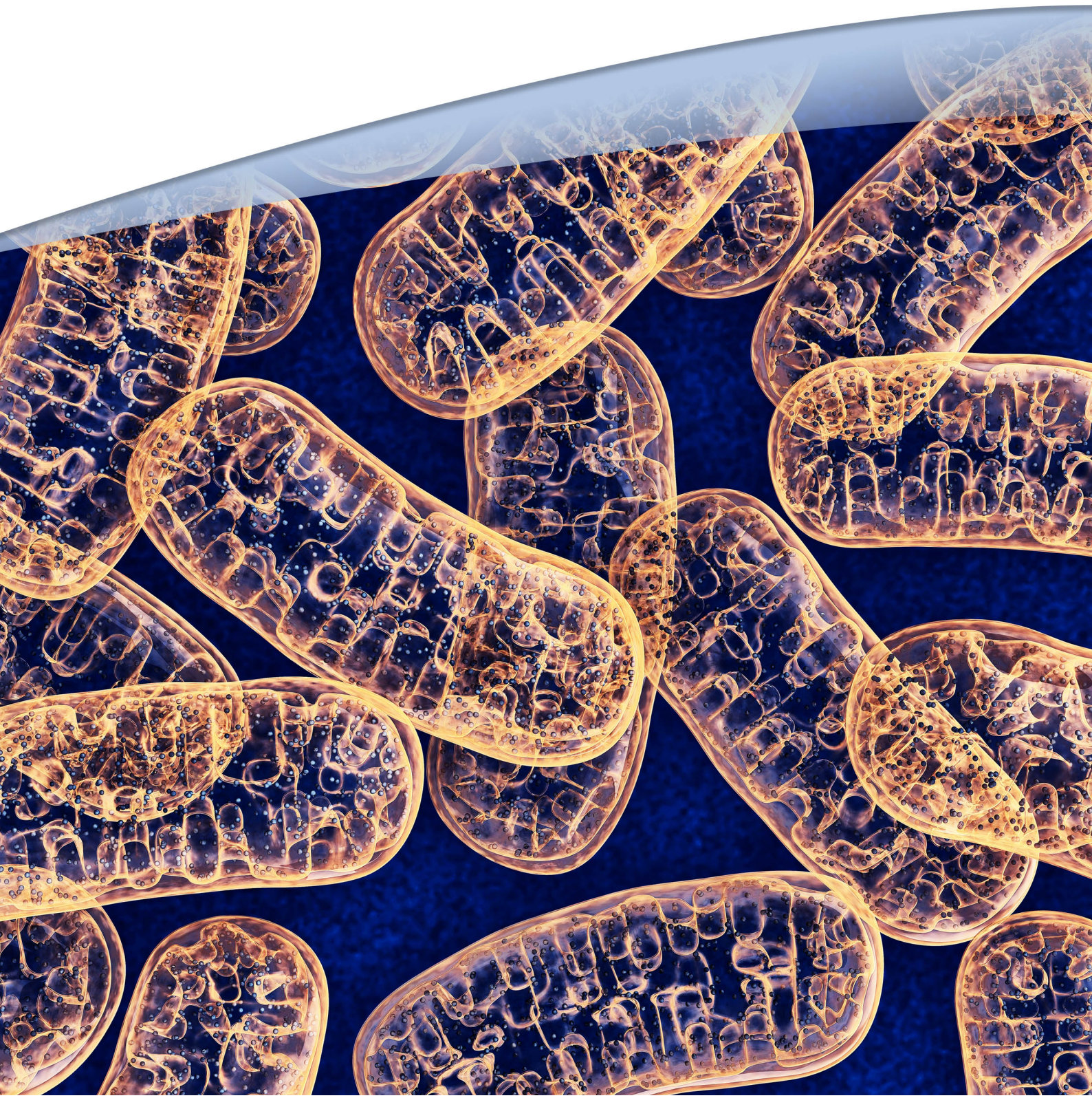
Lifecode GX ®
— Professional Genotype Analysis —

# Metabolics Report



Report for Giedre Babrauskiene (CP00078645)

Metabolism refers to all the chemical reactions that take place within each cell and are essential for life. It involves many interconnected pathways that can be divided into anabolism and catabolism. Anabolism uses energy to synthesise sugars, fats, proteins and nucleic acids, whereas catabolism releases energy in the form of ATP (adenosine triphosphate), alongside carbon dioxide, water and ammonia.

All living organisms, including humans, use their environment to survive by taking in nutrients to support movement, growth, development and reproduction. Most are metabolically flexible, enabling them to adapt to environmental changes and challenges such as scarcity of nutrients (famine), cold and hot climates, and oxygen availability (high altitude).

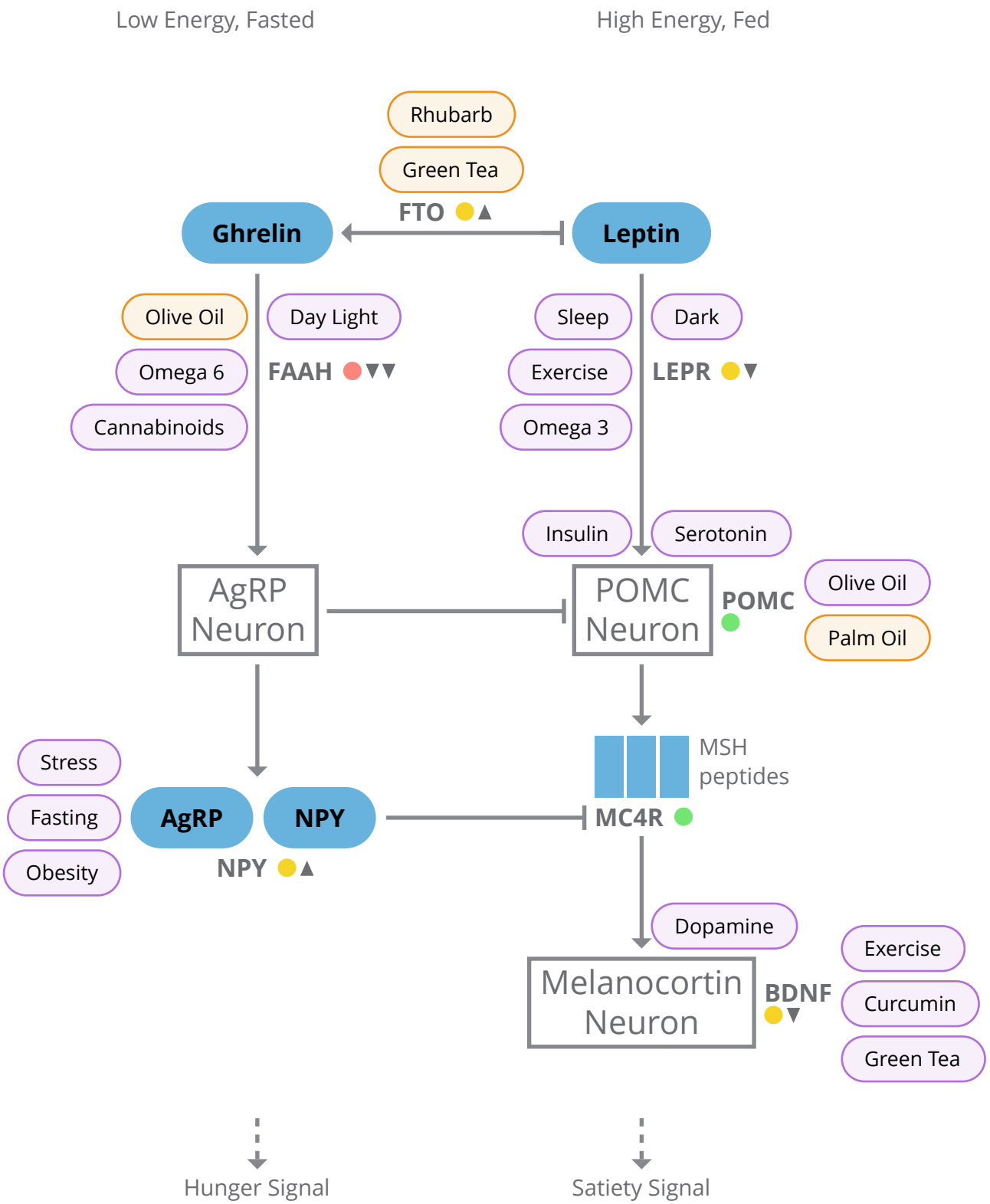
In recent decades, many populations have experienced increased availability of high calorie-low fibre, processed foods, which alongside decreased physical activity have contributed to metabolic dysfunction, and ultimately metabolic syndrome (MetS). However, these conditions are also affected by genetic make up, quality and composition of food, psychosocial stressors, environmental pollutants and gut microbes. Indeed, over a billion people, about a quarter of the world's population, is now affected by MetS – characterised by abdominal obesity, insulin resistance, hypertension and hyperlipidemia; which can lead to type 2 diabetes, cardiovascular and neurodegenerative diseases and cancer.

This Metabolics report describes how nutrients are absorbed and metabolised, and the genetic, nutrient and environmental factors that support metabolic flexibility or can lead to dysfunction. It provides six interconnected personalised pathways and detailed results, followed by a generic metabolics guide. The pathways covered are:

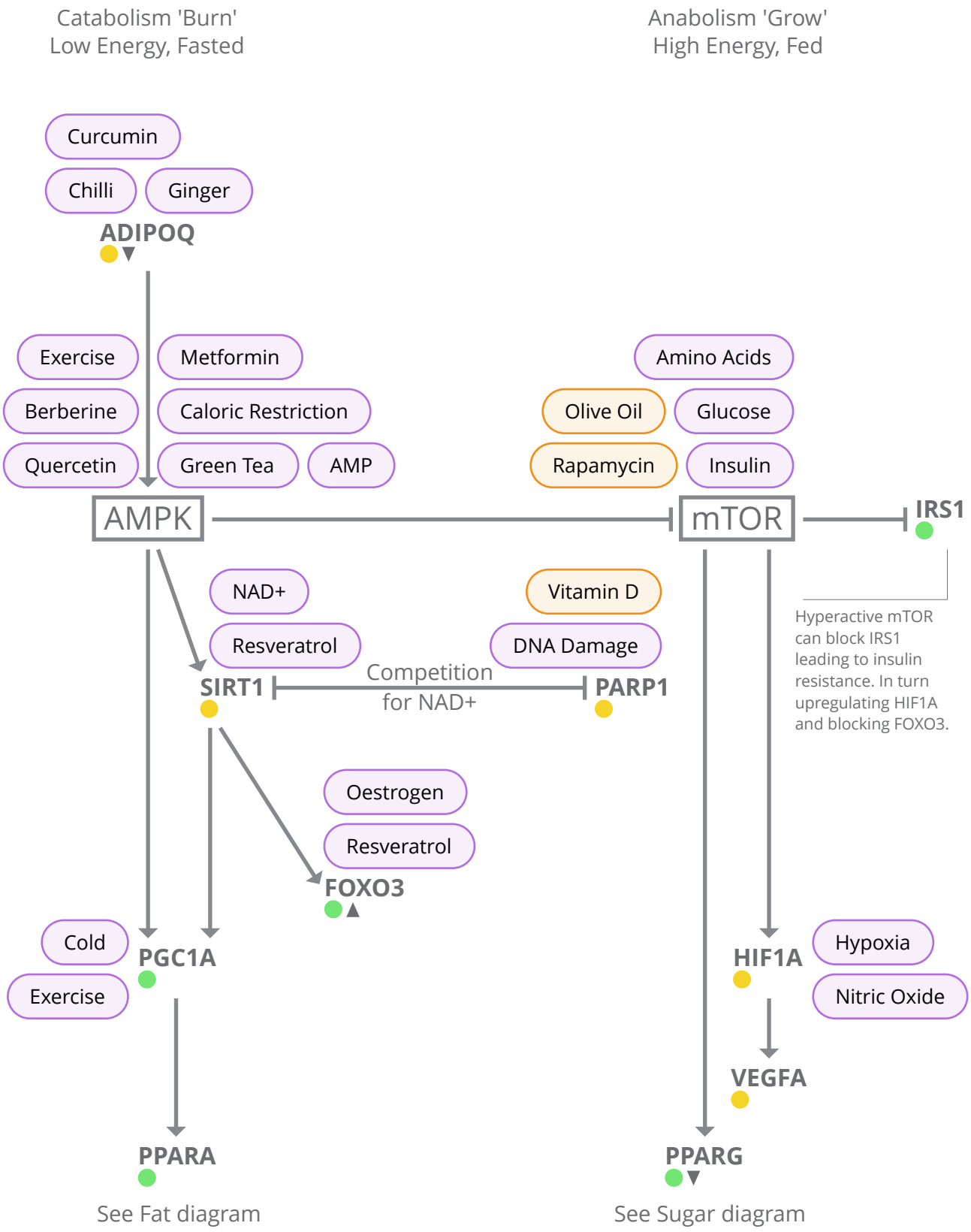
- Appetite regulation
- Nutrient sensing
- Sugar metabolism
- Fat metabolism
- Cholesterol and bile
- Mitochondria and inflammation

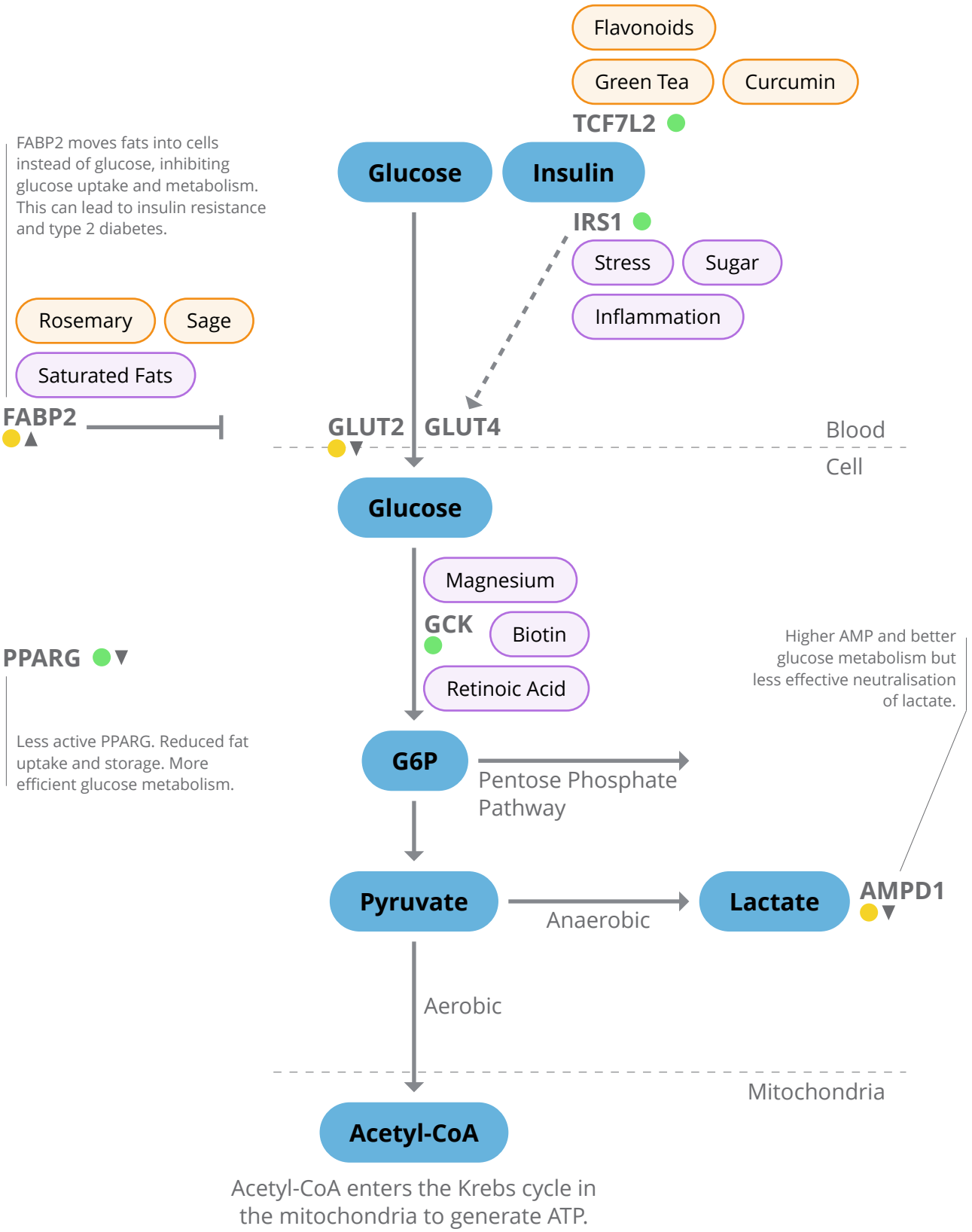
## Appetite Regulation



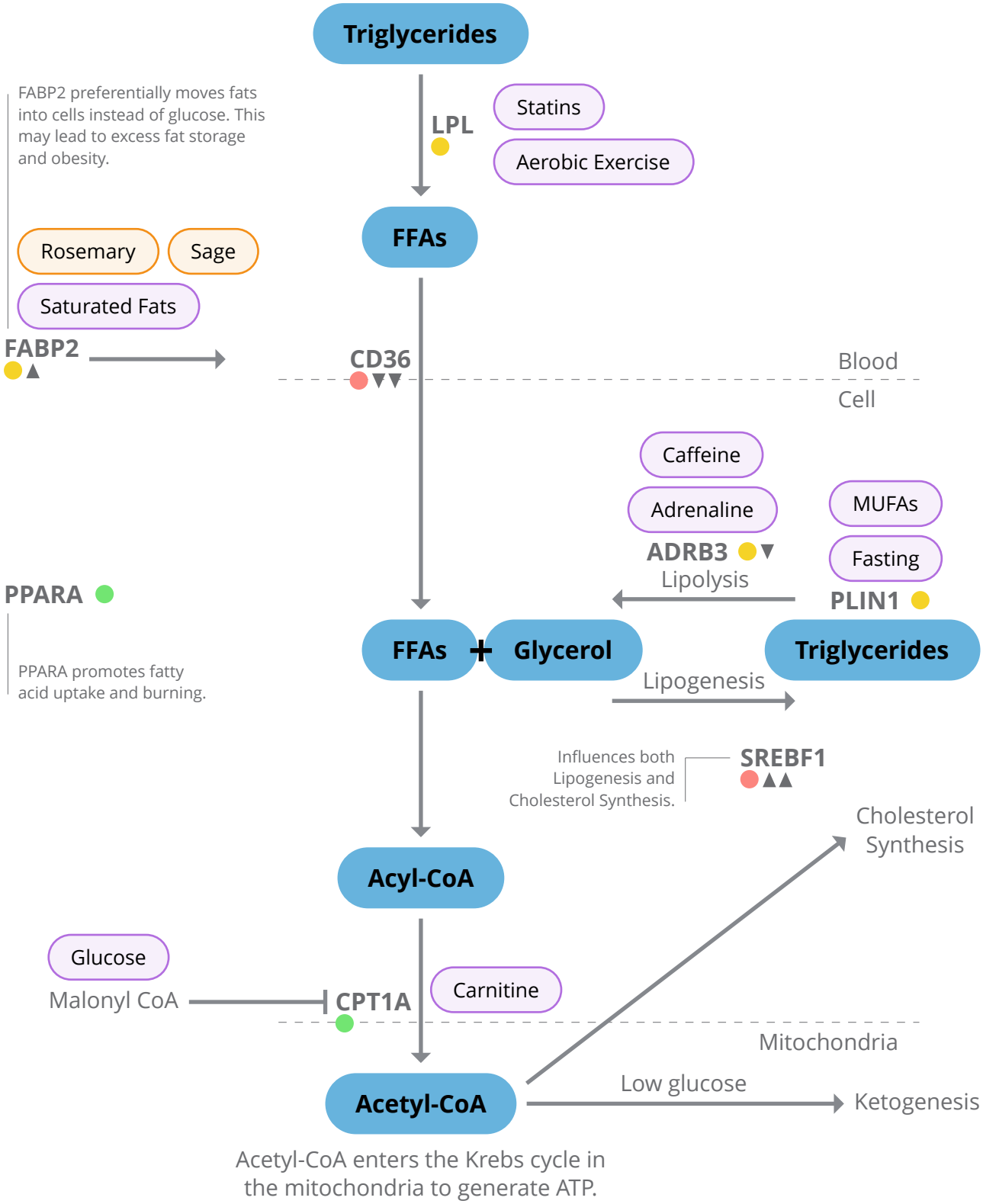
## Nutrient Sensing



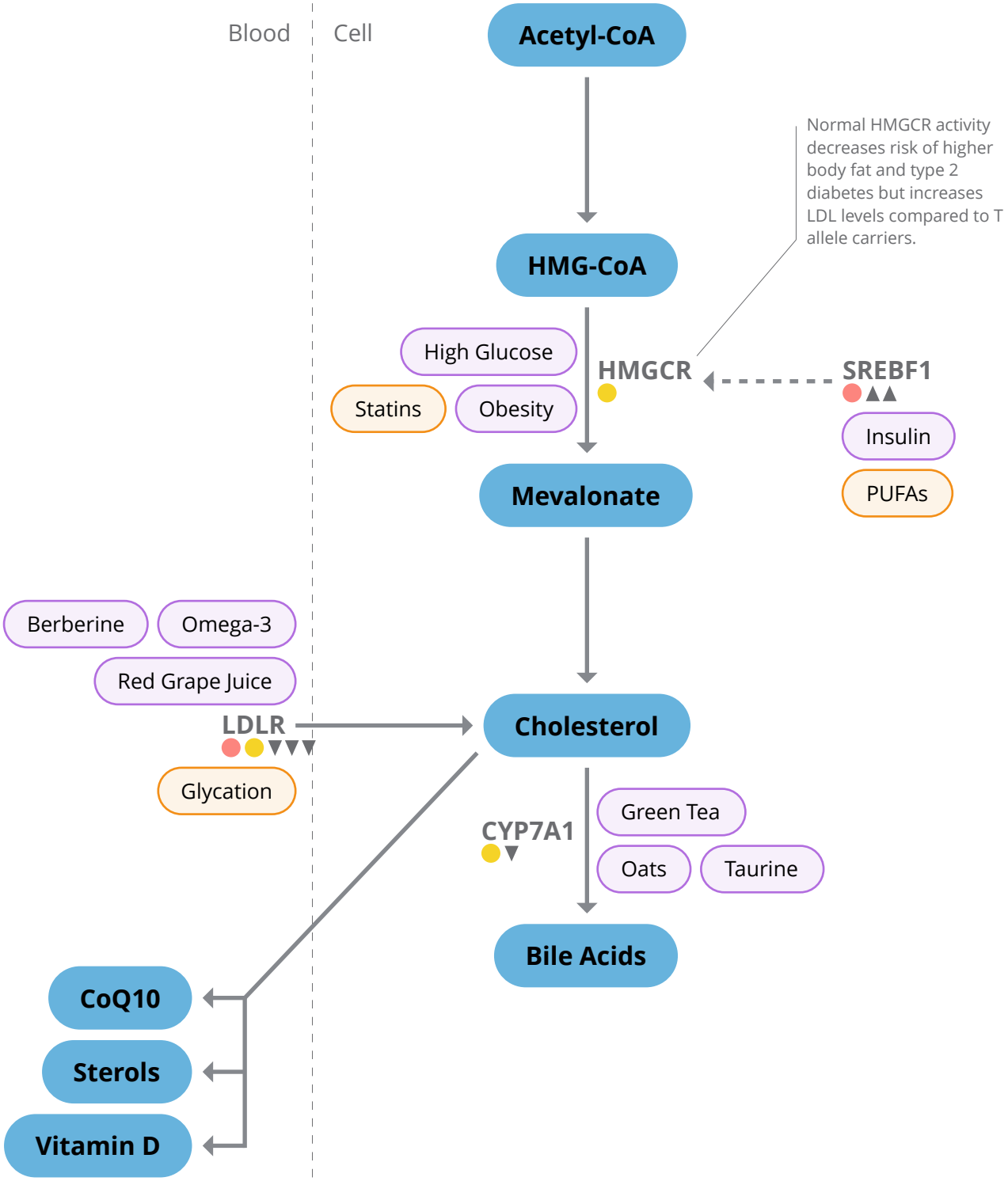
## Sugar Metabolism



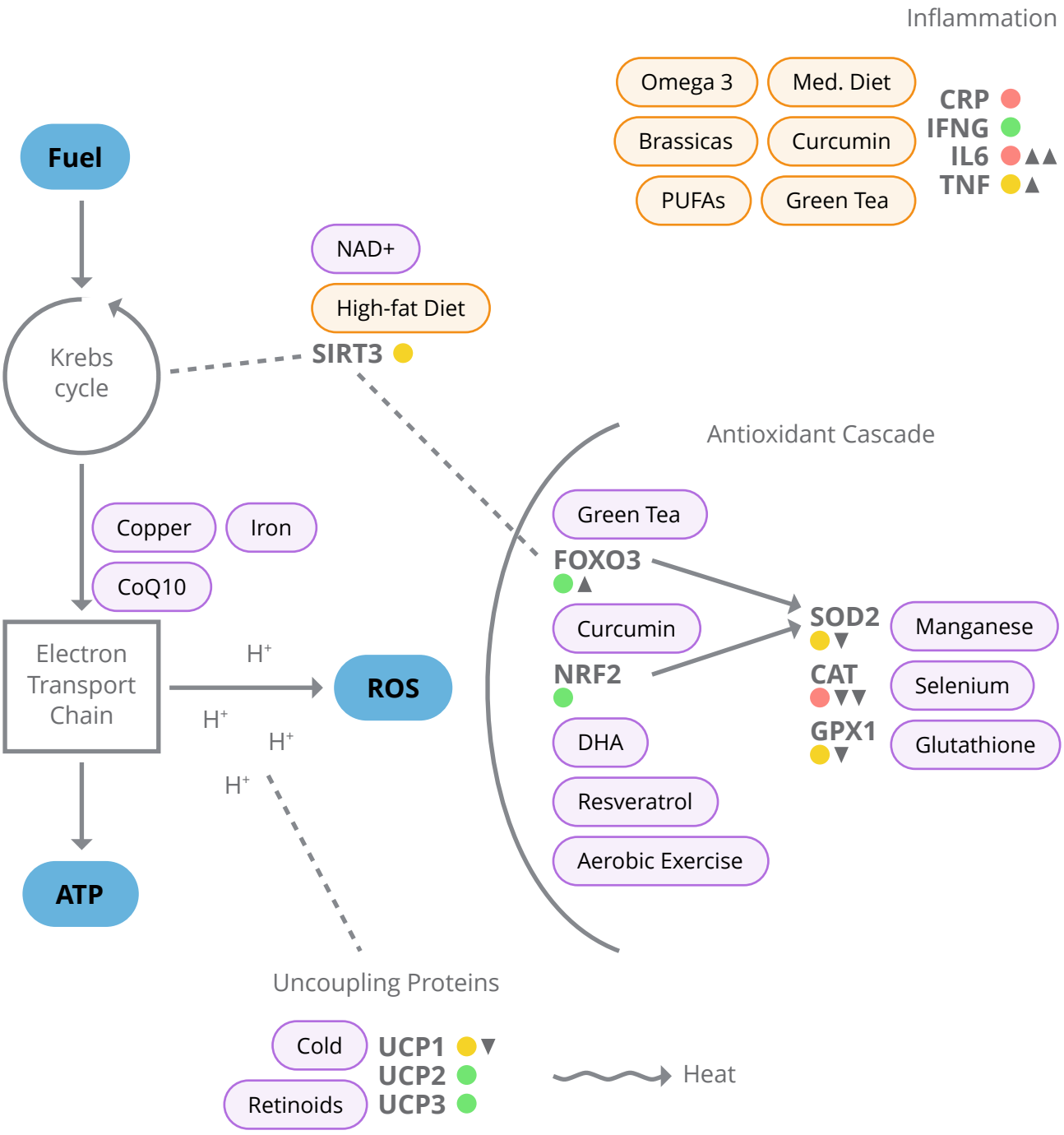
## Fat Metabolism



## Cholesterol and Bile



## Mitochondria and Inflammation



## Appetite Regulation

| | | |
|---|---|---|
| **BDNF**<br>rs6265 | TC ▼ | Lower brain-derived neurotrophic factor activity. Associated with increased appetite and risk of overeating.<br><br>Increase BDNF with intense exercise, vitamin D, vitamin B3 (niacin), curcumin, green tea, DHA (a component of omega-3 fatty acid) and resveratrol. |
| **FAAH**<br>rs324420 | AA ▼▼ | Significantly lower FAAH activity (up to 50%) and slower deactivation of cannabinoids, which may contribute to higher levels. This can lead to higher ghrelin, increased appetite and weight gain.<br><br>Limit intake of omega-6 fats which can increase cannabinoid levels, snacking, and risk of over-eating. Oleic acid, in olive oil, can help to regulate cannabinoids and ghrelin. |
| **FTO**<br>rs9939609 | AT ▲ | The A allele confers over-expression of FTO, subsequent increase in ghrelin (hunger), and reduced satiety after meals. Preference for calorie-dense (sweet and high fat) foods and increased risk of obesity.<br><br>This SNP confers on average 3kg more than the wild genotype. Proteins and complex carbohydrates are preferable to a high-fat diet. Rhubarb and green tea are both FTO inhibitors. |
| **LEPR**<br>rs1137101 | GA ▼ | Lower sensitivity to leptin (the 'satiety hormone'), resulting in increased appetite, lower metabolism, and increased risk of obesity.<br><br>Omega-3 fatty acids (in oily fish), exercise and sleep improve leptin sensitivity. |
| **MC4R**<br>rs17782313 | TT | Normal (good) melanocortin receptor sensitivity. Good appetite regulation and fat metabolism.<br><br>Also consider other SNPs on the pathway. |
| **NPY**<br>rs16139 | CT ▲ | The rare C allele confers significantly higher NPY and AgRP activity, increased appetite (hunger) and decreased energy expenditure (due to melanocortin inhibition). More 'foraging' behaviour towards food and alcohol.<br><br>NPY is increased in obesity, which can result in a vicious cycle. It is also associated with maladaptive responses to stress (over or under-eating). |

## Appetite Regulation (continued)

| | | |
|---|---|---|
| **POMC**<br>rs1042571 | GG | Normal (not shortened) version of POMC (proopiomelanocortin) and normal production of MSH peptides and appetite regulation. Not associated with over-eating.<br><br>Low serotonin could inactivate POMC and increase appetite. |

## Nutrient Sensing

**ADIPOQ**
rs1501299
TG ▼

The T allele confers lower adiponectin levels, and reduced AMPK stimulation, glucose regulation and fat oxidation. Increased risk of developing metabolic syndrome, cardiovascular disease and type 2 diabetes.

Adiponectin levels can be increased by exercise (especially in overweight individuals), ginger, curcumin, chilli peppers, garlic and manganese.

**FOXO3**
rs2802292
TG ▲

The more active G allele is associated with insulin sensitivity, better physical and cognitive function in older age, and less DNA damage and cardiovascular disease, contributing to longer healthspan and lifespan. Women are less dependent on the G allele as FOXO3 is induced by oestrogen.

Curcumin, green tea catechins, resveratrol, astaxanthin and beta-hydroxybutyric acid (induced by fasting or exercise) have been shown to increase FOXO3 activity.

**HIF1A**
rs11549465
CC

Normal increase of HIF1A in response to hypoxia (low oxygen), and induction of erythropoiesis, inflammation and angiogenesis. Less inhibition of (oxidative) aerobic fat metabolism, switch to anaerobic glycolysis. But less effective repair and rejuvenation of skin, hair and nerves after injury and ageing.

More resilient to hypoxia - high altitude, sleep apnea, asthma, anaemia or carbon monoxide exposure. Hyperbaric oxygen therapy can help to restore oxygen supply.

**IRS1**
rs1801278
CC

Normal IRS1 activity, insulin sensitivity and glucose uptake. Not associated with increased risk of type 2 diabetes or susceptibility to insulin resistance.

Plant based, low carbohydrate (glucose) and ketogenic diets have been shown to reduce mTOR activity and support IRS1.

**PARP1**
rs1136410
AA

Normal (relatively high) PARP1 activity and DNA repair. Shown as amber as more risk of inaccurate DNA repair, inflammation and metabolic inefficiency. Increased demand for NAD+ so less is available for use by sirtuins and other functions.

NAD+ levels can be increased with niacin or NAD+ precursors (NR and NMN). Vitamin D can help to decrease PARP1 activity.

## Nutrient Sensing (continued)

| | | |
|---|---|---|
| **PGC1A**<br>rs8192678 | CC | Normal (relatively high) PGC1A activity and - via PPARA, PPARG and antioxidant genes - regulation of mitochondrial biogenesis and metabolism. Promotes development of slow-twitch muscle fibre - beneficial for endurance performance.<br><br>PGC1A expression can be induced by cold exposure - in brown fat, by exercise - in skeletal muscle, and by fasting - in heart and liver. |
| **PPARA**<br>rs1800206 | CC | Normal (relatively high) PPARA activity associated with more efficient fat metabolism. Relatively low cholesterol and triglycerides and reduced risk of type 2 diabetes.<br><br>PPARA can be further activated in response to fasting/ low energy states, and promotes ketogenesis and glycolysis. Activity can be increased by PUFAs, resveratrol and flavonoids. It is inhibited by excess energy, particularly glucose. |
| **PPARG**<br>rs1801282 | GC▼ | Lower PPARG activity, and less efficient fatty acid uptake and storage. Associated with more opportunity for glucose uptake, and lower risk of insulin resistance and type 2 diabetes.<br><br>This less 'thrifty' genotype is less likely to experience weight gain on a high fat diet. |
| **SIRT1**<br>rs7895833 | AA | Wild (most common) genotype shown as amber due to relatively low sirtuin 1 activity and less protection from metabolic dysfunction - diabetes, obesity, cardiovascular, neurodegenerative and other age-related diseases.<br><br>NAD+ and resveratrol have been shown to increase SIRT1 activity while excess nutrition (particularly high glucose), oxidative stress and inflammation can suppress it. |
| **VEGFA**<br>rs2010963 | GG | Normal (not increased) VEGFA activity and vascularisation. Protective against inflammation, vascular permeability (and diabetic retinopathy) and tumour angiogenesis. Less beneficial for endurance performance.<br><br>VEGFA can be increased with aerobic training, beetroot, citrulline (watermelon) and arginine. |

## Sugar Metabolism

| | | |
|---|---|---|
| **AMPD1**<br>rs17602729 | GA▼ | Deficient AMPD1 gene. Reduced AMP recycling resulting in more AMPK activity and increased glucose uptake. Lower risk of insulin resistance, type 2 diabetes and heart disease.<br><br>However, when energy demand is high, less ammonia is produced to neutralise lactate. Greater muscle fatigue, cramps and muscle pain during and after endurance exercise. |
| **FABP2**<br>rs1799883 | CT ▲ | The T allele confers increased fatty-acid binding and transport into cells, which can crowd out glucose uptake. Increased risk of high BMI, obesity, insulin resistance, hyperinsulinemia, and type 2 diabetes.<br><br>Ensure high intake of PUFAs and MUFAs and limit saturated fats. Polyphenols, and especially carnosic acid (rosemary, sage), inhibit FABP2 activity. |
| **GCK**<br>rs1799884 | CC | Normal glucokinase activity and conversion of glucose to G6P.<br><br>Retinoic acid and biotin are both cofactors of GCK. |
| **GLUT2**<br>rs11920090 | AT ▼ | The A allele confers lower GLUT2 activity and impaired glucose sensing, which may impact insulin secretion and glucose homeostasis. More risk of hyperglycemia, transition to diabetes and hypercholesterolemia. Preference for sugar-containing foods and higher intake.<br><br>Monitor blood glucose levels and avoid sugar rich meals. Regular moderate to vigorous physical activity has been shown to improve insulin sensitivity and beta cell function. |
| **IRS1**<br>rs1801278 | CC | Normal IRS1 activity, insulin sensitivity and glucose uptake. Not associated with risk of type 2 diabetes. |
| **PPARG**<br>rs1801282 | GC▼ | Lower PPARG activity, and less efficient fatty acid uptake and storage. Associated with more opportunity for glucose uptake, and lower risk of insulin resistance and type 2 diabetes.<br><br>This less ‘thrifty’ genotype is less likely to experience weight gain on a high fat diet. |

## Sugar Metabolism (continued)

| | | |
|---|---|---|
| **TCF7L2**<br>rs7903146 | CC | Normal expression of TCF7L2 and regulation of insulin release and blood sugar.<br><br>Flavonoids, curcumin, green tea, resveratrol, lupeol, vitamin A and lycopene can also help to regulate TCF7L2. |

## Fat Metabolism

| | | |
|---|---|---|
| **ADRB3**<br>rs4994 | GA ▼ | The G allele confers lower adrenaline sensitivity, slower lipolysis and fat metabolism. More fat accumulation, obesity and insulin resistance.<br><br>Diet and lifestyle interventios are less effective for weight loss. Adrenaline, caffeine, water, fasting, cold exposure, HIIT, bananas, chocolate and green tea can increase lipolysis. |
| **CD36**<br>rs1761667 | AA ▼▼ | Reduced fat transport into cells and less sensitive taste perception. Greater liking for high-fat foods, creaminess and increased risk of visceral obesity.<br><br>Obesity can downregulate CD36 further resulting in a vicious cycle. See FTO genotype (Appetite Section). |
| **CPT1A**<br>rs2229738 | CC | Normal transport of fat into mitochondria and fat utilisation for energy.<br><br>Carnitine can support CPT1A activity. A ketogenic diet may be beneficial for weight loss. |
| **FABP2**<br>rs1799883 | CT ▲ | The T allele confers preferential fat transport into cells instead of glucose. Increased risk of high BMI and obesity.<br><br>Ensure high intake of PUFAs and MUFAs and limit saturated fats. Polyphenols, and especially carnosic acid (rosemary, sage), inhibit FABP2 activity. |
| **LPL**<br>rs328 | CC | Normal LPL activity and break-down of triglycerides carried in lipoproteins. This is shown as amber as it is less effective than the more active variant (G allele).<br><br>Exercise (especially aerobic), lipid-lowering agents and statins can promote LPL activity. |
| **PLIN1**<br>rs894160 | CC | Normal (high) expression of PLIN1 and protection from lipase activity. Normal (not increased) rates of lipolysis and normal (not reduced) risk of obesity. This is shown as amber because the variant (T allele) is beneficial.<br><br>Normal weight loss response on an energy-restricted diet. |

## Fat Metabolism (continued)

| | | |
|---|---|---|
| **PPARA**<br>rs1800206 | CC | Normal PPARA activity, fat metabolism and less risk of obesity.<br><br>Resveratrol, isoflavones, flavonoids and PUFAs can increase PPARA activity. A ketogenic diet may be beneficial for weight loss. |
| **SREBF1**<br>rs11868035 | AA ▲▲ | Higher SREBF1 activity associated with higher LDL and total cholesterol, and increased risk of coronary artery disease, type 2 diabetes and non-alcoholic fatty liver disease.<br><br>PUFAs - in oily fish, nuts and vegetable oils - inhibit SREBF1 activity while glucose increases it. |

## Cholesterol and Bile

**CYP7A1**
rs3808607

TG ▼

The T allele confers slower break-down of cholesterol to bile acids. Associated with increased cholesterol levels and lower bile acid production.

Oats, taurine and green tea can support CYP7A1 activity and help remove cholesterol.

**HMGCR**
rs12916

CC

Normal (higher) conversion of HMG-CoA to mevalonate, and synthesis of cholesterol, CoQ10 and vitamin D. Lower LDLR sensitivity, higher risk of coronary artery disease than T allele carriers, but decreased risk of type 2 diabetes.

To reduce cholesterol naturally, avoid trans and saturated fats, increase exercise and omega-3 fats.

**LDLR**
rs6511720

GG▼▼

Lower LDLR sensitivity and reduced LDL uptake. Most common genotype - associated with higher circulating LDL and increased risk of coronary heart disease.

Increase intake of red grape juice (polyphenols), berberine and omega-3 fats, and limit fructose which can cause glycation.

**LDLR**
rs688

TC ▼

The T allele confers lower LDLR sensitivity. Associated with increased circulating LDL and increased risk of Alzheimer's disease (especially in men).

Increase intake of red grape juice (polyphenols), berberine and omega-3 fats, and limit fructose which can cause glycation.

**SREBF1**
rs11868035

AA ▲▲

Increased SREBF1 activity, which promotes cholesterol synthesis. Associated with higher LDL and total cholesterol, and increased risk of coronary artery disease, type 2 diabetes and non-alcoholic fatty liver disease.

Insulin (via mTOR) increases SREBF1 activity while PUFAs (oily fish, nuts, vegetable oils) decrease it.

## Mitochondria and Inflammation

| | | |
|---|---|---|
| **CAT**<br>rs1001179 | TT ▼▼ | Reduced break-down of hydrogen peroxide which can lead to increased free radicals. Associated with various conditions - infertility in men (pathospermia), grey hair, increased risk of cancer, diabetes and obesity.<br><br>Support catalase with manganese - green vegetables, wholegrain bread and cereal. |
| **CRP**<br>rs1205 | CC | Higher C-reactive protein activity associated with increased inflammatory diseases - cardiovascular, high blood pressure, diabetes and rheumatoid arthritis.<br><br>A Mediterranean diet (especially fish) is associated with lower CRP levels. PUFAs can also reduce them. |
| **FOXO3**<br>rs2802292 | TG ▲ | The G allele confers higher antioxidant activity. Associated with increased longevity.<br><br>Curcumin and green tea can further upregulate FOXO3 activity. |
| **GPX1**<br>rs1050450 | AG ▼ | The A allele confers decreased break-down of hydrogen peroxide and antioxidant activity. Higher risk of neurodegenerative diseases such as Alzheimer's and Parkinson's, as well as increased risk of coronary heart disease, type 2 diabetes and DNA damage.<br><br>Support GPX1 with selenium (brazil nuts) and glutathione (sulphur foods, melon). |
| **IFN-gamma**<br>rs2430561 | AA | Normal (not increased) immune response to infections and normal metabolism.<br><br>An anti-inflammatory diet includes omega-3 (found in oily fish) and brassica foods. |
| **IL6**<br>rs1800795 | GG▲▲ | Increased inflammatory and autoimmune activity associated with increased risk of type 2 diabetes, hyperglycaemia, obesity and metabolic syndrome.<br><br>Ensure intake of anti-inflammatory nutrients such as omega 3 fatty acids in oily fish, like sardines, salmon and mackerel. |

## Mitochondria and Inflammation (continued)

| | | |
|---|---|---|
| **NRF2**<br>rs6721961 | GG | Normal (higher) activity of the master antioxidant regulator NRF2.<br><br>Increase NRF2 activity with intermittent fasting, curcumin, resveratrol, naringenin - in citrus peel, and cruciferous vegetables including broccoli. |
| **SIRT3**<br>rs11555236 | CC | Normal activity (not increased) - fatty acid oxidation, ATP synthesis, and antioxidant defence . Although this is the most common genotype, it is reported amber due to increased risk of metabolic dysfunction.<br><br>SIRT3 can be upregulated by caloric restriction, fasting, exercise and cofactor NAD+. A high-fat diet and age reduce its expression. |
| **SOD2**<br>rs4880 | GA ▼ | The G allele confers slower break-down of superoxide and increased free radical damage. Increased risk of type 2 diabetes, cardiovascular diseases and DNA damage.<br><br>Increase intake of manganese to support SOD2 activity and antioxidants to reduce free radical damage. Rich sources of manganese include whole grains, nuts, leafy vegetables and tea. |
| **TNF**<br>rs1800629 | AG ▲ | Increased immune response and susceptibility to various inflammatory health conditions, including chronic fatigue, metabolic syndrome, arthritis, asthma, migraine and Alzheimer's.<br><br>Reduce inflammation with curcumin, green tea, echinacea, and omega-3 fatty acids found in oily fish. |
| **UCP1**<br>rs1800592 | CT ▼ | The C allele confers reduced thermogenesis activity. Associated with promotion of energy storage, increased BMI and development of obesity (especially lower body).<br><br>Purine nucleotides (high fructose corn syrup, seafood, organ meat, alcohol) inhibit UCP1. It is induced by cold exposure as well as leptin, exercise, adrenaline, green tea, cabbage, berries, spinach and capsaicin. |

## Mitochondria and Inflammation (continued)

| | | |
|---|---|---|
| **UCP2**<br>rs660339 | GG | Normal fat metabolism and ROS protection.<br><br>Capsaicin in chilli peppers, mustard and wasabi helps to stimulate UCP2 as does moderate exercise. However, over-training can generate excess ROS and inhibit energy production. |
| **UCP3**<br>rs1800849 | GG | UCP3 protects mitochondria from lipid-induced oxidative stress by removing excess fatty acids. It is mainly expressed in skeletal muscle. This genotype is associated with higher resting metabolic rate and decreased risk of metabolic dysfunction.<br><br>Protective in the context of a high fat diet. UCP3 activity is increased by exercise. |

# A Guide to Metabolics

This guide contains detailed explanations of the pathways, genes and dietary/environmental factors involved in metabolism. It looks at appetite regulation, nutrient sensing, sugar and fat metabolism, cholesterol and bile synthesis, and mitochondrial function and inflammation.

## Appetite Regulation

The brain plays an important role in food intake, energy expenditure and body weight regulation. The gut controls the brain's feeding behaviour via hunger and satiety signals. These signals are mediated by two opposing hormones – ghrelin and leptin – which interact with the central melanocortin system.

Ghrelin is commonly called the 'hunger hormone' as it stimulates appetite, increases food intake and promotes fat storage, via receptors in the brain. As ghrelin is under circadian control, it is higher in the morning (daylight), prompting food seeking (foraging) behaviour.

Leptin is the 'satiety hormone' which inhibits hunger after eating and stimulates metabolism. Levels are higher in the evening (darkness) and when they drop the brain interprets this as a loss of energy and hunger increases.

In summary, ghrelin is associated with a low energy, fasted state and leptin with a high energy, fed state.

**Low Energy, Fasted**

FTO (fat mass and obesity-associated protein) is commonly called the 'fat gene' due to its connection with increased appetite. It is highly expressed in the brain as well as the heart, kidneys and fat cells. Over-expression of FTO, due to genetic variance, is associated with lower leptin levels, higher ghrelin levels, and an increased preference for calorie-dense (sweet and high fat) foods. A SNP on FTO has been consistently associated with higher body fat, BMI, waist circumference and obesity (on average 3kg heavier). Rhubarb and green tea are both FTO inhibitors.

Cannabinoids promote ghrelin, food intake and energy accumulation. FAAH (fatty acid amide hydrolase) metabolises endogenous cannabinoids including AEA (N-arachidonoylethanolamine, known as anandamide) and 2-AG (2-arachidonoylglycerol) which are involved in the perception of pain, regulation of appetite and immune system function. A SNP on FAAH has lower activity and thus increased levels of cannabinoids. This can confer increased appetite (higher ghrelin), food intake and weight gain. Limit intake of omega-6 fats which can increase cannabinoid levels, ghrelin driven foraging behaviour (snacking), and risk of over-eating. Oleic acid, in olive oil, can help to regulate cannabinoids and ghrelin.

NPY (neuropeptide Y) and AgRP (agouti-related peptide) promote food consumption and energy accumulation. They are stimulated by ghrelin and inhibit the melanocortin pathway (via MC4R), which together increase appetite. Conversely, when energy is higher after eating, neurons that express POMC (proopiomelanocortin) are recruited to antagonise the actions of NPY and AgRP to reduce food intake and stimulate metabolism. AgRP and POMC neurons compose a unique neural circuit known as the melanocortin system.

The NPY gene is expressed in the central nervous system and influences many processes, including stress response, food intake, circadian rhythms, and cardiovascular function. A SNP confers significantly higher NPY and AgRP activity, increased appetite and decreased energy expenditure. This is associated with more 'foraging' behaviour towards food and alcohol, and greater risk of obesity and metabolic dysfunction. NPY is increased in obesity, which can result in a vicious cycle. It is also associated with maladaptive responses to stress (over or under-eating).

The conclusion of this pathway is hunger.

**High Energy, Fed**

Leptin interacts via its receptor LEPR in the brain, tells it there is enough energy, and sends the message of satiety and suppression of hunger. As adipocytes (fat cells) produce leptin, greater adiposity (fatness) results in higher leptin levels. This can lead to 'leptin resistance' (loss of sensitivity of the receptor) so one never feels full. Variances on the LEPR gene can have the same effect – lower sensitivity to leptin and reduced satiety. Leptin sensitivity can be increased with omega-3 fatty acids, exercise and sleep.

After activation by leptin, the POMC protein is cut into smaller pieces including MSH (melanocortin) peptides. A SNP on POMC can result in a shorter version of the protein and fewer MSH peptides and less binding to MC4R (melanocortin-4 receptor), resulting in greater interest in food and impaired satiety. A high protein diet including tryptophan (in chicken and almonds) and olive oil can increase POMC and help reduce appetite. Serotonin activates POMC, resulting in similar satiety effects as leptin. In addition to negative impacts on mood and mental health, low serotonin has been linked to weight gain, obesity and diabetes. Insulin is also an inducer of POMC, while palm oil inhibits it.

MC4R is an important regulator of energy homeostasis, food intake and body weight via its binding to BDNF (brain-derived neurotrophic factor). A SNP on MC4R indicates a less sensitive receptor, and weaker satiety signalling and metabolism. It is the single most impactful genetic polymorphism predisposing to obesity. Carriers should limit portion size of meals, choose smaller plates and avoid the buffet (and seconds).

BDNF promotes growth, differentiation and survival of neurons and synapses in the central and peripheral nervous systems. In the melanocortin system, BDNF plays an essential role in regulating appetite and energy balance. A SNP can reduce its activity and increase the risk of obesity. BDNF can be increased by intense exercise, vitamin D, curcumin, green tea, omega-3-fatty acids and resveratrol.
The neurotransmitter dopamine also plays a role in controlling eating behaviours, by activating the melanocortin neuron.

The conclusion of this pathway is satiety.

## Nutrient Sensing

The mTOR (mechanistic target of rapamycin), AMPK (AMP-activated protein kinase), and sirtuin family of proteins play essential roles in the regulation of metabolic stress and energy balance, enabling biological adaptations in response to environmental signals.

This section of the report describes how genetic variances and environmental factors impact these signalling pathways and balance catabolism ('burn') and anabolism ('grow') to support healthspan and longevity.

**Catabolism 'Burn'**

When energy levels are low, for example in a fasted state, cells activate pathways to restore energy (ATP) by stimulating glycolysis and lipolysis and autophagy ('self-eating') – whereby old proteins are broken down and recycled.

Adiponectin, coded by ADIPOQ, is a hormone released by adipose tissue that initiates fat burning and glucose uptake. This signal is delivered via adiponectin receptors that activate AMPK. A SNP on ADIPOQ confers lower adiponectin levels, and higher risk of obesity, cardiovascular disease, insulin resistance and type 2 diabetes. Adiponectin can be increased by exercise (especially in overweight individuals), ginger, curcumin, chilli peppers, garlic and manganese.

AMPK is key to maintaining the balance between anabolism and catabolism according to nutrient supply and energy demand. As its name suggests, in response to high AMP (low energy), AMPK stimulates glucose and fatty acid break-down and promotes autophagy. And by blocking mTOR inhibits protein synthesis and fat storage. Given its impacts on appetite, insulin signalling, fat and glucose homeostasis, body weight, and mitochondrial biogenesis, AMPK is a major therapeutic target for the treatment of type 2 diabetes, obesity and other metabolic diseases.

Low energy status may be due to low glucose, fasting, exercise, hypoxia (low oxygen) or damage to mitochondria. Mild mitochondrial toxins including polyphenols – epigallocatechin gallate (EGCG) in green tea, quercetin in red onions, apples, berberine, curcumin, genistein in soy beans, and metformin (the anti-diabetic drug) can have a similar effect. Salicylate (aspirin) is a direct activator of AMPK and acts synergistically with other activators. Alpha-lipoic acid (ALA) has been shown to activate AMPK by increasing cellular calcium (Ca++). Finally, AMPK is activated under conditions of oxidative stress (ROS) independently of cellular ATP status.

The sirtuin (silent information regulator 2 (SIRT)) family of genes influence many biological processes including DNA repair, energy metabolism, autophagy, apoptosis and circadian rhythm. In humans, SIRTs 1, 6 and 7 regulate gene expression in the cell nucleus, SIRT2 is active in the cytoplasm and SIRTs 3, 4 and 5 are located in mitochondria where they regulate metabolism.

SIRTs are induced by, and sensitive to, their cofactor NAD+ and inhibited by NADH. Raised NAD+ (relative to NADH) signals low cellular energy (metabolic stress), similarly to AMP (relative to ATP). As AMPK raises cellular NAD+ levels, the same conditions that induce AMPK also stimulate SIRT1 activity. Conversely, excess nutrition (particularly high glucose), inflammation or insufficient NAD+ supply can inhibit SIRT1.

SIRT1 regulates other genes, inhibiting p53 (tumour protein P53) and NF-KB (nuclear factor kappa-beta), and inducing PGC1A (PPAR-gamma coactivator 1-alpha), FOXO3 (forkhead box protein O3) and SREBF1 (sterol regulatory-element binding transcription factor 1) with various effects on metabolism.

The DNA repair protein PARP1 (poly ADP-ribose polymerase 1) also requires NAD+ as a cofactor, and when DNA is damaged (by environmental toxins, and ageing), increased PARP1 activity can divert NAD+ supply away from SIRT1. Conversely, up-regulation of SIRT1 can balance excess PARP1 activity.

Moderately increased NAD+, AMPK and SIRT1 are considered beneficial to healthspan and lifespan. Increased SIRT1 expression protects against metabolic diseases such as diabetes, obesity and cardiovascular disease.

NAD+ (nicotinamide adenine dinucleotide) can be synthesised from tryptophan or from nicotinic acid, or from precursors – NAM (nicotinamide), a form of vitamin B3 found in yeast, meat, milk and green vegetables, NR (nicotinamide riboside) and NMN (nicotinamide mononucleotide). NAD+ deficiency can occur due to excess consumption by PARP1, for example, insufficient dietary intake, age and genetic variance. Exercise has been shown to reverse age-related declines in NAD+. In laboratory conditions, supplementation with NAD+ precursors (NR and NMN) has been shown to be protective against age-related diseases.

As a transcription factor, PGC1A (PPAR-gamma coactivator 1-alpha) regulates other genes including PPARA (PPAR-alpha), PPARG (PPAR-gamma), SIRT3 and NRF (nuclear respiratory factor). It is involved in mitochondrial biogenesis fatty acid oxidation, glucose utilisation, thermogenesis, angiogenesis and muscle fibre-type conversion toward type I (slow-twitch) fibre. Genetic variances on PGC1A are associated with lower activity and greater risk of developing obesity, and other symptoms of metabolic syndrome.

Caloric restriction, fasting, exercise, ketogenic (high-fat) diet, heat shock therapy (hot tubs, heated pools and saunas), cold exposure, ROS (reactive oxygen species) and other cellular stressors can induce PGC1A, directly and via SIRT1 and AMPK.

PPARA is a major regulator of fat metabolism. It is activated under conditions of energy deprivation and is necessary for ketogenesis, an adaptive response to fasting. It is active in tissues that break down fatty acids – the liver, cardiac, and skeletal muscle. PPARA expression is higher in type I (slow-twitch) muscle, and supports adaptive responses to endurance training, including using fat for fuel. A SNP on PPARA is associated with lower activity, and higher risk of obesity. Resveratrol, isoflavones, flavonoids and PUFAs (polyunsaturated fatty acids) can help to increase PPARA function.

FOXO3 is an important regulator of genes involved in cellular homeostasis, stress response, and longevity. When energy is low, SIRT1 induces FOXO3 which activates other genes involved in gluconeogenesis, and mitochondrial respiration, restoring cellar energy levels. FOXO3 is also activated by oxidative stress (ROS), hypoxia, heat shock, and DNA damage, and induces antioxidant compensatory activities. However, in cancer cells, it can mediate cell survival upon chemotherapy induced genotoxic stress.

A SNP on FOXO3 has been consistently and significantly associated with better healthspan and longevity. The more active version of the gene confers higher insulin sensitivity, better physical and cognitive function in older age, and lower prevalence of cancer and cardiovascular disease. Curcumin, green tea catechins, resveratrol, astaxanthin, beta-hydroxybutyric acid (induced by fasting or exercise), and oestrogen have been shown to increase FOXO3 activity.

**Anabolism 'Grow'**

When energy levels are high (in a fed state), cells can activate pathways to induce cell maintenance and growth. Whilst growth is vital for younger people, and maintenance is important in mid and older age, excessive nutrient intake can overstimulate mTOR with detrimental effects.

mTOR is a complex of proteins, including mTOR1 (the main target of rapamycin), and mTOR2, which regulate growth and metabolism. mTOR senses amino acids, glucose, growth factors (such as growth hormone and insulin), energy levels and stressors (such as low oxygen). When nutrients (particularly amino acids and glucose) are plentiful, mTOR drives synthesis – of proteins, lipids (via SREBF1) and purines (via a mitochondrial folate cycle). However, when nutrients are excessive, mTOR can become dysregulated leading to insulin resistance and conditions such as diabetes, obesity and depression. Overactive mTOR can promote excessive cell division with increased risk of DNA copying errors leading to cancer. Conversely, mTOR is inhibited by AMPK and therefore by anything that induces AMPK – such as polyphenols and fasting. mTOR is directly

inhibited by limiting intake of the amino acids, in particular methionine and leucine.

In summary, mTOR is an important regulator of growth and metabolism. In a scenario of nutrient excess and reduced physical activity, mTOR can become dysregulated and overactive. Limiting intake of animal protein, intermittent fasting, and regular exercise can prevent mTOR excess and support healthspan and lifespan.

The IRS1 (insulin receptor substrate 1) protein transmits signals to insulin and insulin-like growth (IGF-1R) receptors to facilitate glucose uptake by cells. In normal circumstances, mTOR regulates this process by uncoupling (blocking) IRS1 interaction with other receptors, thus creating a negative feedback loop. However, hyperactive mTOR can increase degradation of IRS1, resulting in insulin resistance and type 2 diabetes. In addition, a SNP on IRS1 confers lower activity, with similar consequences.

PARP1 (poly(ADP-ribose) polymerase 1) acts as a first responder that detects DNA damage and then facilitates the choice of repair pathway. It is activated by ROS (reactive oxygen species), elevated glucose, and infection, and promotes transcription of inflammatory genes, including TNF and IL6. Both SIRT1 and PARP1 have a roughly equal affinity for NAD+ but DNA damage can increase PARP1 activity more than 100-fold, depleting NAD+ available to SIRT1. Although PARP1 has important roles to play, over-expression can result in highly inaccurate DNA repair. PARP inhibitor drugs reduce inflammation, improve cardiac and endothelial function, and as a cancer treatment, stop PARP from doing its repair work in cancer cells.

A SNP on PARP1 is associated with up to 50% reduced activity, higher HDL cholesterol, lower 8-OHdG (a measure of DNA damage) and decreased risk of coronary artery disease. Reduced PARP1 activity can increase the availability of NAD+ to support SIRT functions, including energy production and DNA synthesis and repair. Vitamin D is a suppressor of PARP1 activity.

PPARG is a key regulator of glucose homeostasis and adipogenesis. It inhibits the release of free fatty acids and adipocytokines (TNF and leptin) and increases production of adiponectin, which together lead to improved insulin sensitivity in liver and skeletal muscle. It also promotes fat storage (and differentiation of white and brown fat). A SNP on PPARG confers a reduced expression, better insulin sensitivity and glucose utilisation, and lower risk of type 2 diabetes. Carriers also have less weight gain on a high-fat diet. Omega-3 and polyphenols – quercetin and kaempferol (beans, spinach, kale, tea and broccoli) are helpful PPARG modulators. PPARG is upregulated by HIF1A.

HIF1A (hypoxia-inducible factor 1-alpha) regulates cellular responses to hypoxic (low oxygen) conditions, and is also upregulated by growth factors, via mTOR. It induces the expression of hundreds of genes including VEGFA and erythropoietin (EPO) which help increase oxygen delivery to hypoxic regions (to compensate for hypoxia). HIF1A also regulates genes that impact energy metabolism – promoting glucose uptake and metabolism (via PPARG), repressing fatty acid oxidation (via PGC1A and PPARA), and supporting cell proliferation and survival.

A SNP on HIF1A is associated with higher activity and reduced risk of developing diabetes (types 1 and 2), and improved wound healing, but dysregulated lipid metabolism associated with atherosclerosis, fatty liver disease (NAFLD), obesity, and cancer. This SNP has been reported as beneficial to athletes participating in power sports, due to increased glucose metabolism and muscle building, with the wild genotype being beneficial to endurance athletes.

VEGFA (vascular endothelial growth factor A) helps to restore and improve oxygen supply by creating new blood vessels in response to injury, exercise and during growth. The variance is associated with significantly higher VEGFA, which is beneficial for endurance and aerobic capability. However, it is also associated with diabetic retinopathy, and tumour growth in the context of cancer. Natural inhibitors of angiogenesis include resveratrol, green tea, ginkgo biloba, quercetin, ginger, cinnamon, curcumin, melon, flavonoids and vitamin E.

## Sugar Metabolism

Carbohydrates are sugar molecules and are the body's favoured fuel source, providing immediate energy. They are broken down into glucose which constitutes blood sugar.

Glucose can come from three different sources: i) intestinal absorption of dietary carbohydrates (sugar, starches and fibre), ii) glycogenolysis – breakdown of glycogen, and iii) gluconeogenesis – formation of glucose from non-carbohydrate precursors including lactate, pyruvate, glycerol and amino acids.

After glucose enters the bloodstream, insulin is released which allows it to enter the cells. Insulin is produced by the pancreas and is the body's primary anabolic hormone. It regulates the metabolism of carbohydrates, fats and proteins. Once in the cell, glucose can be used for energy production (aerobic or anaerobic) and nucleotide synthesis via the pentose phosphate pathway (PPP). Impairment of a pathway due to SNPs or environmental factors can lead to conditions such as insulin resistance, diabetes, weight gain, chronic fatigue or cancer.

### Blood Glucose

The TCF7L2 (transcription factor 7-like 2) gene is involved in regulating blood sugar by influencing the production of insulin. Variants on TCF7L2 lead to over-expression, reduced insulin release and risk of hyperglycaemia. This can lead to insulin resistance, type 2 diabetes, and risk of developing gestational diabetes. Natural modulators of TCF7L2 include flavonoids, curcumin, green tea, resveratrol, retinoids and lupeol – found in olives, mangoes, strawberries, green peppers, tomatoes.

Insulin binds to its receptor and interacts with IRS1 (insulin receptor substrate 1) to facilitate glucose uptake via increased activity of GLUT4, a glucose transporter. A SNP on IRS1 results in reduced activity and impaired insulin signalling. Obesity, stress and inflammation can further promote insulin resistance. Exercise (especially aerobic) induces GLUT4 activity. GLUT2 is another transporter which controls glucose uptake in the liver. However, unlike GLUT4, it does not rely on insulin and acts as a glucose sensor. A SNP on GLUT2 can lead to a down-regulated activity and is associated with risk of gestational diabetes and noninsulin-dependent diabetes.

Glucose uptake can be influenced by several other factors. FABP2 (fatty acid-binding protein 2) has high affinity for saturated long-chain fatty acids and is involved in their uptake and metabolism. Increased FABP2 expression preferentially moves fats into cells instead of glucose, which increases the risk of insulin resistance and type 2 diabetes. PPARG (peroxisome proliferator-activated receptor gamma) is also involved in glucose uptake as it promotes fat storage which can crowd out the glucose from entering the cell. A SNP on PPARG downregulates its activity, which is beneficial and is associated with increased insulin sensitivity and glucose utilisation. Carriers of this SNP are particularly sensitive to omega-3s, which help to reduce triglyceride levels.

### Cellular Glucose

Once glucose has entered the cell, it is broken down by a process called glycolysis. It is firstly converted to G6P (glucose-6-phosphate) by a glucokinase, encoded by the GCK gene. Glucokinase diabetes is a type of familial diabetes often called MODY (maturity-onset diabetes of the young). Variants on GCK reduce its activity and may increase blood glucose and risk of type 2 diabetes. Carriers of this SNP may benefit from a higher intake of whey proteins, retinoic acid and biotin.

G6P can be directed to the PPP to generate NADPH to activate glutathione and ribose-5-phosphate for nucleotide synthesis or – more typically to produce pyruvate, with NAD+ and magnesium as cofactors. In the mitochondria, pyruvate is converted to acetyl-CoA, which goes into the Krebs cycle to produce ATP.

In anaerobic conditions (hypoxia/low oxygen), pyruvate is converted to lactate by fermentation. This can occur during strenuous exercise or due to infection or shock. While this produces less ATP, it can support rapid cellular division, which can be beneficial for muscle growth but detrimental in abnormal conditions (Warburg effect).

AMPD1 codes for adenosine monophosphate (AMP) deaminase 1, a component of the purine nucleotide cycle. It plays a role in energy metabolism by recycling AMP back to IMP (inosine monophosphate), and ammonia. A SNP results in AMPD1 deficiency, which increases the levels of AMP and leads to activation of AMPK. This is beneficial as it has been associated with improved insulin sensitivity and glucose utilisation, and less risk of type 2 diabetes. Metformin, one of the best known drugs used to reverse insulin resistance, has a similar effect to the SNP, inhibiting AMPD1 activity and inducing AMPK. However, individuals with AMPD1 deficiency are more likely to experience muscle fatigue, cramps and pain during and after endurance exercise. This is due to slower conversion of AMP to IMP, and less ammonia production to neutralise lactate. Well-trained, fuelled and hydrated athletes have lower risk of experiencing muscle dysfunction symptoms.

**Glucose vs Fats**

Excess glucose intake promotes fat storage and inhibits fat burning. In this case, acetyl-CoA is converted into malonyl-CoA, which is a building block of triglycerides (fat droplets) in adipose tissue. Malonyl-CoA also suppresses fatty acid utilisation by inhibiting the action of CPT1A (carnitine palmitoyltransferase 1A), which transports fatty acids into the mitochondria.

## Fat Metabolism

Fats are an essential energy source and have structural, metabolic and immune functions. They impact brain development and cognitive function, cardiovascular health and inflammation, and help absorption of fat-soluble vitamins (A, D, E and K).
There are four major types of dietary fats: saturated fats, trans fats, monounsaturated fats and polyunsaturated fats.

**Saturated fats** are made up of carbon chains that are all bonded (saturated) with hydrogen. They are mainly found in animal sources, such as meat, butter and cheese, and some plant sources such as coconut oil. Historically, saturated fats have been considered as detrimental to health as their overconsumption is one of the leading causes of obesity.

**Unsaturated fats** have spaces along the chain of carbon atoms, instead of being saturated with hydrogen. **Monounsaturated fats (MUFAs)** contain one unsaturated bond. As they help to increase 'good' cholesterol and lower 'bad' cholesterol, MUFAs are considered healthy. Examples include olives, avocados and pumpkin seeds.
**Polyunsaturated fats (PUFAs)** contain more than one double bond in their carbon chain. They include omega-3 and omega-6 fatty acids, which are essential as the body can't produce them. They are found in a variety of animal and plant-based sources – oily fish, nuts and vegetable oils.

**Trans fats** are a type of unsaturated fat that has been hydrogenated. Although trans fats occur naturally (in milk, for example) the majority, including hydrogenated vegetable oil, margarine and baked goods (olive oil spreads, crisps, biscuits, cakes and pizzas), are manufactured. Trans fats are considered the worst fats to consume as a diet high in these fats increases the risk of heart disease.

### Circulating Fats

Triglycerides are the most common form of dietary fats. As they are not water-soluble, triglycerides and cholesterol are packaged as lipoproteins for transport to target tissues and cells. There are different types and functions of lipoproteins such as chylomicrons, VLDL (very-low-density lipoprotein), LDL (low-density lipoprotein) and HDL (high-density lipoprotein). LDL is considered a 'bad' cholesterol as it contributes to fat buildups in arteries (atherosclerosis) as opposed to HDL being considered 'good'.

Lipoprotein lipase coded by the LPL gene is located on the surface of the cells. LPL breaks down triglycerides in lipoproteins to free fatty acids (FFAs) which can then be taken up by muscle cells or adipocytes for energy production or storage. Once emptied of triglycerides, the lipoproteins evolve to become HDL. A SNP on LPL is associated with increased activity – lower triglyceride levels, higher HDL and reduced risk of coronary artery disease. Exercise (especially aerobic), lipid-lowering agents and statins can also promote LPL activity.

Fatty acid transport proteins (FATPs) and CD36 (also called FAT) facilitate the uptake of FFAs into adipocytes and muscle cells. CD36 is the free fatty acid equivalent of the GLUT transporters (for glucose). It also impacts taste and dietary fat perception. Reduced CD36 sensitivity due to genetic variance is associated with a greater liking for high-fat foods and increased risk of visceral obesity.

Although carbohydrates are the cell's favoured fuel source, this order can be disrupted by fatty acid binding protein (FABP2). A SNP on FABP2 increases activity, preferentially moving fats into the cell, and crowding out glucose. This increases the risk of insulin resistance, hyperinsulinemia, and type 2 diabetes. SNP carriers benefit from limiting intake of saturated fats. Polyphenols, especially carnosic acid found in rosemary and sage, can inhibit FABP2 activity.

### Cellular Fats

When fatty acids enter the cell, they can either be directly used for energy production or be stored as triglycerides (fat droplets).

When glucose levels are low, the body uses fat as an alternative energy source. Lipolysis is the process through which lipases break down

triglycerides to their constituent molecules – FFAs and glycerol. PPARA (peroxisome proliferator-activated receptor alpha) is activated when energy levels are low and initiates fat metabolism. A SNP is associated with lower activity and is less compatible with a ketogenic diet. Resveratrol, isoflavones, flavonoids and PUFAs can increase PPARA function.

Several genes are involved in regulation of lipolysis including PLIN1 (perilipin 1) and ADRB3 (adrenaline receptor beta 3). PLIN1 controls access to adipocyte triglycerides and protects them from being broken down by lipases. A SNP on PLIN1 is associated with lower expression, higher rates of lipolysis and less risk of obesity. However, it can also confer resistance to weight loss on an energy-restricted diet. Conversely, ADRB3 induces fat break-down by stimulating lipases. A SNP confers reduced sensitivity to adrenaline, slower lipolysis and oxidation, and increased fat accumulation. Carriers of this SNP might also experience resistance to weight loss in response to lifestyle interventions combining diet and exercise. In this case, adrenaline, caffeine, water, fasting, cold exposure, high intensity exercise, bananas, chocolate and green tea can induce lipolysis.

FFAs are converted to acyl-CoA, which is transported across the mitochondrial membrane by CPT1A (carnitine palmitoyltransferase 1A). When glucose is present, malonyl-CoA restricts acyl-CoA (and carnitine) from entering the mitochondria. However, in a low glucose state AMPK lowers malonyl-CoA, enabling entry. Acyl-CoA then undergoes beta-oxidation to produce acetyl-CoA. After beta-oxidation, acetyl-CoA enters the Krebs cycle to produce ATP.

A SNP on CPT1A results in a decreased activity and transport of fatty acids into the mitochondria. This can cause multiple symptoms such as fatigue, dizziness, abdominal pain, muscle pain or weakness, low blood sugar, and low ketone levels (especially during fasting or illness). A high-fat (ketogenic) diet is not advised for carriers of this SNP as it is more likely that fat will be stored rather than burned. Avoid skipping meals, exposure to cold, stress and strenuous exercise. Medium chain triglyceride (MCT) oil and L-carnitine supplementation may be helpful. Conversely, individuals with CPT1A wild genotype are likely to benefit from a ketogenic diet.

Ketogenesis is an alternative pathway which produces ketone bodies. It produces energy for the brain, heart and skeletal muscle during low glucose states such as fasting, prolonged physical activity and sleep. A ketogenic diet can have many health benefits such as weight loss, improved blood sugar, improved metabolic profile and heart health. Alcohol is a potent inhibitor.

Lipogenesis is the opposite of lipolysis, converting acetyl-CoA back to fat for storage. It is upregulated by insulin, glucose, and high energy state and downregulated by leptin. SREBF1 (sterol regulatory element-binding factor 1) activates lipogenic genes and some glycolytic ones too (GCK). It facilitates the storage of excess fatty acids as triglycerides and promotes cholesterol synthesis. Both low and high activity of SREBF1 contribute to insulin resistance and type 2 diabetes. A SNP on this gene is associated with higher SREBF1 expression, higher LDL and total cholesterol and increased risk of type 2 diabetes and non-alcoholic fatty liver disease. SREBF1 is downregulated by high cholesterol and PUFAs.

## Cholesterol and Bile

Cholesterol is a fatty substance which supports cell membrane fluidity, bile acid production, and synthesis of sex steroid hormones, CoQ10 (coenzyme Q10) and vitamin D.

Most (approximately 80%) cholesterol is synthesised in the liver, and the remainder is obtained from the diet. Dietary sources include red meat, eggs, liver, kidney, shellfish and butter. Excess fat and sugar intake promote cholesterol synthesis.

As described in the Fats Section, cholesterol is packaged with triglycerides into lipoproteins. There are several types of lipoproteins but the two most common are LDL (low-density lipoprotein) – considered to be 'bad' cholesterol – and HDL (high-density lipoprotein) – often called 'good' cholesterol.

Cholesterol is regulated by negative feedback. When cholesterol is too high, synthesis is suppressed and liver uptake is reduced (by inhibiting LDL receptors). This causes LDL to accumulate in the blood, which can initiate atherosclerosis. Cholesterol-lowering drugs, such as statins, also exploit the feedback system by blocking cholesterol synthesis, but conversely increase the activity of LDLRs (LDL receptors).

### Cholesterol Synthesis

Acetyl-coA is converted to cholesterol via the mevalonate pathway. This series of reactions (30+ steps) is primarily regulated by HMGCR (HMG-CoA reductase) which converts HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) into mevalonate.

HMGCR is upregulated in obesity and high glucose and is inhibited by statins. A SNP on this gene decreases its expression, lowers circulating LDL and increases LDLR sensitivity, mimicking the mechanism of statins. This reduces the risk of coronary heart disease.

However, this SNP is associated with lower plasma phosphatidylcholine and sphingomyelin levels (which are important for cell membranes), as well as GLUT4 (glucose transporter 4) inhibition which increases BMI, body fat and risk of type 2 diabetes. Lower HMGCR activity can also lead to reduced CoQ10 and vitamin D production, needed for metabolic, antioxidant and mitochondrial functions. Therefore, for carriers of this SNP, it may be preferable to lower cholesterol naturally, through dietary changes such as increasing fibre and limiting saturated and trans fats, as an alternative to statins.

SREBF1 (sterol regulatory element-binding factor 1) facilitates storage of fatty acids as triglycerides by inducing lipogenesis, and promotes cholesterol synthesis by inducing HMGCR activity. A SNP on SREBF1 increases its expression, is associated with higher LDL and total cholesterol, and increased risk of type 2 diabetes and non-alcoholic fatty liver disease. Insulin (via mTOR) increases SREBF1 activity while PUFAs (polyunsaturated fatty acids) – such as oily fish, nuts and vegetable oils – decrease it.

### Cholesterol Uptake and Metabolism

LDL receptors enable uptake of cholesterol by the liver, which removes about 70% of LDL from the bloodstream. LDLRs therefore have an essential role in LDL regulation. Some rare mutations in LDLR and other genes can cause a form of high cholesterol called familial hypercholesterolemia. Common SNPs that decrease LDLR sensitivity can lead to higher total cholesterol and LDL levels, increased risk of coronary heart disease and Alzheimer's disease (especially in men). Red grape juice (polyphenols), berberine and omega-3 fatty acids can increase LDLR sensitivity. Conversely, high fructose intake can increase the risk of glycation which negatively impacts LDLR.

Finally, cholesterol is converted to bile acids via CYP7A1 (cholesterol 7 alpha-hydroxylase 1). Bile acids are needed to absorb and digest fats in the small intestine. This is also the primary mechanism for removing cholesterol from the body. A SNP on CYP7A1 lowers its activity, leading to a slower conversion to bile acids, and therefore, higher cholesterol levels. Oats, taurine and green tea can support CYP7A1 activity and help remove cholesterol.

## Mitochondria and Inflammation

Mitochondria are tiny organelles inside cells that generate energy from food in the form of ATP (adenosine triphosphate). This process is known as cellular respiration. It is for this reason that mitochondria are often referred to as powerhouses of the cell. Mitochondrial function is particularly impacted by sirtuins (SIRTs), uncoupling proteins (UCPs), antioxidant and inflammatory genes.

As seen in the Nutrient Sensing section, SIRTs are an NAD+ (nicotinamide adenine dinucleotide) dependent family of signalling proteins involved in metabolic regulation. Sirtuin 3 (SIRT3) is expressed in the mitochondria and hence plays an important role in regulating energy metabolism – fatty acid oxidation, the Krebs cycle, the ETC (electron transport chain) and ROS (reactive oxygen species) detoxification.

The Krebs cycle is the main source of energy for cells. It takes in Acetyl-CoA (from glucose and fats) and with the help of cofactors NAD+, FAD (flavin adenine nucleotide), generates NADH, FADH2 and ATP. Subsequently, the protons (H+ ions) and electrons released from NADH and FADH2, are processed by the ETC with cofactors CoQ10, iron and copper. The protons couple with ATP synthase to produce ATP.

### Uncoupling Proteins

Uncoupling proteins return the free, uncoupled, protons from the (mitochondria) intermembrane space to the matrix and release energy in the form of heat. By removing protons, the UCPs help prevent ROS production and mitochondrial damage.

Brown adipose tissue (BAT) is activated in cold conditions and has a high concentration of UCPs, enabling greater metabolic activity. It is more present in women than in men, decreases with age, and can be induced by PGC1A, cold exposure, leptin, exercise, adrenaline, green tea, cabbage, berries, spinach and capsaicin. UCP1, known as thermogenin, is exclusively found in BAT.

A SNP on UCP1 is associated with reduced expression, impaired energy metabolism and lower resting metabolic rate. This can promote fat storage, increased BMI and obesity (especially lower body). It is also associated with high triglycerides, high LDL and low HDL. Purine nucleotides (found in high fructose corn syrup, seafood, organ meat and alcohol) inhibit UCP1, whereas fatty acids activate it.

UCP2 and UCP3 specifically regulate fatty acid oxidation and reduce the formation of ROS. A SNP on UCP2 is associated with lower activity and risk of higher BMI, obesity and type 2 diabetes. UCP3 protects from lipid-induced oxidative stress by removing excess fatty acids. A polymorphism on UCP3 is associated with decreased expression, inflammation, higher risk of obesity, insulin resistance, higher LDL cholesterol, non-alcoholic fatty liver disease, type 2 diabetes and other symptoms of metabolic dysfunction, particularly in Asian populations. Physical activity has been shown to increase UCP3 activity. A high-fat diet is not recommended for SNP carriers.

### Antioxidant Cascade

During cellular respiration, ROS (free radicals) are formed within the mitochondria. These by-products include superoxide anion, hydrogen peroxide (H2O2), and hydroxyl radical, which are highly reactive. While ROS are essential signalling molecules, excess can lead to oxidative stress, which can damage cells, proteins, lipids and DNA, and contribute to biological ageing. Oxidative stress also leads to symptoms of metabolic syndrome – obesity, diabetes, cancer, neurodegenerative and cardiovascular diseases.

Antioxidant defence is the ROS scavenging mechanism activated by SIRT3. By binding to FOXO3 (forkhead box family member 3), this sirtuin stimulates catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPX) which all have an antioxidant action. A SNP on SIRT3 is associated with increased activity, and improved metabolic function, healthier ageing and longer lifespan. SIRT3 is upregulated by caloric restriction, fasting, exercise, and its cofactor NAD+. However, SIRT3 activity reduces with age and a high-fat diet. Related to its antioxidant function, FOXO3 has been identified

as a strong contributor to exceptional longevity. Curcumin and green tea help to induce FOXO3.

Working alongside FOXO3 to activate the antioxidant cascade is NRF2 (nuclear factor erythroid 2-related factor 2), often called the master antioxidant regulator. It also stimulates mitochondrial biogenesis. A SNP on NRF2 is associated with lower activity and reduced antioxidative capacity – due to knock-on effects on SOD2, CAT and GPX1. Aerobic exercise, caloric restriction/fasting, DHA (docosahexaenoic acid) – a type of omega-3 fat, and resveratrol have been shown to increase NRF2 activity.

The first step of the antioxidant defence mechanism is led by SOD2, which transforms superoxide into hydrogen peroxide and oxygen. A SNP on this gene can reduce SOD2 activity, leading to more oxidative stress and increased risk of free radical damage. Manganese is the main cofactor for SOD2.

In the second step, CAT and GPX1 convert hydrogen peroxide into oxygen and water. Polymorphisms on these genes reduce their antioxidant activity too and increase ROS levels. Their cofactors are manganese (for CAT), selenium and glutathione (for GPX1). Other small antioxidants that aid in mitochondrial protection are lipoic acid, vitamin E, CoQ10 and carnitine.

**Inflammation**

Mitochondrial ROS can lead to chronic inflammation. In return, pro-inflammatory compounds can also increase ROS levels, triggering a 'vicious cycle'. Increased activity of IL6 (interleukin 6), CRP (C-reactive protein), IFNG (interferon-gamma) and TNF (tumour necrosis factor), due to SNPs and environmental factors, can contribute to oxidative stress and stimulate metabolic, inflammatory and autoimmune diseases. Anti-inflammatory nutrients include omega-3 fatty acids, curcumin and green tea.

## How to Read the Report

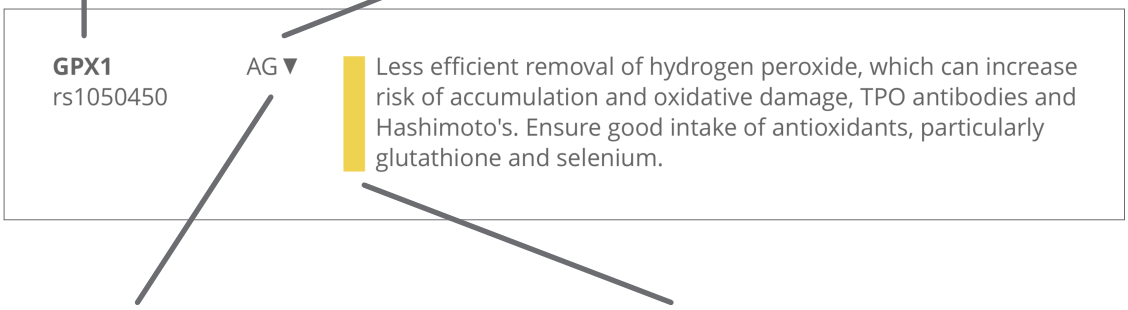
### Genes

Results are listed in order of the gene short name. The 'rs' number is the reference sequence number that identifies a specific location on the genome. It is also known as a SNP (Single Nucleotide Polymorphism) pronounced 'snip', polymorphism or mutation.

### Personalised Result

Your genotype result is shown as two letters (A,G,T or C) which represent the DNA bases present at that location.

Multiple attempts are made to achieve the required level of statistical confidence, but if that cannot be met it is reported as **'No result'**.




### Arrow Direction

The direction of the arrow indicates the potential effect of the SNP on gene expression, where applicable – it can increase or decrease activity, or neither.

▲ up-regulates or increases the activity and effect on the gene

▼ down-regulates or decreases the activity and effect on the gene

No arrow – no effect on the activity of the gene

### Highlight Colour

The genotype result highlight indicates the potential effect of the SNP on gene function in a particular context.

**RED** the effect of the variant is negative

**AMBER** the effect of the variant is somewhat negative

**GREEN** no variation, or the effect of the variant is positive

### Pathway Diagram Key

Cofactor  Inhibitor

# References


## **ADIPOQ** Adiponectin, C1Q and collagen domain containing

Alimi M, Goodarzi MT, Nekoei M. Adiponectin gene polymorphisms and risk of type 2 diabetes: an updated evidence for meta-analysis. Diabetol Metab Syndr. 2021 Nov 17;13(1):133. doi: 10.1186/s13098-021-00749-x. PMID: 34789338; PMCID: PMC8596906. (https://pubmed.ncbi.nlm.nih.gov/34789338/)

## **ADRB3** adrenoceptor beta 3

Chenyao Xie, Wenxi Hua, Yuening Zhao, Jingwen Rui, Jiarong Feng, Yanjie Chen, Yu Liu, Jingjing Liu, Xiaoqin Yang & Xiaojing Xu (2020) The ADRB3 rs4994 polymorphism increases risk of childhood and adolescent overweight/obesity for East Asia's population: an evidence-based meta-analysis, Adipocyte, 9:1, 77-86, DOI: 10.1080/21623945.2020.1722549. (https://www.tandfonline.com/doi/full/10.1080/21623945.2020.1722549)

## **AMPD1** Adenosine Monophosphate Deaminase 1

Cheng J, Morisaki H, Toyama K, Sugimoto N, Shintani T, Tandelilin A, Hirase T, Holmes EW, Morisaki T. AMPD1: a novel therapeutic target for reversing insulin resistance. BMC Endocr Disord. 2014 Dec 15;14:96. doi: 10.1186/1472-6823-14-96. PMID: 25511531; PMCID: PMC4274759. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4274759/)

Ginevičienė V, Jakaitienė A, Pranculis A, Milašius K, Tubelis L, Utkus A. AMPD1 rs17602729 is associated with physical performance of sprint and power in elite Lithuanian athletes. BMC Genetics. 2014;15:58. doi:10.1186/1471-2156-15-58. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4032451/)

Jinnah HA, Sabina RL, Van Den Berghe G. Metabolic disorders of purine metabolism affecting the nervous system. Handb Clin Neurol. 2013;113:1827-36. doi: 10.1016/B978-0-444-59565-2.00052-6. PMID: 23622405; PMCID: PMC4215161. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4215161/)

## **BDNF** Brain Derived Neurotrophic Factor

Singh, R., Takahashi, T., Tokunaga, M., Wilczynska, A., Kim, C., Meester, F., Handjieva-Darlenska, T., Cheema, S., Wilson, D., Milovanovic, B., Fedacko, J., Hristova, K. and Chaves, H., 2014. Effect of Brain Derived Neurotrophic Factor, In Relation to Diet and Lifestyle Factors, for Prevention of Neuropsychiatric and Vascular Diseases and Diabetes. The Open Nutraceuticals Journal, 7(1), pp.5-14. (https://benthamopen.com/contents/pdf/TONUTRAJ/TONUTRAJ-7-5.pdf)

## **CAT** Catalase

Goulas A, Agapakis D, Apostolidis A, Gouda D, Anastassiadis S, Trakatelli C, Savopoulos C, Hatzitolios AI. Association of the Common Catalase Gene Polymorphism rs1001179 With Glycated Hemoglobin and Plasma Lipids in Hyperlipidemic Patients. Biochem Genet. 2017 Feb;55(1):77-86. doi: 10.1007/s10528-016-9777-2. Epub 2016 Oct 4. PMID: 27704307. (https://pubmed.ncbi.nlm.nih.gov/27704307/)

## **CD36** fatty acid transporter

Karthi M, Deepankumar S, Vinithra P, Gowtham S, Vasanth K, Praveen Raj P, Senthilkumar R, Selvakumar S. Single nucleotide polymorphism in CD36: Correlation to peptide YY levels in obese and non-obese adults. Clin Nutr. 2021 May;40(5):2707-2715. doi: 10.1016/j.clnu.2021.02.044. Epub 2021 Mar 6. PMID: 33933736. (https://pubmed.ncbi.nlm.nih.gov/33933736/)

Zhao, L., Li, Y., Ding, Q., Li, Y., Chen, Y. and Ruan, X., 2021. CD36 Senses Dietary Lipids and Regulates Lipids Homeostasis in the Intestine. Frontiers in Physiology, 12, https://doi.org/10.3389/fphys.2021.669279. (https://www.frontiersin.org/articles/10.3389/fphys.2021.669279/full)

## **CPT1A** carnitine palmitoyltransferase 1A

Gobin S, Thuillier L, Jogl G, Faye A, Tong L, Chi M, Bonnefont JP, Girard J, Prip-Buus C. Functional and structural basis of carnitine palmitoyltransferase 1A deficiency. J Biol Chem. 2003 Dec 12;278(50):50428-34. doi: 10.1074/jbc.M310130200. Epub 2003 Sep 29. PMID: 14517221. (https://pubmed.ncbi.nlm.nih.gov/14517221/)

Robitaille J, Houde A, Lemieux S, Pérusse L, Gaudet D, Vohl MC. Variants within the muscle and liver isoforms of the carnitine palmitoyltransferase I (CPT1) gene interact with fat intake to modulate indices of obesity in French-Canadians. J Mol Med (Berl). 2007 Feb;85(2):129-37. doi: 10.1007/s00109-006-0116-7. Epub 2006 Nov 7. PMID: 17089095. (https://pubmed.ncbi.nlm.nih.gov/17089095/)

## **CRP** C-Reactive Protein

Arouca AB, Meirhaeghe A, Dallongeville J, Moreno LA, Lourenço GJ, Marcos A, Huybrechts I, Manios Y, Lambrinou CP, Gottrand F, Kafatos A, Kersting M, Sjöström M, Widhalm K, Ferrari M, Molnár D, González-Gross M, Forsner M, De Henauw S, Michels N; HELENA Study Group. Interplay between the Mediterranean diet and C-reactive protein genetic polymorphisms towards inflammation in adolescents. Clin Nutr. 2020 Jun;39(6):1919-1926. doi: 10.1016/j.clnu.2019.08.016. Epub 2019 Aug 23. PMID: 31500937. (https://pubmed.ncbi.nlm.nih.gov/31500937/)

Bordoni L, Petracci I, Zhao F, Min W, Pierella E, Assmann TS, Martinez JA, Gabbianelli R. Nutrigenomics of Dietary Lipids. Antioxidants (Basel). 2021 Jun 22;10(7):994. doi: 10.3390/antiox10070994. PMID: 34206632; PMCID: PMC8300813. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8300813/)

## **CYP7A1** Cytochrome P450 Family 7 Subfamily A Member 1

Abdullah MMH, Vazquez-Vidal I, Baer DJ, House JD, Jones PJH, Desmarchelier C. Common Genetic Variations Involved in the Inter-Individual Variability of Circulating Cholesterol Concentrations in Response to Diets: A Narrative Review of Recent Evidence. Nutrients. 2021 Feb 22;13(2):695. doi: 10.3390/nu13020695. PMID: 33671529; PMCID: PMC7926676. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7926676/)

Takahashi M, Nagata M, Kinoshita T, Kaneko T, Suzuki T. CYP7A1, NPC1L1, ABCB1, and CD36 Polymorphisms Are Associated with Increased Serum Coenzyme Q10 after Long-Term Supplementation in Women. Antioxidants (Basel). 2021 Mar 11;10(3):431. doi: 10.3390/antiox10030431. PMID: 33799730; PMCID: PMC7998724. (https://pubmed.ncbi.nlm.nih.gov/33799730/)

## **FAAH** Fatty Acid Amide Hydrolase

Doris, J., Millar, S., Idris, I. and O'Sullivan, S., 2018. Genetic polymorphisms of the endocannabinoid system in obesity and diabetes. Diabetes, Obesity and Metabolism, 21(2), pp.382-387. (https://dom-pubs.onlinelibrary.wiley.com/doi/10.1111/dom.13504)

## **FABP2** FATTY ACID-BINDING PROTEIN 2

Liu PJ, Liu YP, Qin HK, Xing T, Li SS, Bao YY. Effects of polymorphism in FABP2 Ala54Thr on serum lipids and glycemic control in low glycemic index diets are associated with gender among Han Chinese with type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2019 Mar 27;12:413-421. doi: 10.2147/DMSO.S196738. PMID: 30988637; PMCID: PMC6441458. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6441458/)

Mauro Gaya, Victoria Repetto, Judith Toneatto, Claudia Anesini, Graciela Piwien-Pilipuk, Silvia Moreno, Antiadipogenic effect of carnosic acid, a natural compound present in Rosmarinus officinalis, is exerted through the C/EBPs and PPAR pathways at the onset of the differentiation program, Biochimica et Biophysica Acta (BBA) - General Subjects, Volume 1830, Issue 6, 2013, Pages 3796-3806, ISSN 0304-4165, https://doi.org/10.1016/j.bbagen.2013.03.021. (https://www.sciencedirect.com/science/article/abs/pii/S0304416513000998)

## **FOXO3** Forkhead Box O3

AMA Style Fasano C, Disciglio V, Bertora S, Lepore Signorile M, Simone C. FOXO3a from the Nucleus to the Mitochondria: A Round Trip in Cellular Stress Response. Cells. 2019; 8(9):1110. https://doi.org/10.3390/cells8091110. (https://www.mdpi.com/2073-4409/8/9/1110/htm)

Chung WH, Dao RL, Chen LK, Hung SI. The role of genetic variants in human longevity. Ageing Res Rev. 2010 Nov;9 Suppl 1:S67-78. doi: 10.1016/j.arr.2010.08.001. Epub 2010 Aug 12. PMID: 20708717; PMCID: PMC7105197. (https://pubmed.ncbi.nlm.nih.gov/20708717/)

Ni X, Wang Z, Gao D, Yuan H, Sun L, Zhu X, Zhou Q, Yang Z. A description of the relationship in healthy longevity and aging-related disease: from gene to protein. Immun Ageing. 2021 Jun 25;18(1):30. doi: 10.1186/s12979-021-00241-0. PMID: 34172062; PMCID: PMC8229348. (https://pubmed.ncbi.nlm.nih.gov/34172062/)

Sanese P, Forte G, Disciglio V, Grossi V, Simone C. FOXO3 on the Road to Longevity: Lessons From SNPs and Chromatin Hubs. Comput Struct Biotechnol J. 2019;17:737-745. Published 2019 Jun 13. doi:10.1016/j.csbj.2019.06.011. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6606898/)

Zhao, Y. and Liu, Y., 2021. Longevity Factor FOXO3: A Key Regulator in Aging-Related Vascular Diseases. Frontiers in Cardiovascular Medicine, 8. (https://www.frontiersin.org/articles/10.3389/fcvm.2021.778674/full)

## **FTO** Fat Mass and Obesity-Associated Gene

Dougkas A., Yaqoob P., Givens I.D., Reynolds C.K., Minihane A.M. (2013). The impact of energy related SNP on appetite and energy intake, The British Journal of Nutrition, 110(6): pp. 1151-6. (http://search.proquest.com/openview/b5d7af2301cfb1e390d703f5fff9eab2/1?pq-origsite=gscholar)

Moleres A., Ochoa M.C., Rendo-Urteaga T., Martínez-González M.A., Azcona- Sanjulián M.C., Martínez J.A. and Marti A., on behalf of the GENOI study group. (2011). Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the FTO gene in a Spanish children case-control study. Br J Nutr.;107(4): pp. 533-82. (http://dadun.unav.edu/bitstream/10171/19253/1/BrJNutrmoleres11.pdf)

Shoulders C. (2008). The FTO (fat mass and obesity-associated) gene: big in adipocyte lipolysis? The Journal of Lipid Research, volume 49, pp. 495-496. (http://www.jlr.org/content/49/3/495.full)

## **GCK** Glucokinase

Da Silva MS, Chartrand D, Vohl MC, Barbier O, Rudkowska I. Dairy Product Consumption Interacts with Glucokinase (GCK) Gene Polymorphisms Associated with Insulin Resistance. J Pers Med. 2017 Aug 30;7(3):8. doi: 10.3390/jpm7030008. PMID: 28867816; PMCID: PMC5618154. (https://pubmed.ncbi.nlm.nih.gov/28867816/)

Qi Q, Wu Y, Li H, Loos RJ, Hu FB, Sun L, Lu L, Pan A, Liu C, Wu H, Chen L, Yu Z, Lin X. Association of GCKR rs780094, alone or in combination with GCK rs1799884, with type 2 diabetes and related traits in a Han Chinese population. Diabetologia. 2009 May;52(5):834-43. doi: 10.1007/s00125-009-1290-2. Epub 2009 Feb 25. PMID: 19241058. (https://pubmed.ncbi.nlm.nih.gov/19241058/)

Rose CS, Ek J, Urhammer SA, Glümer C, Borch-Johnsen K, Jørgensen T, Pedersen O, Hansen T. A -30G>A polymorphism of the beta-cell-specific glucokinase promoter associates with hyperglycemia in the general population of whites. Diabetes. 2005 Oct;54(10):3026-31. doi: 10.2337/diabetes.54.10.3026. PMID: 16186409. (https://pubmed.ncbi.nlm.nih.gov/16186409/)

## **GLUT2** solute carrier family 2 member 2

Dupuis J, Langenberg C, Prokopenko I, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk [published correction appears in Nat Genet.2010 May;42(5):464]. Nat Genet. 2010;42(2):105-116. doi:10.1038/ng.520. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3018764/?report=reader)

## **GPX1** glutathione peroxidase 1

Chen H, Yu M, Li M, Zhao R, Zhu Q, Zhou W, Lu M, Lu Y, Zheng T, Jiang J, Zhao W, Xiang K, Jia W, Liu L. Polymorphic variations in manganese superoxide dismutase (MnSOD), glutathione peroxidase-1 (GPX1), and catalase (CAT) contribute to elevated plasma triglyceride levels in Chinese patients with type 2 diabetes or diabetic cardiovascular disease. Mol Cell Biochem. 2012 Apr;363(1-2):85-91. doi: 10.1007/s11010-011-1160-3. Epub 2011 Dec 14. PMID: 22167619. (https://pubmed.ncbi.nlm.nih.gov/22167619/)

Huang JQ, Zhou JC, Wu YY, Ren FZ, Lei XG. Role of glutathione peroxidase 1 in glucose and lipid metabolism-related diseases. Free Radic Biol Med. 2018 Nov 1;127:108-115. doi: 10.1016/j.freeradbiomed.2018.05.077. Epub 2018 May 22. PMID: 29800654; PMCID: PMC6168395. (https://pubmed.ncbi.nlm.nih.gov/29800654/)

## **HIF1A** hypoxia inducible factor 1 subunit alpha

Gladek I, Ferdin J, Horvat S, Calin GA, Kunej T. HIF1A gene polymorphisms and human diseases: Graphical review of 97 association studies. Genes Chromosomes Cancer. 2017 Jun;56(6):439-452. doi: 10.1002/gcc.22449. Epub 2017 Mar 31. PMID: 28165644; PMCID: PMC5395341. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5395341/)

Nagy G, Kovacs-Nagy R, Kereszturi E, et al. Association of hypoxia inducible factor-1 alpha gene polymorphism with both type 1 and type 2 diabetes in a Caucasian (Hungarian) sample. BMC Med Genet. 2009;10:79. Published 2009 Aug 19. doi:10.1186/1471-2350-10-79. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2736933/)

## **HMGCR** 3-hydroxy-3-methylglutaryl-CoA reductase

Deichmann R, Lavie C, Andrews S. Coenzyme q10 and statin-induced mitochondrial dysfunction. Ochsner J. 2010 Spring;10(1):16-21. PMID: 21603349; PMCID: PMC3096178. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3096178/)

Khan SU, Rahman H, Okunrintemi V, Riaz H, Khan MS, Sattur S, Kaluski E, Lincoff AM, Martin SS, Blaha MJ. Association of Lowering Low-Density Lipoprotein Cholesterol With Contemporary Lipid-Lowering Therapies and Risk of Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2019 Apr 2;8(7):e011581. doi: 10.1161/JAHA.118.011581. PMID: 30898075; PMCID: PMC6509736. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6509736/)

Li S, Schooling CM. A phenome-wide association study of genetically mimicked statins. BMC Med. 2021 Jun 30;19(1):151. doi: 10.1186/s12916-021-02013-5. PMID: 34187478; PMCID: PMC8244164. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8244164/)

Sarsenbayeva A, Jui BN, Fanni G, Barbosa P, Ahmed F, Kristófi R, Cen J, Chowdhury A, Skrtic S, Bergsten P, Fall T, Eriksson JW, Pereira MJ. Impaired HMG-CoA Reductase Activity Caused by Genetic Variants or Statin Exposure: Impact on Human Adipose Tissue, -Cells and Metabolome. Metabolites. 2021 Aug 25;11(9):574. doi: 10.3390/metabo11090574. PMID: 34564389; PMCID: PMC8468287. (https://pubmed.ncbi.nlm.nih.gov/34564389/)

Yang G, Schooling CM. Investigating genetically mimicked effects of statins via HMGCR inhibition on immune-related diseases in men and women using Mendelian randomization. Sci Rep. 2021 Dec 3;11(1):23416. doi: 10.1038/s41598-021-02981-x. PMID: 34862478; PMCID: PMC8642420. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8642420/)

## **IFN-gamma** Interferon Gamma

Lee YH, Bae SC. Association between interferon-gamma +874 T/A polymorphism and susceptibility to autoimmune diseases: A meta-analysis. Lupus. 2016;25(7):710–18. (https://www.ncbi.nlm.nih.gov/pubmed/26703437)

Li P, Zhao Y, Wu X, Xia M, Fang M, Iwasaki Y, Sha J, Chen Q, Xu Y, Shen A. Interferon gamma (IFN- ) disrupts energy expenditure and metabolic homeostasis by suppressing SIRT1 transcription. Nucleic Acids Res. 2012 Feb;40(4):1609-20. doi: 10.1093/nar/gkr984. Epub 2011 Nov 7. PMID: 22064865; PMCID: PMC3287208. (https://pubmed.ncbi.nlm.nih.gov/22064865/)

## **IL6** Interleukin 6

Boeta-Lopez K, Duran J, Elizondo D, Gonzales E, Rentfro A, Schwarzbach AE, Nair S. Association of interleukin-6 polymorphisms with obesity or metabolic traits in young Mexican-Americans. Obes Sci Pract. 2017 Dec 14;4(1):85-96. doi: 10.1002/osp4.138. PMID: 29479468; PMCID: PMC5818745. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5818745/)

M Erdogan, M Kulaksizoglu, S Ganidagli, A Berdeli, Genetic variations in interleukin 6 rs1800795 polymorphism and the association with susceptibility to Hashimoto's thyroiditis, Meta Gene, Volume 12, 2017, Pages 1-3, ISSN 2214-5400, https://doi.org/10.1016/j.mgene.2016.12.010. (https://www.sciencedirect.com/science/article/pii/S2214540016300974)

## **IRS1** insulin receptor substrate 1

Jellema A, Zeegers MP, Feskens EJ, Dagnelie PC, Mensink RP. Gly972Arg variant in the insulin receptor substrate-1 gene and association with Type 2 diabetes: a meta-analysis of 27 studies. Diabetologia. 2003 Jul;46(7):990-5. doi: 10.1007/s00125-003-1126-4. Epub 2003 Jun 18. PMID: 12819898. (https://pubmed.ncbi.nlm.nih.gov/12819898/)

## **LDLR** Low Density Lipoprotein Receptor

Fairoozy RH, White J, Palmen J, Kalea AZ, Humphries SE (2016) Identification of the Functional Variant(s) that Explain the Low-Density Lipoprotein Receptor (LDLR) GWAS SNP rs6511720 Association with Lower LDL-C and Risk of CHD. PLOS ONE 11(12): e0167676. https://doi.org/10.1371/journal.pone.0167676. (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0167676)

Zhu H, Tucker HM, Grear KE, Simpson JF, Manning AK, Cupples LA, Estus S. A common polymorphism decreases low-density lipoprotein receptor exon 12 splicing efficiency and associates with increased cholesterol. Hum Mol Genet. 2007 Jul 15;16(14):1765-72. doi: 10.1093/hmg/ddm124. Epub 2007 May 21. PMID: 17517690; PMCID: PMC2361133.. (https://pubmed.ncbi.nlm.nih.gov/17517690/)

Zou F, Gopalraj RK, Lok J, Zhu H, Ling IF, Simpson JF, Tucker HM, Kelly JF, Younkin SG, Dickson DW, Petersen RC, Graff-Radford NR, Bennett DA, Crook JE, Younkin SG, Estus S. Sex-dependent association of a common low-density lipoprotein receptor polymorphism with RNA splicing efficiency in the brain and Alzheimer's disease. Hum Mol Genet. 2008 Apr 1;17(7):929-35. doi: 10.1093/hmg/ddm365. Epub 2007 Dec 8. PMID: 18065781; PMCID: PMC2361153. (https://pubmed.ncbi.nlm.nih.gov/18065781/)

## **LEPR** Leptin Receptor

den Hoed M, Westerterp-Plantenga MS, Bouwman FG, Mariman EC, Westerterp KR. (2009). Postprandial responses in hunger and satiety are associated with the rs9939609 single nucleotide polymorphism in FTO, Am J Clin Nutr, 90 (5): pp. 1426-32. (https://www.ncbi.nlm.nih.gov/pubmed/19793853?dopt=Abstract)

## **LPL** Lipoprotein Lipase

Agirbasli M, Sumerkan MC, Eren F, Agirbasli D. The S447X variant of lipoprotein lipase gene is inversely associated with severity of coronary artery disease. Heart Vessels. 2011 Jul;26(4):457-63. doi: 10.1007/s00380-010-0077-1. Epub 2010 Dec 3. PMID: 21127884. (https://pubmed.ncbi.nlm.nih.gov/21127884/)

Clee SM, Loubser O, Collins J, Kastelein JJ, Hayden MR. The LPL S447X cSNP is associated with decreased blood pressure and plasma triglycerides, and reduced risk of coronary artery disease. Clin Genet. 2001 Oct;60(4):293-300. doi: 10.1034/j.1399-0004.2001.600407.x. PMID: 11683775. (https://pubmed.ncbi.nlm.nih.gov/11683775/)

## **MC4R** Melanocortin receptor 4

Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, Williams T, Ferreira M, Tang V, McGovern RA, Kenny CD, Christiansen LM, Edelstein E, Choi B, Boss O, Aschkenasi C, Zhang CY, Mountjoy K, Kishi T, Elmquist JK, Lowell BB. Divergence of melanocortin pathways in the control of food intake and energy expenditure. Cell. 2005 Nov 4;123(3):493-505. doi: 10.1016/j.cell.2005.08.035. PMID: 16269339. (https://pubmed.ncbi.nlm.nih.gov/16269339/)

Hammad MM, Abu-Farha M, Hebbar P, et al. MC4R Variant rs17782313 Associates With Increased Levels of DNAJC27, Ghrelin, and Visfatin and Correlates With Obesity and Hypertension in a Kuwaiti Cohort. Front Endocrinol (Lausanne). 2020;11:437. Published 2020 Jul 7. doi:10.3389/fendo.2020.00437. (https://www.frontiersin.org/articles/10.3389/fendo.2020.00437/full)

## **NPY** Neuropeptide Y

Katus U, Villa I, Ringmets I, Veidebaum T, Harro J. Neuropeptide Y gene variants in obesity, dietary intake, blood pressure, lipid and glucose metabolism: A longitudinal birth cohort study. Peptides. 2021 May;139:170524. doi: 10.1016/j.peptides.2021.170524. Epub 2021 Feb 27. PMID: 33652060. (https://pubmed.ncbi.nlm.nih.gov/33652060/)

## **NRF2** NFE2 like bZIP transcription factor 2

Shimizu S, Mimura J, Hasegawa T, Shimizu E, Imoto S, Tsushima M, Kasai S, Yamazaki H, Ushida Y, Suganuma H, Tomita H, Yamamoto M, Nakaji S, Itoh K. Association of single nucleotide polymorphisms in the NRF2 promoter with vascular stiffness with aging. PLoS One. 2020 Aug 11;15(8):e0236834. doi: 10.1371/journal.pone.0236834. PMID: 32780748; PMCID: PMC7418968. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7418968/)

Sorour NE, Abd El-Kareem HM, Ibrahim AE, Salem RM. Nuclear Factor Erythroid-2-related Factor 2 Gene Polymorphisms in Vitiligo. J Clin Aesthet Dermatol. 2021 Jun;14(6):14-17. Epub 2021 Jun 1. PMID: 34804349; PMCID: PMC8594532. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8594532/)

Wang J, Yu M, Chen J, Zhu L, Liu J, Xu J. Association of Nuclear Factor Erythroid-2-Related Actor 2 Gene Polymorphisms with Diabetic Nephropathy in Chinese Patients. Int J Gen Med. 2021 Apr 7;14:1231-1237. doi: 10.2147/IJGM.S300152. PMID: 33854365; PMCID: PMC8039206. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8039206/)

## **PARP1** poly(ADP-ribose) polymerase 1

Magdolna Szántó, Rebecca Gupte, W. Lee Kraus, Pal Pacher, Peter Bai, PARPs in lipid metabolism and related diseases, Progress in Lipid Research, Volume 84, 2021, 101117, ISSN 0163-7827, https://doi.org/10.1016/j.plipres.2021.101117. (https://www.sciencedirect.com/science/article/pii/S0163782721000333)

Sarah Hurtado-Bagès, Gunnar Knobloch, Andreas G. Ladurner, Marcus Buschbeck, The taming of PARP1 and its impact on NAD+ metabolism, Molecular Metabolism, Volume 38, 2020, 100950, ISSN 2212-8778, https://doi.org/10.1016/j.molmet.2020.01.014. (https://www.sciencedirect.com/science/article/pii/S2212877820300223)

Wang XB, Cui NH, Zhang S, Guo SR, Liu ZJ, Ming L. PARP-1 Variant Rs1136410 Confers Protection against Coronary Artery Disease in a Chinese Han Population: A Two-Stage Case-Control Study Involving 5643 Subjects. Front Physiol. 2017;8:916. Published 2017 Nov 14. doi:10.3389/fphys.2017.00916. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5694467/)

## **PGC1A** PPAR-Gamma Coactivator 1-Alpha

Roxanne Vandenbeek, Naveen P Khan, Jennifer L Estall; Linking Metabolic Disease With the PGC-1 Gly482Ser Polymorphism, Endocrinology, Volume 159, Issue 2, 1 February 2018, Pages 853–865, https://doi.org/10.1210/en.2017-00872. (https://www.ncbi.nlm.nih.gov/pubmed/29186342)

## **PLIN1** perilipin 1

Dolores Corella, Lu Qi, José V. Sorlí, Diego Godoy, Olga Portolés, Oscar Coltell, Andrew S. Greenberg, José M. Ordovas, Obese Subjects Carrying the 11482G>A Polymorphism at the Perilipin Locus Are Resistant to Weight Loss after Dietary Energy Restriction, The Journal of Clinical Endocrinology & Metabolism, Volume 90, Issue 9, 1 September 2005, Pages 5121–5126, https://doi.org/10.1210/jc.2005-0576. (https://academic.oup.com/jcem/article/90/9/5121/2838670)

## **POMC** proopiomelanocortin

Srivastava A, Mittal B, Prakash J, Srivastava P, Srivastava N. Analysis of MC4R rs17782313, POMC rs1042571, APOE-Hha1 and AGRP rs3412352 genetic variants with susceptibility to obesity risk in North Indians. Ann Hum Biol. 2016 May;43(3):285-8. doi: 10.3109/03014460.2015.1061597. Epub 2015 Jul 31. PMID: 26226973. (https://www.tandfonline.com/doi/full/10.3109/03014460.2015.1061597)

Williams KW, Scott MM, Elmquist JK. Modulation of the central melanocortin system by leptin, insulin, and serotonin: co-ordinated actions in a dispersed neuronal network. Eur J Pharmacol. 2011 Jun 11;660(1):2-12. doi: 10.1016/j.ejphar.2010.11.042. Epub 2011 Jan 3. PMID: 21211525; PMCID: PMC3085544. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3085544/)

## **PPARA** Peroxisome Proliferator-Activated Receptor Alpha

Duszka K, Gregor A, Guillou H, König J, Wahli W. Peroxisome Proliferator-Activated Receptors and Caloric Restriction-Common Pathways Affecting Metabolism, Health, and Longevity. Cells. 2020 Jul 16;9(7):1708. doi: 10.3390/cells9071708. PMID: 32708786; PMCID: PMC7407644. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7407644/)

Qi S, Wang C, Zhang Y, Cheng Y, Wang S, Zhao Y. The association of peroxisome proliferator-activated receptor with diabetic retinopathy, and additional gene-obesity interaction in Chinese type 2 diabetes mellitus patients. Obes Res Clin Pract. 2016 Sep;10 Suppl 1:S103-S109. doi: 10.1016/j.orcp.2015.11.002. Epub 2015 Dec 3. PMID: 26671228. (https://pubmed.ncbi.nlm.nih.gov/26671228/)

## **PPARG** Peroxisome proliferator-activated receptor gamma

Claussnitzer M, Dankel SN, Klocke B, Grallert H, Glunk V, Berulava T, Lee H, Oskolkov N, Fadista J, Ehlers K, Wahl S, Hoffmann C, Qian K, Rönn T, Riess H, Müller-Nurasyid M, Bretschneider N, Schroeder T, Skurk T, Horsthemke B; DIAGRAM+Consortium, Spieler D, Klingenspor M, Seifert M, Kern MJ, Mejhert N, Dahlman I, Hansson O, Hauck SM, Blüher M, Arner P, Groop L, Illig T, Suhre K, Hsu YH, Mellgren G, Hauner H, Laumen H. Leveraging cross-species transcription factor binding site patterns: from diabetes risk loci to disease mechanisms. Cell. 2014 Jan 16;156(1-2):343-58. doi: 10.1016/j.cell.2013.10.058. PMID: 24439387; PMCID: PMC7116609. (https://www.cell.com/cell/fulltext/S0092-8674(13)01535-3?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867413015353%3Fshowall%3Dtrue)

Ek J, Andersen G, Urhammer SA, Hansen L, Carstensen B, Borch-Johnsen K, Drivsholm T, Berglund L, Hansen T, Lithell H, Pedersen O. Studies of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 (PPAR-gamma2) gene in relation to insulin sensitivity among glucose tolerant caucasians. Diabetologia. 2001 Sep;44(9):1170-6. doi: 10.1007/s001250100629. PMID: 11596673. (https://pubmed.ncbi.nlm.nih.gov/11596673/)

Garaulet M, Smith CE, Hernández-González T, Lee YC, Ordovás JM. PPAR Pro12Ala interacts with fat intake for obesity and weight loss in a behavioural treatment based on the Mediterranean diet. Mol Nutr Food Res. 2011;55(12):1771-1779. doi:10.1002/mnfr.201100437. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951915/)

Picard F, Auwerx J. PPAR(gamma) and glucose homeostasis. Annu Rev Nutr. 2002;22:167-97. doi: 10.1146/annurev.nutr.22.010402.102808. Epub 2002 Jan 4. PMID: 12055342. (https://pubmed.ncbi.nlm.nih.gov/12055342/)

Sarhangi N, Sharifi F, Hashemian L, Hassani Doabsari M, Heshmatzad K, Rahbaran M, Jamaldini SH, Aghaei Meybodi HR, Hasanzad M. PPARG (Pro12Ala) genetic variant and risk of T2DM: a systematic review and meta-analysis. Sci Rep. 2020 Jul 29;10(1):12764. doi: 10.1038/s41598-020-69363-7. PMID: 32728045; PMCID: PMC7391673. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7391673/)

## **SIRT1** Sirtuin 1

Tao TT, Lin XH, Tang SJ, Gui WW, Zhu WF, Li H. Association of genetic variants in the Sirt1 and Nrf2 genes with the risk of metabolic syndrome in a Chinese Han population. BMC Endocr Disord. 2022;22(1):84. Published 2022 Apr 1. doi:10.1186/s12902-022-00965-0. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8973505/)

Zillikens MC, van Meurs JB, Rivadeneira F, Amin N, Hofman A, Oostra BA, Sijbrands EJ, Witteman JC, Pols HA, van Duijn CM, Uitterlinden AG. SIRT1 genetic variation is related to BMI and risk of obesity. Diabetes. 2009 Dec;58(12):2828-34. doi: 10.2337/db09-0536. Epub 2009 Sep 9. PMID: 19741164; PMCID: PMC2780870. (https://pubmed.ncbi.nlm.nih.gov/19741164/)

## **SIRT3** Sirtuin 3

Kincaid B, Bossy-Wetzel E. Forever young: SIRT3 a shield against mitochondrial meltdown, aging, and neurodegeneration. Front Aging Neurosci. 2013 Sep 6;5:48. doi: 10.3389/fnagi.2013.00048. PMID: 24046746; PMCID: PMC3764375. (https://pubmed.ncbi.nlm.nih.gov/24046746/)

Rose G, Dato S, Altomare K, Bellizzi D, Garasto S, Greco V, Passarino G, Feraco E, Mari V, Barbi C, BonaFe M, Franceschi C, Tan Q, Boiko S, Yashin AI, De Benedictis G. Variability of the SIRT3 gene, human silent information regulator Sir2 homologue, and survivorship in the elderly. Exp Gerontol. 2003 Oct;38(10):1065-70. doi: 10.1016/s0531-5565(03)00209-2. PMID: 14580859. (https://pubmed.ncbi.nlm.nih.gov/14580859/)

## **SOD2** Superoxide Dismutase 2, Mitochondrial

Martha-Spyridoula Katsarou, Maria Giakoumaki, Andriana Papadimitriou, Nikolaos Demertzis, Vasileios Androutsopoulos, Nikolaos Drakoulis, Genetically driven antioxidant capacity in a Caucasian Southeastern European population, In Mechanisms of Ageing and Development, 2017, , ISSN 0047-6374, https://doi.org/10.1016/j.mad.2017.08.010. (https://www.ncbi.nlm.nih.gov/pubmed/28844971)

## **SREBF1** sterol regulatory element binding transcription factor 1

Giovanni Musso, Simona Bo, Maurizio Cassader, Franco De Michieli, Roberto Gambino, Impact of sterol regulatory element-binding factor-1c polymorphism on incidence of nonalcoholic fatty liver disease and on the severity of liver disease and of glucose and lipid dysmetabolism, The American Journal of Clinical Nutrition, Volume 98, Issue 4, October 2013, Pages 895–906, https://doi.org/10.3945/ajcn.113.063792. (https://academic.oup.com/ajcn/article/98/4/895/4577194)

Harding AH, Loos RJ, Luan J, O'Rahilly S, Wareham NJ, Barroso I. Polymorphisms in the gene encoding sterol regulatory element-binding factor-1c are associated with type 2 diabetes. Diabetologia. 2006 Nov;49(11):2642-8. doi: 10.1007/s00125-006-0430-1. Epub 2006 Sep 20. PMID: 17019602; PMCID: PMC2668914. (https://pubmed.ncbi.nlm.nih.gov/17019602/)

Vargas-Alarcon G, Gonzalez-Pacheco H, Perez-Mendez O, Posadas-Sanchez R, Cardoso-Saldaña G, Ramirez-Bello J, Escobedo G, Nieto-Lima B, Fragoso JM. SREBF1c and SREBF2 gene polymorphisms are associated with acute coronary syndrome and blood lipid levels in Mexican population. PLoS One. 2019 Sep 6;14(9):e0222017. doi: 10.1371/journal.pone.0222017. PMID: 31490983; PMCID: PMC6730878. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6730878/)

## **TCF7L2** Transcription Factor 7-Like 2

Ding W, Xu L, Zhang L, et al. Meta-analysis of association between TCF7L2 polymorphism rs7903146 and type 2 diabetes mellitus. BMC Medical Genetics. 2018;19:38. doi:10.1186/s12881-018-0553-5. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5842570/)

Lyssenko V, Lupi R, Marchetti P, et al. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. Journal of Clinical Investigation. 2007;117(8):2155-2163. doi:10.1172/JCI30706. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1934596/)

## **TNF** Tumor Necrosis Factor

Catherine M. Phillips. Nutrigenetics and Metabolic Disease: Current Status and Implications for Personalised Nutrition. Nutrients 2013, 5(1), 32-57; doi:10.3390/nu5010032. (http://www.mdpi.com/2072-6643/5/1/32/htm)

Cormier, H., Rudkowska, I., Couture, P., Lemieux, S. and Vohl, M., 2014. Gene-diet interaction effects during a supplementation with n-3 PUFA on both plasma and gene expression levels of inflammatory markers (1037.9). The FASEB Journal, 28(S1). (https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.28.1_supplement.1037.9)

## **UCP1** Uncoupling Protein 1

Chathoth S, Ismail MH, Vatte C, Cyrus C, Al Ali Z, Ahmed KA, Acharya S, Al Barqi AM, Al Ali A. Association of Uncoupling Protein 1 (UCP1) gene polymorphism with obesity: a case-control study. BMC Med Genet. 2018 Nov 20;19(1):203. doi: 10.1186/s12881-018-0715-5. PMID: 30458724; PMCID: PMC6247512. (https://pubmed.ncbi.nlm.nih.gov/30458724/)

Nakayama K, Miyashita H, Yanagisawa Y, Iwamoto S. Seasonal effects of UCP1 gene polymorphism on visceral fat accumulation in Japanese adults. PLoS One. 2013 Sep 25;8(9):e74720. doi: 10.1371/journal.pone.0074720. PMID: 24086366; PMCID: PMC3783463. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3783463/)

## **UCP2** Uncoupling Protein 2

Huang R, Cai T, Zhou Y, Wang Y, Wang H, Shen Z, Xia W, Liu X, Ding B, Luo Y, Yan R, Li H, Wu J, Ma J. Ethnicity Differences in the Association of UCP1-3826A/G, UCP2-866G/A and Ala55Val, and UCP3-55C/T Polymorphisms with Type 2 Diabetes Mellitus Susceptibility: An Updated Meta-Analysis. Biomed Res Int. 2021 Oct 19;2021:3482879. doi: 10.1155/2021/3482879. PMID: 34712730; PMCID: PMC8548105. (https://pubmed.ncbi.nlm.nih.gov/34712730/)

Pravednikova, A.E., Shevchenko, S.Y., Kerchev, V.V. et al. Association of uncoupling protein (Ucp) gene polymorphisms with cardiometabolic diseases. Mol Med 26, 51 (2020). https://doi.org/10.1186/s10020-020-00180-4. (https://molmed.biomedcentral.com/articles/10.1186/s10020-020-00180-4)

## **UCP3** Uncoupling Protein 3

Dalgaard LT, Pedersen O. Uncoupling proteins: functional characteristics and role in the pathogenesis of obesity and Type II diabetes. Diabetologia. 2001 Aug;44(8):946-65. doi: 10.1007/s001250100596. PMID: 11484071. (https://pubmed.ncbi.nlm.nih.gov/11484071/)

## **VEGFA** Vascular Endothelial Growth Factor A

Ahmetov I. I. et al. The combined impact of metabolic gene polymorphisms on elite endurance athlete status and related phenotypes, 2009, Original Investigation, Hum Genet, 2009. (https://www.ncbi.nlm.nih.gov/pubmed/19653005)

DNA sequence variation in the promoter region of the VEGF gene impacts VEGF gene expression and maximal oxygen consumption Steven J. Prior, James M. Hagberg, Chad M. Paton, Larry W. Douglass, Michael D. Brown, John C. McLenithan, Stephen M. Roth American Journal of Physiology - Heart and Circulatory Physiology May 2006, 290 (5) H1848-H1855; DOI: 10.1152/ajpheart.01033.2005. (http://ajpheart.physiology.org/content/290/5/H1848.long)

Lifecode GX ®

— Professional Genotype Analysis —

**Disclaimer**

The information provided should not be used for diagnostic or treatment purposes and is not a substitute for personal medical advice. Use the information provided by Lifecode Gx® solely at your own risk.

Lifecode Gx® makes no warranties or representations as to the accuracy of information provided herein. If you have any concerns about your health, please consult a qualified health professional.