J.M. 2006.

COL1A1 1546 G>T

COLLAGEN 1A1

Background

Type 1 collagen is the major protein of bone, which is formed from two collagen alpha-1 chains and one collagen alpha-2 chain.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GT	Heterozygote	Moderate
TT	Homozygote	High

The **T allele** influences the ratio of collagen alpha chains produced by bone cells, leading to abnormal mineralization of bone and reduced bone strength. Women with the TT genotype are at significantly increased risk of bone loss at the spine. This effect may be nullified by the use of HRT. Individuals with the T allele have increased risk of fracture and greater bone loss when calcium is low.

Recommendation: T allele

Ensure adequate calcium intake and incorporate load-bearing exercises into the exercise routine.

Ralston, S. H. 2002.

INSULIN SENSITIVITY

Insulin resistance syndrome is a term used to describe a combination of illnesses that have a common link – abnormalities in how the body uses insulin to metabolise sugars. These health disorders include: obesity, type 2 diabetes, hypertension, hypercholesterolemia and heart disease.

In insulin resistance, the body's cells have a diminished ability to respond to the action of the insulin hormone, which under normal conditions would remove glucose from the bloodstream by regulating entry into cells. Clustering of type 2 diabetes in certain families points to a strong genetic background for the disease, however environmental factors such as obesity and a sedentary lifestyle are usually required to unmask the genes.

If a number of gene variants in this panel convey moderate to high risk impacts, in combination with other phenotypic and lifestyle risk factors, it may be prudent to test an individual's insulin sensitivity and blood glucose levels.

PPARG Pro12Ala C>G

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR γ

Background

The PPARs are lipid sensing transcription factors that are primarily known for modulating energy metabolism, lipid storage and transport, and inflammation. Peroxisome proliferator-activated receptor-gamma (PPARG) protein is abundantly expressed in fat cells. It is a ligand-activated transcription factor activated by fatty acids, eicosanoids and thiazolidinediones, and plays an important role in the expression of adipocyte-specific genes and the formation of fat cells.

It is involved in the regulation of glucose and lipid metabolism and has been identified as the nuclear receptor for the thiazolidinedione class of insulin-sensitizing drugs.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	Moderate
CG	Heterozygote	Beneficial
GG	Homozygote	Beneficial

The G allele is associated with reduced promoter activation, reduced transcriptional activity and reduced adipocyte differentiation. As a result the G allele has been associated with lower fasting insulin, improved insulin sensitivity and reduced risk of insulin resistance and type 2 diabetes mellitus (T2DM).

The Pro12 Pro genotype (CC) has a 1.25 fold risk for diabetes; and may also predict the conversion from impaired glucose tolerance to T2DM, with a 3 fold increased T2DM risk in the Pro12 homozygotes compared to Ala allele carriers. However, in obese individuals the diabetes risk is almost doubled among the Pro12 allele carriers; therefore, obesity appears to exacerbate the detrimental effect of the PPARG Pro12 allele on insulin sensitivity.

Recommendation: CC genotype

Increase MUFA's and decrease saturated fatty acids. All diet and lifestyle variables that impact insulin sensitivity should also be addressed.

Gouda, H. N. et al. 2010. & Razquin, C., et al. 2009.

TCF7L2 rs7903146 C>T

TRANSCRIPTION FACTOR 7-LIKE 2

Background

TCF7L2 gene encodes a transcription factor that regulates blood glucose homeostasis. This SNP influences both insulin secretion and sensitivity and has been associated with an increased risk of insulin resistance and type 2 diabetes mellitus. TCF7L2 is thought to operate via impaired glucagon-like peptide 1 (GLP-1) secretion, which is stimulated more by fat than by carbohydrate ingestion. GLP-1 may contribute to body weight regulation through appetite, adipose tissue metabolism and insulin signalling.

It is expressed in subcutaneous and visceral fat tissue and a decrease in TCF7L2 expression in adipose tissue could be demonstrated through caloric restriction. T allele carriers have reduced insulinotropic action of GLP-1. Meal ingestion is the primary physiological stimulus for GLP-1 secretion.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	No Impact
CT	Heterozygote	Mild
TT	Homozygote	Moderate

Individuals with the T allele, especially the TT genotype, are more susceptible to insulin resistance and diabetes. T allele carriers are at approximately 1.4-fold increased risk of T2DM, and TT homozygotes present with approximately a 2.0-fold increase in T2DM risk when compared with CC homozygotes. Diet and exercise intervention is very important for T allele carriers to reduce risk of insulin resistance (IR).

Recommendation: T allele

T allele carriers require more long term intervention to manage weight and prevent IR and diabetes.

T allele carriers lose more weight on a low fat, hypo-energetic diet compared to a high fat diet. A low glycaemic load (GL) diet and all interventions to manage insulin resistance are also recommended.

Corella, D. et al. 2013. & Phillips, C. M. 2013.

FTO T>A

FAT MASS AND OBESITY-ASSOCIATED GENE

Background

Fat-mass-and-obesity-associated (FTO) gene is present at high levels in several metabolically active tissues, including, heart, kidney, and adipose tissue, and is most highly expressed in the brain, particularly in the hypothalamus which is concerned with the regulation of arousal, appetite, temperature, autonomic function, and endocrine systems. It has been suggested that the FTO gene plays a role in appetite regulation and that it is associated with energy expenditure, energy intake, and diminished satiety.

Gene impact and information

Genotype		Diet Impact
TT	Wild type	No Impact
TA	Heterozygote	Mild
AA	Homozygote	Moderate

The **A allele** has been associated with higher BMI, body fat percentage and waist circumference, especially in individuals with a sedentary lifestyle. Overweight individuals with the A allele are at increased risk for insulin resistance and diabetes, especially when there is a high fat intake.

Recommendation: A allele

Following a low saturated fat diet, that is higher in lean protein and with adequate sources of polyunsaturated fats (omega 3 FA), and ensuring adequate physical activity levels, will decrease the risk for insulin resistance in A allele carriers.

Steemburgo, T., et al. 2013. & Zheng, Y., et al. 2015.

GLUT2 coded by SLC2A2 Thr110Ile (C>T)

GLUCOSE TRANSPORTER TYPE 2 CODED BY SLC2A2

Background

GLUT2, coded by the SLC2a2 gene, is a member of the facilitative glucose transport protein (GLUT) family and is expressed in the pancreas, liver, small intestine, kidney, and brain. GLUT2 facilitates the first step in glucose induced insulin secretion, with the entry of glucose into the pancreatic β cell. Because of its low affinity for glucose, it has been suggested as a glucose sensor, and is considered to be important in the postprandial state, and is involved in food intake and regulation. GLUT2-null mice fail to control their food intake in response to glucose, suggesting a potential role for this transporter as a glucose sensor in the brain.

Gene impact and information

Genotype		Diet Impact
CC	Wildtype	Low/No Impact
CT	Heterozygote	Mild
TT	Homozygote	Moderate

The T allele is associated with risk of Type 2 diabetes. Individuals with the GLUT2 CT and TT genotype have a higher daily intake of sugars, more so from sweets, such as baked goods, chocolate and sweetened beverages, rather than fruit. Compared with individuals with the Thr/Thr (CC) genotype, carriers of the Ile (T) allele had a significantly higher intake of sugars, suggesting an underlying glucose-sensing mechanism, rather than glucose/insulin levels, that regulates food intake.

Recommendation: T allele

It is important to avoid all high-sugar foods in the diet, especially foods that contain refined carbohydrates. Decrease total carbohydrate intake and include strategies to manage blood glucose levels.

Eny, K.M. 2008. & Marty N. et al. 2007.

FOOD RESPONSIVENESS

Particular nutrients and certain food components in different foodstuffs can affect individuals in different ways. With new research coming to light in this area, specific genes can be tested to give more insight to how an individual might respond to a particular food component. The areas of food responsiveness covered in this panel include: Lactose intolerance, Polyunsaturated Fat (PUFA) metabolism, caffeine sensitivity, and iron overload.

Lactose Intolerance

MCM6 –13910C>T

Background

Adult lactase deficiency is a common condition with a decrease in the ability of the epithelial cells in the small intestine to digest lactose, owing to a physiological decline in the lactase enzyme. After ingestion of milk or other dairy products, Individuals who suffer from this condition may experience abdominal cramps, bloating, distension, flatulence and diarrhoea.

Gene impact and information

SNP	Genotype		Diet Impact
MCM6 –13910C>T	CC	Homozygote	High
	CT	Heterozygote	Mild
	TT	Wildtype	No Impact

The CC genotype is associated with adult hypolactasia in the Caucasian population. Individuals with this genotype should avoid intake of dairy products. The CT and TT genotypes are associated lactase persistence in the Caucasian population.

Recommendation: C allele

Avoid all lactose containing foods and drinks. General tolerance level is at about 12g of lactose per day (1 cup milk).

Swallow, D.M. 2003.

HFE Cys282Tyr (C282Y) HFE His63Asp (H63D)

HEMOCHROMATOSIS

Background

Hereditary hemochromatosis is a genetic disorder in which there is excessive accumulation of iron in the body, leading to iron overload. It is considered to be one of the most common hereditary diseases in populations of Caucasian origin with European Caucasians showing a prevalence of 1:400.

The HFE protein regulates the production of another protein called hepcidin, which is located on the surface of cells, primarily liver and intestinal cells. Hepcidin is considered the "master" iron regulatory hormone. Hepcidin determines how much iron is absorbed from the diet and determines how much is released from storage sites in the body. When the proteins involved in iron sensing and absorption are functioning properly, iron absorption is tightly regulated. On average, the body absorbs about 10 percent of the iron obtained from the diet. In individuals with hereditary hemochromatosis, the daily absorption of iron from the intestines is greater than the amount needed to replace losses. Since the normal body cannot increase iron excretion, the absorbed iron accumulates in the body.

Individuals who carry the genes for hereditary hemochromatosis may have no symptoms or signs and the disease is treatable if detected early. However severe symptoms and signs of iron overload include sexual dysfunction, heart failure, joint pains, liver cirrhosis, diabetes mellitus, fatigue, and hypermelanotic pigmentation.

Depending on genotype and other factors, an individual's iron processing deficiency may not reach the level of formally being diagnosed as hemochromatosis. Hemochromatosis is easily diagnosed through an iron panel of blood tests. If hemochromatosis is diagnosed, it can be easily treated by phlebotomy or regular donation of blood to reduce blood iron levels. A low-iron diet can also help control accumulation of iron.

Gene impact and information

SNP	Genotype	Impact
HFE Cys282Tyr (C282Y) & HFE His63Asp (H63D)	C282C & H63H	No Impact
	C282C & H63D	No Impact
	C282Y & H63H	No Impact
	C282C & D63D	Moderate
	C282Y & H63D	Moderate
	Y282Y & H63H	High

The homozygous mutation resulting in amino acid 282 Cys (C) changed to Tyr (Y) accounts for around 90% of hemochromatosis patients. The HFE 63DD genotype can lead to a mild form of the disease, accounting for another 5% of affected patients. The compound heterozygote for HFE Cys282Tyr (C282Y) and HFE His63Asp (H63D) may also cause the disease. Depending on genotype and other factors, an individual's iron processing deficiency may not reach the level of formally being diagnosed as Hemochromatosis. Hemochromatosis is easily diagnosed through an iron panel of blood tests.

Recommendation:

HFE C282C & D63D, C282Y & H63D, and Y282Y & H63H genotypes

A low-iron diet can help control accumulation of iron. Those affected should avoid vitamin supplements containing iron and also heavy vitamin C and alcohol consumption which can interfere with iron processing.

If Hemochromatosis is diagnosed, it can be easily treated by phlebotomy or regular donation of blood to reduce blood iron levels.

Hansen, E. et al. 2001. & Waalen, J. et al. 2006.

TAS2R38 145 C>G (Pro49Ala), 785 C>T (Ala262Val) & 886 G>A (Val296Ile)

BITTER TASTE

TASTE RECEPTOR TYPE 2 GENE 38

Background

Taste is an important determinant of food acceptance or rejection behaviour, and also enables individuals to distinguish between nutrient-rich food and poisonous or harmful substances. Taste sensitivity has great inter-individual variability and can strongly influence food preferences, nutritional status and health.

Bitter taste is based on an individual's ability to taste the compounds phenylthiocarbamide (PTC) and propylthiouracil (PROP). The bitter taste gene, TAS2R38, is responsible for the sensitivity to the bitter compounds PTC and PROP. Variations in this gene will determine an individual's sensitivity to bitter foods. Of particular relevance is inter-individual variation in perception and preference for various oral stimuli including high-fat/high-energy foods, smoking habits, selection of fruits and vegetables, as well as body composition, plasma anti-oxidant status and colon cancer risk.

The three TAS2R38 SNPs; rs713598 (145 C>G), rs1726866 (785 C>T), rs10246939 (886 G>A), give rise to 3 non-synonymous coding exchanges (Proline49Alanine, Alanine262Valine, and Valine296Isoleucine). These substitutions result in 2 major haplotypes: PAV (Proline, Alanine, Valine), which is the dominant taster variant, and AVI (Alanine, Valine, Isoleucine), which is the recessive non-taster variant.

Gene impact and information

Genotype	Impact
AVI/AVI	No impact: non-taster
PAV/AVI	Moderate impact: medium taster
PAV/PAV	High impact: super-taster

Having a strong sensitivity to taste bitter compounds may impact dietary sugar intake, as observed in the study by Joseph et al. Medium- and super-bitter tasters were also observed to have a lower vegetable intake, especially from cruciferous, and dark green leafy vegetables, thus possibly affecting overall nutritional status of these individuals. The bitter taste variant has been associated with increased BMI and a possible increased risk for colon cancer.

Recommendation: PAV genotype

Medium- and super-bitter tasters have been associated with having a decreased intake of vegetables, especially cruciferous, and dark green leafy vegetables, and a preference for sweet foods and sucrose. Understanding your clients' food choices and taste preferences will give insight to compliance and guide recommendations. Advising on more palatable vegetable options with the use of other ingredients in an effort to lessen the bitter taste, may improve intake.

Recommendation: AVI/AVI genotype

Be aware of inability to taste bitter foods. Bitter taste can often be related to poisonous/harmful substances and so more caution should be taken in this regard. Non-tasters for the bitter taste have been associated with an increased affinity to start and to continue to smoke. Being aware of this from early on may lessen the chance of developing a smoking habit.

Joseph, P. et al. 2014. & Sollai, G. et al. 2017.

ALDH2 rs671 G>A

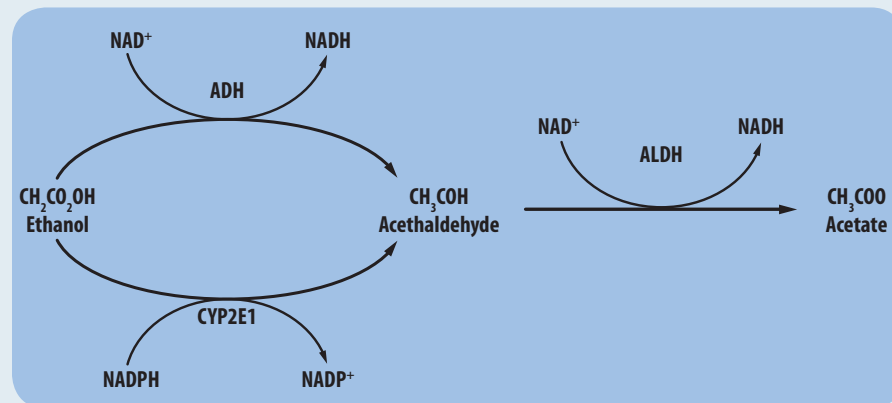
ALCOHOL METABOLISM

ALDEHYDE DEHYDROGENASE-2

Background

Aldehyde dehydrogenase 2 (ALDH2) is an enzyme that is expressed in the liver and is responsible for the detoxification of toxic, carcinogenic aldehydes to acetate. These toxic aldehydes include acetaldehyde – derived from ethanol (alcohol), as well as 4-hydroxynonenal and malondialdehyde – generated by lipid peroxidation. This enzyme therefore plays a key role in the protection from oxidative stress. The SNP determines the activity of the ALDH2 enzyme, and thus blood acetaldehyde concentrations after alcohol consumption.

Pathway of ethanol metabolism in the liver



KEY: ALDH=acetaldehyde dehydrogenase; NAD^+ =nicotinamide adenine dinucleotide; NADH = reduced NAD^+ ; NADP^+ =nicotinamide adenine dinucleotide phosphate; NADPH =reduced NADP^+ ; ADH = alcohol dehydrogenase; CYP2E1 = cytochrome P-450 isoform 2E1.

Gene impact and information

Genotype	Impact
GG	No impact
GA	Moderate impact
AA	High impact

The variant is a G-to-A transition resulting in a glutamate to lysine amino acid substitution at codon 487 in the protein, which inactivates the enzyme. High levels of aldehydes, especially acetaldehyde, in the blood have been shown to interfere with DNA synthesis and repair, and have been associated with increased risk for oxidative stress, cancer and cardiovascular disease. Preliminary studies have also linked the SNP with an increased risk for non-alcoholic fatty liver disease.

This SNP is highly prevalent among the East Asian population, yet extremely rare in the Caucasian and African populations.

Recommendation: A allele

Usually, moderate alcohol consumption (defined as 1 to 2 servings of alcohol per day for women and men respectively) can be recommended for the general population. In individuals who carry the A allele (GA or AA genotype) are advised to completely avoid alcohol. General health promotion in A allele carriers would also be advantageous.

Testing GGT (gamma-glutamyl transferase) blood levels may give further insight for at risk individuals.

Cai, Q. et al. 2015. & Oniki, K. et al. 2016.

PUFA Metabolism

FADS1 rs174537 G>T

Background

Tissue availability of polyunsaturated fatty acids (PUFAs) depends on dietary intake and metabolic turnover. Optimal levels and ratios of PUFAs have a major impact on human health. Some functions include: mediating inflammation, supporting infant growth, neural development, and immune function.

The delta 5 and delta 6 desaturases, encoded by FADS1 and FADS2 genes, are key enzymes in polyunsaturated fatty acid (PUFA) metabolism that catalyze the conversion of linoleic acid (LA) into arachidonic acid (AA) and that of α -linolenic acid (ALA) into eicosapentaenoic acid (EPA). SNPs in the FADS locus have been associated with blood concentrations of long-chain PUFAs as well as with cholesterol concentrations. Based on genetic variation, individuals may require different amounts of dietary PUFAs or LC-PUFAs to achieve comparable biological effects.

Gene impact and information

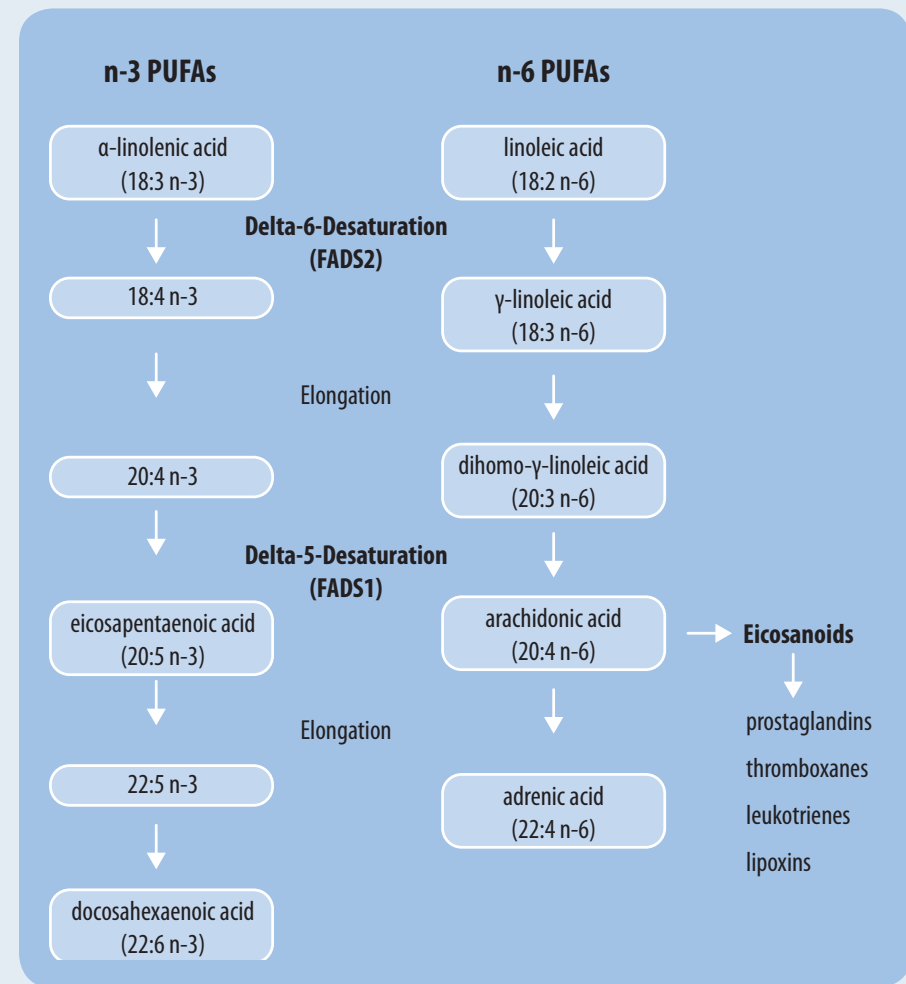
SNP	Genotype	Diet Impact
FADS1 rs174537 G>T	GG	High
	GT	Moderate
	TT	No Impact

The G allele is associated with enhanced conversion of DGLA to AA due to increased enzymatic efficiency and thus appears to be associated with higher levels of AA, systemic inflammation and inflammatory disorders especially in the presence of a modern western diet where LA intake is generally high.

Recommendation: G allele

Decrease pro-inflammatory fat intake generally found in a modern western diet. Ensure adequate intake of EPA and DHA. Consider testing blood fatty acid status in high risk individuals.

Mathias, R.A. et al. 2014.



Caffeine Sensitivity

CYP1A2 A>C

Background

Caffeine is mainly metabolized by the polymorphic cytochrome P450 1A2 (CYP1A2) enzyme. The enzyme is responsible for the demethylation of caffeine into dimethylxanthine metabolites paraxanthine, theobromine, and theophylline.

Gene impact and information

Genotype		Diet Impact
AA	Wildtype	No Impact
AC	Heterozygote	Moderate
CC	Homozygote	High

AA genotype individuals are 'fast' metabolisers of caffeine. Individuals with the C allele are associated with a reduced ability to metabolise caffeine, and may be termed 'slow' caffeine metabolisers. A moderate to high intake of caffeinated beverages, such as coffee, is associated with increased risk of myocardial infarction and a rise in blood pressure. Risk increased with higher intake. It is recommended that these individuals opt for decaffeinated options and decrease total caffeine in the diet.

Recommendation: C allele

Limit caffeinated coffee to not more than 2 cups per day. It would be prudent to avoid all caffeine-containing foods and beverages.

Cornelis, M.C. 2006.

Salt Sensitivity

ACE I/D

Background

ACE codes for the angiotensin-converting enzyme and is part of the renin-angiotensin system, which controls blood pressure by regulating the volume of fluids in the body.

Gene impact and information

SNP	Genotype	Diet Impact
ACE I/D	II	High
	ID	Mild
	DD	No Impact

Studies show that patients with essential hypertension homozygous for the insertion allele of the ACE gene had a significantly higher blood pressure increase with high salt intake compared to DD individuals.

Recommendation: Insertion

Decrease salt intake in II individuals to avoid spikes in blood pressure.

AGT M235T / rs699 T>C

Background

AGT is the gene that encodes for angiotensinogen, which is a precursor to both angiotensin I and angiotensin II. It is the initial component to the renin-angiotensin-aldosterone system (RAAS), the most important regulator of renal sodium transport and the major system involved in the increase in renal sodium transport. This system plays an integral role in regulating blood volume and blood pressure.

Gene impact and information

SNP	Genotype	Diet Impact
AGT M235T / rs699 T>C	CC	High
	TC	Mild
	TT	No Impact

Individuals who carry the C allele are associated with increased risk for hypertension, however incidence of hypertension was found to be significantly lower among these individuals who reduced sodium intake.

Recommendation: C allele

Decrease salt (sodium) intake in individuals who carry the C allele.

Armando, I. et al. 2015. & Meneton, P. et al. 2005.

DNA Diet

Introduction

Genes involved in regulation of energy expenditure, appetite, and fat metabolism, all play an important role in weight regulation. In fact, 40% to 80% of the variance in body weight is due to genetic factors. A prolific amount of new research being published has put forward additional gene variations, giving even more insight into the role of genes in an individual's risk for weight gain and ability to lose weight. This research touched on a number of metabolic processes and variables that contribute to weight gain such as insulin sensitivity, snacking, binge eating, saturated fat intake and carbohydrate intake, and exercise.

This helps to explain why not everyone becomes obese even though people may be exposed to similar environments. Genetics determines an individual's susceptibility to obesity when exposed to an unfavourable environment. It also explores the way in which a person responds to diet and exercise. Knowing more about your client's genetic make-up can go a long way towards personalising and optimising your diet and exercise advice.

DNA DIET is a weight management test that includes well-researched and clinically useful gene variations that impact obesity risk and weight management. The 13 SNPs included in the test have been analysed in order to understand how an individual's genetic profile will impact their response to what we believe to be the three most cutting-edge, scientifically proven, and effective weight loss plans i.e. Low fat, Mediterranean, and Low Carbohydrate. Research suggests that individuals do respond differently to different diets and no ONE diet plan is right for everyone.

By analysing an individual's DNA DIET results we are able to recommend the BEST DIET POSSIBLE for that individual. Of course, the choice of which diet to follow will be based on the clients' diagnosis, personal preferences, diet history, and eating attitudes, as discussed with an accredited practitioner.

DNA DIET will also provide additional insight into the role of carbohydrate, saturated fat and exercise on the ability of an individual to lose weight, allowing you, the practitioner, to further personalise the diet plan to suit your client's needs. This test, we believe, will become an indispensable tool in the hands of trained practitioners.

FABP2 Ala54Thr G>A

FATTY ACID BINDING PROTEIN 2

Background

Fatty acid binding protein 2, encoded by FABP2, is a member of the FABPs; a family of small, highly conserved, cytoplasmic proteins that bind long-chain fatty acids and other hydrophobic ligands and participate in fatty acid uptake, transport, and metabolism. Polymorphisms in the gene result in greater binding of the fatty acids, which are released in the intestine from dietary fat consumption, and in turn results in higher absorption of fat.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GA	Heterozygote	Moderate
AA	Homozygote	Moderate

The Thr54 (A) allele is associated with a 2-fold higher affinity for binding long chain fatty acids. The variant A allele is associated with obesity, elevated BMI, increased abdominal fat, insulin resistance and higher insulin levels, and hypertriglyceridemia.

A allele carriers have greater fat absorption and higher circulating free fatty acids, especially in the presence of a high-saturated fat diet.

Recommendation: A allele

Clinical studies have indicated that these individuals will improve their weight management outcome by reducing saturated fat to less than 7% total energy (TE) and avoiding trans-fats, while increasing mono-unsaturated fats and omega-3 fatty acid sources, and moderating the carbohydrate in their diet.

Marín, C. et al. 2005. & Martinez-Lopez, E. et al. 2013.

PPARG Pro12Ala C>G

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR- γ

Background

The PPARs are lipid sensing transcription factors that are primarily known for modulating energy metabolism, lipid storage and transport, and inflammation. Peroxisome proliferator-activated receptor-gamma (PPARG) protein is abundantly expressed in fat cells.

It is a ligand-activated transcription factor activated by fatty acids, eicosanoids and thiazolidinediones, and plays an important role in the expression of adipocyte-specific genes and the formation of fat cells.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	No Impact
CG	Heterozygote	Moderate
GG	Homozygote	Moderate

The Ala12 (G) allele is associated with impaired transcriptional activity in adipose tissue. The G allele is associated with increased obesity risk in the presence of an obesogenic environment. Energy content and composition of the diet may have a greater effect on BMI, body composition, and metabolic parameters in Ala (G) allele carriers compared to individuals with the CC genotype.

Recommendation: G allele

Focusing on a calorie-restricted diet and increasing physical activity levels in G allele carriers has been associated with improved weight management outcomes. By implementing a diet with a high poly-unsaturated fat:saturated fat ratio, improved results with regards to decreasing VAT was observed.

Lindi, V.I. et al. 2002. & Yao, Y.-s. et al. 2015.

ADRB2 Arg16Gly G>A

β 2 ADRENERGIC RECEPTOR

Background

ADRB2 is a cell membrane-spanning beta-adrenergic receptor that interacts with epinephrine (adrenaline), a hormone and neurotransmitter. This ADRB2 receptor protein is 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 defence against obesity.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	Moderate
GA	Heterozygote	Moderate
AA	Homozygote	No impact

Compared to AA individuals, individuals with the G allele have been associated with obesity, and G allele carriers are more likely to gain and regain weight and lose weight more slowly. These carriers are less able to mobilize fat stores in response to exercise.

In these individuals it is important to emphasize diet for weight management as exercise may be less effective.

Recommendation: G allele

Adjust weight management goals and weight loss targets. It is also recommended that these individuals focus on increasing physical activity and emphasise the use of diet for weight management.

Ellsworth, D. et al. 2002. & Lagou, V. et al. 2011.

ADRB2 Gln27Glu C>G

β2 ADRENERGIC RECEPTOR

Background

ADRB2 is a cell membrane-spanning beta-adrenergic receptor that interacts with epinephrine (adrenaline), a hormone and neurotransmitter. This ADRB2 receptor protein is 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 defence against obesity.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	No impact
CG	Heterozygote	Moderate
GG	Homozygote	High

The G allele has been associated with increased BMI and fat mass. Carriers of the G allele are less able to use fat stores as a source of fuel during exercise compared to the CC genotype.

Individuals with the G allele have been shown to have a greater risk of obesity and elevated insulin levels when carbohydrate intake is greater than 49% of total energy. Decreasing intake of CHO has been shown to reduce insulin levels and is beneficial in weight management.

Recommendation: G allele

Weight management may be ineffective without appropriate dietary intervention. Reduce total carbohydrate intake to improve weight management results. It is also recommended that these individuals focus on increasing physical activity.

Martínez, J. A. et al. 2003. & Martínez, J. A., & Milagro, F. I. 2015.

ADRB3 Trp64Arg T>C

β3 ADRENERGIC RECEPTOR

Background

The beta-3 adrenergic receptor (ADRB3) protein is expressed primarily in visceral adipose tissue, more specifically in brown and white adipose tissue, where it is involved in the regulation of lipolysis (break down of fat stores) and thermogenesis.

The Trp64Arg polymorphism in the gene results in reduced lipolysis in response to a specific agonist in cells carrying the Arg64 allele. The variant is associated with increased abdominal obesity and a tendency to have a lower metabolic rate.

Gene impact and information

Genotype		Exercise Impact
TT	Wild type	No Impact
TC	Heterozygote	Moderate
CC	Homozygote	High

The **C allele** is associated with increased BMI and weight loss resistance. These individuals do not break down abdominal fat in response to exercise as expected. As a result they may have a slower energy metabolism and are less responsive to the beneficial effects of exercise for weight management. Clinical studies have shown an increased risk of obesity for sedentary C allele carriers. The higher risk of obesity among carriers of the C allele may be diminished by above average levels of vigorous physical activity.

Recommendation: C allele

For improved weight management, a very high intensity exercise program would be recommended for individuals with this genotype.

Csernus, K. et al. 2015. & Marti, A. et al. 2002.

APOA2 -265 T>C

APOLIPOPROTEIN A2

Background

Apolipoprotein A2 (APOA2), the second most abundant apolipoprotein in HDL, plays a complex and relatively undefined role in lipoprotein metabolism, insulin resistance, obesity and atherosclerosis susceptibility.

Gene impact and information

Genotype		Diet Impact
TT	Wild type	No Impact
TC	Heterozygote	Mild
CC	Homozygote	Moderate

The **CC genotype** is associated with obesity and increased food consumption, especially total fat and saturated fat intake is high (>22g per day), the CC genotype is strongly associated with increased BMI, a higher fat percentage and obesity risk. This diet-gene interaction may also play a role in insulin resistance and diabetes.

Recommendation: CC genotype

In CC individuals, attention should be paid to reducing total dietary saturated fat intake.

Corella, D. et al. 2009. & Zaki, M. E. et al. 2013.

TCF7L2 rs7903146 C>T

TRANSCRIPTION FACTOR 7-LIKE 2

Background

TCF7L2 gene encodes a transcription factor that regulates blood glucose homeostasis. This SNP influences both insulin secretion and sensitivity and has been associated with an increased risk of insulin resistance and type 2 diabetes mellitus.

TCF7L2 is thought to operate via impaired glucagon-like peptide 1 (GLP-1) secretion, which is stimulated more by fat than by carbohydrate ingestion. GLP-1 may contribute to body weight regulation through appetite, adipose tissue metabolism and insulin signalling.

It is expressed in subcutaneous and visceral fat tissue and a decrease in TCF7L2 expression in adipose tissue can be demonstrated through caloric restriction. T allele carriers have reduced insulinotropic action of GLP-1. Meal ingestion is the primary physiological stimulus for GLP-1 secretion.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	No Impact
CT	Heterozygote	Moderate
TT	Homozygote	High

Individuals with the **T allele**, and more so the **TT genotype**, are more susceptible to insulin resistance and diabetes, and experience less weight loss than the CC genotype. Long-term diet and exercise intervention is very important for T allele carriers to prevent weight regain, insulin resistance and diabetes.

T allele carriers displayed lower reduction in BMI and total body fat, especially when fat intake is high.

Recommendation: T allele

Long term diet and lifestyle intervention to manage weight and blood sugar is required. A low glycaemic load diet and all interventions to manage insulin are recommended.

Corella, D. et al. 2013. & Phillips, C. M. 2013.

FTO rs9939609 T>A

FAT MASS AND OBESITY-ASSOCIATED GENE

Background

FTO gene is present at high levels in several metabolically active tissues, including, heart, kidney, and adipose tissue. It is most highly expressed in the brain, particularly in the hypothalamus, which is concerned with the regulation of arousal, appetite, temperature, autonomic function, and endocrine systems. It has been suggested that the FTO gene plays a role in appetite regulation and that it is associated with eating behaviour, energy expenditure, energy intake, and diminished satiety.

Gene impact and information

Genotype		Diet Impact
TT	Wild type	No Impact
TA	Heterozygote	Moderate
AA	Homozygote	High

The **A allele** has been associated with higher BMI, higher body fat percentage and higher waist circumference, especially in individuals with a sedentary lifestyle. Overweight individuals with the A allele are at increased risk for insulin resistance and diabetes, especially when there is a high fat intake.

A allele carriers are reported to consume more fat and total energy, and experience less satiety, especially in children.

Low physical activity and a diet high in fat accentuates the susceptibility to obesity in individuals with the A allele.

Recommendation: A allele

Following a low saturated fat diet, that is higher in lean protein and with adequate sources of polyunsaturated fats, and ensuring adequate physical activity levels, will decrease the risk for obesity in A allele carriers.

Grau, K. et al. 2009. & Rankinen, T. et al. 2010.

CLOCK 3111 T>C

CIRCADIAN LOCOMOTOR OUTPUT CYCLES KAPUT

CLOCK is an essential element of the positive regulatory arm in the human biological clock, and is involved in metabolic regulation. The CLOCK 3111 T>C variation leads to a change in protein levels, and has an effect on circadian rhythms and sleep duration.

Gene impact and information

Genotype		Diet Impact
TT	Wild type	No Impact
TC	Heterozygote	Mild
CC	Homozygote	Moderate

Individuals with the C allele are associated with obesity susceptibility, and a higher kilojoule intake. C allele carriers lose less weight, and are more weight loss resistant compared to the the TT genotype when on a weight management program. In addition, those with the C allele have reduced sleep, report morning fatigue and eat breakfast later, and show an evening preference for activities.

Sleep reduction, changes in ghrelin values, alterations of eating behaviours and evening preference could affect weight and weight loss among CLOCK 3111C carriers.

Recommendation: C allele

Incorporate a healthy, regular daily eating and sleeping routine. Avoid high carbohydrate foods before sleep, and at bedtime ensure the bedroom is completely dark, with all electronic and electric devices turned off. Emphasis should be placed on regular physical activity.

Garaulet, M. et al. 2010. & Zanquetta, M. M. et al. 2010.

APOA5 –1131 T>C

APOLIPOPROTEIN A5

Background

Apolipoprotein A5 encodes a protein that plays an important role in regulating plasma triglyceride levels. Evidence of APOA5-diet interactions has been previously demonstrated for plasma lipoprotein metabolism as well as BMI.

Gene impact and information

Genotype		Diet Impact
TT	Wild type	Moderate
TC	Heterozygote	Mild
CC	Homozygote	No Impact

The **T allele** has been associated with greater weight, and reduced weight loss, especially when on a high fat, high saturated fat diet. A high total fat intake increases obesity risk in T allele carriers, but there is good responsiveness to dietary intervention.

The **C allele** has been previously associated with increased triglyceride concentrations, but is also associated with greater weight loss. MUFA intake has a positive effect on BMI and TG levels in individuals with the C allele.

Recommendation: TT genotype

Decrease total fat intake in individuals with the TT genotype to improve weight management outcomes.

Corella et al., 2009

PLIN 11482 G>A

PERILIPIN

Background

Perilipin is a class of protein-coating lipid droplets found in adipocytes and steroidogenic cells and play a critical role in energy and glucose metabolism. Perilipin knockout mice are lean and resistant to diet-induced obesity. PLIN1 limits lipase access to stored triglycerides during the fed state or facilitates hormonally stimulated lipolysis during the fasted state.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GA	Heterozygote	Moderate
AA	Homozygote	High

The **A allele** is associated with greater obesity risk, weight loss resistance and greater decrease in lipid oxidation rate compared to the GG genotype. PLIN 11482 A allele carriers were resistant to weight loss, suggesting that this polymorphism may predict outcome of body weight reduction strategies based on low-energy diets.

Recommendation: A allele

Set realistic weight loss goals and ensure regular follow-up and support for sustained weight management. A higher complex carbohydrate and low saturated fat diet is protective against obesity in individuals with the A allele. Avoid all refined carbohydrate.

Martínez, J. A., & Milagro, F. I. 2015. & Smith, C. E., & Ordovás, J. M. 2012.

MC4R T>C

MELANOCORTIN-4 RECEPTOR

Background

Melanocortin-4 Receptor gene is expressed, amongst other places, in the hypothalamus, which is a crucial centre for energy balance and regulation of food intake. MC4R is a strong obesity candidate gene significantly associated with energy intake and expenditure.

Gene impact and information

Genotype		Diet Impact
TT	Wild type	No Impact
TC	Heterozygote	Moderate
CC	Homozygote	High

The C allele leads to reduced MC4R receptor function, and is associated with obesity, higher BMI and waist circumference, and hyperinsulinemia. The risk C allele is associated with reduced satiety, greater total fat intake, overeating and greater total energy intake. Individuals with the C allele tend to show greater snacking behaviour, hunger, and eating large amounts of food, especially in children.

Recommendation: C allele

Provide a personalised, calorie-restricted eating plan that includes mindful eating strategies and methods to promote satiety. Plan for 5 meals through the day (3 main meals with 2 snacks) and avoid skipping meals, increase fibre intake, opt for low GI carbohydrate sources, and include protein and/or fat at each meal for improved blood sugar levels.

Jaaskelainen, A. et al. 2013. & Xi, B. et al. 2012.

TNFA -308 G>A

TUMOUR NECROSIS FACTOR- α

Background

Tumour necrosis factor- α (TNF α), a pro-inflammatory cytokine secreted by both macrophages and adipocytes, has been shown to alter whole body glucose homeostasis and has been implicated in the development of obesity, obesity-related insulin resistance and dyslipidaemia.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GA	Heterozygote	Mild
AA	Homozygote	Moderate

The **A allele** results in a 2-fold increase of TNF- α transcription and subsequent increase in TNF α production. It is also associated with low-grade chronic inflammation, obesity risk and fat mass, obesity-related insulin resistance and altered serum lipid concentrations, especially with increased fat intake.

Recommendation: A allele

The priority is to manage inflammation by achieving and maintaining a healthy weight, incorporating a low GL diet, an anti-inflammatory diet and ensuring adequate n-3 fatty acids.

Joffe, Y. et al., 2010

DRD2 (Taq1A)

D2 DOPAMINE RECEPTOR GENE

Background

Midbrain dopamine circuits may play an important role in both addiction and normal eating behaviour as they are involved in reward processing, particularly dopaminergic signalling via dopamine receptor 2 (DRD2).

This gene has commonly been linked to alcoholism, other addictive behaviours and overeating.

Gene impact and information

SNP	Genotype		Diet Impact
DRD2 rs1800497	TT	Homozygote	High
	TC	Heterozygote	Moderate
	CC	Wildtype	No Impact

The **T allele** is associated with obesity, co-morbid substance use disorders, cravings and reward-seeking. Low DRD2 density is associated with the rs1800497 T allele, putatively making individuals less sensitive to the activation of dopamine-based reward circuitry and rendering them more likely to overeat. Consumption of sweet or high-fat foods increases dopamine concentrations, activating the dopaminergic reward pathways of the brain. Greater sugar consumption and increased BMI is associated with the variant.

Recommendation: T allele

Avoid all high-sugar foods and reduce total carbohydrate intake. Include methods for mindful eating and identify triggers for binge eating.

Epstein, L. H. et al. 2007. & Heber, D., & Carpenter, C. L. 2011.

TAS1R2 Ile191Val

TASTE RECEPTOR, TYPE 1, MEMBER 2

Background

Twin studies indicated genetics explained 33% of the variance in intensity ratings for a supra-threshold sweet solution and 53% variance in frequency use of sweet foods.

Taste is an important determinant of food consumption, and genetic variations in the sweet taste receptor subunit TAS1R2 may contribute to inter-individual variations in sugar consumption. The diverse tissue distribution of TAS1R2 gene affects food intake beyond the detection of sweet taste on the tongue and palate. These tissues include the gastrointestinal tract, pancreas and hypothalamus, tissues known for regulating metabolic and energy homeostasis.

Gene impact and information

SNP	Genotype		Diet Impact
TAS1R2 Ile191Val	AA	Wildtype	High
	AG	Heterozygote	Moderate
	GG	Homozygote	No Impact

Compared with individuals homozygous for the A allele (Ile191Ile), there is a lower consumption of sugars in the G (Val) allele.

Recommendation: A allele

It is important to decrease intake of high-carbohydrate containing foods, especially high sugar foods.

Eny, K.M. 2010.

GLUT2 coded by SLC2A2 Thr110Ile

GLUCOSE TRANSPORTER TYPE 2 (GLUT2) CODED BY THE SLC2A2 Thr110Ile

Background

GLUT2, coded by the SLC2A2 gene, is a member of the facilitative glucose transport protein (GLUT) family and is expressed in the pancreas, liver, small intestine, kidney, and brain. GLUT2 facilitates the first step in glucose induced insulin secretion, with the entry of glucose into the pancreatic β cell. Because of its low affinity for glucose, it has been suggested as a glucose sensor, and is considered to be important in the postprandial state, and is involved in food intake and regulation. GLUT2-null mice fail to control their food intake in response to glucose, suggesting a potential role for this transporter as a glucose sensor in the brain.

Gene impact and information

Genotype		Diet Impact
CC	Wildtype	No Impact
CT	Heterozygote	Mild
TT	Homozygote	Moderate

Individuals with the TT genotype have a higher daily intake of sugars, more so from sweets, such as baked goods, chocolate and sweetened beverages, rather than fruit. Compared with individuals with the CC genotype, carriers of the T allele had a significantly higher intake of sugars, suggesting an underlying glucose-sensing mechanism, rather than glucose/insulin levels, that regulates food intake. The T variant is also associated with risk of Type 2 diabetes.

Recommendation: T allele

It is important to avoid all high-sugar foods in the diet, especially foods that contain refined sugars. Decrease total carbohydrate intake and include strategies to manage blood glucose levels.

Eny, K.M. 2008. & Marty N. et al. 2007.

ADIPOQ -11391 G>A

ADIPOQ -11391 G>A

Background

ADIPOQ encodes adiponectin, which is expressed in adipose tissue and is an effective insulin sensitiser that regulates energy homeostasis and glucose tolerance thus promoting lipid oxidation in the muscle and liver. Obese subjects tend to have lower circulating levels of adiponectin, and hypoadiponectinemia seems to play an important causal role in development of insulin resistance, type 2 diabetes, and the metabolic syndrome.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	Moderate impact
GA	Heterozygote	Mild impact
AA	Homozygote	Moderate impact

Individuals with the A allele tend to have higher levels of adiponectin and have been associated with lower BMI, as well as other improved obesity parameters such as low waist:hip ratio and higher insulin sensitivity. Studies have shown an association with the A allele and a lower BMI, but only when mono-unsaturated fatty acid (MUFA) intake comprised more than 13% of total energy (TE) intake. As a general trend, the G allele carriers tend to have lower adiponectin levels and higher risk for increased BMI.

Recommendation: A allele

To maintain a healthy BMI, individuals with the A allele should consume a diet high in MUFA (>13% TE) and focus on increased intake of omega 3 fatty acids.

Recommendation: GG genotype

Individuals with the GG genotype are able to manage their BMI when following a low-calorie diet. Continued follow-up and support is recommended for these individuals in order to control risk factors associated with the metabolic syndrome.

Enns, E. et al. 2011. & Goyenechea, et al. 2009.

UCP1 -3826 A>G, UCP2 -866 G>A, UCP3 -55 C>T

UNCOUPLING PROTEIN 1, 2 AND 3

Background

The uncoupling proteins 1, 2 and 3 belong to the family of mitochondrial transporter proteins that allow protons to re-enter the mitochondrial matrix without phosphorylating ADP (adenosine diphosphate), thus uncoupling the connection between oxidative metabolism and energy production, releasing energy as heat. The uncoupling proteins may therefore play an important role in energy homeostasis. These proteins share structural similarities, but are expressed in different tissues.

UCP1 is mainly expressed in brown adipose tissue and has a central function in thermogenesis and energy homeostasis, as well as reducing the production of reactive oxygen species in the mitochondria. Under certain pathological conditions, such as hyperglycemia, UCP1 has been found to also be expressed in skeletal muscle, white adipose tissue, retinal cells and pancreatic beta cells.

UCP2 is expressed across a wide range of tissue and cell types, and UCP3 is mainly restricted to expression in skeletal muscle cells. Both UCP2 and 3 are important in regulating free fatty acid metabolism.

SNPs in the UCP genes may contribute to variation in energy balance, and the possible development of obesity as well as risk for metabolic syndrome and type 2 diabetes.

Gene impact & information: UCP1 -3826 A>G

Genotype		Diet Impact
AA	Wild type	No impact
AG	Heterozygote	Mild impact
GG	Homozygote	Moderate impact

The UCP1 -3826G allele leads to decreased mRNA expression and is associated with an increased risk for higher BMI, and to gain weight more easily. G allele carrier may also exhibit a stronger resistance to a hypocaloric diet.

Recommendation: G allele

Due to the possible weight loss resistance that G allele individuals may face, it is important to set realistic weight management goals. It is important to focus on interventions that will improve the individual's ability to burn fat. An example of an

intervention is to include more high intensity exercise, or interval training, in the weight management plan. Regular follow up and practitioner support will also help to improve weight management outcomes.

Gene impact & information: UCP2 -866G>A

Genotype		Diet Impact
GG	Wild type	No impact
GA	Heterozygote	No impact
AA	Homozygote	Beneficial

Compared to the G allele, the UCP2 -866A allele is associated with higher rates of transcription from the UCP2 promotor, and thus increased activity. A recent meta-analysis showed that the A allele may be protective in the development of obesity, and may be more responsive to the weight loss effects of a calorie-restricted diet.

Recommendation: G allele

The A allele may offer protection against a higher BMI. It has been shown that by following a hypocaloric diet, UCP2 and UCP3 expression can be significantly increased in adipose and skeletal muscle cells. G allele carriers would therefore benefit from restricting total energy intake and engaging in regular physical activity.

Gene impact & information: UCP3 -55CT

Genotype		Diet Impact
CC	Wild type	No impact
CT	Heterozygote	Beneficial
TT	Homozygote	Beneficial

Compared to the C allele, the UCP3 -55T allele has been associated with greater transcriptional activity, and higher resting energy expenditure (REE) and thus a decreased risk for obesity.

Recommendation: C allele

The T allele offers protection against a higher BMI. It has been shown that by following a hypocaloric diet, UCP2 and UCP3 expression can be significantly increased in adipose and skeletal muscle cells. C allele carriers would therefore benefit from restricting total energy intake.

Csernus, K. et al. 2015., Nicoletti, C. et al. 2016. & Salopuro, T. et al. 2009

DNA Oestrogen

Introduction

Oestrogen hormones affect the growth, differentiation and function of a number of target tissues. Improving oestrogen metabolism is of benefit to women who suffer from oestrogen-dominant conditions such as endometriosis, premenstrual syndrome and uterine fibroid tumours, or where there is a family history of breast, uterine or ovarian cancer.

The importance of both oestrogen and progesterone in breast cancer development is well established. However, considerable inter-individual variability has been observed in carcinogen metabolism, metabolism of steroid hormones, and phase I and phase II detoxification.

Variations in genes involved in these biological processes help identify a sub-population of women with higher lifetime exposure to oestrogens, oestrogen metabolites and other carcinogens. Understanding an individual's genetic variability will allow for targeted diet, lifestyle and hormone intervention.

The Nordic DNALysis Oestrogen Metabolism and Detoxification test includes 12 gene variants involved in oestrogen biosynthesis, oestrogen metabolism, and phase I and phase II detoxification. The results provide unique information to guide personalised diet, lifestyle, hormone and nutraceutical recommendations.

CYP1A1 Ile462Val A>G and CYP1A1 Msp1 6235 T>C

CYTOCHROME P450 1A1

Background

The CYP1A1 gene encodes a phase I cytochrome P450 enzyme that converts environmental procarcinogens such as polycyclic aromatic hydrocarbons (PAHs) and aromatic amines to reactive intermediates having carcinogenic effects. In addition, CYP1A1 is involved in the oxidative metabolism of oestrogens, which may play a critical role in the aetiology of breast and prostate cancer. The CYP1A1 enzyme catalyses the 2-hydroxylation of oestradiol (E1 and E2) in several extra hepatic tissues including breast tissue. It is also involved in activating cigarette smoke, diet and environmental pollutants, and producing carcinogens.

Gene impact and information

Ile462Val A>G polymorphism			Msp 1 T>C polymorphism		
Genotype		Diet Impact	Genotype		Diet Impact
AA	Wild type	No Impact	TT	Wild type	No Impact
AG	Heterozygote	Moderate	TC	Heterozygote	Moderate
GG	Homozygote	High	CC	Homozygote	High

Ile462Val A>G polymorphism

An A to G substitution leads to an amino acid substitution (ile to val) of its protein. The association between this SNP and cancer has been well documented.

The **GG genotype** is associated with increased enzyme activity resulting in increased rates of carcinogen activation and subsequently DNA damage.

Msp1 T>C polymorphism

The variant **allele C** is associated with increased enzyme activity resulting in elevated levels of activated metabolites and DNA damage, and is associated with increased production of catechol oestrogens and oestrogen quinones in breast tissue.

Recommendation: C and G alleles

Reduce exposure to dietary and environmental procarcinogens i.e. PAHs, aromatic amines, nitrates and smoking. Also use diet, and supplements, to optimise phase II detoxification.

Kadluba F., 2003

CYP17A 34 T>C

CYTOCHROME P450 17A1

Background

The cytochrome P450 proteins are mono-oxygenases that catalyse many reactions involved in drug metabolism and synthesis of cholesterol, steroids, and other lipids.

CYP17A mediates both steroid 17 α -hydroxylase and 17,20-lyase activities, and catalyses a rate-limiting step in ovarian and adrenal biosynthesis leading to the precursor, dehydroepiandrosterone (DHEA).

Gene impact and information

Genotype		Diet Impact
TT	Wild type	No Impact
TC	Heterozygote	Moderate
CC	Homozygote	Moderate

The **C allele** increases enzyme activity, thereby increasing the amount of bioavailable oestrogen. For individuals with the C allele beneficial modulation of oestrogen metabolism can be accomplished through dietary and lifestyle modifications.

Recommendation: C allele

Increase insoluble fibre, avoid refined carbohydrates, increase phytoestrogens, achieve and maintain ideal weight, and increase exercise.

Kadluba F., 2003

CYP1B1 1294 C>G

CYTOCHROME P450 1B1

Background

CYP1B1 enzymes catalyses the 4-hydroxylation of oestradiol, and it also activates many polycyclic aromatic hydrocarbons (PAHs) and aryl amines.

Gene impact and information

Genotype		Diet Impact
CC	Wild type	No Impact
CG	Heterozygote	Moderate
GG	Homozygote	High

This SNP has been found to have the most profound impact on the catalytic properties of CYP1B1, with the 4-hydroxylase activity of the **G allele** displaying three-fold higher activity compared to the C allele.

Recommendation: G allele

Reduce exposure to dietary and environmental procarcinogens i.e. PAHs, aromatic amines, nitrates and smoking. Also use diet and supplements to optimise phase II detoxification.

Kadluba F., 2003

COMT 472 G>A

CATECHOL-O-METHYLTRANSFERASE

Background

COMT catalyses the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. This O-methylation results in one of the major degradative pathways of the catecholamine transmitters. In addition to its role in the metabolism of endogenous substances, COMT is important in the metabolism of catechol drugs used in the treatment of hypertension, asthma, and Parkinson disease.

Soluble catechol-O-methyltransferase (S-COMT) helps control the levels of certain hormones and is involved in methylation and inactivation of catechol oestrogens. Accumulation of oestrogen metabolites appears to confer increased risk of breast cancer via oxidative DNA damage.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GA	Heterozygote	Moderate
AA	Homozygote	High

The **A allele** is associated with a 3-4 fold reduction in the methylation activity of the COMT enzyme.

For A allele carriers beneficial modulation of oestrogen metabolism can be accomplished through dietary and lifestyle modifications.

Recommendation: A allele

Achieve and maintain an ideal weight and include moderate intensity exercise. Increase intake of insoluble fibre and avoid refined carbohydrates. Also increase intake of phytoestrogens and include nutrients such as cruciferous vegetables that support preferred oestrogen pathways.

Cerne, J. et al., 2005

SULT1A1 638 G>A

SULFOTRANSFERASE 1A1

Background

Sulfotransferase 1A1 (SULT1A1) is involved in the inactivation of oestrogens and bio-activation of heterocyclic amines and polycyclic aromatic hydrocarbons.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GA	Heterozygote	Moderate
AA	Homozygote	Moderate

A allele carriers have a substantially lower activity of this enzyme. Women who carry the A allele have been associated with a greater risk for post-menopausal breast cancer, which is increased with higher BMI, and longer exposure to endogenous hormones.

For individuals with the A allele, beneficial modulation of oestrogen metabolism can be accomplished through dietary and lifestyle modifications.

Recommendation: A allele

Increase insoluble fibre, avoid refined carbohydrates and increase phytoestrogens. Also increase exercise and achieve and maintain ideal weight.

Yang, Gong et. al., 2005

Factor V 1691 G>A

FACTOR V

Background

Factor V functions as a cofactor to allow factor Xa to activate the enzyme thrombin, which in turn cleaves fibrinogen to form fibrin, polymerizing it to form the dense meshwork that makes up the majority of a clot. Activated protein C (aPC) is a natural anticoagulant which limits the extent of clotting by cleaving and degrading factor V.

Factor V Leiden is an inherited defect associated with risk of venous thrombosis. It is characterised by a poor anticoagulant response to aPC and an increased risk for venous thromboembolism (VTE). Deep venous thrombosis (DVT) is the most common VTE, especially in legs, however VTE can also occur in other parts of the body.

Gene impact and information

Genotype		Impact
GG	Wild type	No Impact
GA	Heterozygote	Moderate
AA	Homozygote	High

GA alleles have a slightly increased risk for venous thrombosis.

AA genotypes have much greater thrombotic risk, particularly in veins. They have aPC-resistant Factor V, which affects cleavage by aPC, thus aPC cannot effectively degrade the cofactor, resulting in increased thrombin, then excess fibrin, and finally excess clotting.

Women with Factor V Leiden have a substantially increased risk of clotting in the form of pulmonary embolism and deep vein thrombosis when on oestrogen-containing contraceptive pills or hormone replacement therapy, as well as during pregnancy. Women also have a slightly increased risk of developing preeclampsia, giving birth to low birth weight babies, miscarriage and stillbirths due to clotting in the placenta, umbilical cord or the foetus – foetal clotting may depend on whether the baby has inherited the gene.

Recommendation: A allele

Consider other forms of contraception to oestrogen-containing contraceptive pills and other treatment methods to oestrogen hormone replacement therapy.

DNA Oestrogen also includes the SNPs:

- GSTM1 I/D
- GSTT1 I/D
- NQO1
- MnSOD -28 C>T
- MTHFR 677 C>T

For information on these SNPs, please refer to the DNA Health section.

DNA Sport

Introduction

Over the past 3 decades, multiple genetic association studies have identified genes that correlate to athletic performance, training responsiveness, injury-related traits and the ability to recover from exercise training. It is now a contemporary notion that exercise regimes can be tailored to the genetics of an individual. The interest in genetics within the field of sport and exercise lies with talent spotting and understanding individual training potential. Although there are ethical considerations around the topic of talent searching, genetic testing can allow individual athletes (and coaches) to learn more about optimal training patterns in order to gain as much as possible from training sessions and exploit potential advantages, as well as identify weaknesses that need to be worked on. Genetic insight can also be used to make appropriate nutrition choices in an attempt to prevent injury as well as optimise recovery time in order to perform at one's best.

It is important to highlight that athletic success is not just about genetic predisposition. The athletic phenotype is highly complex and can be considered a multi-factorial manifestation of many genetic and environmental factors. Success with regards to athletic performance therefore results firstly from personalising a sport-specific training strategy that optimises your genetic potential, and secondly choosing the right lifestyle, nutritional and environmental interactions to optimally express your inherited genes.

The DNA Sport test is divided into three categories relating to sport performance:

1. **Injury Susceptibility:** examines genes involved in the structural integrity and remodelling of soft tissues. Certain polymorphisms are implicated in increased risk for tendon and ligament injuries.
2. **Recovery:** includes genes involved in inflammation and oxidative stress which may impact the need for focussed nutritional support as well as extended recovery times between training sessions and exercise repetitions.
3. **Power and Endurance Performance:** this section examines genes involved in various physiological process that impact sporting potential such as blood flow and respiration, energy mobilisation and fuel metabolism, as well as looking at musculoskeletal properties. Each of the genes tested impact an athlete's response to a training modality.

COL1A1 Sp1 G>T

COLLAGEN 1 ALPHA-1

Background

The COL1A1 gene encodes the major protein component of type I collagen; the main fibrillar collagen found in most connective tissues, including tendons, ligaments and cartilage. This gene encodes the alpha-1 chain of type I collagen which combines with the alpha 2 chain of type I collagen to produce type I pro-collagen. These triple-stranded, rope-like pro-collagen molecules arrange themselves into long, thin fibrils that cross-link with one another, forming very strong mature type I collagen fibres.

Gene impact and information

Genotype		Injury Impact
GG	Wild type	High
GT	Heterozygote	Moderate
TT	Homozygote	No Impact

The G to T substitution on the Sp1 site of COL1A1 has been associated with increased gene expression and collagen production, which has been speculated to increase the tensile strength of tendons and ligaments. The T allele appears to be protective against ligament injuries in sport, even though it is a risk factor for osteoporosis. Weight-bearing exercises are important for strengthening bone in these cases.

GG genotypes are at an increased risk for tendon and ligament injuries. Regular participation in sports, particularly those which involve a sudden deceleration or change in direction, in combination with this genotype, may place an individual at up to ten times greater risk of ACL rupture.

Recommendation: G allele

Base strength conditioning, as well as resistance and flexibility training are important components of injury prevention for at risk individuals.

Khoschnau S, 2008

Collins M, 2009

COL5A1 BstUI RFLP C>T

COLLAGEN 5 ALPHA-1

Background

The COL5A1 gene encodes for the alpha-1 chain of type V collagen, one of the minor fibrillar collagens. Type V collagen molecules intercalate into the tendon and ligament fibrils where, along with other proteins, they play an important role in regulating fibrillogenesis and modulating fibre diameter within the connective tissues. Type V collagen appears to regulate the assembly of heterotypic fibres, which are composed of both type I and type V collagen.

Gene impact and information

Genotype		Injury Impact
CC	Wild type	No Impact
CT	Heterozygote	Moderate
TT	Homozygote	High

The C>T polymorphism in the COL5A1 gene has been associated with an increased risk of soft tissue injuries including Achilles tendinopathy and ACL rupture.

The CC genotype is associated with greater range of motion and considered to be protective against injury. The CC genotype has also been associated with a decreased risk of ACL injury in females.

The T allele is associated with increased injury susceptibility; however the TT genotype has been associated with better running economy and therefore faster running times.

Recommendation: T allele

Conditioning and flexibility training are important parts of injury prevention for at risk individuals.

*Posthumus M, 2009
September AV, 2009*

GDF5 5' UTR C>T

GROWTH DIFFERENTIATION FACTOR 5

Background

The GDF5 gene encodes for Growth Differentiation Factor 5, a protein that is closely related to the bone morphogenetic protein (BMP) family and is a member of the transforming growth factor beta (TGF-beta) superfamily. GDF5 is expressed in the developing central nervous system and plays a role in the development and healing of skeletal, joint and soft tissues. GDF5 has therefore been shown to influence susceptibility to injuries and the ability to recover from them.

Gene impact and information

Genotype		Injury Impact
CC	Wild type	No Impact
CT	Heterozygote	Moderate
TT	Homozygote	High

The TT genotype of GDF5 correlates with reduced expression of the GDF5 protein in human soft tissue. In line with this observation, the major T allele is thought to raise the risk of sports and training injuries, specifically Achilles tendon pathology by up to 2-fold.

The T allele has also been linked to osteoarthritis (critically of the knee) and to an increased risk of congenital dislocation of the hip.

Recommendation: T allele

Resistance and flexibility training are important components of injury prevention for at risk individuals.

Posthumus M, 2010

IL-6 -174 G>C

INTERLEUKIN 6

Background

IL-6 is a cytokine secreted by T cells and macrophages, which stimulates an immune response to strenuous exercise, leading to inflammation in the muscle and fatty tissue. IL-6 is also known as a myokine (muscle cytokine) and regulates the expression of the gene encoding CRP. The inflammatory response of an athlete is affected by the intensity and duration of exercise training - the inevitable muscle damage results in a repair process mediated by inflammatory cytokines such as IL-6. Overtraining syndrome (OTS) has been hypothesised to be caused by excess cytokine release during exercise, resulting in a chronic inflammatory state.

Gene impact and information

Genotype		Injury & Recovery Impact
GG	Wild type	No Impact
GC	Heterozygote	Moderate
CC	Homozygote	High

The GG genotype has been linked to power performance due to the hypothesized improved muscle repair after eccentric exercise.

The C allele has been linked to increased IL-6 and CRP production in muscle cells in response to exercise, which may induce more pronounced fatigue due to excess inflammation and prolong recovery times. Higher IL-6 levels are also associated with lower VO2max, which may affect aerobic capacity. The C allele has been linked to increases in the muscle damage marker, creatine kinase, following exercise.

Recommendation: C allele

Insure adequate recovery time between training sessions. Focus on an anti-inflammatory diet and avoid pro-inflammatory foods, taking into account other inflammatory markers.

Yamin C, 2008

Ruiz JR, 2010

IL-6R Asp358Ala A>C

INTERLEUKIN 6 RECEPTOR

Background

The interleukin 6 receptor (IL-6R) is a type I cytokine receptor made up of a protein complex consisting of an IL-6 receptor subunit (IL-6R) and a signal transducer (gp130). The IL-6R gene specifically encodes this IL-6R subunit, which in-turn influences IL-6 cytokine action. Proteolytic cleavage of the membrane-bound IL-6R protein leads to the generation of a soluble form of the IL-6R (sIL-6R), which is able to bind to IL-6. The resulting IL-6/sIL-6R complex is also capable of binding to gp130 and inducing intracellular signalling, increasing the biological activity and half-life of IL-6. The resulting IL-6-induced inflammatory response has been linked to fatigue during exercise, the ability to recover from training sessions and potentially the risk of overtraining. Regular exercise reduces baseline long-term inflammatory biomarkers, but single high-intensity exercise sessions will acutely increase local inflammation.

Gene impact and information

Genotype		Recovery Impact
AA	Wild type	No Impact
AC	Heterozygote	Moderate
CC	Homozygote	High

An A to C SNP on the IL-6R gene has been shown to have an effect on sIL-6R and consequently IL-6 levels.

Subjects with the C allele may have higher levels of sIL-6R and IL-6, thereby increasing the acute inflammatory effects of exercise.

Recommendation: C allele

These individuals are generally advised to increase their recovery time between training bouts and training sessions, increase anti-inflammatory nutrition support and check their inflammatory biomarkers if they phenotypically struggle with recovery.

Rafiq S, 2007

CRP 219 G>A

C-REACTIVE PROTEIN

Background

C-reactive protein (CRP) is an acute-phase protein, which rises in response to inflammation in the body: interleukin-6 (IL-6) and other inflammatory cytokines trigger the synthesis of CRP and fibrinogen by the liver. Its physiological role is to bind phosphocholine, which is expressed on the surface of dead or dying cells, in order to activate the complement system which is part of the innate immune system. CRP is used as a biomarker for acute or chronic inflammation. Regular exercise and favourable dietary habits can reduce baseline long-term inflammatory biomarkers (such as CRP), whereas single high-intensity exercise sessions will acutely increase local inflammation.

Gene impact and information

Genotype		Recovery Impact
GG	Wild type	High
GA	Heterozygote	Moderate
AA	Homozygote	No Impact

The G allele is associated with raised CRP levels. Higher circulating levels of IL-6, CRP and fibrinogen may be associated with lower VO2max levels.

Studies showed that AA homozygotes have significantly lower CRP levels than G allele carriers. CRP levels decrease significantly with 24 weeks of exercise training and following a low-fat diet (although GG genotypes still had the highest CRP levels). The A allele has also been associated with endurance performance.

Recommendation: G allele

Focus on anti-inflammatory nutrition and avoid pro-inflammatory foods.

Obisesan TO, 2004

TNFA -308 G>A

TUMOUR NECROSIS FACTOR ALPHA

Background

TNFA encodes the pro-inflammatory cytokine, tumour necrosis factor alpha. It is produced chiefly by activated macrophages and is a member of a group of cytokines that stimulate the acute phase reaction. The primary role of TNF is in the regulation of immune cells, and it is able to induce fever, apoptotic cell death, sepsis (through IL-1 and IL-6 production) and inflammation, as well as inhibit tumour growth and viral replication. Like other inflammatory cytokines, TNF levels increase during and after intensive exercise.

Gene impact and information

Genotype		Recovery Impact
GG	Wild type	No Impact
GA	Heterozygote	Moderate
AA	Homozygote	High

The minor A allele has been shown to cause 2-fold greater levels of TNFA transcription compared to the G form. The A allele is therefore associated with increased circulating TNF levels. An A allele carrier, with greater TNF levels, may experience increased levels of fatigue and poorer recovery times.

Recommendation: A allele

Accommodate extended recovery times. Polyunsaturated fatty acids (n-3 PUFA), glutamine, arginine, S-amino acids and nucleotides can be included in a nutrition program taking into account inflammatory phenotype. Diet is more effective than exercise in reducing CRP.

Moldoveanu AI, 2000

Lakka HM, 2006

SOD2 Val16Ala -28 C>T

SUPEROXIDE DISMUTASE 2

Background

The SOD2 gene encodes manganese superoxide dismutase, which is a potent free radical scavenger within the cell, especially the mitochondria. The SOD2 enzyme converts superoxide free radicals to hydrogen peroxide. The mitochondrion is commonly referred to as the powerhouse of the cell and is therefore the site of many oxidative reactions during energy production leading to the generation of free radicals. There is evidence that oxidation within the cell contributes to muscular fatigue and extreme exercise can cause increased lipid peroxidation and depleted levels of vitamin E. Long-term moderate- and low-intensity training can increase base levels of SOD2, whereas short-term bursts of intense activity will increase oxidative stress.

Gene impact and information

Genotype		Recovery Impact
CC	Wild type	High
CT	Heterozygote	Moderate
TT	Homozygote	No Impact

All types of strenuous exercise increase muscle damage, inflammation and oxidative stress. The SOD2 C allele has however been associated with higher oxidative stress biomarkers and people with this genotype who consume low levels of fruit and vegetables are at increased risk of developing long-term disease.

Recommendation: C allele

Oxidative stress in C allele individuals can be reduced with a diet rich in antioxidants from fruit and vegetables. Long term regular low- and moderate-intensity exercise can also lead to increased levels of SOD2 and other anti-oxidant enzymes.

Ambrosone CB, 1999

Bastaki M, 2006

eNOS Asp298Glu 984 G>T

ENDOTHELIAL NITRIC OXIDE SYNTHASE

Background

The endothelium-derived nitric oxide (NO) plays a key role in the regulation of vascular tone and peripheral resistance. It also has vasoprotective effects by suppressing platelet aggregation, leukocyte adhesion and smooth muscle cell proliferation. Decreased activity of this enzyme has been associated with an increase in free radicals.

Gene impact and information

Genotype		Recovery Impact
GG	Wild type	No Impact
GT	Heterozygote	Moderate
TT	Homozygote	High

The T allele affects proteolytic cleavage of the enzyme, thereby reducing nitric oxide bio-availability in the blood vessel wall. As a result, it is associated with atherosclerosis, essential hypertension, end stage renal disease and preeclampsia, due to an increase in the presence of free radicals, damaging to tissues. These individuals are likely to experience delayed recovery times from strenuous exercise.

Recommendation: T allele

Individuals with the T-allele should ensure adequate intake of n-3 fatty acids as well as antioxidant and nitric oxide rich foods.

Ferguson JF, 2010

AGT Met238Thr T>C

ANGIOTENSINOGEN

Background

The protein encoded by this gene, angiotensinogen, is expressed in the liver and is cleaved by the enzyme renin in response to lowered blood pressure. It is an essential component of the renin-angiotensin system (RAS), a potent regulator of blood pressure, body fluid and electrolyte homeostasis.

Plasma angiotensinogen levels are increased by corticosteroids, oestrogen, thyroid hormone, and angiotensin II. Angiotensinogen is a precursor of angiotensin, which causes vasoconstriction, increased blood pressure, and release of aldosterone from the adrenal cortex.

Gene impact and information

Genotype		Power Impact
TT	Wild type	No Impact
TC	Heterozygote	No Impact
CC	Homozygote	Moderate

The CC genotype of the AGT Met235Thr polymorphism is associated with power sports performance.

Recommendation: CC genotype

Emphasize strength and power training. Monitor heart rate and blood pressure (BP) during strenuous exercise in at risk individuals.

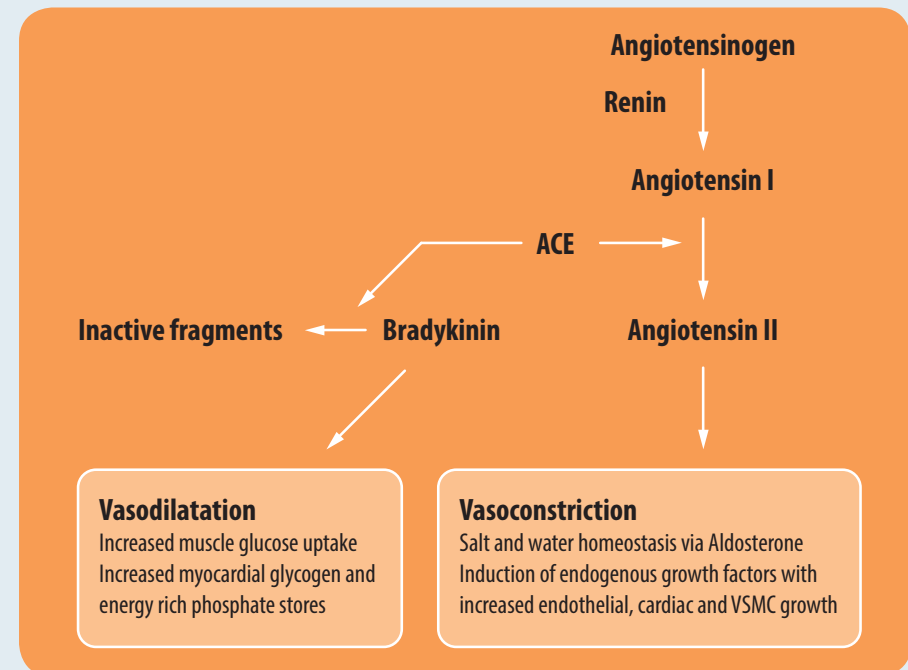
Gomez-Gallego F, 2009

ACE Insertion/Deletion

ANGIOTENSIN 1-CONVERTING ENZYME

Background

The ACE I/D polymorphism is strongly associated with circulating angiotensin 1-converting enzyme levels and is related to an individual's physical performance. ACE is a key enzyme in blood pressure regulation. It is responsible for the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor of the renin-angiotensin system; it can also inactivate bradykinin, a vasodilator of the kallikrein-kinin system.



Gene impact and information

Genotype		Power Impact	Endurance Impact
I/I	Wild type	No Impact	High
I/D	Heterozygote	Moderate	Moderate
D/D	Homozygote	High	No Impact

ACE Insertion/Deletion continued:

Recommendation: II genotype

Increased muscle efficiency can be achieved with aerobic type exercise or low level repetitive weight training. These individuals will cope less well with anaerobic, strength type exercises, such as heavy weights. As II individuals may be more comfortable with aerobic exercises, modulate routines accordingly e.g. when weight training, start with lighter weights and build up gradually, perhaps do more repetitions with lighter weights. Exercise may be better directed towards muscle efficiency rather than muscle strength.

Recommendation: ID genotype

There is an intermediate balance between power and endurance. The I allele is linked to increased muscle efficiency with aerobic type exercise or low level repetitive weight training and the D allele is associated with an advantage for strength and power training. The ACE D allele is also associated with increased left ventricular growth in response to training. D allele carriers should monitor cardio parameters such as blood pressure and heart rate - avoid excessive training at maximal heart rate. Serious athletes should monitor left ventricular growth regularly. D allele carriers are also prone to increased fat deposition, especially visceral fat, in the absence of exercise – therefore motivation for exercise is important.

Recommendation: DD genotype

DD individuals are better at strength exercises, rather than endurance, and may have difficulty if trying to train specifically to improve muscle efficiency (taking into account other genetic variations). There is enhanced muscle growth with weight bearing exercise in DD carriers. The ACE D allele is associated with increased left ventricular growth in response to training, especially in DD athletes after long periods of training. Individuals may get better results from power type exercise and be less successful at endurance sports - take into consideration in training routines. Aerobic training is important but condition expectations. D allele carriers should monitor cardio parameters such as blood pressure and heart rate - avoid excessive training at maximal heart rate. Serious athletes should regularly monitor left ventricular growth. D allele carriers are also prone to increased fat deposition, especially visceral fat, in the absence of exercise – therefore motivation for exercise is important.

Jones A, 2002

Di Mauro M, 2010

Nicklas BJ, 2010

BDKRB2 Rpt sequence exon 1 C>T

BRADYKININ RECEPTOR B2

Background

Bradykinin is an endothelial dependent vasodilator that acts via the Bradykinin B2 receptor. The B2 receptor forms a complex with angiotensin I converting enzyme (ACE), believed to play a role in the cross-talk between the renin-angiotensin and the kinin-kallikrein systems.

Gene impact and information

Genotype		Endurance Impact
CC	Wild type	No Impact
CT	Heterozygote	Moderate
TT	Homozygote	High

Recommendation: C allele

The C allele is associated with increased thirst and fluid loss, which could make it a handicap for endurance sports. Monitor fluid loss as these individuals may need to drink more during exercises.

Recommendation: T allele

The T allele is associated with increased Bradykinin B2 mRNA expression, which is associated with an increase in the efficiency of muscular contraction (i.e. the amount of energy used per unit of power output). Training focus should include endurance exercise in these individuals.

Bray MS, 2009

Tsianos GI, 2010

VEGF -634 C>G

VASCULAR ENDOTHELIAL GROWTH FACTOR

Background

VEGF is an endothelial cell proliferator involved in angiogenesis (blood vessel growth) to match the needs of the active tissue. VEGF levels therefore affect peripheral circulation and capillary blood flow, increasing oxygenation to the muscles and impacting VO2max. Muscle VEGF levels can increase up to 4-fold in response to training.

Gene impact and information

Genotype		Power Impact	Endurance Impact
CC	Wild type	Moderate	High
CG	Heterozygote	No Impact	No Impact
GG	Homozygote	No Impact	No Impact

The CC genotype of the VEGF gene is associated with higher VEGF levels and increased VO2max at baseline and in response to training. No differences have been reported in muscle strength gain between genotypes, which suggests that the higher VEGF producers (CC genotype) experience an increase in muscle efficiency with no change in muscular strength.

Recommendation: CC genotype

Incorporate all types of training (muscle efficiency and muscle strength). Visible improvements in VO2max should aid motivation.

The GG genotype has lower VEGF levels, which is poorer for muscle efficiency, and possibly poorer for muscle growth. Guide appropriate expectations for training induced improvements (taking into account full genetic profile). Look for improvements in other areas beyond muscle characteristics (body composition, glucose, inflammation, etc.).

Recommendation: G allele

Experiment with training strategies designed to increase blood flow and capillary growth to overcome the SNP "weakness" – monitor results carefully, some trial and error is required to determine the best routines.

Prior SJ, 2006

Ahmetov II, 2009

NRF2 A>G

NUCLEAR RESPIRATORY FACTOR 2

Background

The NRF2 gene encodes the NRF2 protein that improves respiratory capacity and increases the rate of ATP ("the unit of energy") production during exercise. It is important in the induction of mitochondrial biogenesis and also regulates several genes that encode mitochondrial proteins: these include cytochrome C and TFAM. NRF2 also regulates heme biosynthesis.

Gene impact and information

Genotype		Endurance Impact
AA	Wild type	No Impact
AG	Heterozygote	High
GG	Homozygote	High

The very rare G allele of the NRF2 gene is associated with greater improvements in VO2max with an endurance training programme: around 50 to 60% better results. The AA genotype however makes up approximately 98% of the population.

Recommendation: G allele

Individuals with the G allele should put emphasis on endurance training to maximise VO2 max potential.

Eynon N, 2009

PPARGC1A Gly482Ser G>A

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA CO-ACTIVATOR-1

Background

PPARGC1A (otherwise known as PGC-1α) is a co-activator of PPAR-gamma and other nuclear hormone receptors and plays an essential role in energy homeostasis. It is involved in mitochondrial biogenesis, fatty acid oxidation, adipocyte differentiation, glucose utilisation, thermogenesis, angiogenesis and muscle fibre type conversion towards type I fibres. It is expressed in tissues with high energy demands and is therefore abundant in mitochondria and is consequently associated with endurance performance. It appears that the activation of PPARGC1A may mediate the initial phase of the exercise-induced adaptive increases in muscle mitochondria. Additionally, the subsequent increase in the PPARGC1A protein sustains and enhances the increase in mitochondrial biogenesis that is associated with exercise training.

Gene impact and information

Genotype		Endurance Impact
GG	Wild type	High
GA	Heterozygote	No Impact
AA	Homozygote	No Impact

The serine allele (A allele) is associated with lower levels of PPARGC1A and consequently reduced aerobic improvements with exercise training when compared to the glycine allele (G allele). Following 9 months of training the A allele was linked to less aerobic improvements in comparison to the G allele. AA individuals also had a lower VO₂max (therefore endurance capacity) than GG individuals. Furthermore, the A allele was found to be less frequent among endurance athletes. PPARGC1A GG genotypes were more frequently found in elite endurance athletes compared to sprinters and control subjects.

Recommendation: GG genotype

GG individuals should focus on including endurance-style training in their program.

Eynon N, 2010

PPARA Intron7 G>C

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-ALPHA

Background

PPAR-alpha is a transcription factor and a major regulator of lipid and glucose metabolism in the liver, skeletal muscle and heart. It is also involved in energy homeostasis. PPAR-alpha is activated under nutrient-deficient conditions and is necessary for the process of ketogenesis, a key adaptive response to conditions of low carbohydrate availability. Activation of PPAR-alpha promotes uptake, utilisation, and catabolism of fatty acids by up regulation of genes involved in fatty acid transport and peroxisomal and mitochondrial fatty acid metabolism. Endurance training increases the use of non-plasma fatty acids and may enhance skeletal muscle oxidative capacity by influencing PPARA gene expression.

Gene impact and information

Genotype		Power Impact	Endurance Impact
GG	Wild type	No Impact	High
GC	Heterozygote	Moderate	Moderate
CC	Homozygote	High	No Impact

The PPARA G allele is associated with endurance performance and type I muscle fibre specialisation. For example, G allele frequencies have been shown to be higher in endurance-orientated compared to power-orientated athletes and GG homozygotes are thought to have significantly higher percentages of slow twitch fibres compared to CC homozygotes.

The PPARA C allele has been associated with greater power in sports, as well as left ventricular growth with training.

Recommendation: G allele

Emphasise endurance sports/training.

Recommendation: C allele

Emphasise power sports/training.

Ahmetov II, 2006

Ahmetov II, 2007

ADRB2

BETA 2 ADRENERGIC RECEPTOR

Background

The ADRB2 gene encodes for Beta 2 Adrenergic receptors, which play a part in the regulation of cardiac, pulmonary, vascular and endocrine functions, and the central nervous system. Adrenaline, predominantly via the Beta 2 adrenergic receptors, plays a major role in maintaining blood glucose levels by promoting glycogenolysis during prolonged exercise.

ADRB2 Arg16Gly A>G

A polymorphism between arginine and glycine in position 16 of the ADRB2 gene has been associated with altered vasodilator responses to catecholamines during stress, and so modulates the pressor response (increasing cardiac output), as driven by the sympathetic nervous system.

Gene impact and information

Genotype		Endurance Impact
AA	Wild type	High
AG	Heterozygote	Moderate
GG	Homozygote	No Impact

Arg16 (A allele) carriers have a better VO₂max at baseline and in response to training. Arg16Arg (AA) genotypes had faster marathon running times compared to Gly (G allele) carriers and the A allele was also associated with lower blood pressure at rest, during and after exercise.

Recommendation: A allele

Individuals with the A allele should focus on endurance training, which is good for VO₂max efficiency.

G alleles seem to have lower VO₂max. They maintain bronchodilation for longer after exercise and have good forearm blood flow and vasodilation. G alleles may be better at a pressor response in the face of increased peripheral vasodilation. Thus, they have better blood flow, but higher heart rate. GG genotypes tend not to burn fat with exercise as effectively as those with the AA genotype.

Recommendation: GG genotype

Vary types of exercise to determine which are more effective. Allow for the possibility of needing more rest between exercises and monitor heart rate. For fat loss, increase exercise intensity, and focus on diet composition.

ADRB2 Gln27Glu C>G

A polymorphism between glutamine and glutamate at position 27 of the gene has been associated with endurance performance and the ability to lose weight as a result of an exercise programme.

Gene impact and information

Genotype		Endurance Impact
CC	Wild type	High
CG	Heterozygote	Moderate
GG	Homozygote	No Impact

Gln27 (C allele) carriers show good VO₂max/efficiency and endurance potential. Exercise is particularly effective for burning fat.

Recommendation: C allele

Emphasise endurance training.

Individuals with the Glu27Glu (GG) genotype have a lower VO₂max. Lipolysis and fat oxidation during an exercise test also appeared to be blunted in the GG group.

Recommendation: GG genotype

Vary exercise intensities to try and stimulate lipolysis and fat oxidation.

Wolfarth B, 2007

Sarpeshkar V, 2010

TRHR T>G

THYROTROPIN RELEASING HORMONE RECEPTOR

Background

The TRHR gene encodes the Thyrotropin-releasing hormone (TRH) receptor. TRH is a hormone that stimulates the release of thyroid-stimulating hormone (TSH) and prolactin from the anterior pituitary. TSH in turn stimulates the release of Thyroxine (T4) and Triiodothyronine (T3) from the thyroid gland. T3 and T4 increase metabolic rate, help catecholamines to mobilise fuels during exercise and are involved in growth..

Gene impact and information

Genotype		Power Impact
CC	Wild type	No Impact
CT	Heterozygote	No Impact
TT	Homozygote	High

The TT genotype is significantly associated with increased lean body mass compared to the CC genotype. These individuals have favourable increases in lean body mass and therefore strength and power advantages.

Recommendation: TT genotype

Emphasise strength and power training.

Lui XG, 2009

Roth SM, 2011

CYP1A2 -163 C>A

CYTOCHROME P450 1A2

Background

Caffeine is a central nervous system and metabolic stimulant that is used to reduce physical fatigue. In athletics, moderate doses of caffeine have been known to improve both sprint and endurance performance. Cytochrome P450 1A2 (CYP1A2) is one of the main enzymes that catalyses the oxidation of caffeine in humans.

Gene impact and information

Genotype		Impact
AA	Wild type	Moderate
CA	Heterozygote	High
CC	Homozygote	High

The C allele of CYP1A2 is associated with a reduced ability to metabolise caffeine. These individuals are at increased risk for heart disease and should monitor caffeine intake.

Recommendation: C allele

C allele carriers may need to take in caffeine a while before the start of a race/event in order to gain from the effects.

Individuals with the AA genotype are able to metabolise caffeine at a fast rate. They have also been noted to experience a greater ergogenic effect with caffeine ingestion in comparison to C allele carriers.

Recommendation: AA genotype

AA individuals are advised to take in caffeine less than an hour before a race in order to benefit from any effects. Depending on how long a race is, AA individuals could take in caffeine during the race as well.

Womack CJ, 2012

ACTN3 577 R/X

ALPHA-ACTININ 3

Background

Alpha-actinins are a family of actin-binding proteins that maintain the cytoskeleton. The ACTN3 gene encodes alpha-actinin 3, which is only present in type II (fast twitch) muscle fibres and also has a low expression in brain tissue. Alpha-actinins are found at the Z-line of the muscle where they anchor actin filaments and help to maintain the structure of the sarcomere. Alpha-actinins also interact with a signalling factor that plays a role in the specialisation of muscle fibre type, diameter and metabolism.

Gene impact and information

Genotype		Power Impact	Endurance Impact
RR	Wild type	High	No Impact
RX	Heterozygote	Moderate	No Impact
XX	Homozygote	No Impact	Moderate

The RR genotype has an advantage for strength, sprint and power activities, especially in females. Muscle efficiency improvements should be as normal, but muscle growth may be enhanced. Including more power-type exercises is advised.

Recommendation: RR genotype

Emphasise strength and power exercises.

The RX genotype is tipped towards power potential.

Recommendation: RX genotype

Balance power and endurance exercise, with slightly more emphasis on power.

The XX genotype has a minor association with endurance potential.

Recommendation: XX genotype

Balance power and endurance exercise, with slightly more emphasis on endurance.

Yang N, 2003
Roth SM, 2008

VDR Taq1 T>C

VITAMIN D RECEPTOR

Background

The VDR gene encodes the nuclear hormone receptor for vitamin D3 and is expressed by cells in most organs. VDR activation in the intestines, bones, kidneys and parathyroid glands leads to the maintenance of calcium and phosphorus levels in the blood and bone. VDR is also involved in cell proliferation and affects the immune system, organ maintenance and even lipolysis and insulin secretion. Stress hormones such as cortisol are known to decrease the expression of VDR.

Gene impact and information

Genotype		Power Impact
TT	Wild type	No Impact
TC	Heterozygote	No Impact
CC	Homozygote	Moderate

The Taq1 CC homozygotes have shown to have better baseline strength and muscle torque in various muscles tested. This genotype favours strength gains with training. The CC genotypes have also been shown to have higher fasting glucose and insulin levels when physical activity was low, but this was responsive to training adaptations. These individuals also tend to have decreased bone mineral density when calcium intake is inadequate and caffeine intake exceeds 300mg.

Recommendation: CC genotype

Focus on strength training and bone-loading exercises. Ensure adequate calcium intake and reduce caffeine intake to under 300 mg/d.

Bozsodi A, 2016

DNA Single SNPs

Introduction

Although the bulk of Nordic DNALysis SNP tests are grouped into convenient panels for the ease of use by practitioners, additional SNPs are now also available as either stand-alone tests or in combination with the other panels.

These single SNPs are slightly more 'high penetrance' in nature in that the outcome of testing can be diagnostic e.g. Factor V Leiden, or can assist in deciding the most appropriate intervention for treatment or management.

DIO2 Rs225014 T>C

TYPE II IODOTHYRONINE DEIODINASE (D2)

Background

Three iodothyronine deiodinase enzymes are responsible for the activation and deactivation of thyroid hormones and for the conversion of thyroxine (T4), via the removal of an iodine residue, to the active or inactive form of triiodothyronine (T3).

D2 is the only enzyme able to convert T4 to T3 in the brain and is likely to play a key role in determining the brain's ability to respond to circulating T4 levels, thus a common variation in D2 activity may represent the best available marker of intracellular T3 levels in the brain.

Despite titration of T4 replacement to adequate serum levels of thyroid hormone and normalisation of TSH in patients diagnosed with hypothyroidism, a significant number of patients still report on-going symptoms.

Gene impact and information

Genotype		Impact
TT	Wild type	No Impact
TC	Heterozygote	Moderate
CC	Homozygote	High

The **TT genotype** appears to have normal enzyme function and thus individuals presenting with hypothyroidism should be managed effectively with T4 monotherapy.

The **C allele** is indicated to have an effect on ubiquitination, thus impairing its ability to increase its activity with low T4 levels. This reduces the ability to maintain homeostasis and increases dependence on serum T3 as a source of T3 in the brain. The C allele may also predict both poorer psychological well-being on T4 monotherapy and improved response to combination T4/T3 therapy. The CC genotype is also linked to increased risk of osteoarthritis.

Recommendation: C allele

Combined T4/T3 therapy is likely to be the best choice of thyroid replacement therapy. Ensure adequate nutrition for bone health.

NAT2 rs1495741 G>A

ARYLAMINE N-ACETYLTRANSFERASE 2

Background

N-Acetylation is a phase II conjugation reaction mediated by the N-acetyltransferase (NAT) enzymes. By their influence in three distinct coenzyme-A dependant pathways, these enzymes both activate and deactivate arylamines and arylhydrazines drugs and carcinogens, which includes drugs, caffeine, cigarette chemicals and xenobiotics

The NAT2 gene encodes NAT2 enzymes. Polymorphisms in this gene are responsible for dividing people into rapid, intermediate, and slow acetylators based on a normal or faster than normal addition of an acetyl group to these toxins.

Drugs metabolised by NAT2 include isoniazid, sulfadimidine, hydralazine, dapsone, procaine amide, sulfapyridine and nitrazepam.

Gene impact and information

Genotype		Diet Impact
GG	Wild type	No Impact
GA	Heterozygote	No Impact
AA	Homozygote	Moderate

AA genotypes are slow acetylators. In general they have higher rates of certain types of cancer, such as bladder cancer, and are more susceptible to side effects from chemicals metabolised by NAT2 enzymes than AG and GG genotype. Also, tuberculosis patients with the AA genotype have a significantly increased susceptibility to anti-tuberculosis drug-induced liver injury, compared to AG and GG genotypes.

Recommendation: AA genotype

Avoid caffeine, smoking, xenobiotics, aromatic amines. Consider alternative medication to drugs metabolised by NAT2.

Gluten Intolerance / Coeliac disease risk HLA DQ2/DQ8

HUMAN LEUKOCYTE ANTIGEN

Background

Coeliac disease (CD) is a common, autoimmune disorder affecting about 1% of the population, in which the small intestine is damaged in response to a severe gluten intolerance. The classical symptoms of CD include gastrointestinal-related symptoms such as diarrhea, steatorrhea and weight loss due to malabsorption. Approximately 50% of CD patients present extra-intestinal or atypical symptoms, such as anemia, osteoporosis, dermatitis herpetiformis, neurological problems and dental enamel hypoplasia.

Specific Human Leukocyte Antigen (HLA) alleles represent the major genetic predisposition. The most important genes associated with susceptibility to coeliac disease are HLA DQ2 and HLA DQ8. A positive HLA test is indicative of genetic susceptibility but does not necessarily mean the disease will develop.

Gene impact and information

SNP	Genotype	Diet Impact
HLA DQ2/DQ8	DQ2	High
	DQ8	High
	DQ2/DQ8	High
	DQ2 / DQ8 negative	Low/No Impact

Individuals carrying the **HLA DQ2 and DQ8** genotypes have a significantly greater chance of developing coeliac disease when on a diet high in gluten. The long term consequences of untreated CD are related to chronic systemic inflammation, poor nutrition and malabsorption of nutrients. This is not a diagnosis of coeliac disease, but coeliac disease cannot be excluded. While 30% of the population carry one or both of these genes, only 1 in 30 of these people (approximately) will develop coeliac disease.

Recommendation: HLA DQ2 / DQ8

Consider further diagnostic tests to confirm CD, especially if typical and/or atypical symptoms of CD are present. CD diagnosis is based on presence of predisposing genetic factor human leukocyte antigen (HLA) DQ2/8, with positive biopsy and serological antibodies upon gluten contained diet. If a positive diagnosis is determined, then a gluten free diet should be followed.

World J Gastroenterol 2012 November 14; 18(42): 6036-6059

Factor V 1691 G>A

FACTOR V

Background

Factor V functions as a cofactor to allow factor Xa to activate the enzyme thrombin, which in turn cleaves fibrinogen to form fibrin, polymerizing it to form the dense meshwork that makes up the majority of a clot. Activated protein C (aPC) is a natural anticoagulant which limits the extent of clotting by cleaving and degrading factor V.

Factor V Leiden is an inherited defect associated with risk of venous thrombosis. It is characterised by a poor anticoagulant response to aPC and an increased risk for venous thromboembolism (VTE). Deep venous thrombosis (DVT) is the most common VTE, especially in legs, however VTE can also occur in other parts of the body.

Gene impact and information

Genotype		Impact
GG	Wild type	No Impact
GA	Heterozygote	Moderate
AA	Homozygote	High

GA alleles have a slightly increased risk for venous thrombosis.

AA genotypes have much greater thrombotic risk, particularly in veins. They have aPC-resistant Factor V, which affects cleavage by aPC, thus aPC cannot effectively degrade the cofactor, resulting in increased thrombin, then excess fibrin, and finally excess clotting.

Women with Factor V Leiden have a substantially increased risk of clotting in the form of pulmonary embolism and deep vein thrombosis when on oestrogen-containing contraceptive pills or hormone replacement therapy, as well as during pregnancy. Women also have a slightly increased risk of developing preeclampsia, giving birth to low birth weight babies, miscarriage and stillbirths due to clotting in the placenta, umbilical cord or the foetus – foetal clotting may depend on whether the baby has inherited the gene.

Recommendation: A allele

Consider other forms of contraception to oestrogen-containing contraceptive pills and other treatment methods to oestrogen hormone replacement therapy.

Appendix

Diet Plan Principles

Low Carbohydrate Diet

Low carb diets have a positive impact on obesity, serum lipids, impaired glucose metabolism and hypertension, but it is important to understand what constitutes a low carbohydrate diet. There is no need to completely cut out carbohydrates from the diet; the same positive results can still be achieved with a smaller intake of carbohydrates as described in the recommendations below.

A low carbohydrate diet limits intake to 30-130 g of carbohydrate per day, usually starting with the lower level in the first week or two, increasing to 60-70 g/day by week three, eventually maintaining approximately 100-130 g/day.

- Refined carbohydrate, most whole-grains and all sugars should be avoided, including natural sugars.
- Carbohydrate will be consumed in an array of vegetables and fruits, legumes, seeds and nuts, and dairy. All these foods do contain an amount of carbohydrate and need to be accounted for in your diet plan.
- Avoid starchy vegetables as they are high in carbohydrate and include leafy green vegetables where possible. Fruit should also be restricted.
- So long as weight loss is being achieved there is no need to restrict fat intake, however, moderate fat restriction may be necessary if the rate of weight loss decreases.
- Fat intake should focus on mono-unsaturated fatty acids, mostly from olive oil, and n-3 poly-unsaturated fat-rich foods such as fatty fish.
- Eat 3 meals and 2 snacks a day – never skip meals.
- Avoid drinks and foods with artificial sweeteners, and ensure adequate intake of water.
- Learn to read food labels. Most foods contain carbohydrates and you need to learn to identify foods that contain hidden carbohydrates, especially sugar. As an example tomato sauce and salad dressing are both very high in sugar.

Mediterranean Diet

The Mediterranean food patterns are typical of Crete, Greece and Southern Italy in the early 1960's. The term is closely tied to traditional areas of olive cultivation in the Mediterranean region more than 30 years ago, and not to the urbanized diet eaten in these countries today. Several studies have established the health benefits of the Mediterranean diet in reducing the risk of metabolic syndrome, type 2 diabetes, cardiovascular disease, and some neuro-degenerative diseases and cancers. In addition, it has been shown to be an extremely effective eating plan for weight loss.

- Rich in plant foods (whole-grain cereals, fruits, vegetables, legumes, tree nuts, seeds and olives).
- Extra virgin olive oil is the principal source of added fat.
- High to moderate intakes of fish and seafood.
- Moderate consumption of eggs, poultry and low fat dairy products (mainly cheese and yoghurt).
- Low consumption of red meat.
- Moderate intake of alcohol (mainly wine during meals).
- In addition all foods in this diet plan should be as fresh as possible, minimally processed, and local and seasonal foodstuff should be used.

Low Fat

- In general a low fat diet comprises a fat intake of less than 30% total energy, however for the purposes of weight loss it is recommended that fat is reduced to 20% of total energy.
- Consume whole-grains, vegetables, fruits, and legumes.
- Choose lean sources of meat, chicken, fish and dairy (low fat or fat free).
- Attention should be paid to the procurement, preparation and cooking of meals to keep fat content at a minimum.
- Refined carbohydrates and sugar should be avoided.
- A minimum of 3 meals should be eaten, ideally with 2 snacks, and no meals should be skipped!

Introduction to Nordic VMS

The Nordic Group of companies includes Nordic Laboratories, Nordic VMS and Nordic Clinic. As we believe that functional medicine is the future of healthcare, the group's mission is to incorporate a functional medicine approach into modern health practice.

Nordic VMS is an online patient management system that is free to use for both practitioners and patients. Its aim is to help healthcare practitioners better manage their patients, their practice and their time.

Registered practitioners can create patient notes and protocols, order selected tests and supplements for their patients, and pay through the online secure location.

The patient site gives patients access to their treatment protocols, prescribed tests and supplements. They can pay online, on the site, for products delivered directly to their door.

All data on the system is fully encrypted using SSL inscription, and complies with data security laws in the EU.

To sign-up for Nordic VMS go to www.nordicvms.com/practitioner.aspx – it takes just 2 minutes to register.

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