Fo

FoodHealth®

by LIFESTYLEGENOMICS

HEARTGENETICS
GENETICS & BIOTECHNOLOGY

LIFESTYLEGENOMICS®

Dear patient

This report is divided into the following sections:

By clicking on the section you want to access, you will have immediate access to the correct page of the document.

FOR THE PATIENT:

- Section 1: contains information on how to read your report
- Section 4: contains the main messages to keep in mind regarding the integration of genetics and biochemistry
- Section 5: contains a summary of your results for all aspects considered in the test
- Sections 6.1, 6.2, and 6.3: contain your detailed results for the areas of the body, food and behavior, respectively
- Sections 7 - 9: contain technical information about the methodologies used, as well as the scientific support and scientific references used in the generation of this report

FOR THE HEALTHCARE PROFESSIONAL:

- All sections must be read carefully.
- Section 2: contains information about the genetic test
- Section 4: contains the main messages to keep in mind regarding the integration of your user's genetics and biochemistry
- Section 5: contains a summary of the results for all aspects considered in the test
- Sections 6.1, 6.2, and 6.3: contain detailed information for the areas of the body, food and behavior, respectively
- Sections 7 - 9: contain technical information about the methodologies used, as well as the scientific support and scientific references used in the generation of this report

Please contact us if you have any difficulty in accessing or understanding the results.

1. How to read this report

FoodHealth test aims to be a tool to support the definition of health and well-being strategies, according to the genetic and biochemical profile of each person.
The genetic test allows to obtain information on how the genetic predisposition influences (i) the body composition and metabolic parameters; (ii) the metabolism of nutrients; and (iii) the definition of satiety strategies, the sleep habits and the practice of physical exercise. Biochemical tests allow to obtain dynamic information on your current health status. The combination of all this data allows to define personalized nutrition plans and lifestyle changes.
This genetic test analyzes 102 genetic variants, present in 75 genes, and 18 biochemical parameters with impact on 3 major areas: (i) your **BODY**, (ii) your **FOOD**, and (iii) your **BEHAVIOR**.
The individual characteristics evaluated are polygenic, i.e., several genes contribute to the same characteristic. In this context, the computational model used considers all the individual contribution of each genetic variant. The result of the genetic modeling algorithm is a scoring model illustrated with a more or less filled bar.This score bar is proportional to the relevance of the risk or impact of genetic the variants, present in your genome, for the trait under evaluation.
The algorithm, proprietary of HeartGenetics, builds the scoring model based on a high set of parameters. The result of the scoring model is more relevant than the number of genes that may be marked as changed. Each genetic variant should not be interpreted individually. The area of vitamins is an exception because different genes contribute to different vitamins, it is essential to always consult the detail page.

Polygenic scoring model

In this report, two different concepts are used for the relevance of the score obtained in each bar. The **risk concept** is used in the 'Body' area, which describes the genetic predisposition for unfavorable characteristics. For example, the genetic predisposition to a high BMI. The score represented in the bar is higher when the risk for ICM is higher. Thus, a more filled bar translates to a higher predisposition and a less filled one to a lower predisposition. The **concept of impact** is used in the areas 'Food' and 'Behavior', which informs how your genotype interacts with nutrient and food intake and how it can be conditioned by behaviors, qualifying the impact of taking certain actions. For example, for a given genotype, increasing the intake of complex carbohydrates can have a very relevant impact on the management of a healthy weight. In the area of habis, sleep can have a very relevant impact on the management of a healthy weight and on your health in general.

If you find this symbol next to a bar, consider this information as a priority while building your nutritional plan.

The relevance of biochemical analyzes is indicated by a blue or red icon in front of each score bar.

If you find this symbol, consider that at least one parameter of the associated biochemical analysis **is outside** the reference range.

If you find this symbol, consider that all parameters of the associated biochemical analysis **are within** the reference ranges.

The parameters presented here must be considered as a whole. For this reason, it is strongly recommended that a trained health professional guides you in the interpretation of this results. The existence of biochemical parameters outside the reference ranges, being not necessarily the diagnosis of any specific problem, requires discussion with a physician.

2. Lifestyle Genomics

Lifestyle Genomics is a brand of scientifically based products for personalized medicine management. We believe that we all want to live increasingly healthy and plenty of life. We believe that we have to take care of ourselves in all dimensions that make up our well-being - physical, emotional, aesthetic. We believe that in order to achieve this, we need to know our body, and for that we need to evaluate, measure, quantify our health. We believe that for this we need scientifically valid laboratory solutions and with the most rigorous quality control.

3. FoodHealth

3.1. What does this test analyze?

This genetic test analyzes your DNA in order to evaluate 102 genetic variants in 75 genes that, in a determinant way, are associated with well-being, nutrition and weight control.

The associations identified between the genes studied and the body's response to food intake are corroborated by international standard scientific studies referred in this report.

With FoodHealth we go beyond genetics and biochemical parameters are investigated in your blood sample, which allow us to assess whether your genetic heritage is manifesting itself in physiological changes that require medical attention. Biochemical parameters analyzed:

Your body	Glycemia, Glycated hemoglobin, HDL cholesterol, LDL cholesterol, Total cholesterol, Triglycerides, GT range, AST / GOT, ALT / GPT, C-reactive protein
Your diet	Sodium, Potassium, Urea, Creatinine, Vitamin B12, Total vitamin D, Calcium, Phosphorus

3.2. How was this test developed?

The FoodHealth (TM) test results from a collaboration between Centro de Medicina Laboratorial Germano de Sousa (CMLGS), through its Lifestyle Genomics brand, and HeartGenetics. The two companies brought together the ambition to go beyond genetic analysis to develop a test that would match genetic potential with physiological characterization. HeartGenetics carries out genetic testing, CMLGS performs biochemical analyzes that are then integrated into an algorithm developed jointly, combining the medical, genetic and bioinformatics experience of the two companies. The two laboratories ensure that all quality, safety and accuracy criteria are met.

3.3. Limitations of this test

The use of the information provided in this report in the definition of a nutritional plan must be integrated with the information on physical characteristics (eg, age, gender, etc.) and with habits information (eg, eating habits, physical activity, etc.).

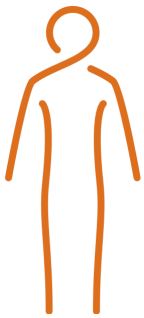
The genetic test results cannot be used for clinical diagnostics, for disease prevention or for the identification of a clinical condition. The genetic test result does not depend on the physical or clinical condition or on the therapeutic management of the individual tested.

It is important to note that these laboratory tests should not be used without a complete assessment of the individual's health by a health professional.

Report

Patient identification		Sample		Requester
Full name:		Specimen type:		Referring physician:
N.A.		**N.A.**		**N.A.**
		Referral number:	**N.A.**	
Date of birth:	**N.A.**	Entry date	**2021-05-27**	
Gender:	**N.A.**	Sample reception date:	**N.A.**	
Age:	**N.A.**	Report issue date:	**N.A.**	

4. Main messages



- The Glicemia, Glycated hemoglobin, LDL Cholesterol value(s) is/are within the reference range, so there is no alarm signal.
- The Gamma GT, AST/GOT value(s) is/are within the reference range, so there is no alarm signal. The genetic result, however, indicates an increased genetic risk. It is recommended to discuss this result with your health professional assistante in order to identify beneficial behaviors that keep the values within the reference ranges.
- The Total Cholesterol value(s) is/are outside the reference ranges. Several factors can cause this change. In your case, in the absence of an increased genetic risk, it will possibly be behavioral factors. In any case, it is strongly recommended to discuss this (s) biochemical change (s) with your healthcare professional assistant.
- The Triglycerides, ALT/GPT value(s) is/are outside the reference ranges. Several factors can cause this change. In your case, we identified an increased genetic risk that could possibly be a reason for this change. It is strongly recommended to discuss this biochemical and genetic result with your healthcare professional assistante.

- The Sodium value(s) is/are within the reference range, so there is no alarm signal.
- The Vitamin B12, Total vitamin D value(s) is/are outside the reference ranges. Several factors can cause this change. In your case, we identified an increased genetic risk that could possibly be a reason for this change. It is strongly recommended to discuss this biochemical and genetic result with your healthcare professional assistante.

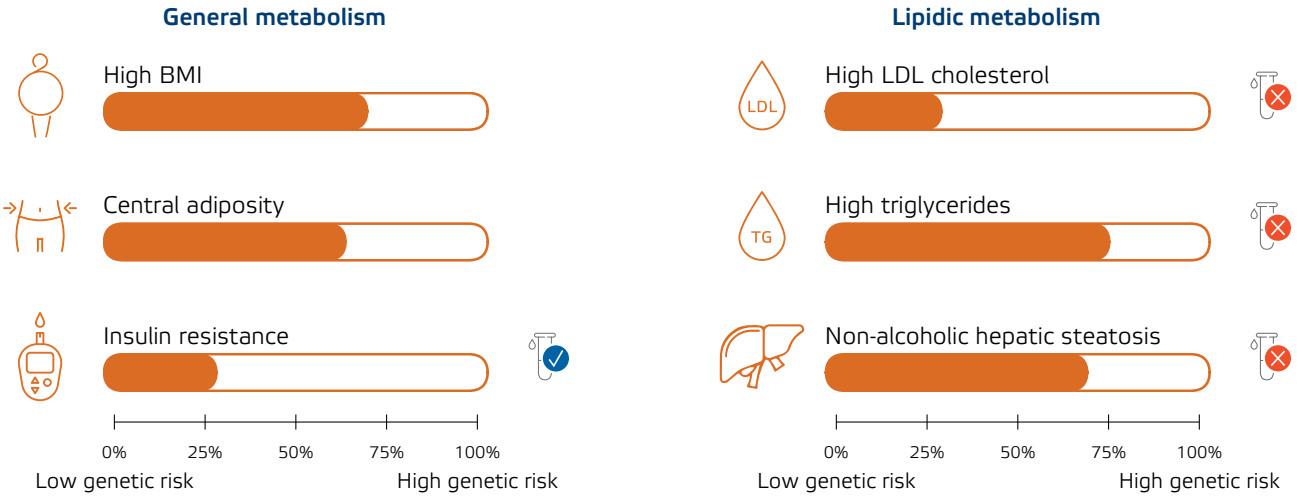
5. Summary of your genetic and biochemical profile

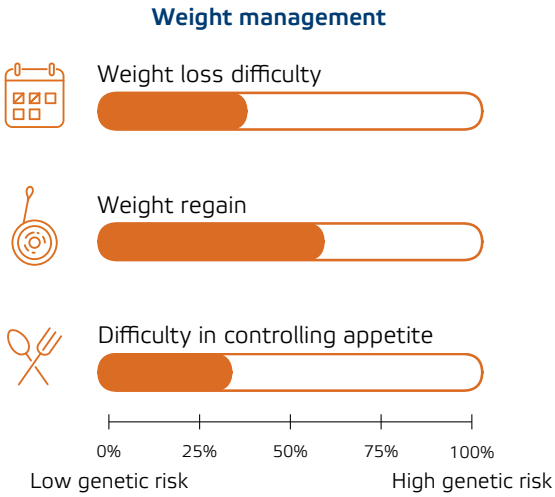
Your body

Discover your body structure genetic predisposition.

Genetics influences the body structure of each individual, contributing to weight control and nutritional metabolism. The impact of your genetic predisposition on body composition can be modified by food and behaviour appropriate to your genetic profile.

Here you have your genetic predisposition for the following body characteristics. For more details, see section 6.1.





If you find this symbol, consider that at least one parameter of the associated biochemical analysis **is outside** the reference range.

If you find this symbol, consider that all parameters of the associated biochemical analysis **are within** the reference ranges.

Your diet

Discover the actionable nutritional plan ideal for your body.

By adopting the most appropriate nutritional plan for your genetic predisposition you will be improving your body's performance. Find out the foods that are most suited to you, and which actions you should prioritise.

Your genetic profile suggests the following impact of nutrient intake, relevant to the development of a nutritional plan for healthy weight maintenance and metabolic balance. For more details, see section 6.2.

Positive impact

- Complex carbohydrates
- Fibre
- Polyunsaturated fats
- Monounsaturated fats
- Protein
- Vitamins
- Caloric restriction

0% 25% 50% 75% 100%

Negative impact

- Total fats
- Salt
- Caffeine

0% 25% 50% 75% 100%

Primary lactose intolerance

Your genotype is associated with primary lactose intolerance.

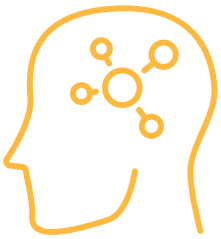
Gluten intolerance

Your genetic profile is compatible with an intermediate predisposition to gluten intolerance.

If you find this symbol next to a bar, consider this information as a priority while building your nutritional plan.

If you find this symbol, consider that at least one parameter of the associated biochemical analysis **is outside** the reference range.

If you find this symbol, consider that all parameters of the associated biochemical analysis **are within** the reference ranges.

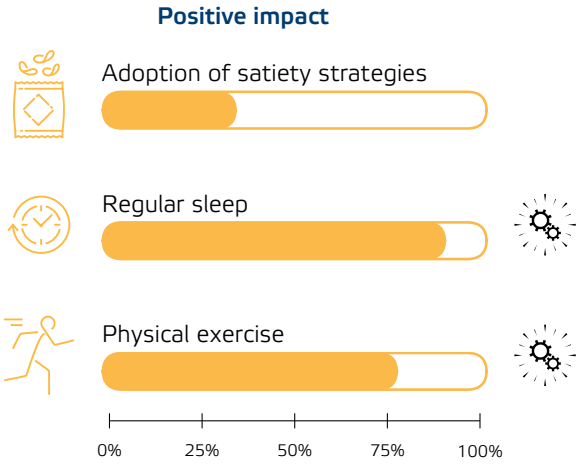


Your behaviour

Discover your behavioural actionable plan ideal for healthy weight management.

Adopting satiety strategies, adopting a regular sleep pattern and practicing physical exercise are behaviours impacting weight management. Take your genetic predisposition into account in these actions and follow recommendations for the best results.

Your genes indicate how certain behaviours can have a significant impact on managing a healthy weight. For more details, see section 6.3.



If you find this symbol next to a bar, consider this information as a priority for managing your weight and your well-being.

6. Details on your genetic and biochemical profile

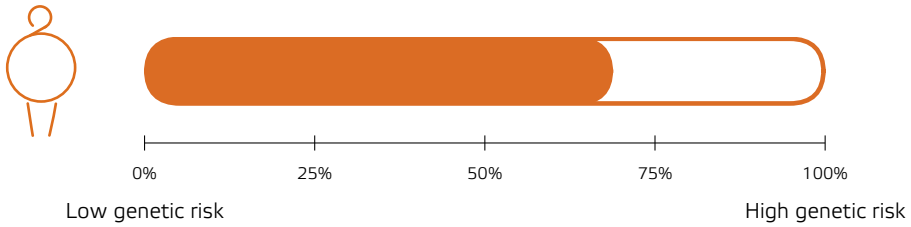
6.1. Your body

6.1.1. General metabolism

6.1.1.1 High BMI

BMI is a measure that relates height to weight and is a good indicator of general adiposity [1]. High overall adiposity, i.e. overweight, results from a calorie intake that exceeds the needs of the body [2]. To maintain a healthy weight, it is essential to maintain a balance between calorie intake and energy expenditure [2].

Genetic result

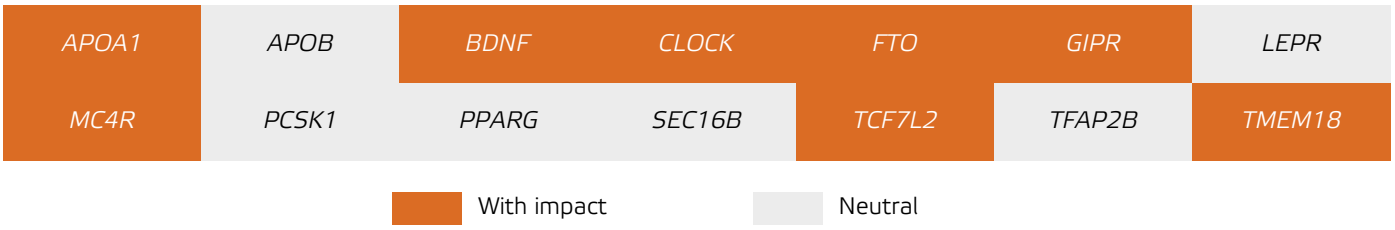


Result analysis

- Your genetic profile suggests a higher predisposition for increased body mass index (BMI).

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Appetite control	*BDNF*	rs10767664	c.-22+16205A>T	–	TA
Appetite control and energy expenditure	*MC4R*	rs11152221	g.60350016C>T	–	T
		rs17700633	g.60262199G>A	–	GA
		rs2229616	c.307A>G	p.Ile103Val	G
		rs52820871	c.751C>A	p.Leu251Ile	A
	TMEM18	rs2867125	g.622827T>C	–	C

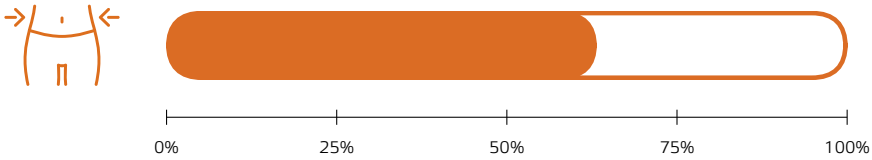
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Circadian rhythm	*CLOCK*	rs1801260	c.*213T>C	–	TC
		rs3749474	c.*897G>A	–	GA
Energy expenditure	*FTO*	rs1121980	c.46-34805G>A	–	A
		rs1558902	c.46-40478T>A	–	A
		rs9939609	c.46-23525T>A	–	TA
Glucose metabolism	*TCF7L2*	rs7903146	c.382-41435C>T	–	C
Insulin secretion	*GIPR*	rs2287019	c.886+14T>C	–	CT
Lipid metabolism	*APOA1*	rs670	c.-113A>G	–	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.1.1.2 Central adiposity

Central adiposity refers to a particular form of distribution of body fat which it is concentrated in the abdomen / belly zone. There are two types of abdominal fat: subcutaneous, which is located directly below the skin, and visceral, which is found around the organs, in the intra-abdominal cavity. The latter is an important risk factor for metabolic change, particularly with regard to the development of insulin resistance [3].

Genetic result



Result analysis

- Your genes suggest that you have an intermediate predisposition to build up abdominal fat, which is generally associated with the accumulation of fat around the cells and organs.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

The following table lists all variants whose identified result is relevant for this parameter.

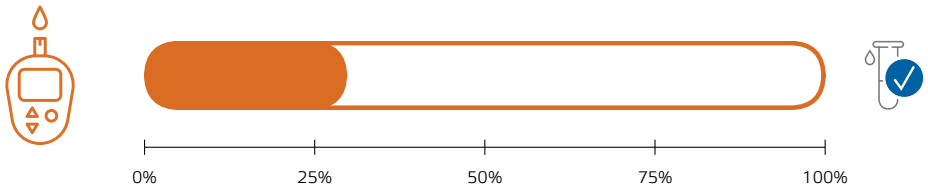
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Circadian rhythm	*PER2*	rs2304672	c.-12C>G	–	C
Endogenous antioxidant system	*MSRA*	rs545854	g.9860080C>G	–	CG
Energy expenditure	*FTO*	rs1121980	c.46-34805G>A	–	A
		rs9939609	c.46-23525T>A	–	TA
Hydrolysis of uncharacterised substrates	*LYPLAL1*	rs2605100	g.219470882A>G	–	G
Insulin signalling	*GRB14*	rs10195252	g.165513091C>T	–	TC
Lipid metabolism	*APOA1*	rs670	c.-113A>G	–	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).
Note: There is a sexual dimorphism for the association between the studied variants on the *GRB14* and the *LYPLAL1* genes and this parameter. These variants are only considered for female gender.

6.1.1.3 Insulin resistance

The main function of insulin is to promote the transport of glucose to cells in tissues such as skeletal muscle, heart muscle, liver and white adipose tissue. Consequently, insulin can control circulating glucose levels and favours lipid synthesis (lipogenesis) in liver and white adipose tissue [4]. Insulin resistance consists of a diminished response to its action on the target tissues, leading to an increase in blood glucose levels [4].

Genetic result



Biochemical result

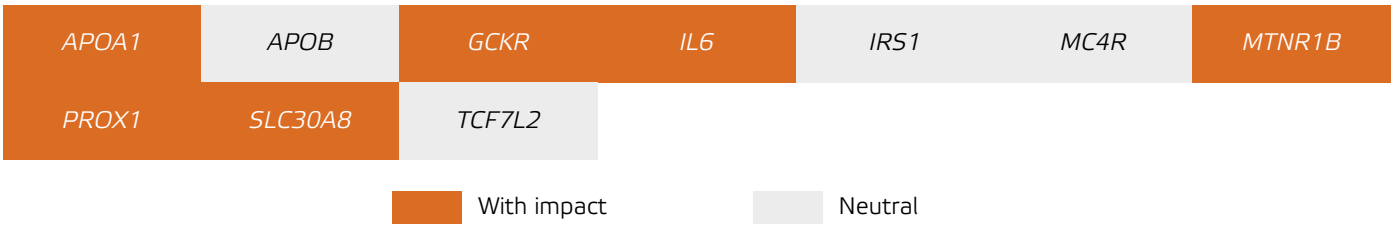
Clinical analysis	Result	Reference values	Units
Glicemia	85.0	70 – 110	mg / dL
Glycated hemoglobin	34.0	< 42	mmol / mol

Result analysis

- Your genes indicate a lower predisposition for increased insulin resistance, which is a metabolic state in which your body needs to oversecrete insulin in order to maintain healthy blood glucose levels.
- The Glicemia, Glycated hemoglobin value(s) is/are within the reference range.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Circadian rhythm	*MTNR1B*	rs10830963	c.223+5596C>G	–	CG

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Glucose metabolism	*GCKR*	rs780094	c.1423-418T>C	–	CT
Inflammation	*IL6*	rs1800795	c.-237G>C	–	GC
Insulin secretion	*SLC30A8*	rs13266634	c.826C>T	p.Arg276Trp	C
Lipid metabolism	*APOA1*	rs670	c.-113A>G	–	G
Regulation of circadian rhythm and metabolism	*PROX1*	rs340874	c.-68+2590T>C	–	CT

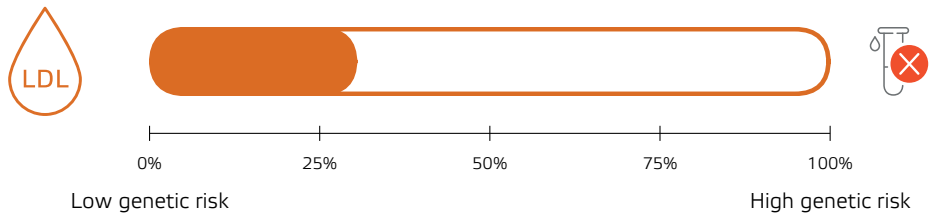
[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.1.2. Lipidic metabolism

6.1.2.1 High LDL cholesterol

The genetic predisposition towards high LDL cholesterol levels indicates an association with a lipid profile with a negative impact on health and weight control [5]. Control of plasma levels (in blood circulation) of LDL cholesterol is important to preserve cardiovascular health. A healthy diet and lifestyle favour the increase in plasma levels of HDL cholesterol and decrease the concentrations of LDL cholesterol in the blood, leading to a lower cardiovascular risk [6].

Genetic result



Biochemical result

Clinical analysis	Result	Reference values	Units
Total Cholesterol	206.0	< 190	mg / dL
HDL Cholesterol	74.0	M: 35 – 55, F: 45 – 65	mg / dL
LDL Cholesterol	82.0	< 115	mg / dL

Result analysis

- Your genetic profile suggests a lower predisposition for increased circulating levels of LDL cholesterol (bad cholesterol).
- The HDL Cholesterol, Total Cholesterol value(s) is/are outside the reference ranges.
- The LDL Cholesterol value(s) is/are within the reference range.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

The following table lists all variants whose identified result is relevant for this parameter.

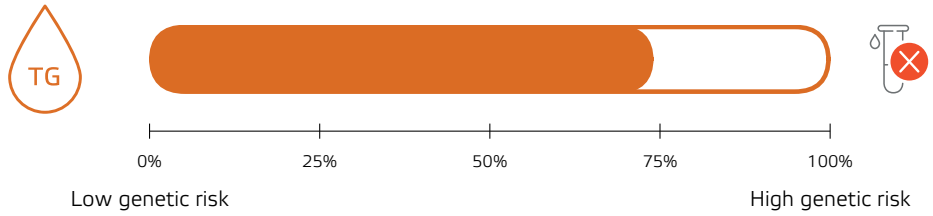
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Lipid metabolism	*LDLR*	rs6511720	c.67+2015G>T	–	GT
	PNPLA3	rs738409	c.444C>G	p.Ile148Met	C
	TM6SF2	rs58542926	c.499G>A	p.Glu167Lys	G
Protein trafficking	*SORT1*	rs629301	c.*1635G>T	–	GT

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.1.2.2 High triglycerides

Triglycerides are the human body's main form of energy storage and the main form of fat in food. They consist of one molecule of glycerol and three fatty acids. Naturally occurring triglycerides are referred to as mixed, because they contain two or three different types of fatty acids: saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA) [7]. High plasma triglyceride levels are a cardiovascular risk factor, are associated with obesity and insulin resistance [8] and contribute to a low-grade inflammatory state [9]. Control of blood triglycerides requires adequate weight control through changing eating habits and regular exercise [6].

Genetic result



Biochemical result

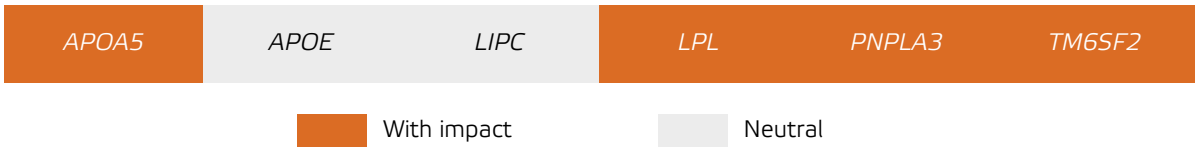
Clinical analysis	Result	Reference values	Units
Triglycerides	252.0	< 150	mg / dL

Result analysis

- Your genes indicate a higher predisposition for increased triglyceride levels.
- The Triglycerides value(s) is/are outside the reference ranges.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

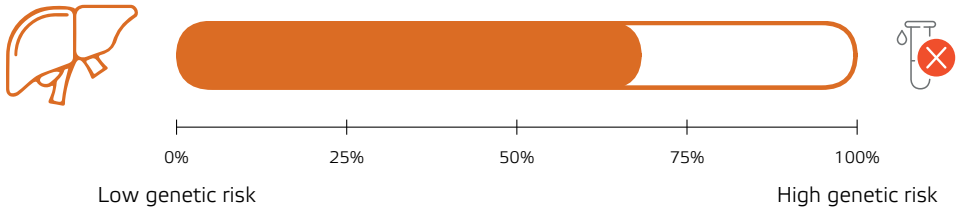
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Lipid metabolism	*APOA5*	rs662799	c.-620C>T	–	TC
	LPL	rs285	c.1019-1582C>T	–	T
		rs328	c.1421G>C	p.Term474Ser	C
	PNPLA3	rs738409	c.444C>G	p.Ile148Met	C
	TM6SF2	rs58542926	c.499G>A	p.Glu167Lys	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.1.2.3 Non-alcoholic hepatic steatosis

Hepatic steatosis, commonly known as fatty liver disease, is characterized by an excessive accumulation of fat in the liver. Scientific evidence has shown that hereditary factors have a strong influence on its development and progression [10]. The presence of certain pathologies and conditions, such as obesity, diabetes and dyslipidaemia, has also been associated with this type of hepatic steatosis [11]. Lifestyle changes such as regular practice of aerobic exercise and the implementation of a Mediterranean-style diet [12] with energy restriction for weight loss are fundamental [13].

Genetic result



Biochemical result

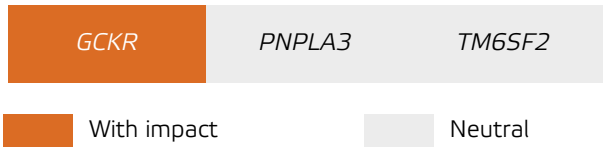
Clinical analysis	Result	Reference values	Units
ALT/GPT	<9	10 – 49	U / L
AST/GOT	19.0	< 34	U / L
C-reactive protein	0.513	< 1	mg / dL
Gamma GT	8.0	M: < 73, F: < 38	U / L

Result analysis

- Your genetic profile is associated with increased predisposition to store high amounts of fat in liver cells, a condition usually referred to as fatty liver.
- The ALT/GPT value(s) is/are outside the reference ranges.
- The Gamma GT, AST/GOT, C-reactive protein value(s) is/are within the reference range.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Glucose metabolism	*GCKR*	rs780094	c.1423-418T>C	–	CT

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

As shown in the results above, genetics has a direct impact on the predisposition for non-alcoholic hepatic steatosis, through deregulation of fat and sugar metabolism. In addition, it influences the capacity for endogenous production (i.e. by the body itself) of a nutrient, a deficiency of which contributes to the development of steatosis: choline. In this regard, a variant of the *PEMT* gene is studied, shown below.

Choline plays an important role in hepatic function and its deficiency has been associated with the development of non-alcoholic steatosis [14, 15, 16]. It is also a precursor of the neurotransmitter acetylcholine. Choline is obtained through the diet and is also endogenously synthesised in the liver, in a reaction catalyzed by the enzyme phosphatidylethanolamine N-methyltransferase (PEMT). The expression of the *PEMT* gene is induced by oestrogen. For this reason, most women (pre-menopausal or postmenopausal treated with oestrogen) have lower choline requirements than men and postmenopausal women not receiving oestrogen therapy [14, 16]. Notwithstanding, the induction of *PEMT* expression by oestrogen can be abolished by the presence of a specific polymorphism, thereby altering nutritional requirements [17, 18]

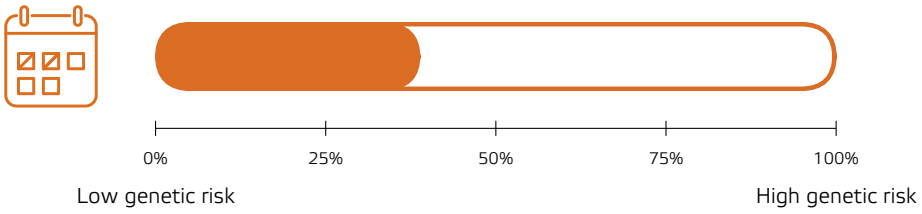
- You are not a carrier of the *PEMT* genetic variant that renders the expression of this gene irresponsive to the presence of oestrogen. This means that you are likely to have a normal capacity to synthesise choline endogenously in the liver. It is important, however, to take into account that during menopause not enough oestrogen is produced to fully induce the expression of *PEMT*. In this situation, it is particularly important to ensure an adequate intake of choline. Some of the main sources of choline are beef liver, beef, eggs, soybeans, chicken, cod, mushrooms, potatoes, kidney beans, quinoa, and dairy.

6.1.3. Weight management

6.1.3.1 Weight loss difficulty

Difficulty in losing weight often results from eating errors associated with a sedentary lifestyle and less favourable genetic factors [19]. In order to optimize the weight loss strategy, it is important to consider our genetic profile [20]. Knowing that we have an intrinsic difficulty to reduce body weight alerts us to an increased need for adherence to the defined strategy and to permanently adopt a lifestyle that allows us to maintain a healthy weight [21, 22].

Genetic result



Result analysis

- Your genetic profile predisposes to an intermediate difficulty in losing weight.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

The following table lists all variants whose identified result is relevant for this parameter.

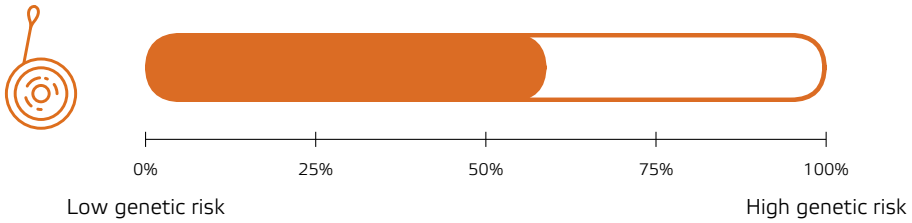
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Circadian rhythm	*CLOCK*	rs1801260	c.*213T>C	–	TC
	MTNR1B	rs10830963	c.223+5596C>G	–	CG
Orexigenic stimulus	*GHSR*	rs490683	g.172175074C>G	–	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).
Note: There is a sexual dimorphism for the association between the studied variants on the *ADRB2* and the *MTNR1B* genes and this parameter. The *ADRB2* variant is only considered for the male gender and the *MTNR1B* variant for the female gender.

6.1.3.2 Weight regain

Maintenance of body weight is regulated by the interaction of several processes, encompassing genetic, environmental and behavioural factors [23, 24]. Acquiring and maintaining healthy eating habits and a lifestyle appropriate to one's genetic profile is a determining factor for successful weight management and health promotion [25, 26].

Genetic result



Result analysis

- Your results show an intermediate predisposition to easily recover lost weight.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

The following table lists all variants whose identified result is relevant for this parameter.

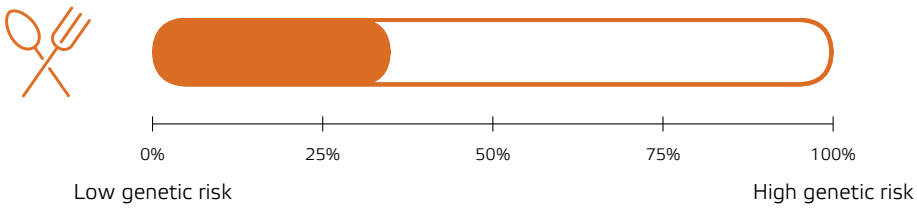
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Adipogenesis, lipogenesis and glucose homeostasis	*PPARG*	rs1801282	c.34C>G	p.Pro12Ala	C
Energy expenditure	*ADIPOQ*	rs17300539	c.-1138A>G	–	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).
Note: There is a sexual dimorphism for the association between the studied variant on the *ADRB2* gene and this parameter. This variant is only considered for the male gender.

6.1.3.3 Difficulty in controlling appetite

Appetite control is an essential factor in controlling body weight. Eating behaviour is the result of a complex interaction of physiological, psychological, social and genetic factors influencing the timing of meals, the amount of food ingested and food preferences [27]. In various areas of the brain, information on gustatory stimuli is integrated with signs of hunger, satiety, and appetite [28]. The feeling of hunger leads to a greater intake of food, which in turn induces satiety. Control of the size of the meal is mainly determined by satiety. Control of the frequency of meals is essentially determined by the onset of hunger. Eating behaviour is a hereditary characteristic [29], and several genetic variants are described in the scientific literature that affect the control of energy homeostasis and food intake [30, 31, 32].

Genetic result



Result analysis

- According to your genetic profile, you have an intermediate predisposition to the deregulation of appetite control mechanisms.
- Individuals with the same variant of the *CLOCK* gene as you do tend to eat more calories, having greater energy intake than necessary.
- You carry a genetic variant of *CLOCK* that predisposes you to secrete higher levels of ghrelin (the hunger hormone), which is associated with increased hunger. Moreover, individuals with this profile often have a higher intake of saturated fat.
- You have sensitive gene variants in your genome that have been associated with predisposition to false hunger and/or difficulty in controlling appetite.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

CLOCK	*DRD2*	*FTO*	*MC4R*	*OPRM1*	*PER2*	*SIRT1*
SLC2A2						

With impact Neutral

The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Circadian rhythm	*CLOCK*	rs1801260	c.*213T>C	–	TC
		rs3749474	c.*897G>A	–	GA
Energy expenditure	*FTO*	rs9939609	c.46-23525T>A	–	TA

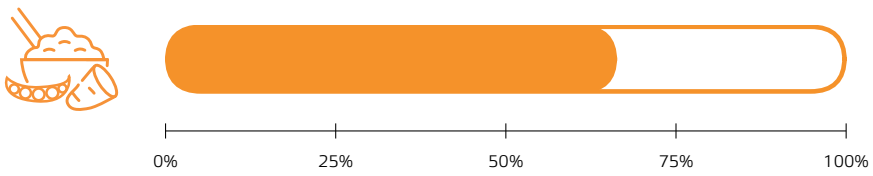
[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.2. Your diet

6.2.1. Complex carbohydrates

Carbohydrates (CH) are the most abundant organic substances in food, being widely distributed in the tissues of animals and plants and in the form of reserves in seeds, tubers and starches. They are the main energy source from most diets, accounting for approximately half of the energy consumed [33]. They can be divided into complex and simple CH. The former, also known as polysaccharides, are slowly absorbed, prolonging the sensation of satiety and leading to a gradual increase in blood glucose [34].

Genetic result



Result analysis

Your genetic results suggest that you benefit from a nutritional plan enriched in complex carbohydrates, comparing to the recommended daily allowance.

- Your genotype for the *PPARG* gene is associated with a greater tolerance to the intake of complex carbohydrate with regard to weight management.
- A low glycaemic index diet improves insulin resistance by reducing the glycaemic (blood sugar) peaks after a meal. Your genotype of *PPM1K* is particularly sensitive to this intervention, suggesting that you should adopt such a dietary strategy.
- Your genotype for the *CRY1* gene suggests that you do not have an increased predisposition to insulin resistance by adopting a diet enriched in complex carbohydrates.
- Your genotype is associated with a greater benefit in adopting a low glycemic index (GI) diet in order to achieve weight loss and improved insulin resistance. You can have a lower GI diet by replacing simple carbohydrates (such as refined grains and sugars) with complex carbohydrates (such as whole grains).

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

The following table lists all variants whose identified result is relevant for this parameter.

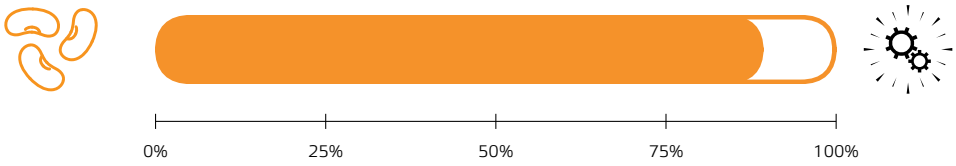
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Adipogenesis, lipogenesis and glucose homeostasis	*PPARG*	rs1801282	c.34C>G	p.Pro12Ala	C
Circadian rhythm	*CRY1*	rs2287161	c.-562G>C	–	CG
Insulin secretion	*GIPR*	rs2287019	c.886+14T>C	–	CT
	PPM1K	rs1440581	n.133-6526T>C	–	C

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.2.2. Fibre

Diet fibres are essential for the proper functioning of the organism and are obtained from food of plant origin [7]. Insoluble fibres contribute to the regulation of bowel movements and feed the good bacteria in our digestive tract, collaborating in several metabolic processes [35]. In turn, soluble fibres absorb large amounts of water in the digestive tract, giving rise to a paste with gel consistency, which promotes the feeling of satiety [36]. This is how fibres contribute to weight management, regulating the intake and absorption of the various nutrients and their constituents (e.g. sugars, fats and cholesterol) [37].

Genetic result



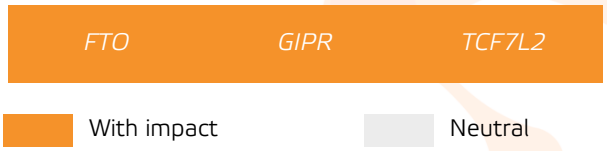
Result analysis

Your genetic results suggest that you benefit from a nutritional plan highly enriched in fiber.

- Individuals carrying a specific variant of the *GIPR* gene (found in your genome) have shown improved insulin sensitivity when consuming a high fibre diet. Fibre improves satiety and delays the glycaemic (blood sugar) peaks after a meal.
- Particular gene variants in your genome have been associated with greater weight loss when individuals consume a diet rich in fibre. This may be either due to improved satiety or due to reduced overall energy intake.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

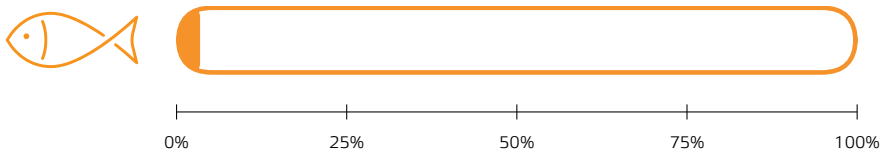
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Energy expenditure	*FTO*	rs8050136	c.46-27777C>A	–	CA
Glucose metabolism	*TCF7L2*	rs7903146	c.382-41435C>T	–	C
Insulin secretion	*GIPR*	rs2287019	c.886+14T>C	–	CT

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.2.3. Polyunsaturated fats

Polyunsaturated fats (PUFAs) are essential for the proper functioning of the body. They regulate the body's inflammatory response, stimulate brain function, play a key role in body's growth, development and repair, and are very important in modelling the cardiovascular system [38]. The essential fatty acids (linoleic and linolenic) of PUFAs must be obtained through diet, since they cannot be produced by the body. Western diets tend to be very rich in ω-6 fatty acids (linoleic acid, LA) and deficient in ω-3 (linolenic acid, ALA). Since the ω-6 fatty acids compete for the same enzymes as the ω-3 fatty acids, the excess of the former in the diet saturates the enzymes and prevents the conversion of ALA to other ω-3 (EPA and DHA). The genetic profile is also a relevant factor with regard to the adequate intake of PUFA [39], and the basic principles of healthy eating must be constantly considered. Therefore, a balanced diet containing ALA, EPA and DHA is recommended to improve the ratio of ω-6:ω-3 [40]. Functional ω-3 fatty acids are highly available in fatty fish, fish oils, nuts, and seeds, and have important roles in terms of cognitive function and anti-inflammatory mechanisms.

Genetic result

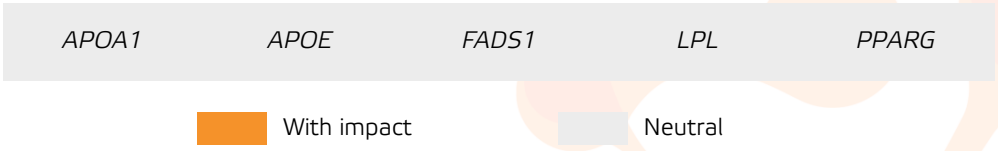


Result analysis

Your genetic results suggest that there is no additional benefit in enriching the diet with polyunsaturated fats and that you should follow the recommended daily allowance.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

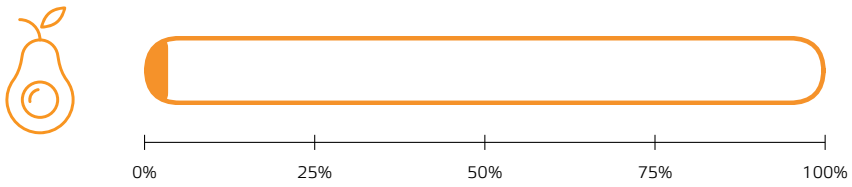


No genetic variants with significant impact.

6.2.4. Monounsaturated fats

In nature, there are more than 100 types of monounsaturated fatty acids (MUFAs), but some are very rare. Oleic acid is the most well-known MUFA and can be found in large proportions in olive, canola or peanut oil, as well as in some dried fruits [41]. Daily consumption of olive oil has been associated with a decline in cardiovascular risk [42], as well as the adoption of Mediterranean, DASH and other diets, [43]. Scientific evidence has shown that replacing carbohydrates with MUFA increases HDL-cholesterol levels and that replacing saturated fat with monounsaturated fat lowers LDL-cholesterol and improves the HDL/LDL ratio [41].

Genetic result

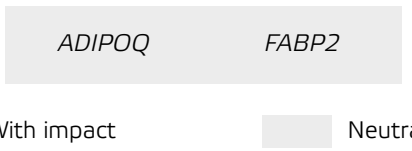


Result analysis

Your genetic results suggest that there is no additional benefit in enriching the diet with monounsaturated fats and that you should follow the recommended daily allowance.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

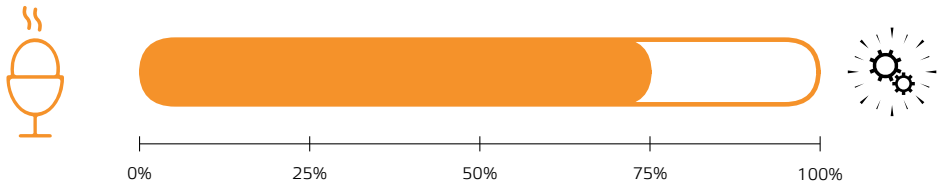


No genetic variants with significant impact.

6.2.5. Protein

Proteins (made up of chains of amino acids) have structural, immune, catalytic, regulatory and transport functions. They can provide energy when the intake of carbohydrates and fats is not adequate [7]. Amino acids are considered to be non-essential when the body is capable of producing them and essential when they cannot be endogenously synthesized and must be obtained through food. The nutritional value of the protein is determined by its digestibility and amino acid content and ratio [44]. If the amino acid profile of a food is not compatible with human nutritional requirements, the amino acid present in the lowest amount is considered to be the limiting factor. The nutritional value of animal protein is higher than that of vegetable protein [45]. However, the appropriate combination of various types of plant foods (e.g. legumes and cereals) normally provides the appropriate amounts of essential amino acids to meet protein requirements [45]. High-protein diets contribute to increased satiety and favour weight management [46], while simultaneously increasing renal acid load. Some genetic variants have been associated with greater benefits in weight control [47] and improved insulin resistance [48] when high-protein diets are adopted.

Genetic result



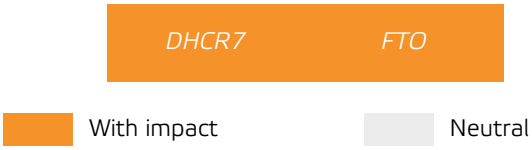
Result analysis

Your genetic results suggest that you benefit from a nutritional plan highly enriched in protein.

- A low energy high-protein diet has been shown to improve insulin resistance in individuals who carry the same *DHCR7* gene variant that was identified in your genome. Good lean sources of protein include poultry and chicken, legumes (e.g., beans, peas, lentils), non-fatty dairy and egg whites.
- A high protein diet has been shown to improve weight loss in individuals carrying a particular variant of the *FTO* gene (such as yourself).
- As result of your *FTO* genotype, protein intake is particularly beneficial in reducing food cravings and appetite during a low-energy weight-loss strategy.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

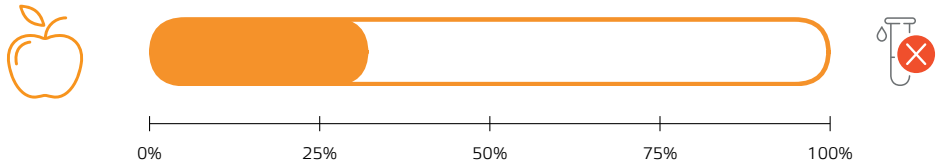
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Energy expenditure	*FTO*	rs1558902	c.46-40478T>A	–	A
		rs9939609	c.46-23525T>A	–	TA
Vitamin D synthesis	*DHCR7*	rs12785878	c.146+1233T>G	–	GT

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.2.6. Vitamins

Vitamins are essential nutrients the body needs to maintain a healthy life and are obtained through a variety of foods. The reference values for the European population are defined by the European Food Safety Authority (EFSA) [40], although there are also other International Organizations (e.g. WHO [49]) that present reference values for this micro-nutrient.

Genetic result



Biochemical result

Clinical analysis	Result	Reference values	Units
Calcium	9.6	8.7 – 10.4	mg / dL
Phosphorus	4.0	2.4 – 5.1	mg / dL
Vitamin B12	158.0	211 – 911	pg / mL
Total vitamin D	28.2	30 – 100	ng / mL

Result analysis

Your genetic results suggest that you benefit from a nutritional plan enriched in the vitamins mentioned below.

The Vitamin B12, Total vitamin D value(s) is/are outside the reference ranges.

The Calcium, Phosphorus value(s) is/are within the reference range.

- You have a non-favourable variant from a well-known gene (*FUT2*) important in the absorption of vitamin B_{12}. This suggests that you benefit from a nutritional plan enriched in foods with vitamin B_{12} (most foods from animal sources, including dairy and eggs).
- An intergenic variant (rs12272004) present in your genome has been associated with lower circulating levels of Vitamin E, a powerful antioxidant molecule. Increasing consumption of foods rich in vitamin E (vegetable oils, such as wheat germ, sunflower, almond, and olive oils, nuts and seeds) is helpful to prevent pro-oxidation.
- A genetic variant of *SLC23A1*, present in your genome, has been associated with lower circulating levels of Vitamin C, which is a crucial vitamin for several body functions including immunity and detoxification. Since humans cannot synthesize vitamin C endogenously, it is important - particularly for you - to consume enough foods rich in vitamin C (most raw vegetables and fresh fruits).
- According to your genotype of *SOD2* you might benefit from food rich in liposoluble (fat-soluble) antioxidants, such as vitamins A and E. These vitamins can be found in eggs, liver, vegetable oils (e.g., wheat germ, sunflower, almond, and olive oils) nuts and seeds and also, in less quantities, in colourful (yellow and orange) vegetables.
- You have genetic variants in your genome that have been associated with a decreased bioavailability of vitamin D within your body. Individuals who have these variables in their genomes appear to benefit from a nutritional plan enriched with foods containing higher amounts of vitamin D. Being soluble in fats, vitamin D can be predominantly found in fatty fish, dairy products, eggs and beef liver.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

ALPL	*AMDHD1*	*BCO1*	*CYP24A1*	*CYP2R1*	*DHCR7*	*FUT2*
GC	*IM11*	*IRS1*	*MTHFR*	*SEC23A*	*SLC23A1*	*SOD2*

With impact Neutral

The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Endogenous antioxidant system	*SOD2*	rs4880	c.47T>C	p.Val16Ala	T
Protein trafficking	*SEC23A*	rs8018720	g.39086981G>C	–	C
Vitamin B12 absorption	*FUT2*	rs602662	c.772A>G	p.Ser258Gly	GA
Vitamin C transport	*SLC23A1*	rs33972313	c.790G>A	p.Val264Met	AG
Vitamin D synthesis	*CYP2R1*	rs10741657	g.14914878A>G	–	GA
	DHCR7	rs12785878	c.146+1233T>G	–	GT
Vitamin D transport	*GC*	rs2282679	c.*26-796A>C	–	CA
Vitamin E transport	*IM11*	rs12272004	g.116733008C>A	–	C

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).
Note: There is a sexual dimorphism for the association between the studied variant on the *IRS1* gene and this parameter. This variant is only considered for the female gender.

General information:

Vitamin A

It is a fat-soluble vitamin that plays an important role in vision, bone growth, reproduction and cell division, and also helps to regulate the immune system in fighting infections [7]. It can be found in its active form in foods of animal origin in the form of retinoids (e.g. retinol) and in its inactive (pro-vitamin) form in foods of plant origin rich in some carotenoids (e.g. β-carotene, α-carotene y β-cryptoxanthin) [50]. Its known antioxidant function is essentially associated with the action of carotenoids from the diet [51].

Vitamin B_6

Vitamin B_6 is present in foods in three interconvertible forms: pyridoxine, pyridoxamine and pyridoxal. They can all be converted to pyridoxal-5-phosphate (PLP), the main biological form of this vitamin [52]. PLP is a coenzyme of several enzymes involved in virtually all reactions in the metabolism of amino acids (e.g. tryptophan), some stages of the metabolism of neurotransmitters (e.g. serotonin and melatonin), glycogen, sphingolipids, heme group and steroids [53]. It also has an essential function in the metabolism of homocysteine [54]. It is widely distributed in foods but has greater bioavailability in animal foods [7]. The benefits of eating foods rich in vitamin B_6 are increased for those genetically predisposed for lowering concentrations of this vitamin in the blood.

Vitamin B_9

Vitamin B_9, or folate, can be found in various foods, but the best sources are dark green leafy vegetables, legumes, seeds, fruits (e.g. citrus and red fruits) and cereals (if fortified) [7]. This vitamin performs several functions in the body and is necessary for DNA synthesis, protein metabolism and formation of haemoglobin [55]. It is also crucial for the prevention of foetal malformations and the metabolism of homocysteine [56]. Poor folate intake has been associated with a number of health problems [55]. Although it is a widely distributed vitamin in foods, its bioavailability is lower than that of folic acid supplements[57], and its absorption is more efficient when associated with vitamin B_{12} and C [58]. Individuals who are genetically predisposed to a low serum vitamin B_9 level need to consume better dietary sources of this vitamin.

Vitamin B_{12}

Vitamin B_{12} (cobalamin) is a water soluble vitamin which exists essentially in foods of animal origin, such as meat, fish, dairy products and eggs [59]. In order to be absorbed it has to bind to a glycoprotein (intrinsic factor) which is released by gastric secretions during digestion and is then absorbed into the intestine after binding to the specific receptor [60]. Vitamin B_{12} is vital for the functioning of the nervous system and nucleic acid synthesis. It also participates in carbohydrate and fat metabolism, haemoglobin formation, and folic acid activation, associated with the conversion of homocysteine to methionine [61]. Strict vegetarians with a genetic predisposition for low vitamin B_{12} serum concentrations must take special care with their intake, either by combining some plant food sources containing the vitamin [62] or by supplementing them.

Vitamin C

It is one of the most important water-soluble vitamins, being present mainly in uncooked food of plant origin [63] but it also can be found in other types of food, in the form of an additive [64]. It is a food antioxidant with a cofactor function for many enzymes. Its reduced form, L-ascorbic acid, is the main biologically active form of this vitamin and is an effective antioxidant. Vitamin C is also important for the formation of collagen, absorption of dietary iron, stimulation of the immune system [65], minimization of allergic reactions [66], folate metabolism and synthesis of various hormones and neurotransmitters [67]. Other functions of this vitamin, still under study, include possible action on ageing and prevention of dementia [68]. Adequate levels of vitamin C are important in the prevention of chronic diseases [69]. Adequate intake of this vitamin is especially relevant for individuals who associate genetic and environmental factors (e.g. smokers) that predispose to lower concentrations of vitamin C in the blood.

Vitamin D

Vitamin D (calciferol) is a fat-soluble vitamin, which can be obtained in foods or through sun exposure. It is formed from two provitamins, one of vegetable origin (ergosterol) and the other of animal origin (7-dehydrocholesterol), which are respectively converted into forms D2 (ergocalciferol) and D3 (cholecalciferol), still without biological activity. These need to be doubly hydroxylated in the liver and kidneys to produce the biologically active form of vitamin D [70]. It is a vital nutrient, whose main functions are to aid the absorption of calcium in the intestines and its deposition in the bones, and to control levels of calcium in the blood [71]. Individuals who are genetically predisposed to low vitamin D [72] benefit from foods rich in this vitamin [73].

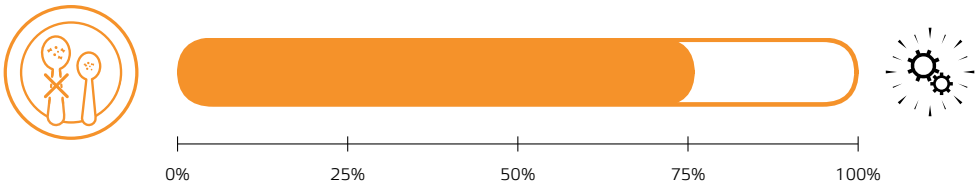
Vitamin E

Vitamin E consists of two groups of compounds, tocopherols and the tocotrienols. The compound with the highest biological activity is the α-Tocopherol [74]. Tocopherols and tocotrienols are only synthesized by plants, so vitamin E is only present in foods of plant origin [75]. It mainly serves as an antioxidant that protects cell membranes from the damaging action of free radicals [76]. The antioxidant function of vitamin E can be affected by the plasma levels of other nutrients (e.g. vitamin C and selenium) [77]. It also contributes to the proper functioning of the immune system, protecting the body from infections [78]. Individuals who are predisposed to a low plasma concentration of vitamin E will have greater benefit in increasing the intake of good dietary sources of this vitamin [75].

6.2.7. Caloric restriction

Caloric restriction (CR) is a methodology based on low daily calorie intake (low-calorie diet), with a reduction of 20-50 % of people's daily energy ingested [79]. It is commonly used in clinical practice for weight loss, improvement of metabolic biomarkers and in the treatment of non-alcoholic hepatic steatosis [80]. Scientific evidence has shown that CR is an intervention strategy that promotes healthy ageing and longevity, but its mechanisms are not well known yet [81]. CR, combined with intermittent fasting and liquid meals, is a successful strategy for weight loss in obese people and for cardiovascular risk reduction [82], but its adherence and maintenance in the medium and long term is difficult and sometimes leads to the recovery of lost weight [81]. Strategies for weight loss focus on a change of eating habits and lifestyle. However, the response to nutritional intervention programmes has evidenced a wide inter-individual variation, influenced by genetic determinants [83]. People with certain genetic variants have different responses to caloric restriction programmes [25, 84, 85, 86, 87, 87, 88, 89].

Genetic result



Result analysis

Your genetic results suggest a very favorable response to caloric restriction, should this be a goal to you.

- Overweight individuals carrying the same variant of the *ADIPOQ* gene as you do benefit particularly from a caloric restriction strategy to reduce the risk of metabolic syndrome.
- You carry genetic variants that predispose you to respond well to a hypoenergetic diet as a strategy to lose weight, meaning that you are likely to lose more weight in response to caloric restriction compared with people who do not carry these variants.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Adipogenesis, lipogenesis and glucose homeostasis	*PPARG*	rs1801282	c.34C>G	p.Pro12Ala	C

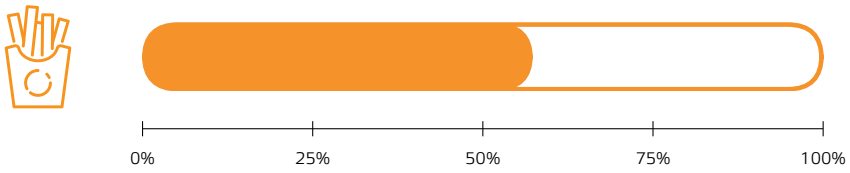
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Energy expenditure	*ADIPOQ*	rs17300539	c.-1138A>G	–	G
Lipid metabolism	*FABP2*	rs1799883	c.163G>A	p.Ala55Thr	G
	PLIN	rs894160	c.772-799G>A	–	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).
Note: There is a sexual dimorphism for the association between the studied variant on the *ADRB2* gene and this parameter. This variant is only considered for the male gender.

6.2.8. Total fats

Lipids, or fats, are the macronutrient that provides the most energy per gram of intake (9 kcal). In addition to their energy function, they also regulate cell function, are indispensable for the absorption of fat-soluble vitamins (A, E, D and K) and for the regulation of the endocrine system. Fats are classified into three types: saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA). Cholesterol is also a type of fat, found in cell membranes and transported in the blood plasma of all animals. According to the EFSA recommendation, 20-35 % of the Daily Energy Value (TEV) must come from fats [40]. Fat consumption must be moderate, especially SFA (max. 7 % of TEV), trans fat (max. 1 % of TEV) and cholesterol (max. 300 mg/day) [6]. Fat ingested in excess contributes to weight gain, abdominal fat accumulation, LDL-cholesterol increase, and insulin resistance [90, 91, 92]. The Mediterranean diet is low in saturated fats, trans fat and cholesterol and has excellent food sources of MUFA. It is therefore promoted by the Portuguese national programme for the promotion of healthy eating and represents an adequate strategy to improve the lipid profile [93]. According to current knowledge, tolerance to fat intake is partially regulated by genes associated with the use and accumulation of energy [94, 95, 96, 97, 98].

Genetic result



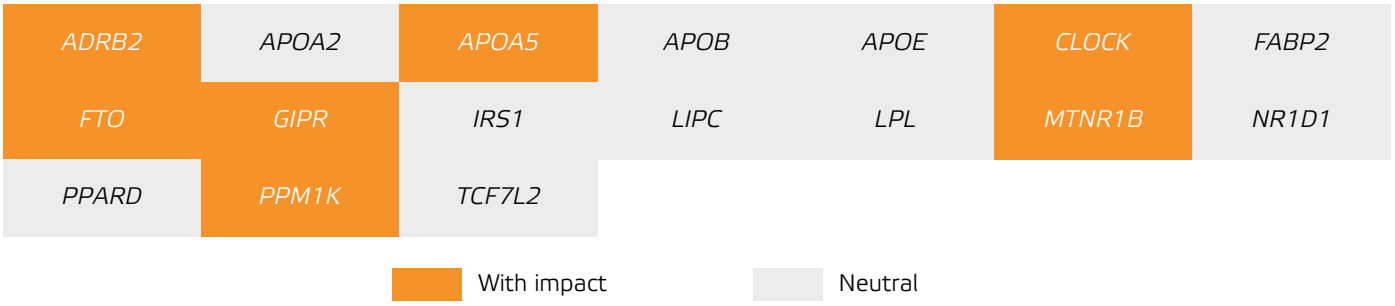
Result analysis

Your genetic results suggest a reduction in the consumption of saturated fats, comparing to the recommended daily allowance.

- Your genotype of *APOA5* suggests that your cholesterol and triglyceride levels may be improved if you consume less fat in your regular diet. This is particularly important if you are someone who is predisposed to an unfavourable lipid profile.
- Individuals carrying the same *ADRB2* gene variant as you have been found to have improvements in their LDL cholesterol (also known asbad cholesterol) and overall lipid profile when consuming a low-fat diet.
- Research has shown that your genetic profile benefits from a low-fat diet. This means eating less fatty foods to improve your body weight management.
- Decreased fat intake has been shown to improve insulin resistance in individuals sharing your genetic profile.
- You carry a genetic variant of *MTNR1B* that predisposes to greater reductions in total cholesterol and LDL cholesterol (bad cholesterol) levels in response to a decreased intake of dietary fat. This same variant is also associated with greater weight loss when adopting such a nutritional strategy.
- Research has shown that your genetic profile benefits from a low-fat diet to improve body weight management but also to prevent the development of insulin resistance (IR). IR is a condition in which cells are less responsve to the effect of insulin (a hormone), which causes them to have problems metabolizing carbohydrates.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

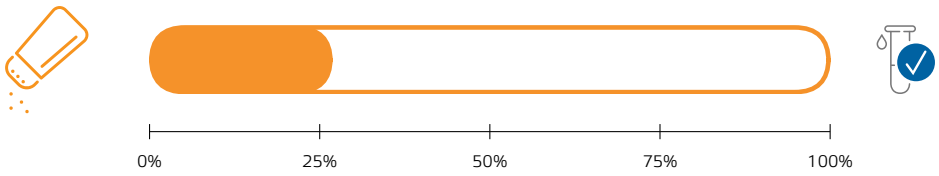
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Circadian rhythm	*CLOCK*	rs3749474	c.*897G>A	–	GA
	MTNR1B	rs10830963	c.223+5596C>G	–	CG
Energy expenditure	*ADRB2*	rs1042713	c.46A>G	p.Arg16Gly	G
	FTO	rs1121980	c.46-34805G>A	–	A
Insulin secretion	*GIPR*	rs2287019	c.886+14T>C	–	CT
	PPM1K	rs1440581	n.133-6526T>C	–	C
Lipid metabolism	*APOA5*	rs3135506	c.56G>C	p.Trp19Ser	G
		rs662799	c.-620C>T	–	TC

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.2.9. Salt

Salt contains sodium, which is an electrolyte whose primary function is the control of body fluids. It is also necessary to maintain acid-base balance in the body, heart rate and muscle contraction [7]. According to EFSA recommendations, daily salt intake must not exceed 5 g, which represents 2 g/day of sodium [40]. Several studies have shown a strong positive association between salt intake and an increase in systolic blood pressure, as well as its decrease after adherence to a salt-restricted diet [99]. High blood pressure is a major risk factor for cardiovascular disease, accounting for about 62% of acute myocardial infarction and 49% of coronary heart disease cases [100]. Type 2 diabetes also accounts for death from high blood pressure, the latter being twice as frequent in people with diabetes [101]. One of the most common diets for restricting salt intake and promoting potassium intake is the DASH diet [102], although the Mediterranean diet is also an excellent alternative. Each person's salt sensitivity associated with increased blood pressure is very variable [99]. More than 50 % of people with high blood pressure are sensitive to salt. Several genetic variants have been identified as being associated with salt sensitivity [103, 104, 105, 106, 107, 108, 109]. Therefore, the most susceptible people should adopt a preventive strategy, restricting the consumption of salt and processed foods through a healthy diet and promoting the consumption of fruits and vegetables.

Genetic result



Biochemical result

Clinical analysis	Result	Reference values	Units
Creatinine	0.59	M: 0.7 – 1.3, F: 0.5 – 1.1	mg / dL
Potassium	4.7	3.5 – 5.5	mmol / L
Sodium	140.0	132 – 146	mmol / L
Urea	17.0	< 50	mg / dL

Result analysis

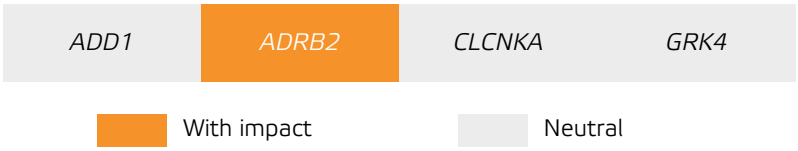
Your genetic results suggest a reduction in the consumption of salt, comparing to the recommended daily allowance.

The Sodium, Potassium, Urea, Creatinine value(s) is/are within the reference range.

- Given the total number of genetic variants that contribute to this area, the overall impact of those identified in your genome is not very significant.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

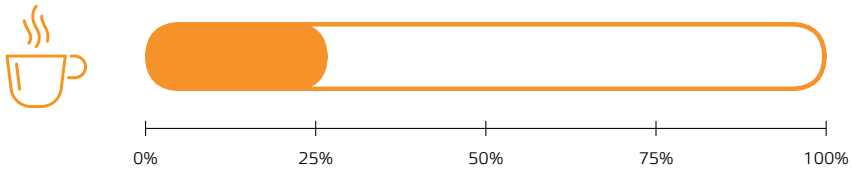
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Energy expenditure	*ADRB2*	rs1042713	c.46A>G	p.Arg16Gly	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.2.10. Caffeine

Caffeine is the most consumed phytoactive compound in the world. The natural sources of caffeine are coffee, tea (theine) and chocolate [110], but several other food sources containing synthetic caffeine are available on the market. Several health benefits [111] have been associated with the consumption of up to 400 mg/day of caffeine [112]. However, excessive consumption of this phytochemical is also associated with health risks [113]. In Portugal, caffeine content in a full, medium and short coffee is 88 mg, 72 mg and 62 mg, respectively [114]. An average consumption of 2 to 3 coffees/day in healthy adults is advised, but always dependent on each person's susceptibility to caffeine. Genetics is clearly involved in each person's different levels of tolerance to caffeine consumption [115, 116, 117] and its effects on their pattern and quality of sleep [118]. Therefore, less tolerant people present a slower caffeine metabolism, prolonging its "alertness" effect, with possible changes in their biological rhythm (e.g. sleep rhythm). A change in a person's biological rhythm is a relevant factor for body weight management [119]. People who are susceptible to caffeine should control the consumption of foods rich in this compound and substitute it with other foods (e.g. herbal teas, decaf, chicory, guaraná, purple willow bark, cayenne pepper and ginger). In addition, it is important to note the interaction between the environment and the expression of the *CYP1A2* gene, which encodes for the main enzyme implicated in the metabolism of caffeine. In particular, *CYP1A2* expression is induced by smoke, cruciferous vegetables, polyamines from grilled meat and proton pump inhibitors such as omeprazol, and reduced by oral contraceptives, the antidepressant fluvoxamine and fluoroquinolone antibiotics [120].

Genetic result



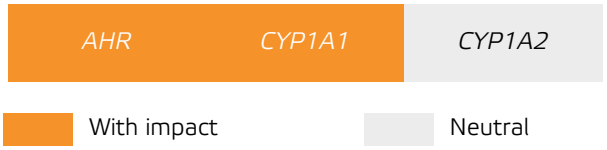
Result analysis

Your genetic results suggest a reduction in the consumption of caffeine, comparing to the recommended daily allowance.

- Given the total number of genetic variants that contribute to this area, the overall impact of those identified in your genome is not very significant.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Caffeine metabolism	*AHR*	rs4410790	g.17284577T>C	–	TC
	CYP1A1	rs2470893	c.-1694G>A	–	AG
		rs2472297	g.74735539C>T	–	CT

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

The genetic profile study enables not only the capacity for metabolising caffeine to be studied, shown above, but also the variability of response to this nutrient with regard to its anxiety-promoting effect. To that end, the *ADORA2A* and *COMT* genes are assessed, as described below.

The studied variants of the *ADORA2A* and *COMT* genes have an impact on the caffeine-induced anxiety and on the response to stress, respectively. It is relevant to evaluate its genotype in the context of caffeine metabolism since caffeine has a stimulating effect that may contribute to a more adverse response to anxiety-triggering situations.

- Carriers of the same genotype of *ADORA2A* that was identified on your genome report greater anxiety after the intake of caffeine, especially those who are not regular consumers (< 120 mg caffeine/day). When in an anxiogenic environment, it is particularly important that you consider restricting caffeine intake.
- Your genotype for the *COMT* gene is associated with an advantage in the processing of stress and with a lower predisposition to anxiety-related behaviors. On the other hand, individuals with this genotype have worse performance in working memory and attention-related tasks.

The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Neurotransmisson and vascular tone	*ADORA2A*	rs5751876	g.24837301T>C	–	T

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.2.11. Primary lactose intolerance

Lactose is a disaccharide that exists in large amounts in mammalian milk [121]. It is hydrolysed in the intestine through the action of the lactase enzyme [122]. Intolerance to this sugar is developed by the low activity of lactase, leading to the appearance of symptoms whenever a person ingests food with lactose. The severity of the symptoms depends on the amount of lactose ingested, the level of reduction of lactase activity, intestinal flora, motility and sensitivity of the gastrointestinal tract [123]. Some individuals only report symptoms with milk consumption (main source of lactose), while others develop symptoms with the consumption of several dairy products (e.g. yoghurt, cottage cheese) [121]. Common symptoms are pain, swelling, flatulence and colic, but also soft stools and diarrhoea can occur [124]. A significant percentage of the world's adult population has primary lactose intolerance and its distribution is very variable. At the European level, it is more frequent in the countries of the South than the North [125]. Individuals with genetic variants associated with lactose intolerance should adopt the strategy of replacing foods rich in lactose with other equivalents without the disaccharide (e.g. soy beverages) and/or taking lactase.

Genetic result

Your genotype is associated with primary lactose intolerance.

Result analysis

- You do not carry any of the *MCM6* gene variants associated with lactase persistence. This means that your ability to digest lactose is very likely to be lost in adult life (primary lactose intolerance), therefore resulting in intolerance symptoms when products containing lactose are ingested.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Lactase expression	*MCM6*	rs4988235	c.1917+326C>T	–	C
		rs182549	c.1362+117G>A	–	G
		rs41380347	c.1917+321T>G	–	T
		rs145946881	c.1917+226G>C	–	G
		rs41525747	c.1917+329C>G	–	C

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.2.12. Gluten intolerance

Gluten is a protein blend (mostly composed of gliadin and glutenin) to which some people are intolerant [126]. The nutritional value of gluten is inferior to that of proteins of animal origin, but the main advantages of using it are its physical and functional characteristics and its low cost [126]. Gluten is widely used for different purposes in the food industry. It is often found in products intended for vegetarian food, as a protein substitute and coating agent [127]. People's tolerance to the intake of foods containing gluten is variable and is associated with genetic factors [128].

Celiac disease is an enteropathy of immune origin, triggered by the ingestion of gluten in genetically susceptible people and has a prevalence of about 1% in the world population [129, 130]. The symptoms of celiac disease, which may be intestinal and extraintestinal, are variable and include diarrhoea, weight loss, constipation, iron deficiency, flatulence, chronic fatigue, and abdominal pain [130]. Symptoms may develop as early as adulthood and precede the diagnosis by several years [130, 131]. The presence of haplotypes DQ2 (DQ2.2 or DQ2.5) or DQ8, evaluated in this test, is necessary for the development of celiac disease, but it is not sufficient to determine the existence of this condition [132], since these haplotypes are present in about 30% of the healthy population [133]. These haplotypes are also present in up to 50% of people with non-celiac gluten sensitivity (NCGS) [133]. NCGS has been associated with irritable bowel syndrome, with improved symptoms following the initiation of a low-FODMAP (fermentable carbohydrate) diet [134], indicating that other foods are also important in the nutritional treatment of non-celiac gluten sensitivity.

In the presence of genetic susceptibility to gluten intolerance, it is particularly important to pay attention to the development of symptoms of intolerance and to discuss with the health professional the relevance of complementary diagnostic tests for celiac disease.

Genetic result

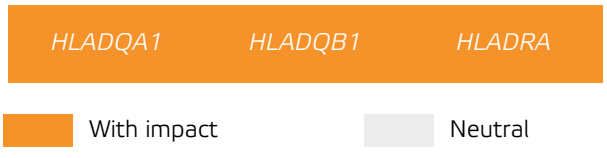
Your genetic profile is compatible with an intermediate predisposition to gluten intolerance.

Result analysis

- Your genetic profile for the *HLA* markers relevant to gluten sensitivity suggests that you have an intermediate predisposition to develop symptoms of intolerance [135]. Genetic variation in *HLA* is necessary but not sufficient to determine the presence of intolerance [132]. It is important to monitor the development of symptoms to evaluate the benefit of a gluten-free diet in the prevention of intestinal inflammation.
- In certain situations, it is not possible to unambiguously identify the presence of a DQ2.2 haplotype, due to limitations inherent in the technique, common to most genotyping techniques. In these cases, the result is described as DQX, and the estimated genetic predisposition may be lower than the real one.

Details of genetic analysis

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Immune response	*HLADQA1*	rs2187668	g.32638107C>T	–	CT
	HLADQB1	rs4713586	g.32691805A>G	–	A
	HLADRA	rs2395182	c.*406+494G>T	–	T

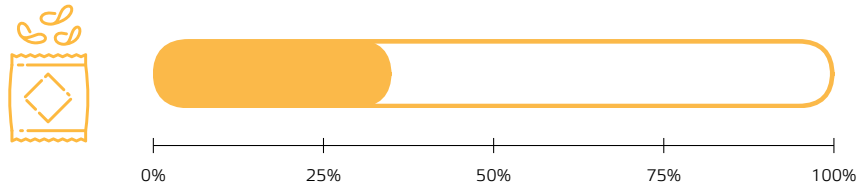
[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.3. Your behaviour

6.3.1. Adoption of satiety strategies

Levels of appetite and satiety result from the balance between nutrient intake, metabolism and energy expenditure. This balance may be altered due to the disruption of hormones that regulate appetite and satiety, notably ghrelin, serotonin and dopamine. As a result, a preference for consuming more caloric or satiating foods, often with higher fat or sugar content, may occur. The trend towards consuming food outside main mealtimes may also occur, or the trend towards consuming larger portions. In reality, this type of behaviour occurs without the body having an actual need, but rather because the brain requires higher levels of stimulation in the sense of brain reward. These impulsive behaviours may occur in situation of stress, or make up part of your daily life, due to having a genetic profile with a predisposition for such behaviours. This type of genetic predisposition may be circumvented by practicing physical exercise, regular sleep and a diet favouring foods rich in fibre and protein.

Genetic result



Result analysis

Your genetic results suggest that you benefit from the adoption of dietary strategies to increase satiety.

- Results from your genetic test suggest that you benefit from eating meals at regular times to avoid experiencing false hunger throughout the day and to keep your metabolism at a stable rate, avoiding a drop in energy expenditure. In your particular case, there is also benefit from adopting nutritional strategies within each meal to control appetite and hunger: have foods rich in fibre (e.g. vegetables, non-tropical fruits and whole grain cereals), and protein (e.g. meat clean from visible fat, dairy, egg whites, legumes, nuts) at every meal.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

CLOCK	*DRD2*	*FTO*	*MC4R*	*OPRM1*	*PER2*	*SIRT1*
SLC2A2						

With impact Neutral

The following table lists all variants whose identified result is relevant for this parameter.

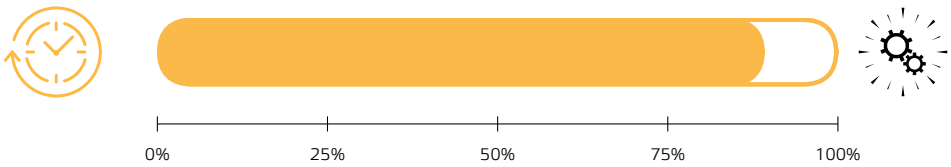
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Circadian rhythm	*CLOCK*	rs1801260	c.*213T>C	–	TC
		rs3749474	c.*897G>A	–	GA
Energy expenditure	*FTO*	rs9939609	c.46-23525T>A	–	TA

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.3.2. Regular sleep

A regular sleep pattern is essential for maintaining a healthy weight. During sleep, the balance between the energy that resulted from the ingestion of nutrients, energy expenditure and the metabolism of fats and carbohydrates is regulated. Sleeping poorly or having little restful sleep decreases the body's energy metabolism, resulting in a greater trend towards fat accumulation, particularly in the abdominal area. Disruption of hormones that regulate appetite and satiety (ghrelin, serotonin and leptin) may also occur, which may foster a preference for consuming more caloric or satiating foods (higher fat or sugar content) and often outside mealtimes. This type of behaviour occurs without the body having an actual need. As a result, weight gain may occur, with difficulty in losing weight. It is recommended that all individuals have a regular bedtime schedule, and hours of sleep should fall within the following ranges: 1) for adolescents (aged 13-18 years), between 8-10 hours daily; 2) for adults, between 7-8 hours daily. For restful sleep, avoid consumption of energy drinks before bedtime.

Genetic result

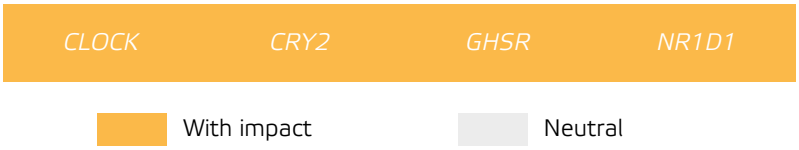


Result analysis

Your genetic results suggest that you benefit significantly from a regular sleep pattern.

- Your test indicates a genetic profile that is extremely sensitive to sleep deprivation and to a lack of regular sleeping patterns. Ways to overcome this genetic predisposition involve sleeping 6 to 8 hours/day at night time (8 to 10 hours/day if you are a teenager, up to 18 years old), in order to maximise the control of your circadian rythms.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

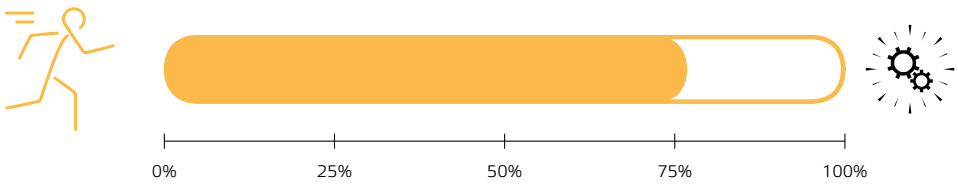
Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Circadian rhythm	*CLOCK*	rs1801260	c.*213T>C	–	TC
	CRY2	rs11605924	c.32+4259A>C	–	CA
	NR1D1	rs12941497	c.31+723C>T	–	T
Orexigenic stimulus	*GHSR*	rs490683	g.172175074C>G	–	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

6.3.3. Physical exercise

Physical exercise is important for weight management and the body's metabolic balance. Along with an appropriate diet, it enables the reduction of BMI, the loss of fat mass and excess weight and prevents the gain of lost weight. From a metabolic standpoint, it enables the reduction of LDL cholesterol and the reduction of insulin resistance. Various types of exercise can be recommended according to specific goals. For example, if the goal is to lose abdominal fat, resistance exercises will be the most suitable. On the other hand, more intense exercises contribute to the regulation of hormones associated with appetite. Genetics plays a very important role in the area of exercise associated with weight management. It is known that certain genes associated with body composition, lipid metabolism, insulin resistance and appetite control are conditioned by the practice of physical exercise.

Genetic result



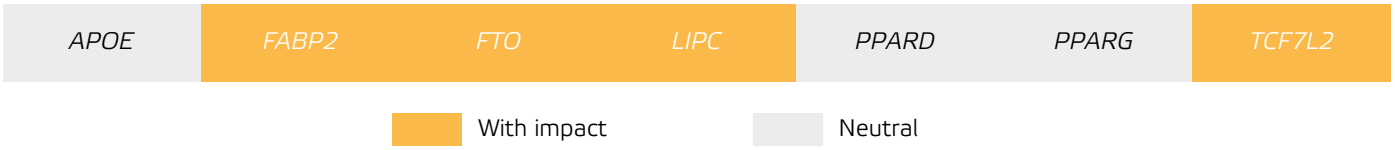
Result analysis

According to the World Health Organization (WHO), regular physical activity of moderate intensity, such as walking, cycling or playing sports, has significant health benefits at all ages.

Your genetic results suggest that you benefit very significantly from the practice of physical exercise, for the purposes identified below.

- Your results indicate that you benefit from physical activity to lose weight, suggesting that you have an increased energy expenditure (burn more calories) when practising exercise.
- Considering the identified genetic variant of *LIPC*, physical activity is particularly beneficial to increase insulin sensitivity. This means that, in your particular case, practising exercise may facilitate the insulin action on the muscle cells, causing fuel to be utilized more efficiently, hence improving your overall metabolism.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
Energy expenditure	*FTO*	rs1121980	c.46-34805G>A	–	A
		rs8050136	c.46-27777C>A	–	CA
Glucose metabolism	*TCF7L2*	rs7903146	c.382-41435C>T	–	C
Lipid metabolism	*FABP2*	rs1799883	c.163G>A	p.Ala55Thr	G
	LIPC	rs1800588	c.-557C>T	–	C

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (**http://www.ensembl.org**).

7. Technical information

7.1. Genetic analysis methodology

1. The DNA extraction was done in the automatic extraction equipment MagNA Pure Compact (ROCHE) through the use of the MagNA Pure Compact Nucleic Acid Isolation Kit I kit (ROCHE). The concentration and quality evaluation was done through the use of the Spectrophotometer MultiskanGo (Thermo Scientific).
2. Genotyping was made through the study of 102 genetic variants in 75 genes, described as nutrition and weight management-related.
3. Genotyping was achieved using a high-throughput DNA Microchip platform, the iPLEX® MassARRAY® system (Agena Bioscience, Inc.). This array platform allows an optimal genetic analysis by combining the benefits of accurate primer extension chemistry with MALDI-TOF mass spectrometry. The different masses of each generated PCR product are then converted into genotype information.
4. In accordance with Agena Bioscience's iPLEX® chemistry flyer, the MassARRAY® system performs SNP genotyping with a high level of accuracy and reproducibility (>99% accuracy on validated assays).

7.2. Genetic panel

ADD1	**Adducin 1 (alpha)** | ENSG00000087274
ADIPOQ	**Adiponectin, C1Q and collagen domain containing** | NM_004797.3
ADORA2A	**Adenosine A2a receptor** | NC_000022.10
ADRB2	**Adrenoceptor Beta 2** | ENSG00000169252
AHR	**Aryl Hydrocarbon Receptor** | NM_001621.4
ALPL	**Alkaline Phosphatase, Liver Bone Kidney** | NM_000478.4
AMDHD1	**Amidohydrolase domain containing 1** | NC_000012.12
APOA1	**Apolipoprotein A1** | ENSG00000118137
APOA2	**Apolipoprotein A2** | ENSG00000158874
APOA5	**Apolipoprotein A5** | ENSG00000110243
APOB	**Apolipoprotein B** | ENSG00000084674
APOE	**Apolipoprotein E** | ENSG00000130203
BCO1	**Beta-Carotene Oxygenase 1** | NM_017429.2
BDNF	**Brain Derived Neurotrophic Factor** | NM_001143805.1
CLCNKA	**Chloride voltage-gated channel Ka** | ENSG00000186510
CLOCK	**Clock Circadian Regulator** | ENSG00000134852
COMT	**Catechol-O-methyltransferase** | NM_000754.3
CRY1	**Cryptochrome Circadian Clock 1** | ENSG00000008405
CRY2	**Cryptochrome Circadian Clock 2** | ENSG00000121671
CYP1A1	**Cytochrome P450 Family 1 Subfamily A Member 1** | NM_000499.3
CYP1A2	**Cytochrome P450 Family 1 Subfamily A Member 2** | NM_000761.3
CYP24A1	**Cytochrome P450 family 24 subfamily A member 1** | NC_000020.11
CYP2R1	**Cytochrome P450 family 2 subfamily R member 1** | NC_000011.9
DHCR7	**7-Dehydrocholesterol Reductase** | NM_001360.2
DRD2	**Dopamine Receptor D2** | NM_000795.3
FABP2	**Fatty Acid Binding Protein 2** | NM_000134.3
FADS1	**Fatty Acid Desaturase 1** | NM_013402.4
FTO	**Fat Mass And Obesity Associated** | NM_001080432.2
FUT2	**Fucosyltransferase 2** | NM_000511.5
GC	**GC, Vitamin D Binding Protein** | NM_000583.3
GCKR	**Glucokinase Regulator** | NM_001486.3
GHSR	**Growth Hormone Secretagogue Receptor** | NM_198407.2
GIPR	**Gastric Inhibitory Polypeptide Receptor** | NM_000164.2
GRB14	**Growth Factor Receptor Bound Protein 14** | ENSG00000115290
GRK4	**G Protein-Coupled Receptor Kinase 4** | ENSG00000125388
HLADQA1	**Major Histocompatibility Complex, Class II, DQ Alpha 1** | NC_000006.12
HLADQB1	**Major Histocompatibility Complex, Class II, DQ Beta 1** | NC_000006.12
HLADRA	**Major Histocompatibility Complex, Class II, DR Alpha** | NM_019111.4
IL6	**Interleukin 6** | NM_000600.3
IM11	**Intergenic marker Chr 11** | NC_000011.10
IM19	**Intergenic marker Chr 19** | NC_000019.10
IRS1	**Insulin Receptor Substrate 1** | NM_005544.2
LDLR	**Low Density Lipoprotein Receptor** | NM_000527.4
LEPR	**Leptin Receptor** | NM_001003679.3
LIPC	**Lipase C, Hepatic Type** | NM_000236.2
LPL	**Lipoprotein Lipase** | NM_000237.2
LYPLAL1	**Lysophospholipase Like 1** | NM_138794.4
MC4R	**Melanocortin 4 Receptor** | NM_005912.2
MCM6	**Minichromosome Maintenance Complex Component 6** | NM_005915.5
MSRA	**Methionine Sulfoxide Reductase A** | ENSG00000175806
MTHFR	**methylenetetrahydrofolate reductase (NAD(P)H)** | NM_005957
MTNR1B	**Melatonin Receptor 1B** | NM_005959.3
NR1D1	**Nuclear Receptor Subfamily 1 Group D Member 1** | NM_021724.4
OPRM1	**Opioid receptor Mu 1** | NM_000914.4
PCSK1	**Proprotein convertase subtilisin kexin type 1** | NM_000439.4
PEMT	**Phosphatidylethanolamine N-methyltransferase** | NC_000017.10
PER2	**Period Circadian Clock 2** | NM_022817.2
PLIN	**Perilipin 1** | NM_001145311.1
PNPLA3	**Patatin Like Phospholipase Domain Containing 3** | NM_025225.2
PPARD	**Peroxisome Proliferator Activated Receptor Delta** | NM_006238.4
PPARG	**Peroxisome Proliferator Activated Receptor Gamma** | NM_015869.4
PPM1K	**Protein Phosphatase, Mg2+ Mn2+ Dependent 1K** | NM_152542.4
PROX1	**Prospero Homeobox 1** | NM_001270616.1
SEC16B	**SEC16 homolog B, endoplasmic reticulum export factor** | NC_000001.11
SEC23A	**Sec23 homolog A, COPII coat complex component** | NC_000014.9
SIRT1	**Sirtuin 1** | NM_012238.4
SLC23A1	**Solute Carrier Family 23 Member 1** | NM_005847.4
SLC2A2	**Solute Carrier Family 2 Member 2** | NM_000340.1
SLC30A8	**Solute Carrier Family 30 Member 8** | NM_001172811.1
SOD2	**Superoxide Dismutase 2, Mitochondrial** | NM_000636.2
SORT1	**Sortilin 1** | NM_001408.2
TCF7L2	**Transcription Factor 7 Like 2** | NM_030756.4
TFAP2B	**Transcription Factor AP-2 Beta** | NM_003221.3
TM6SF2	**Transmembrane 6 Superfamily Member 2** | NM_001001524.2
TMEM18	**Transmembrane protein 18** | NC_000002.12

7.3. Risks and limitations

The FoodHealth was built under a rigorous quality control process which may not exclude the possibility of error that might influence the test results. The reliability of the results is always guaranteed as HeartGenetics, Genetics and Biotechnology SA standard quality recommendations have been followed for the execution of this genetic test. The results presented in this report are limited to the available scientific knowledge at the time this test was developed. HeartGenetics, Genetics and Biotechnology SA guarantees the accuracy of the scientific knowledge presented in the report. It has been assumed as truthful all the above declarations about patient and medical identity, the purpose of the study, index case and nature of analysed biological products.

7.4. Quality assurance

HeartGenetics, Genetics and Biotechnology SA is an ISO 9001 certified company for Quality Management System and applies External Quality Assessment programs from INSTAND. The laboratory that performs this genetic test complies, at all times, with all the applicable certifications and Law in its territory.

7.5. Genetic information

This genetic test has identified 63 genetic variants, out of a total of 102 variants evaluated, with an impact on the definition of a nutritional plan and/or promotion of metabolic health. The variants with an impact on each trait can be consulted in the respective detail sections. The genetic variants considered in the preparation of this report are identified in the table below. The results are described according to HGVS nomenclature (`http:www.hgvs.org`) consulted on 1 July 2020.

Gene	Genetic variant references		Nucleotidic change [1]	Aminoacidic change	Result
	HGMD	Ensembl			
ADD1	CM021240	rs4961	c.1378G>T	p.Gly460Trp	G
ADIPOQ	CR052432	rs17300539	c.-1138A>G	–	G
ADORA2A	–	rs5751876	g.24837301T>C	–	T
ADRB2	CM950016	rs1042713	c.46A>G	p.Arg16Gly	G
AHR	–	rs4410790	g.17284577T>C	–	TC
ALPL	–	rs4654748	c.134-9113T>C	–	T
AMDHD1	–	rs10745742	g.95964751C>T	–	T
APOA1	CR900263	rs670	c.-113A>G	–	G
APOA2	CR024268	rs5082	c.-323T>C	–	TC
APOA5	CM023881	rs3135506	c.56G>C	p.Trp19Ser	G
APOA5	CM032546	rs2075291	c.553G>T	p.Gly185Cys	G
APOA5	CR033141	rs662799	c.-620C>T	–	TC
APOB	–	rs512535	c.-965A>G	–	AG
APOE	CM860003	rs7412	c.526C>T	p.Arg176Cys	C
APOE	CM900020	rs429358	c.388T>C	p.Cys130Arg	T
BCO1	CM091857	rs12934922	c.801A>T	p.Arg267Ser	AT
BCO1	CM091858	rs7501331	c.1136C>T	p.Ala379Val	C
BDNF	–	rs10767664	c.-22+16205A>T	–	TA
CLCNKA	–	rs848307	n.530+427C>T	–	C
CLOCK	CR121503	rs3749474	c.*897G>A	–	GA
CLOCK	CR984677	rs1801260	c.*213T>C	–	TC
COMT	CM960420	rs4680	c.472G>A	p.Val158Met	G
CRY1	–	rs2287161	c.-562G>C	–	CG
CRY2	–	rs11605924	c.32+4259A>C	–	CA
CYP1A1	–	rs2470893	c.-1694G>A	–	AG
CYP1A1	–	rs2472297	g.74735539C>T	–	CT
CYP1A2	CR993820	rs762551	c.-9-154C>A	–	A
CYP24A1	–	rs17216707	g.54115823T>C	–	T
CYP2R1	–	rs10741657	g.14914878A>G	–	GA
DHCR7	–	rs12785878	c.146+1233T>G	–	GT
DRD2	CM041241	rs1800497	c.2137G>A	p.Glu713Lys	G
FABP2	CM950433	rs1799883	c.163G>A	p.Ala55Thr	G
FADS1	CR1510437	rs174546	c.*53A>G	–	G
FTO	–	rs1121980	c.46-34805G>A	–	A
FTO	CR119357	rs1558902	c.46-40478T>A	–	A
FTO	CS076623	rs9939609	c.46-23525T>A	–	TA
FTO	CS088104	rs8050136	c.46-27777C>A	–	CA
FUT2	CM042988	rs602662	c.772A>G	p.Ser258Gly	GA
GC	–	rs2282679	c.*26-796A>C	–	CA
GCKR	CR118767	rs780094	c.1423-418T>C	–	CT
GHSR	CR084002	rs490683	g.172175074C>G	–	G
GIPR	–	rs2287019	c.886+14T>C	–	CT
GRB14	–	rs10195252	g.165513091C>T	–	TC
GRK4	CM025429	rs2960306	c.194G>T	p.Arg65Leu	G
GRK4	CM025430	rs1024323	c.425C>T	p.Ala142Val	C
HLADQA1	–	rs2187668	g.32638107C>T	–	CT
HLADQB1	–	rs4713586	g.32691805A>G	–	A
HLADQB1	–	rs7454108	g.32713706T>C	–	T
HLADQB1	–	rs7775228	g.32690302T>C	–	T
HLADRA	–	rs2395182	c.*406+494G>T	–	T

Gene	Genetic variant references HGMD	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
IL6	CR983402	rs1800795	c.-237G>C	–	GC
IM11	–	rs12272004	g.116733008C>A	–	C
IM19	–	rs4420638	g.44919689A>G	–	A
IRS1	CR096329	rs2943641	g.227093745TC>T	–	CT
LDLR	–	rs6511720	c.67+2015G>T	–	GT
LEPR	–	rs11208659	c.-20-51949T>C	–	T
LIPC	CR971949	rs1800588	c.-557C>T	–	C
LPL	CM900164	rs328	c.1421G>C	p.Term474Ser	C
LPL	CS890131	rs285	c.1019-1582C>T	–	T
LPL	CS931395	rs320	c.1322+483G>T	–	GT
LYPLAL1	–	rs2605100	g.219470882A>G	–	G
MC4R	–	rs11152221	g.60350016C>T	–	T
MC4R	–	rs12970134	g.60217517G>A	–	G
MC4R	–	rs17700633	g.60262199G>A	–	GA
MC4R	–	rs17782313	g.60183864T>C	–	T
MC4R	CM030481	rs2229616	c.307A>G	p.Ile103Val	G
MC4R	CM030483	rs52820871	c.751C>A	p.Leu251Ile	A
MCM6	CR024269	rs4988235	c.1917+326C>T	–	C
MCM6	CR024379	rs182549	c.1362+117G>A	–	G
MCM6	CR070424	rs145946881	c.1917+226G>C	–	G
MCM6	CR070425	rs41380347	c.1917+321T>G	–	T
MCM6	CR070426	rs41525747	c.1917+329C>G	–	C
MSRA	–	rs545854	g.9860080C>G	–	CG
MTHFR	CM950819	rs1801133	c.665C>T	p.Ala222Val	C
MTHFR	CM981315	rs1801131	c.1286A>C	p.Glu429Ala	A
MTNR1B	CR110512	rs10830963	c.223+5596C>G	–	CG
NR1D1	–	rs12941497	c.31+723C>T	–	T
NR1D1	–	rs2314339	c.370+106A>G	–	G
OPRM1	CM003770	rs1799971	c.118A>G	p.Asn40Asp	A
PCSK1	CM083013	rs6232	c.661A>G	p.Asn221Asp	A
PCSK1	CM1311914	rs6235	c.2069C>G	p.Thr690Ser	C
PEMT	CR063410	rs12325817	g.17486519C>G	–	C
PER2	–	rs2304672	c.-12C>G	–	C
PER2	–	rs4663302	g.238295120C>T	–	CT
PLIN	CS045669	rs894160	c.772-799G>A	–	G
PNPLA3	CM086892	rs738409	c.444C>G	p.Ile148Met	C
PPARD	CR035869	rs2016520	c.-87C>T	–	T
PPARG	CM981614	rs1801282	c.34C>G	p.Pro12Ala	C
PPM1K	–	rs1440581	n.133-6526T>C	–	C
PROX1	–	rs340874	c.-68+2590T>C	–	CT
SEC16B	–	rs539515	g.177919890A>C	–	A
SEC23A	–	rs8018720	g.39086981G>C	–	C
SIRT1	–	rs1467568	c.1916-864A>G	–	G
SLC23A1	CM0911294	rs33972313	c.790G>A	p.Val264Met	AG
SLC2A2	CM941277	rs5400	c.329C>T	p.Thr110Ile	C
SLC30A8	CM072050	rs13266634	c.826C>T	p.Arg276Trp	C
SOD2	CM962694	rs4880	c.47T>C	p.Val16Ala	T
SORT1	–	rs629301	c.*1635G>T	–	GT
TCF7L2	CS065626	rs7903146	c.382-41435C>T	–	C
TFAP2B	–	rs987237	c.602-724A>G	–	A
TM6SF2	CM143615	rs58542926	c.499G>A	p.Glu167Lys	G
TMEM18	–	rs2867125	g.622827T>C	–	C

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

Identified *APOE* haplotypes:

- *APOE*-$\varepsilon_3/\varepsilon_3$ (T,T) (C,C)

Identified *HLA* haplotypes:

- DQ2.5/DQX

Technical direction
HeartGenetics, Genetics and Biotechnology SA
Cantanhede, Portugal, N.A.

Raquel Lemos
Laboratory Director
Clinical Laboratory Geneticist; Biologist, BSc

Lúcia Gonçalves
Senior Laboratory Technician
Molecular Biologist, MSc

Daniel Luís
Scientific director
Molecular Biologist, MSc

Centro de Medicina Laboratorial Germano de Sousa is the responsible of the biochemical parameters in this test.

Technical direction
Centro de Medicina Laboratorial Germano de Sousa
Lisboa, Portugal

Prof. Dr. Germano de Sousa
Clinical Pathologist
Clinical Director

8. Appendix

8.1. Evidences for genetics impact

This appendix includes a detailed interpretation of the genetic study. All evidences are supported by scientific articles indexed in PubMed (http://www.ncbi.nlm.nih.gov/pubmed), accessed in July 2020.

ADIPOQ, CR052432 / rs17300539

The hormone ADIPOQ (adiponectin) promotes the ability of muscles to use carbohydrates, increases the metabolism of fats and regulates the feeling of satiety and, consequently, the level of appetite. This hormone is produced exclusively by adipocytes, but their levels are inversely correlated with body fat mass, unlike the remaining cytokines secreted by adipose tissue [136]. The G allele of this polymorphism, located in the promoter region, is associated with lower levels of adiponectin [137], which correlate with an increase in appetite. GG genotype carriers are more likely to recover lost weight after finishing a hypoenergetic diet [86]. However, calorie restriction is particularly beneficial to them for reducing the risk of metabolic syndrome if they are overweight [86].

ADORA2A, – / rs5751876

The *ADORA2A* gene encodes for a transmembrane protein that acts as a receptor for adenosine. The signal transduction that results from this interaction is implicated in biological functions such as cardiac rhythm, blood flow, pain regulation, immune function and sleep. Caffeine is able to bind to this receptor, acting as an antagonist of adenosine, inducing psychostimulation and, sometimes, anxiety. Individuals harbouring the TT genotype of the rs5751876 polymorphism have reported greater anxiety, after the ingestion of 100 mg [138] or 150 mg [139] of caffeine, as compared with carriers of the CT or CC genotypes. This effect is less marked among regular caffeine consumers (> 120 mg/day) [138].

ADRB2, CM950016 / rs1042713

The ADRB2 protein is a catecholamine (e.g. adrenaline) receptor, important for lipolysis, i.e. for the mobilisation and consumption of the energy stored in adipocytes. Genotype-phenotype association studies show that male carriers of the GG genotype have greater difficulty in weight loss and greater ease in recovering lost weight [84, 85, 140]. In addition, both men and women with the GG genotype are more likely to benefit from reducing fat intake to decrease LDL- and total cholesterol [141]. The ADRB2 protein is also involved in regulating vasodilation insofar as it induces sodium reabsorption by the kidneys. Carriers of the GG genotype present an increased sensitivity to sodium, which induces fluid retention [106]. The retention of fluids causes swelling and the attendant weight gain.

AHR, – / rs4410790

The AHR protein regulates the activity of the *CYP1A1-CYP1A2* genes, which are associated with caffeine metabolism. Meta-analysis studies indicate that individuals carrying the T allele tend to ingest less caffeine [116, 142]. This allele is associated with decreased caffeine metabolism, as assessed by metabolite analysis [117].

APOA1, CR900263 / rs670

The apolipoprotein A1 (APOA1) is the main protein component of the high-density lipoprotein (HDL) in the plasma. It is synthesised in the liver and in the intestine and acts as a co-factor for the lecithin-cholesterol acetyltransferase, responsible for the esterification of free cholesterol in HDL particles. It is involved in reverse cholesterol transport, promoting the efflux of free cholesterol and phospholipides from the cells. Carriers of the GG genotype have a predisposition to a higher Body Mass Index (BMI), abdominal fat accumulation and insulin resistance [143, 144].

APOA5, CM023881 / rs3135506

The Apo-AV protein regulates lipid metabolism and plasma triglyceride levels. GG genotype carriers have a greater predisposition to being overweight in response to a high fat intake, and therefore benefit from a low-fat diet for risk mitigation [145].

APOA5, CR033141 / rs662799

The Apo-AV protein regulates lipid metabolism and plasma triglyceride levels. Genotype-phenotype association studies indicate that individuals harbouring the C allele have a predisposition to higher triglyceride levels, and therefore benefit from a low-fat diet to decrease plasma triglycerides and total cholesterol [96, 146, 147].

APOE, CM900020 / rs429358 + APOE, CM860003 / rs7412

The Apo-E protein plays a role in the absorption and metabolism of lipoproteins, from which cholesterol is an important component. Apo-E has three major isoforms, encoded by the haplotypes $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$. $\varepsilon 3$ is the most common. $\varepsilon 2$ is associated with lower values of LDL- and total cholesterol and $\varepsilon 4$ allele to the opposite effect, i.e. higher levels of plasma LDL- and total cholesterol [148, 149, 150]. With respect to the impact of fat intake in the variation of total cholesterol levels, carriers of the $\varepsilon 2/\varepsilon 4$ diplotype (combination of haplotypes) are those with the most disadvantageous

response [150] and therefore benefit from a low-fat nutritional plan. $\varepsilon 2/\varepsilon 2$, $\varepsilon 2/\varepsilon 4$ and $\varepsilon 4/\varepsilon 4$ are associated with predisposition to higher triglyceride levels [150]. Carriers of $\varepsilon 2$ benefit from the intake of polyunsaturated fats to reduce triglyceride levels [151].

BDNF, – / rs10767664

The *BDNF* gene encodes for a neurotrophic factor, i.e. a protein that promotes neuron survival and differentiation. It modulates the growth and morphology of dendrites and participates in axonal orientation and growth. It also has a relevant role in synaptic plasticity [152]. The expression of BNDF in the hypothalamus, responsible for appetite regulation mechanisms, has aroused the interest of the scientific community due to the possible impact of its genetic variability on energy balance and consequently on excess weight [153]. Studies with mice have shown that *BDNF* knockout results in hyperphagia and obesity [154], whereas the hypothalamic infusion of BDNF suppresses appetite and results in weight loss [155, 156]. The association of *BDNF* variants with elevated BMI has been demonstrated in humans through several studies [153, 157, 158, 159]. Given the anorexigenic role of BNDF shown in mice, it is likely that genetic variants associated with elevated BMI result either in decreased gene expression or in the production of a protein with reduced activity. In particular, for this genetic variant, the predisposition for high BMI results from the presence of the A allele [157, 158].

CLOCK, CR121503 / rs3749474

The CLOCK protein is a transcriptional activator of several key genes that regulate the circadian rhythm. It thereby influences the balance between energy expenditure and fat, carbohydrate and protein metabolism, among other biological processes. Studies of genotype-phenotype association show that A allele carriers have a predisposition to an increased caloric intake and to a higher Body Mass Index (BMI) [31, 89, 160]. They benefit from a hypoenergetic diet with decreased fat intake, in order to achieve better weight loss results [161].

CLOCK, CR984677 / rs1801260

The CLOCK protein is a transcriptional activator of several key genes that regulate the circadian rhythm. It thereby influences the balance between energy expenditure and fat, carbohydrate and protein metabolism, among other biological processes. Studies of genotype-phenotype association show that C allele carriers have a predisposition to higher Body Mass Index (BMI) and greater difficulty in losing weight [89, 160, 162]. This allele is also associated with short-time sleepers with increased levels of the hunger-inducing hormone ghrelin, and with increased saturated fat intake [89, 160, 162]. Sleeping an appropriate number of hours and having a regular sleep pattern+D91 is beneficial to decrease ghrelin levels in those carrying this allele [163].

CRY1, – / rs2287161

The CRY1 protein participates in the regulation of the circadian rhythm and influences the balance between carbohydrate intake and glucose metabolism. Genotype-phenotype association studies show that G allele carriers are more tolerant to a diet enriched in complex carbohydrates [160, 164]. In particular, these individuals do not have an increased predisposition to insulin resistance by adopting such a diet [160, 164].

CRY2, – / rs11605924

The CRY2 protein participates in the regulation of the circadian rhythm and influences the balance between energy expenditure and food intake. Genotype-phenotype association studies show that A allele carriers have a predisposition to higher energy expenditure. They benefit from a regular sleep pattern of more than 6-7 hours to increase HDL cholesterol levels [165, 166].

CYP1A1, – / rs2470893

The SNP rs2470893 is localized in the bidirectional promoter of the *CYP1A1* and *CYP1A2* genes. Variations in this region may alter CYP1A2 expression, the main enzyme of the caffeine metabolism. Meta-analysis studies indicate that individuals carrying the G allele tend to ingest less caffeine [116, 142, 167, 168]. This allele is associated with decreased caffeine metabolism, as assessed by metabolite analysis [117].

CYP1A1, – / rs2472297

The SNP rs2472297 is localized in the bidirectional promoter of the *CYP1A1* and *CYP1A2* genes. Variations in this region may alter CYP1A2 expression, the main enzyme of caffeine metabolism. Meta-analysis studies indicate that individuals carrying the C allele tend to ingest less caffeine [142, 168, 169]. This allele is associated with decreased caffeine metabolism, as assessed by metabolite analysis [117].

CYP1A2, CR993820 / rs762551

The CYP1A2 enzyme is associated with caffeine metabolism. Studies of genotype-phenotype association show that variation in CYP1A2 results in different levels of enzymatic activity and therefore in different levels of caffeine metabolism, namely fast and slow metabolism. Carriers of the AA genotype have increased caffeine metabolism, i.e. they are fast metabolizers [115, 170, 171, 172].

CYP2R1, – / rs10741657

The *CYP2R1* gene encodes for the 25-hydroxylase enzyme, which catalyses the addition of a hydroxyl group to the 25-carbon of cholecalciferol (vitamin D3) converting it into calcidiol (25-hydroxyvitamin D). The rs10741657 polymorphism has been consistently correlated with variability in the serum levels of 25-hydroxyvitamin D, with the G allele being associated with lower levels [72, 173, 174].

DHCR7, – / rs12785878

The DHCR7 enzyme is involved in the production of cholesterol from 7-dehydrocholesterol, a precursor of vitamin D. Increased DHCR7 activity reduces the 7-dehydrocholesterol that is available for the production of vitamin D through sunlight exposure. The G allele is associated with increased activity of the DHCR7 enzyme, and therefore carriers of this allele present lower plasma levels of vitamin D [72, 173, 174]. For this reason, they are particularly likely to benefit from increased (responsible) sun exposure and from the intake of good dietary sources of vitamin D. On the other hand, carriers of the T allele were shown to benefit from a hypoenergetic protein-rich nutrition plan to decrease insulin resistance [48].

FABP2, CM950433 / rs1799883

The I-FABP protein, encoded by the *FABP2* gene, participates in regulating the absorption of fats in the intestine, and in its metabolism, influencing insulin sensitivity. Genotype-phenotype association studies indicate that carriers of the GG genotype are more likely to have lower intestinal fat absorption [175]. Carriers of this genotype benefit more from the practice of physical exercise for weight loss and also present better response to the adoption of a hypoenergetic diet [88].

FTO, – / rs1121980

The FTO protein plays an important role in regulating body weight, energy expenditure, insulin resistance, appetite, and satiety. Genome-wide association studies (GWAS) consistently associate variation in the *FTO* gene with susceptibility to a higher Body Mass Index (BMI), as it is the gene with the strongest and most replicated correlation [176]. Carriers of the A allele have a predisposition to a higher BMI and accumulation of abdominal fat [177, 178, 179]. Physical exercise is recommended to attenuate this predisposition, which is exacerbated by a sedentary lifestyle [178]. Carriers of the AA genotype benefit from a low-fat nutritional plan in order to achieve better weight loss results [98].

FTO, CR119357 / rs1558902

The FTO protein plays an important role in regulating body weight, energy expenditure, insulin resistance, appetite, and satiety. Genome-wide association studies (GWAS) consistently associate variation in the *FTO* gene with susceptibility to higher Body Mass Index (BMI), being it the gene with the strongest and most replicated correlation [176]. Carriers of the A allele have a predisposition to higher BMI and benefit from a protein-enriched nutritional plan for weight loss [47, 180, 181].

FTO, CS076623 / rs9939609

The FTO protein plays an important role in regulating body weight, energy expenditure, insulin resistance, appetite, and satiety. Genome-wide association (GWA) studies consistently associate the variants of the *FTO* gene with susceptibility to high Body Mass Index (BMI), the gene with the strongest correlation being the most replicated between studies [176]. Individuals with the A allele are more likely to have a lack of control over the amount of food eaten, a high BMI and abdominal fat accumulation [182, 183, 184, 185, 186, 187, 188, 189]. However, there is evidence that a high protein diet is particularly beneficial for them as a strategy to decrease their appetites [190]. In addition, individuals with an AA genotype benefit from physical exercise to mitigate the impact of the variant on adiposity, which is exacerbated by a sedentary lifestyle, as well as from a diet plan with reduced fat intake [98, 182, 184, 185, 186, 188, 191].

FTO, CS088104 / rs8050136

The FTO protein plays an important role in regulating body weight, energy expenditure, insulin resistance, appetite, and satiety. Genome-wide association studies (GWAS) consistently associate variation in the *FTO* gene with susceptibility to a higher Body Mass Index (BMI), as it is the gene with the strongest and most replicated correlation [176]. Carriers of the A allele benefit from a fibre-rich nutrition plan and from physical activity in order to achieve better weight loss results [192, 193, 194].

FUT2, CM042988 / rs602662

The FUT2 enzyme modulates the host-microbiome interaction, thereby influencing microbiome composition. As a result, FUT2 conditions the intestine absorption of vitamin B_{12}, and its circulating levels. Studies of genotype-phenotype association show that those carrying the G allele, associated with increased FUT2 activity, have lower circulating levels of vitamin B_{12}. Vitamin B_{12} is essential to cellular metabolism, especially of the gastrointestinal tract, bone marrow and nerve tissue. It is essential for the synthesis of nucleic acids and is involved in the metabolism of carbohydrates and fats [195, 196, 197].

GC, – / rs2282679

The GC protein participates in vitamin D transport and storage. Several studies indicate that C allele carriers have a lower concentration of circulating

vitamin D [72, 173, 174, 198]. The main source of vitamin D is ultraviolet radiation, essential for its production from 7-dehydrocholesterol. It can also be obtained by vitamin supplementation. The main active form, 1,25-dihydroxyvitamin D (calcitriol), is produced in the kidneys. Vitamin D plays a role in the immune system, reproduction, insulin secretion and keratocyte differentiation. It is also involved in the active transport of phosphate in the intestine and in calcium homoeostasis, promoting its absorption by the bones [72, 199].

GCKR, CR118767 / rs780094

The gene *GCKR* encodes for a glucokinase inhibitory protein, which acts on the liver and pancreatic islets. The glucokinase enzyme is responsible for the catalysis of the first step of glucose metabolism in these tissues. Its inactivation by GCKR controls the influx of glucose into the hepatocytes and thereby regulates lipogenesis *de novo*, i.e. the lipid synthesis pathway from carbohydrates [10]. By influencing glucose internalization, its activity has an impact on the insulin resistance mechanism. In particular, the presence of the C allele is significantly associated with increased fasting insulin and glucose levels and insulin resistance [200, 201].

GHSR, CR084002 / rs490683

The ghrelin (GHS) hormone is produced by the stomach and induces the sensation of hunger, therefore playing an important role in appetite regulation. The concentration of this hormone in the blood is higher during a hypoenergetic diet intervention, which can generate a continuous sensation of hunger, predisposing to the intake of more calories and consequent weight gain. Genotype-phenotype association studies show that individuals carrying the G allele, for this variant of the ghrelin receptor gene (*GHSR*), present greater difficulty in losing weight and decreasing insulin resistance in response to a hypoenergetic nutritional plan [202, 203]. Those with GG genotype, associated with higher GHSR expression, are advised to have a regular sleep rhythm, within the recommended limits, since sleep deprivation is associated with increased levels of ghrelin and consequently with more hunger and appetite [163, 202].

GIPR, – / rs2287019

The GIP hormone is secreted by the K-cells of the intestinal epithelium in response to the intake of carbohydrates and fats, mainly to stimulate insulin secretion. Genotype-phenotype association studies show that T allele carriers benefit from a low-fat nutritional plan, enriched in both complex carbohydrates and fibre, in order to achieve better weight loss results and decrease insulin resistance [204]. The C allele is associated with higher Body Mass Index (BMI) [205, 206].

GRB14, – / rs10195252

The GRB14 protein binds to the insulin receptor and suppresses insulin singnalling. Meta-analysis studies indicate that women carrying the T allele have a predisposition to a higher waist-hip ratio [207, 208, 209].

HLADRA, – / rs2395182 + HLADQB1, – / rs7775228 + HLADQB1, – / rs4713586 + HLADQA1, – / rs2187668 + HLADQB1, – / rs7454108

The major histocompatibility complex is a highly polymorphic genomic region. The *HLA-DQA1* and *-DQB1* genes, located in this region, encode for receptor proteins, which present antigens to T cells at the cell surface level. Recognition of the antigen by these cells triggers the immune response. Some genetic variants in this histocompatibility region result in an increased ability of the encoded proteins to interact with gluten and present it as an antigen. The presence of gluten therefore triggers an immune response whose repetition, over time, leads to a change in the microvilli of the intestinal mucosa and consequently to a decrease in the capacity to absorb nutrients. The *HLA-DQ* diplotype identified is associated with an intermediate risk of gluten intolerance [135, 210]. It is important to note that genetic variation in HLA is required but is not sufficient to determine the presence of celiac disease [132]. In the presence of symptoms of gluten intolerance, a gluten-free diet must be tested, and additional diagnosis methods must be considered by the healthcare provider [211].

IL6, CR983402 / rs1800795

The IL6 cytokine has both pro- and anti-inflammatory properties, and is also involved in the metabolism of fat and carbohydrates. The expression of IL6 is influenced by this genetic variant, with the G allele resulting in increased plasma levels. Carriers of this allele have a predisposition to insulin resistance [212].

IM11, – / rs12272004

The RS12272004 variant is located in an intergenic region near the *APOA5* gene. Studies of genotype-phenotype association indicate that it correlates with plasma levels of α-tocopherol, the main active form of vitamin E. Carriers of the C allele have lower levels of α-tocopherol [213, 214]. These individuals benefit from a vitamin E-enriched diet plan. Vitamin E has antioxidant properties, preventing the peroxidation of polyunsaturated fatty acids and protecting the cell membranes from the harmful action of free radicals.

LDLR, – / rs6511720

The *LDLR* gene encodes the receptor of low density lipoparticles, the major circulating cholesterol-carrying lipoproteins. This receptor is involved in the endocytosis of these particles, i.e. in their internalization by cells, removing them from circulation. Its activity is therefore absolutely critical to the management of plasma cholesterol levels. This genetic variant has been identified in several GWAS studies as one of the most significant in view of the variability of circulating LDL cholesterol levels [215, 216, 217]. The G allele, which is the most frequent in all populations, is associated with higher levels.

LIPC, CR971949 / rs1800588

The LIPC protein is involved in the regulation of plasma triglyceride, LDL and HDL cholesterol levels. Genotype-phenotype association studies show that CC genotype carriers benefit from physical exercise in order to reduce insulin resistance [218].

LPL, CM900164 / rs328

The LPL protein regulates fat metabolism and transport, and also plasma triglyceride levels. Genotype-phenotype association studies show that CC genotype carriers have a predisposition to higher triglyceride and lower HDL cholesterol levels [147, 219, 220].

LPL, CS890131 / rs285

The LPL protein regulates fat metabolism and transport, and also plasma triglyceride levels. Genotype-phenotype association studies show that TT genotype carriers have a predisposition to higher triglyceride and lower HDL cholesterol levels [219].

LPL, CS931395 / rs320

The LPL protein regulates fat metabolism and transport, and also plasma triglyceride levels. Genotype-phenotype association studies show that G allele carriers have a predisposition to lower triglyceride and higher HDL cholesterol levels [147, 219].

LYPLAL1, – / rs2605100

The LYPAL1 protein hydrolyzes short chain substrates. Meta-analysis studies indicate that women carrying the G allele have a predisposition to higher waist-hip ratio. No significant effect was observed in men [221, 222].

MC4R, – / rs11152221

The MC4-R protein plays an important role in regulating body weight, energy expenditure, appetite, and satiety. This variant is associated with partial or total loss of function. Carriers of the T allele have a predisposition to a higher Body Mass Index (BMI) [223].

MC4R, – / rs17700633

The MC4-R protein plays an important role in regulating body weight, energy expenditure, appetite, and satiety. This variant is associated with partial or total loss of function. Carriers of the A allele have a predisposition to a higher Body Mass Index (BMI) [224].

MC4R, CM030481 / rs2229616

The MC4-R protein plays an important role in regulating body weight, energy expenditure, appetite, and satiety. Carriers of the GG genotype have a predisposition to a higher Body Mass Index (BMI) [223, 225, 226, 227, 228, 229].

MC4R, CM030483 / rs52820871

The MC4-R protein plays an important role in regulating body weight, energy expenditure, appetite, and satiety. Genotype-phenotype association studies indicate that AA genotype carriers have a predisposition to higher Body Mass Index (BMI) [223, 225, 226].

MCM6, CR024269 / rs4988235 + MCM6, CR024379 / rs182549 + MCM6, CR070425 / rs41380347 + MCM6, CR070424 / rs145946881 + MCM6, CR070426 / rs41525747

The protein encoded by the *MCM6* gene is essential for the replication of the eukaryotic genome. In addition, this gene presents intronic regions with a regulatory role in the expression of the *LCT* gene, which encodes the lactase enzyme (responsible for the metabolism of lactose). The presence of certain genetic variants in these regions results in increased transcriptional activation of LCT and, as a result, in the persistence of lactase activity, which allows for the digestion of ingested lactose in vitro [230, 231]. These genetic variants are very frequent, due to their positive selection, which is why a considerable fraction of the adult population is able to consume animal milk without any symptoms of intolerance. The variants rs4988235 (c.1917+326C>T, T allele) and rs182549 (c.1362+117G>A, A allele) are very common in Europe, while rs41380347 (c.1917+321T>G, G allele) is mainly found in the Middle East and rs145946881 (c.1917+226G>C, C allele) and rs41525747 (c.1917+329C>G, G allele) in Africa, with varying frequencies [124, 230, 232, 233]. In the absence of all of them, as is the case, there is no persistence of lactase activity in adulthood, and symptoms of intolerance occur when lactose products are consumed.

MSRA, – / rs545854

The MSRA protein is associated with oxidative damage repair in proteins and the restoration of their biological activity. Studies of genotype-phenotype association show that G allele carriers have greater predisposition to accumulate abdominal fat [222, 234, 235].

MTNR1B, CR110512 / rs10830963

The MTNR1B protein is a receptor for melatonin, a hormone synthesised from tryptophan and derived from serotonin that regulates the circadian or biological rhythm. The regulation of the circadian rhythm impacts on the balance between energy expenditure and food intake and glucose metabolism. Genotype-phenotype association studies show that carriers of the G allele have increased expression of MTNR1B, delayed offset of melatonin synthesis and high levels of this hormone for a longer period of time [236, 237]. This allele is associated with reduced beta cell function, with consequent decrease in insulin secretion and increased plasma glucose [160, 165, 200, 237, 238, 239, 240]. Carriers of the G allele benefit from a low-fat nutritional plan to lose weight and reduce LDL- and total cholesterol levels [241, 242]. Women carrying this allele show greater difficulty in losing weight [243].

NR1D1, – / rs12941497

The NR1D1 protein is involved in the regulation of the circadian rhythm, controlling the expression of CLOCK and CRY1 proteins and thereby regulating the balance between energy expenditure and fat, carbohydrate and protein metabolism, among other biological processes. Carriers of the T allele are more likely to be evening type, i.e. to be more active during the evening and have a delayed sleep phase by comparison with morning and intermediate types. They should have a regular sleep rhythm, sleep an appropriate number of hours, and avoid high caloric intake at the end of the day, when the metabolism slows down [244].

PER2, – / rs2304672

The PER2 protein is involved in the regulation of the circadian rhythm, influencing the balance between energy expenditure and fat, carbohydrate and protein metabolism, among other biological processes. Individuals with the CC genotype have a predisposition to a higher waist-to-hip ratio [245].

PLIN, CS045669 / rs894160

The protein encoded by the *PLIN* gene participates in the coating of lipid vesicles used for the storage of lipids in adipocytes. This coating protects the lipids from the action of lipases, which catalyse their degradation. Therefore, this protein works as a modeller of the lipid metabolism. Scientific evidence suggests that the GG genotype for this genetic variant is associated with a better response to calorie restriction. In particular, individuals with this genotype demonstrated greater weight loss [246] and reduction of the abdominal perimeter [247] following such restriction.

PNPLA3, CM086892 / rs738409

The enzyme encoded by the PNPLA3 gene has triglyceride lipase activity and is involved in its use as a source of energy and consequently in its storage. This polymorphism is associated with variability in lipid profile values. In particular, the CC genotype, for which lipase activity is maintained, has a significant correlation with higher levels of triglycerides and circulating LDL cholesterol [248].

PPARG, CM981614 / rs1801282

The PPARG protein participates in the metabolism of lipids and adipogenesis and, therefore, in the regulation of fat storage. The CC genotype of this polymorphism is associated with a more favourable response to a hypoenergetic diet, with less resistance to weight loss [87]. However, individuals with this genotype might recover lost weight more easily [249, 250]. They are also likely to be more tolerant to the intake of complex carbohydrates with regard to weight gain [251].

PPM1K, – / rs1440581

The PPM1K protein participates in the regulation of insulin secretion. Carriers of the CC genotype benefit from a hypoenergetic low-fat plan, enriched in complex carbohydrates, insofar as it induces increased insulin sensitivity [252, 253, 254].

PROX1, – / rs340874

The PROX1 protein functions as a key regulatory protein in the development of the pancreas and as a transcriptional regulator of several metabolic genes. Genotype-phenotype association studies indicate that the C allele is associated with decreased insulin secretion, with a consequent increase in circulating glucose levels [200, 239, 255].

SEC23A, – / rs8018720

The protein encoded by the *SEC23A* gene is implicated in the vesicular trafficking of proteins and lipids between the endoplasmic reticulum and the Golgi complex, where proteins undergo post translational modifications and where exocytosis is initiated. Despite the absence of a known direct link between *SEC23A* and the vitamin D canonical metabolic pathway, the rs8018720 polymorphism has been consistently correlated with variability in plasma levels of 25-hydroxyvitamin D [173, 174]. In particular, the C allele is associated with lower serum levels.

SLC23A1, CM0911294 / rs33972313

The SLC12A31 protein is a carrier of vitamin C (also known as L-ascorbic acid). Several studies have shown that A allele carriers have lower levels of circulating vitamin C [256, 257, 258]. These individuals benefit from a nutritional plan enriched with this vitamin. Vitamin C plays several roles: as an antioxidant, it prevents the peroxidation of polyunsaturated fatty acids and protects the cell membranes from the action of free radicals; it promotes resistance to infection; it enhances the absorption of iron from food; it is involved in the synthesis of various hormones (e.g. norepinephrine and dopamine) and neurotransmitters (e.g. serotonin); it is involved in folate metabolism; it is involved in the production of collagen; it promotes the maintenance of dental and gum health.

SLC30A8, CM072050 / rs13266634

The *SLC30A8* gene encodes for a zinc carrier (ZnT-8), which is expressed essentially at the pancreatic level, in β cells. This carrier is involved in the accumulation of zinc (Zn) in intracellular vesicles, used for the storage of insulin in the form of Zn-insulin crystals [259]. These vesicles function as secretory granules, upon fusion with the cell membrane, resulting in the release of the stored insulin [259]. The C allele of this polymorphism is associated with a lower conversion of the proinsulin into insulin and lower secretion of the latter [260], that is, a functional reduction of β cells. As such, the presence of this allele negatively impacts the glucose metabolism, as demonstrated by several studies [261, 262, 263].

SOD2, CM962694 / rs4880

The reactive oxygen anion superoxide is formed as a by-product of the mitochondrial electron transport chain, therefore increasing along with aerobic metabolism, and is toxic, causing oxidative cell damage. The *SOD2* gene encodes for a mitochondrial superoxide dismutase, which catalyses the conversion of the superoxide into hydrogen peroxide and diatomic oxygen. SOD2 is one of the main endogenous enzymes with antioxidant function thus being vital to protect cells against the oxidative stress caused by free radicals. Some variations in the *SOD2* gene affect the activity of the encoded enzyme, thereby influencing endogenous protection against oxidative damage. The TT genotype is associated with a less efficient production and mitochondrial trafficking of SOD2, and consequently with a decreased capacity of superoxide metabolization [264]. Increased levels of superoxide promote lipid peroxidation by reacting with nitric oxide, therefore damaging biomembranes [265]. Carriers of the TT genotype are likely to benefit from an increased dietary intake of manganese, the co-factor of SOD2, and antioxidants, including the lipid-soluble vitamin E (α-tocopherol) and carotenoids, which are radical-scavenging antioxidants effective against lipid peroxidation [266, 267, 268].

SORT1, – / rs629301

The *SORT1* gene encodes for the sortilin protein required for the transport of proteins in the Golgi apparatus, conditioning their routing to the cell surface or sub-cellular compartments. It therefore has an impact on multiple cellular processes, including lipid metabolism. This genetic variant is one of those with a more significant association, according to several GWAS studies, with the variability of circulating LDL cholesterol levels [215, 216, 217]. The G allele is particularly associated with higher levels.

TCF7L2, CS065626 / rs7903146

The TCF7L2 protein is a regulator of gene expression in beta cells and in other glucose metabolizing tissues. Carriers of the CC genotype have a predisposition to a higher Body Mass Index (BMI) and benefit from fibre intake and physical activity in order to achieve better weight loss results [157, 269, 270, 271].

TM6SF2, CM143615 / rs58542926

The *TM6SF2* gene encodes a transmembrane protein with influence on the secretion of triglycerides and consequently on the content of hepatic lipid vesicles. A functional study has shown that the silencing of this gene results in a lower secretion of VLDL and an increase in hepatic fat [272]. This genetic variant is functional and therefore conditions the activity of this protein. The GG genotype, in particular, corresponds to homozygous for the wild type allele and is therefore associated with maintenance of the TM6SF2 function. However, it contributes to the less favourable lipid profile, more specifically to higher levels of circulating LDL cholesterol and triglycerides [248].

TMEM18, – / rs2867125

Several studies have demonstrated a strong correlation between the genomic region close to the *TMEM18* gene and BMI [206, 235, 273, 274, 275, 276, 277]. The protein encoded by *TMEM18* acts as a transcriptional repressor, and the scientific evidence suggests that it plays a role in appetite control [278]. In animal models, gene deletion induces weight gain, whereas it's hypothalamic overexpression results in reduced food intake and increased energy expenditure [278]. The C allele of the rs2867125 polymorphism is associated with higher BMI [206, 275, 277].

9. References

[1] P. Adab, M. Pallan, and P. H. Whincup, BMJ-BRITISH MEDICAL JOURNAL **361**, k2293 (2018).
[2] K. D. Hall, G. Sacks, D. Chandramohan, C. C. Chow, Y. C. Wang, S. L. Gortmaker, and B. A. Swinburn, The Lancet **378**, 826 (2011).
[3] H. Bays, Current opinion in endocrinology, diabetes, and obesity **21**, 345 (2014).
[4] M. C. Petersen and G. I. Shulman, Physiological reviews **98**, 2133 (2018).
[5] N. P. Greene, J. D. Fluckey, B. S. Lambert, E. S. Greene, S. E. Riechman, and S. F. Crouse, American Journal of Physiology-Endocrinology and Metabolism **303**, E1212 (2012).
[6] A. L. Catapano, I. Graham, G. De Backer, O. Wiklund, M. J. Chapman, H. Drexel, A. W. Hoes, C. S. Jennings, U. Landmesser, T. R. Pedersen, *et al.*, European heart journal **37**, 2999 (2016).
[7] R. A. Roth, *Nutrition & diet therapy* (Cengage Learning, 2013).
[8] V. Ormazabal, S. Nair, O. Elfeky, C. Aguayo, C. Salomon, and F. A. Zuñiga, Cardiovascular diabetology **17**, 122 (2018).
[9] B. G. Nordestgaard, Circulation research **118**, 547 (2016).
[10] M. Eslam, L. Valenti, and S. Romeo, Journal of hepatology **68**, 268 (2018).
[11] A. Lonardo, S. Sookoian, C. J. Pirola, and G. Targher, Metabolism **65**, 1136 (2016).
[12] M. C. Ryan, C. Itsiopoulos, T. Thodis, G. Ward, N. Trost, S. Hofferberth, K. O'Dea, P. V. Desmond, N. A. Johnson, and A. M. Wilson, Journal of hepatology **59**, 138 (2013).
[13] E. A. for the Study of the Liver, E. A. for the Study of Diabetes (EASD, *et al.*, Obesity facts **9**, 65 (2016).
[14] K. D. Corbin and S. H. Zeisel, Current opinion in gastroenterology **28**, 159 (2012).
[15] J. L. Sherriff, T. A. O'Sullivan, C. Properzi, J.-L. Oddo, and L. A. Adams, Advances in nutrition **7**, 5 (2016).
[16] S. H. Zeisel, Annual Review of Food Science and Technology **11**, 71 (2020).
[17] M. E. Resseguie, K.-A. Da Costa, J. A. Galanko, M. Patel, I. J. Davis, and S. H. Zeisel, Journal of Biological Chemistry **286**, 1649 (2011).
[18] L. M. Fischer, K.-A. da Costa, L. Kwock, J. Galanko, and S. H. Zeisel, The American journal of clinical nutrition **92**, 1113 (2010).
[19] R. R. Wing and J. O. Hill, Annual review of nutrition **21**, 323 (2001).
[20] F. Riveros-McKay, V. Mistry, R. Bounds, A. Hendricks, J. M. Keogh, H. Thomas, E. Henning, L. J. Corbin, S. O'Rahilly, E. Zeggini, *et al.*, PLoS genetics **15**, e1007603 (2019).
[21] S. F. Meisel, R. J. Beeken, C. H. van Jaarsveld, and J. Wardle, Obesity **23**, 305 (2015).
[22] S. F. Meisel, C. Walker, and J. Wardle, Obesity **20**, 540 (2012).
[23] F. Greenway, International journal of obesity **39**, 1188 (2015).
[24] K. Elfhag and S. Rössner, Obesity reviews **6**, 67 (2005).
[25] J. A. Martínez and F. I. Milagro, Trends in food science & technology **42**, 97 (2015).
[26] T. Wang, Y. Heianza, D. Sun, T. Huang, W. Ma, E. B. Rimm, J. E. Manson, F. B. Hu, W. C. Willett, and L. Qi, bmj **360**, j5644 (2018).
[27] E. R. Grimm and N. I. Steinle, Nutrition reviews **69**, 52 (2011).
[28] M. de Krom, F. Bauer, D. Collier, R. Adan, and S. E. La Fleur, Annual review of nutrition **29**, 283 (2009).
[29] A. J. Mayhew, M. Pigeyre, J. Couturier, and D. Meyre, Neuroendocrinology **106**, 292 (2018).
[30] F. Stutzmann, S. Cauchi, E. Durand, C. Calvacanti-Proenca, M. Pigeyre, A. Hartikainen, U. Sovio, J. Tichet, M. Marre, J. Weill, *et al.*, International Journal of Obesity **33**, 373 (2009).
[31] M. Garaulet, Y.-C. Lee, J. Shen, L. D. Parnell, D. K. Arnett, M. Y. Tsai, C.-Q. Lai, and J. M. Ordovas, European Journal of Human Genetics **18**, 364 (2010).
[32] J. K. Winkler, A. Woehning, J.-H. Schultz, M. Brune, N. Beaton, T. D. Challa, S. Minkova, E. Roeder, P. P. Nawroth, H.-C. Friederich, *et al.*, Nutrition **28**, 996 (2012).
[33] E. E. Blaak, Current opinion in clinical nutrition and metabolic care **19**, 289 (2016).
[34] A. Pan and F. B. Hu, Current Opinion in Clinical Nutrition & Metabolic Care **14**, 385 (2011).
[35] C. V. De Almeida, M. R. de Camargo, E. Russo, and A. Amedei, World journal of gastroenterology **25**, 151 (2019).
[36] C. J. Rebello, C. E. O'neil, and F. L. Greenway, Nutrition reviews **74**, 131 (2015).
[37] J. L. Slavin, Nutrition **21**, 411 (2005).
[38] R. Zárate, N. el Jaber-Vazdekis, N. Tejera, J. A. Pérez, and C. Rodríguez, Clinical and translational medicine **6**, 25 (2017).
[39] F. Chilton, R. Dutta, L. Reynolds, S. Sergeant, R. Mathias, and M. Seeds, Nutrients **9**, 1165 (2017).
[40] E. F. S. A. (EFSA), EFSA Supporting Publications **14**, e15121E (2017).
[41] Food and A. O. of the United Nations, *Fats and fatty acids in human nutrition Report of an expert consultation* (FAO Food and Nutrition Paper 91, FAO, Rome, 2010).
[42] L. Schwingshackl and G. Hoffmann, Lipids in health and disease **13**, 154 (2014).
[43] N. R. Jones, N. G. Forouhi, K.-T. Khaw, N. J. Wareham, and P. Monsivais, European journal of epidemiology **33**, 235 (2018).
[44] G. Wu, Food & function **7**, 1251 (2016).
[45] M. Lonnie, E. Hooker, J. Brunstrom, B. Corfe, M. Green, A. Watson, E. Williams, E. Stevenson, S. Penson, and A. Johnstone, Nutrients **10**, 360 (2018).
[46] D. H. Pesta and V. T. Samuel, Nutrition & metabolism **11**, 53 (2014).
[47] X. Zhang, Q. Qi, C. Zhang, S. R. Smith, F. B. Hu, F. M. Sacks, G. A. Bray, and L. Qi, Diabetes **61**, 3005 (2012).
[48] Q. Qi, Y. Zheng, T. Huang, J. Rood, G. A. Bray, F. M. Sacks, and L. Qi, Diabetologia **58**, 2791 (2015).
[49] World Health Organization and others, "Vitamin and mineral requirements in human nutrition," (2005).
[50] E. Reboul, Nutrients **5**, 3563 (2013).
[51] J. Fiedor and K. Burda, Nutrients **6**, 466 (2014).
[52] G. F. Combs Jr and J. P. McClung, *The vitamins: fundamental aspects in nutrition and health* (Academic press, 2016).
[53] M. Parra, S. Stahl, and H. Hellmann, Cells **7**, 84 (2018).
[54] D. Dalto and J.-J. Matte, Nutrients **9**, 189 (2017).
[55] S.-C. Liew, Revista da Associação Médica Brasileira **62**, 90 (2016).
[56] Y. Li, T. Huang, Y. Zheng, T. Muka, J. Troup, and F. B. Hu, Journal of the American Heart Association **5**, e003768 (2016).
[57] V. E. Ohrvik and C. M. Witthoft, Nutrients **3**, 475 (2011).
[58] R. M. Winkels, I. A. Brouwer, E. Siebelink, M. B. Katan, and P. Verhoef, The American journal of clinical nutrition **85**, 465 (2007).
[59] F. Watanabe and T. Bito, Experimental Biology and Medicine **243**, 148 (2018).

[60] A. Hunt, D. Harrington, and S. Robinson, bmj **349**, g5226 (2014).
[61] R. Green, Blood **129**, 2603 (2017).
[62] F. Watanabe, Y. Yabuta, T. Bito, and F. Teng, Nutrients **6**, 1861 (2014).
[63] A. Valente, T. G. Albuquerque, A. Sanches-Silva, and H. S. Costa, Food Research International **44**, 2237 (2011).
[64] N. Smirnoff, Free Radical Biology and Medicine **122**, 116 (2018).
[65] A. Sorice, E. Guerriero, F. Capone, G. Colonna, G. Castello, and S. Costantini, Mini reviews in medicinal chemistry **14**, 444 (2014).
[66] C. S. Johnston, in *Subcellular Biochemistry* (Springer, 1996) pp. 189–213.
[67] P. H. Golding, BMC hematology **18**, 13 (2018).
[68] S. Hansen, P. Tveden-Nyborg, and J. Lykkesfeldt, Nutrients **6**, 3818 (2014).
[69] R. H. Fletcher and K. M. Fairfield, Jama **287**, 3127 (2002).
[70] D. D. Bikle, Chemistry & biology **21**, 319 (2014).
[71] S. Basit, British journal of biomedical science **70**, 161 (2013).
[72] T. J. Wang, F. Zhang, J. B. Richards, B. Kestenbaum, J. B. Van Meurs, D. Berry, D. P. Kiel, E. A. Streeten, C. Ohlsson, D. L. Koller, *et al.*, The Lancet **376**, 180 (2010).
[73] R. Bouillon, Nature Reviews Endocrinology **13**, 466 (2017).
[74] E. Reboul, Antioxidants **6**, 95 (2017).
[75] R. García-Closas, A. Berenguer, M. J. Tormo, M. J. Sánchez, J. R. Quiros, C. Navarro, R. Arnaud, M. Dorronsoro, M. D. Chirlaque, A. Barricarte, *et al.*, British Journal of Nutrition **91**, 1005 (2004).
[76] A. Yadav, R. Kumari, A. Yadav, J. Mishra, S. Srivatva, and S. Prabha, Research in Environment and Life Sciences **9**, 1328 (2016).
[77] E. Niki, The Korean journal of internal medicine **30**, 571 (2015).
[78] G. Lee and S. Han, Nutrients **10**, 1614 (2018).
[79] M. Malavolta and E. Mocchegiani, *Molecular basis of nutrition and aging: a volume in the molecular nutrition series* (Academic Press, 2016).
[80] C. Thoma, C. P. Day, and M. I. Trenell, Journal of hepatology **56**, 255 (2012).
[81] G. López-Lluch and P. Navas, The Journal of physiology **594**, 2043 (2016).
[82] M. C. Klempel, C. M. Kroeger, S. Bhutani, J. F. Trepanowski, and K. A. Varady, Nutrition journal **11**, 98 (2012).
[83] L. Goni, M. Cuervo, F. I. Milagro, and J. A. Martínez, The Journal of nutrition **146**, 905S (2015).
[84] I. Rudkowska and L. Pérusse, Progress in Molecular Biology and Translational Science **108**, 347 (2012).
[85] K. Masuo, T. Katsuya, H. Kawaguchi, Y. Fu, H. Rakugi, T. Ogihara, and M. L. Tuck, American Journal of Hypertension **18**, 1508 (2005).
[86] E. Goyenechea, L. Collins, D. Parra, I. Abete, A. Crujeiras, S. O'Dell, and J. Martinez, Hormone and Metabolic Research **41**, 55 (2009).
[87] K. B. Adamo, R. Dent, C. D. Langefeld, M. Cox, K. Williams, K. M. Carrick, J. S. Stuart, S. S. Sundseth, M.-E. Harper, R. McPherson, *et al.*, Obesity **15**, 1068 (2007).
[88] D. De Luis, R. Aller, O. Izaola, M. Gonzalez Sagrado, and R. Conde, Annals of Nutrition and Metabolism **50**, 354 (2006).
[89] M. Garaulet, M. D. Corbalan, J. A. Madrid, E. Morales, J. Baraza, Y.-C. Lee, and J. Ordovas, International Journal of Obesity **34**, 516 (2010).
[90] B. A. Jensen, T. S. Nielsen, A. M. Fritzen, J. B. Holm, E. Fjære, A. K. Serup, K. Borkowski, S. Risis, S. I. Pærregaard, I. Søgaard, *et al.*, Metabolism **65**, 1706 (2016).
[91] B. Sears and M. Perry, Lipids in health and disease **14**, 121 (2015).
[92] J. J. DiNicolantonio and J. H. O'Keefe, "Effects of dietary fats on blood lipids: a review of direct comparison trials," (2018).
[93] I. Pinho, S. Rodrigues, B. Franchini, and P. Graça, (2016).
[94] C. Sánchez-Moreno, J. M. Ordovás, C. E. Smith, J. C. Baraza, Y.-C. Lee, and M. Garaulet, The Journal of Nutrition **141**, 380 (2011).
[95] J. Aberle, D. Evans, F. Beil, and U. Seedorf, Clinical genetics **68**, 152 (2005).
[96] J. Mattei, S. Demissie, K. L. Tucker, and J. M. Ordovas, The Journal of Nutrition **139**, 2301 (2009).
[97] M. Xu, G. A. Bray, D. H. Ryan, F. M. Sacks, G. Ning, L. Qi, *et al.*, The Journal of Nutrition **145**, 1289 (2015).
[98] D. Corella, D. K. Arnett, K. L. Tucker, E. K. Kabagambe, M. Tsai, L. D. Parnell, C.-Q. Lai, Y.-C. Lee, D. Warodomwichit, P. N. Hopkins, *et al.*, The Journal of Nutrition **141**, 2219 (2011).
[99] W. B. Farquhar, D. G. Edwards, C. T. Jurkovitz, and W. S. Weintraub, Journal of the American College of Cardiology **65**, 1042 (2015).
[100] O. M. Dong, BMJ Nutrition, Prevention & Health , bmjnph (2018).
[101] J. R. Petrie, T. J. Guzik, and R. M. Touyz, Canadian Journal of Cardiology **34**, 575 (2018).
[102] S. P. Juraschek, A. C. Gelber, H. K. Choi, L. J. Appel, and E. R. Miller III, Arthritis & Rheumatology **68**, 3002 (2016).
[103] R. A. Felder and P. A. Jose, Nature Clinical Practice Nephrology **2**, 637 (2006).
[104] Z. Wang, C. Zeng, M. V. Van Anthony, S.-Y. Chen, P. Konkalmatt, X. Wang, L. D. Asico, J. E. Jones, Y. Yang, H. Sanada, *et al.*, Hypertension **67**, 325 (2016).
[105] P. Strazzullo and F. Galletti, Current Hypertension Reports **9**, 25 (2007).
[106] E. M. Snyder, S. T. Turner, M. J. Joyner, J. H. Eisenach, and B. D. Johnson, The Journal of Physiology **574**, 947 (2006).
[107] L. Pojoga, N. S. Kolatkar, J. S. Williams, T. S. Perlstein, X. Jeunemaitre, N. J. Brown, P. N. Hopkins, B. A. Raby, and G. H. Williams, Hypertension **48**, 892 (2006).
[108] N. Glorioso, F. Filigheddu, D. Cusi, C. Troffa, M. Conti, M. Natalizio, G. Argiolas, C. Barlassina, and G. Bianchi, Hypertension **39**, 357 (2002).
[109] C. Barlassina, C. Dal Fiume, C. Lanzani, P. Manunta, G. Guffanti, A. Ruello, G. Bianchi, L. Del Vecchio, F. Macciardi, and D. Cusi, Human Molecular Genetics **16**, 1630 (2007).
[110] J. G. Lisko, G. E. Lee, J. B. Kimbrell, M. E. Rybak, L. Valentin-Blasini, and C. H. Watson, Nicotine & Tobacco Research **19**, 484 (2016).
[111] G. Grosso, J. Godos, F. Galvano, and E. L. Giovannucci, Annual review of nutrition **37**, 131 (2017).
[112] European Food Safety Authority, "Scientific opinion on the safety of caffeine by the EFSA panel on dietetic products, nutrition and allergies (NDA)," (2015).
[113] J. L. Temple, C. Bernard, S. E. Lipshultz, J. D. Czachor, J. A. Westphal, and M. A. Mestre, Frontiers in psychiatry **8**, 80 (2017).
[114] S. Casal, R. Alves, E. Mendes, and M. Oliveira, Relatório Técnico (2009).
[115] A. Nehlig, Pharmacological Reviews **70**, 384 (2018).
[116] M. C. Cornelis, K. L. Monda, K. Yu, N. Paynter, E. M. Azzato, S. N. Bennett, S. I. Berndt, E. Boerwinkle, S. Chanock, N. Chatterjee, *et al.*, PLoS Genetics **7**, e1002033 (2011).
[117] M. C. Cornelis, T. Kacprowski, C. Menni, S. Gustafsson, E. Pivin, J. Adamski, A. Artati, C. B. Eap, G. Ehret, N. Friedrich, *et al.*, Human Molecular Genetics **25**, 5472 (2016).
[118] J. L. Treur, M. Gibson, A. E. Taylor, P. J. Rogers, and M. R. Munafo, Journal of sleep research **27**, e12695 (2018).
[119] A. Hutchison, G. Wittert, and L. Heilbronn, Nutrients **9**, 222 (2017).
[120] A. Gunes and M.-L. Dahl, (2008).
[121] P. J. Dekker, D. Koenders, and M. J. Bruins, Nutrients **11**, 551 (2019).

[122] A. Szilagyi and N. Ishayek, Nutrients **10**, 1994 (2018).
[123] B. Misselwitz, D. Pohl, H. Frühauf, M. Fried, S. R. Vavricka, and M. Fox, United European gastroenterology journal **1**, 151 (2013).
[124] Y. Deng, B. Misselwitz, N. Dai, and M. Fox, Nutrients **7**, 8020 (2015).
[125] R. Mattar, D. F. de Campos Mazo, and F. J. Carrilho, Clinical and experimental gastroenterology **5**, 113 (2012).
[126] J. R. Biesiekierski, Journal of gastroenterology and hepatology **32**, 78 (2017).
[127] P. Kumar, M. Chatli, N. Mehta, P. Singh, O. Malav, and A. K. Verma, Critical reviews in food science and nutrition **57**, 923 (2017).
[128] P. Grace-Farfaglia, J. Nutr. Health Food Eng **1**, 14 (2014).
[129] I. Aziz, M. Hadjivassiliou, and D. S. Sanders, Nature Reviews Gastroenterology & Hepatology **12**, 516 (2015).
[130] B. Lebwohl, D. S. Sanders, and P. H. Green, The Lancet **391**, 70 (2018).
[131] V. Fuchs, K. Kurppa, H. Huhtala, M. Mäki, L. Kekkonen, and K. Kaukinen, United European gastroenterology journal **6**, 567 (2018).
[132] L. M. Sollid and B. A. Lie, Clinical Gastroenterology and Hepatology **3**, 843 (2005).
[133] G. Casella, V. Villanacci, C. Di Bella, G. Bassotti, J. Bold, and K. Rostami, Gastroenterology and hepatology from bed to bench **11**, 197 (2018).
[134] B. Lebwohl, J. F. Ludvigsson, and P. H. Green, Bmj **351**, h4347 (2015).
[135] A. J. Monsuur, P. I. de Bakker, A. Zhernakova, D. Pinto, W. Verduijn, J. Romanos, R. Auricchio, A. Lopez, D. A. van Heel, J. B. A. Crusius, *et al.*, PloS one **3**, e2270 (2008).
[136] L. G. Straub and P. E. Scherer, Nature Metabolism **1**, 334 (2019).
[137] M.-F. Hivert, A. K. Manning, J. B. McAteer, J. C. Florez, J. Dupuis, C. S. Fox, C. J. O'Donnell, L. A. Cupples, and J. B. Meigs, Diabetes **57**, 3353 (2008).
[138] P. J. Rogers, C. Hohoff, S. V. Heatherley, E. L. Mullings, P. J. Maxfield, R. P. Evershed, J. Deckert, and D. J. Nutt, Neuropsychopharmacology **35**, 1973 (2010).
[139] E. Childs, C. Hohoff, J. Deckert, K. Xu, J. Badner, and H. De Wit, Neuropsychopharmacology **33**, 2791 (2008).
[140] K. Masuo, T. Katsuya, Y. Fu, H. Rakugi, T. Ogihara, and M. L. Tuck, Circulation **111**, 3429 (2005).
[141] O. Ramos-Lopez, J. Riezu-Boj, F. Milagro, L. Goni, M. Cuervo, and J. Martinez, Nutrition, Metabolism and Cardiovascular Diseases (2017).
[142] A. R. Josse, L. A. Da Costa, H. Campos, and A. El-Sohemy, The American Journal of Clinical Nutrition **96**, 665 (2012).
[143] C. M. Phillips, Nutrients **5**, 32 (2013).
[144] C. M. Phillips, L. Goumidi, S. Bertrais, M. R. Field, R. McManus, S. Hercberg, D. Lairon, R. Planells, and H. M. Roche, Atherosclerosis **214**, 408 (2011).
[145] T. Domínguez-Reyes, C. C. Astudillo-López, L. Salgado-Goytia, J. Muñoz-Valle, A. B. Salgado-Bernabé, I. P. Guzmán-Guzmán, N. Castro-Alarcón, M. E. Moreno-Godínez, and I. Parra-Rojas, Lipids in Health and Disease **14**, 106 (2015).
[146] C.-Q. Lai, D. K. Arnett, D. Corella, R. J. Straka, M. Y. Tsai, J. M. Peacock, X. Adiconis, L. D. Parnell, J. E. Hixson, M. A. Province, *et al.*, Arteriosclerosis, Thrombosis, and Vascular Biology **27**, 1417 (2007).
[147] M.-J. Ariza, M.-Á. Sánchez-Chaparro, F.-J. Barón, A.-M. Hornos, E. Calvo-Bonacho, J. Rioja, P. Valdivielso, J.-A. Gelpi, and P. González-Santos, BMC Medical Genetics **11**, 1 (2010).
[148] D. Pirim, Z. H. Radwan, X. Wang, V. Niemsiri, J. E. Hokanson, R. F. Hamman, E. Feingold, C. H. Bunker, F. Y. Demirci, and M. I. Kamboh, PloS one **14**, e0214060 (2019).
[149] J. M. Ordovas, Obesity **16**, S40 (2008).
[150] K. Wu, R. Bowman, A. A. Welch, R. N. Luben, N. Wareham, K.-T. Khaw, and S. A. Bingham, European Heart Journal **28**, 2930 (2007).
[151] R. Fallaize, A. L. Carvalho-Wells, A. C. Tierney, C. Marin, B. Kieć-Wilk, A. Dembińska-Kieć, C. A. Drevon, C. DeFoort, J. Lopez-Miranda, U. Risérus, *et al.*, Scientific Reports **7**, 6274 (2017).
[152] C. R. Bramham and E. Messaoudi, Progress in neurobiology **76**, 99 (2005).
[153] S.-A. Akbarian, A. Salehi-Abargouei, M. Pourmasoumi, R. Kelishadi, P. Nikpour, and M. Heidari-Beni, Advances in medical sciences **63**, 43 (2018).
[154] S. G. Kernie, D. J. Liebl, and L. F. Parada, The EMBO journal **19**, 1290 (2000).
[155] M. A. Pelleymounter, M. J. Cullen, and C. L. Wellman, Experimental neurology **131**, 229 (1995).
[156] M. Rios, Trends in neurosciences **36**, 83 (2013).
[157] A. E. Locke, B. Kahali, S. I. Berndt, A. E. Justice, T. H. Pers, F. R. Day, C. Powell, S. Vedantam, M. L. Buchkovich, J. Yang, *et al.*, Nature **518**, 197 (2015).
[158] Y. Guo, M. B. Lanktree, K. C. Taylor, H. Hakonarson, L. A. Lange, B. J. Keating, and I. K. S. array BMI Consortium, Human molecular genetics **22**, 184 (2012).
[159] C. H. Sandholt, T. Sparsø, N. Grarup, A. Albrechtsen, K. Almind, L. Hansen, U. Toft, T. Jørgensen, T. Hansen, and O. Pedersen, Diabetes **59**, 1667 (2010).
[160] V. Micó, L. Díez-Ricote, and L. Daimiel, International Journal of Molecular Sciences **17**, 299 (2016).
[161] V. Loria-Kohen, I. Espinosa-Salinas, H. Marcos-Pasero, T. Lourenço-Nogueira, J. Herranz, S. Molina, G. Reglero, and A. R. de Molina, Nutrition **32**, 453 (2016).
[162] M. Garaulet, A. E. Tardido, Y. Lee, C. Smith, L. Parnell, and J. Ordovas, International Journal of Obesity **36**, 1436 (2012).
[163] S. M. Schmid, M. Hallschmid, K. Jauch-Chara, J. Born, and B. Schultes, Journal of Sleep Research **17**, 331 (2008).
[164] H. S. Dashti, C. E. Smith, Y.-C. Lee, L. D. Parnell, C.-Q. Lai, D. K. Arnett, J. Ordovás, and M. Garaulet, Chronobiology International **31**, 660 (2014).
[165] H. S. Dashti, J. L. Follis, C. E. Smith, T. Tanaka, M. Garaulet, D. J. Gottlieb, A. Hruby, P. F. Jacques, J. C. Kiefte-de Jong, S. Lamon-Fava, *et al.*, Diabetes Care **38**, 1456 (2015).
[166] K. Mirzaei, M. Xu, Q. Qi, L. De Jonge, G. A. Bray, F. Sacks, and L. Qi, The American Journal of Clinical Nutrition **99**, 392 (2014).
[167] N. Amin, E. Byrne, J. Johnson, G. Chenevix-Trench, S. Walter, I. Nolte, J. Vink, R. Rawal, M. Mangino, A. Teumer, *et al.*, Molecular Psychiatry **17**, 1116 (2012).
[168] P. Sulem, D. F. Gudbjartsson, F. Geller, I. Prokopenko, B. Feenstra, K. K. Aben, B. Franke, M. den Heijer, P. Kovacs, M. Stumvoll, *et al.*, Human Molecular Genetics **20**, 2071 (2011).
[169] G. McMahon, A. E. Taylor, G. D. Smith, and M. R. Munafó, PloS One **9**, e103448 (2014).
[170] C. F. Thorn, E. Aklillu, T. E. Klein, and R. B. Altman, Pharmacogenetics and Genomics **22**, 73 (2012).
[171] A. Yang, A. A. Palmer, and H. de Wit, Psychopharmacology **211**, 245 (2010).
[172] C. Sachse, J. Brockmöller, S. Bauer, and I. Roots, British Journal of Clinical Pharmacology **47**, 445 (1999).
[173] D. Manousaki, R. Mitchell, T. Dudding, S. Haworth, A. Harroud, V. Forgetta, R. L. Shah, J. Luan, C. Langenberg, N. J. Timpson, *et al.*, The American Journal of Human Genetics **106**, 327 (2020).
[174] X. Jiang, P. F. O'Reilly, H. Aschard, Y.-H. Hsu, J. B. Richards, J. Dupuis, E. Ingelsson, D. Karasik, S. Pilz, D. Berry, *et al.*, Nature communications **9**, 1 (2018).
[175] E. Levy, D. Ménard, E. Delvin, S. Stan, G. Mitchell, M. Lambert, E. Ziv, J. C. Feoli-Fonseca, and E. Seidman, Journal of Biological Chemistry **276**, 39679 (2001).
[176] C. Sandholt, T. Hansen, and O. Pedersen, Nutrition & Diabetes **2**, e37 (2012).
[177] S. Li, J. H. Zhao, J. Luan, R. N. Luben, S. A. Rodwell, K.-T. Khaw, K. K. Ong, N. J. Wareham, and R. J. Loos, The American Journal of Clinical Nutrition **91**, 184 (2009).
[178] K. S. Vimaleswaran, S. Li, J. H. Zhao, J. Luan, S. A. Bingham, K.-T. Khaw, U. Ekelund, N. J. Wareham, and R. J. Loos, The American Journal of Clinical Nutrition **90**,

425 (2009).
[179] C. Dina, D. Meyre, S. Gallina, E. Durand, A. Körner, P. Jacobson, L. M. Carlsson, W. Kiess, V. Vatin, C. Lecoeur, *et al.*, Nature Genetics **39**, 724 (2007).
[180] C. Hardman, P. Rogers, N. Timpson, and M. Munafo, International Journal of Obesity **38**, 730 (2014).
[181] C. S. Fox, Y. Liu, C. C. White, M. Feitosa, A. V. Smith, N. Heard-Costa, K. Lohman, A. D. Johnson, M. C. Foster, D. M. Greenawalt, *et al.*, PLoS Genetics **8**, e1002695 (2012).
[182] C. Celis-Morales, C. F. Marsaux, K. M. Livingstone, S. Navas-Carretero, R. San-Cristobal, C. B. O'donovan, H. Forster, C. Woolhead, R. Fallaize, A. L. Macready, *et al.*, Obesity (2016).
[183] L. Brunkwall, U. Ericson, S. Hellstrand, B. Gullberg, M. Orho-Melander, and E. Sonestedt, Food & Nutrition Research **57** (2013).
[184] E. Sonestedt, B. Gullberg, U. Ericson, E. Wirfält, B. Hedblad, and M. Orho-Melander, International Journal of Obesity **35**, 1041 (2011).
[185] H.-J. Lee, I. kyoung Kim, J. H. Kang, Y. Ahn, B.-G. Han, J.-Y. Lee, and J. Song, Clinica Chimica Acta **411**, 1716 (2010).
[186] E. Sonestedt, C. Roos, B. Gullberg, U. Ericson, E. Wirfält, and M. Orho-Melander, The American Journal of Clinical Nutrition **90**, 1418 (2009).
[187] M. Tanofsky-Kraff, J. C. Han, K. Anandalingam, L. B. Shomaker, K. M. Columbo, L. E. Wolkoff, M. Kozlosky, C. Elliott, L. M. Ranzenhofer, C. A. Roza, *et al.*, The American Journal of Clinical Nutrition **90**, 1483 (2009).
[188] C. H. Andreasen, K. L. Stender-Petersen, M. S. Mogensen, S. S. Torekov, L. Wegner, G. Andersen, A. L. Nielsen, A. Albrechtsen, K. Borch-Johnsen, S. S. Rasmussen, *et al.*, Diabetes **57**, 95 (2008).
[189] R. A. Price, W.-D. Li, and H. Zhao, BMC Medical Genetics **9**, 1 (2008).
[190] T. Huang, Q. Qi, Y. Li, F. B. Hu, G. A. Bray, F. M. Sacks, D. A. Williamson, and L. Qi, The American journal of clinical nutrition **99**, 1126 (2014).
[191] T. M. Frayling, N. J. Timpson, M. N. Weedon, E. Zeggini, R. M. Freathy, C. M. Lindgren, J. R. Perry, K. S. Elliott, H. Lango, N. W. Rayner, *et al.*, Science **316**, 889 (2007).
[192] F. Hosseini-Esfahani, G. Koochakpoor, M. S. Daneshpour, P. Mirmiran, B. Sedaghati-khayat, and F. Azizi, Scientific Reports **7**, 18057 (2017).
[193] J. A. Mitchell, T. S. Church, T. Rankinen, C. P. Earnest, X. Sui, and S. N. Blair, Obesity **18**, 641 (2010).
[194] T. Rankinen, T. Rice, M. Teran-Garcia, D. C. Rao, and C. Bouchard, Obesity **18**, 322 (2010).
[195] A. Hazra, P. Kraft, R. Lazarus, C. Chen, S. J. Chanock, P. Jacques, J. Selhub, and D. J. Hunter, Human Molecular Genetics **18**, 4677 (2009).
[196] T. Tanaka, P. Scheet, B. Giusti, S. Bandinelli, M. G. Piras, G. Usala, S. Lai, A. Mulas, A. M. Corsi, A. Vestrini, *et al.*, The American Journal of Human Genetics **84**, 477 (2009).
[197] A. Hazra, P. Kraft, J. Selhub, E. L. Giovannucci, G. Thomas, R. N. Hoover, S. J. Chanock, and D. J. Hunter, Nature Genetics **40**, 1160 (2008).
[198] B. R. Santos, N. C. Costa, T. R. Silva, K. Oppermann, J. A. Magalhães, G. Casanova, and P. M. Spritzer, Plos one **14**, e0226215 (2019).
[199] J. Ahn, K. Yu, R. Stolzenberg-Solomon, K. C. Simon, M. L. McCullough, L. Gallicchio, E. J. Jacobs, A. Ascherio, K. Helzlsouer, K. B. Jacobs, *et al.*, Human molecular genetics **19**, 2739 (2010).
[200] J. Dupuis, C. Langenberg, I. Prokopenko, R. Saxena, N. Soranzo, A. U. Jackson, E. Wheeler, N. L. Glazer, N. Bouatia-Naji, A. L. Gloyn, *et al.*, Nature Genetics **42**, 105 (2010).
[201] M. Bi, W. H. L. Kao, E. Boerwinkle, R. C. Hoogeveen, L. J. Rasmussen-Torvik, B. C. Astor, K. E. North, J. Coresh, and A. Köttgen, PloS one **5**, e11690 (2010).
[202] M. E. Matzko, G. Argyropoulos, G. C. Wood, X. Chu, R. J. McCarter, C. D. Still, and G. S. Gerhard, Obesity Surgery **22**, 783 (2012).
[203] U. Mager, T. Degenhardt, L. Pulkkinen, M. Kolehmainen, A.-M. Tolppanen, J. Lindström, J. G. Eriksson, C. Carlberg, J. Tuomilehto, M. Uusitupa, *et al.*, PLoS One **3**, e2941 (2008).
[204] Q. Qi, G. A. Bray, F. B. Hu, F. M. Sacks, and L. Qi, The American Journal of Clinical Nutrition **95**, 506 (2012).
[205] I. K. S. array BMI Consortium *et al.*, Human molecular genetics **22**, 184 (2012).
[206] E. K. Speliotes, C. J. Willer, S. I. Berndt, K. L. Monda, G. Thorleifsson, A. U. Jackson, H. L. Allen, C. M. Lindgren, R. Mägi, J. C. Randall, *et al.*, Nature Genetics **42**, 937 (2010).
[207] J. A. Nettleton, J. L. Follis, J. S. Ngwa, C. E. Smith, S. Ahmad, T. Tanaka, M. K. Wojczynski, T. Voortman, R. N. Lemaitre, K. Kristiansson, *et al.*, Human molecular genetics **24**, 4728 (2015).
[208] D. Shungin, T. W. Winkler, D. C. Croteau-Chonka, T. Ferreira, A. E. Locke, R. Mägi, R. J. Strawbridge, T. H. Pers, K. Fischer, A. E. Justice, *et al.*, Nature **518**, 187 (2015).
[209] I. M. Heid, A. U. Jackson, J. C. Randall, T. W. Winkler, L. Qi, V. Steinthorsdottir, G. Thorleifsson, M. C. Zillikens, E. K. Speliotes, R. Mägi, *et al.*, Nature Genetics **42**, 949 (2010).
[210] M. P. Horan, S. Y. Chai, N. Munusamy, K. H. Tay, L. Wienholt, J. A. Tye-Din, J. Daveson, M. Varney, and T. Badrick, Journal of clinical pathology **71**, 900 (2018).
[211] C. Catassi and A. Fasano, The American journal of medicine **123**, 691 (2010).
[212] Y. Hamid, C. Rose, S. Urhammer, C. Glümer, R. Nolsøe, O. Kristiansen, T. Mandrup-Poulsen, K. Borch-Johnsen, T. Jorgensen, T. Hansen, *et al.*, Diabetologia **48**, 251 (2005).
[213] J. M. Major, K. Yu, W. Wheeler, H. Zhang, M. C. Cornelis, M. E. Wright, M. Yeager, K. Snyder, S. J. Weinstein, A. Mondul, *et al.*, Human Molecular Genetics **20**, 3876 (2011).
[214] L. Ferrucci, J. R. Perry, A. Matteini, M. Perola, T. Tanaka, K. Silander, N. Rice, D. Melzer, A. Murray, C. Cluett, *et al.*, The American Journal of Human Genetics **84**, 123 (2009).
[215] T. M. Teslovich, K. Musunuru, A. V. Smith, A. C. Edmondson, I. M. Stylianou, M. Koseki, J. P. Pirruccello, S. Ripatti, D. I. Chasman, C. J. Willer, *et al.*, Nature **466**, 707 (2010).
[216] S. Kathiresan, O. Melander, C. Guiducci, A. Surti, N. P. Burtt, M. J. Rieder, G. M. Cooper, C. Roos, B. F. Voight, A. S. Havulinna, *et al.*, Nature genetics **40**, 189 (2008).
[217] C. J. Willer, S. Sanna, A. U. Jackson, A. Scuteri, L. L. Bonnycastle, R. Clarke, S. C. Heath, N. J. Timpson, S. S. Najjar, H. M. Stringham, *et al.*, Nature genetics **40**, 161 (2008).
[218] M. Teran-Garcia, N. Santoro, T. Rankinen, J. Bergeron, T. Rice, A. S. Leon, D. Rao, J. S. Skinner, R. N. Bergman, J.-P. Després, *et al.*, Diabetes **54**, 2251 (2005).
[219] G. S. Sagoo, I. Tatt, G. Salanti, A. S. Butterworth, N. Sarwar, M. van Maarle, J. W. Jukema, B. Wiman, J. J. Kastelein, A. M. Bennet, *et al.*, American Journal of Epidemiology **168**, 1233 (2008).
[220] E. Boes, S. Coassin, B. Kollerits, I. M. Heid, and F. Kronenberg, Experimental Gerontology **44**, 136 (2009).
[221] R. Wagner, F. Machicao, A. Fritsche, N. Stefan, H.-U. Häring, and H. Staiger, Drug Discovery Today: Disease Mechanisms **10**, e5 (2013).
[222] C. M. Lindgren, I. M. Heid, J. C. Randall, C. Lamina, V. Steinthorsdottir, L. Qi, E. K. Speliotes, G. Thorleifsson, C. J. Willer, B. M. Herrera, *et al.*, PLoS Genetics **5**, e1000508 (2009).
[223] D. S. Evans, M. A. Calton, M. J. Kim, P.-Y. Kwok, I. Miljkovic, T. Harris, A. Koster, Y. Liu, G. J. Tranah, N. Ahituv, *et al.*, PloS One **9**, e96805 (2014).

[224] R. J. Loos, C. M. Lindgren, S. Li, E. Wheeler, J. H. Zhao, I. Prokopenko, M. Inouye, R. M. Freathy, A. P. Attwood, J. S. Beckmann, *et al.*, Nature Genetics **40**, 768 (2008).
[225] A. Hinney, A.-L. Volckmar, and N. Knoll, Progress in Molecular Biology and Translational Science **114**, 147 (2013).
[226] F. Stutzmann, V. Vatin, S. Cauchi, A. Morandi, B. Jouret, O. Landt, P. Tounian, C. Levy-Marchal, R. Buzzetti, L. Pinelli, *et al.*, Human Molecular Genetics **16**, 1837 (2007).
[227] E. H. Young, N. J. Wareham, S. Farooqi, A. Hinney, J. Hebebrand, S. Scherag, Andréand O'Rahilly, I. Barroso, and M. S. Sandhu, International Journal of Obesity **31**, 1437 (2007).
[228] I. Heid, C. Vollmert, A. Hinney, A. Döring, F. Geller, H. Löwel, H. Wichmann, T. Illig, J. Hebebrand, and F. Kronenberg, Journal of Medical Genetics **42**, e21 (2005).
[229] F. Geller, K. Reichwald, A. Dempfle, T. Illig, C. Vollmert, S. Herpertz, W. Siffert, M. Platzer, C. Hess, T. Gudermann, *et al.*, The American Journal of Human Genetics **74**, 572 (2004).
[230] A. Liebert, S. López, B. L. Jones, N. Montalva, P. Gerbault, W. Lau, M. G. Thomas, N. Bradman, N. Maniatis, and D. M. Swallow, Human genetics **136**, 1445 (2017).
[231] L. C. Olds and E. Sibley, Human molecular genetics **12**, 2333 (2003).
[232] F. Imtiaz, E. Savilahti, A. Sarnesto, D. Trabzuni, K. Al-Kahtani, I. Kagevi, M. Rashed, B. Meyer, and I. Järvelä, Journal of medical genetics **44**, e89 (2007).
[233] N. S. Enattah, T. Sahi, E. Savilahti, J. D. Terwilliger, L. Peltonen, and I. Järvelä, Nature genetics **30**, 233 (2002).
[234] E. Yeung, L. Qi, F. B. Hu, and C. Zhang, International Journal of Molecular Epidemiology and Genetics **2**, 138 (2011).
[235] A. Scherag, C. Dina, A. Hinney, V. Vatin, S. Scherag, C. I. Vogel, T. D. Müller, H. Grallert, H.-E. Wichmann, B. Balkau, *et al.*, PLoS Genet **6**, e1000916 (2010).
[236] J. M. Lane, A.-M. Chang, A. C. Bjonnes, D. Aeschbach, C. Anderson, B. E. Cade, S. W. Cain, C. A. Czeisler, S. A. Gharib, J. J. Gooley, *et al.*, Diabetes **65**, 1741 (2016).
[237] V. Lyssenko, C. L. Nagorny, M. R. Erdos, N. Wierup, A. Jonsson, P. Spégel, M. Bugliani, R. Saxena, M. Fex, N. Pulizzi, *et al.*, Nature Genetics **41**, 82 (2009).
[238] A. Jonsson, C. Ladenvall, T. S. Ahluwalia, J. Kravic, U. Krus, J. Taneera, B. Isomaa, T. Tuomi, E. Renström, L. Groop, *et al.*, Diabetes **62**, 2978 (2013).
[239] A. K. Manning, M.-F. Hivert, R. A. Scott, J. L. Grimsby, N. Bouatia-Naji, H. Chen, D. Rybin, C.-T. Liu, L. F. Bielak, I. Prokopenko, *et al.*, Nature Genetics **44**, 659 (2012).
[240] C. Holzapfel, M. Siegrist, M. Rank, H. Langhof, H. Grallert, J. Baumert, C. Irimie, N. Klopp, B. Wolfarth, T. Illig, *et al.*, European Journal of Endocrinology **164**, 205 (2011).
[241] L. Goni, D. Sun, Y. Heianza, T. Wang, T. Huang, M. Cuervo, J. A. Martínez, X. Shang, G. A. Bray, F. M. Sacks, *et al.*, Journal of Lipid Research **59**, 155 (2018).
[242] L. Goni, D. Sun, Y. Heianza, T. Wang, T. Huang, J. A. Martínez, X. Shang, G. A. Bray, S. R. Smith, F. M. Sacks, *et al.*, European Journal of Nutrition , 1 (2018).
[243] L. Goni, M. Cuervo, F. I. Milagro, and J. A. Martínez, Journal of Nutrigenetics and Nutrigenomics **7**, 232 (2014).
[244] J. I. Kang, C. I. Park, K. Namkoong, and S. J. Kim, Chronobiology International **32**, 568 (2015).
[245] M. Garaulet, M. D. Corbalán-Tutau, J. A. Madrid, J. C. Baraza, L. D. Parnell, Y.-C. Lee, and J. M. Ordovas, Journal of the American Dietetic Association **110**, 917 (2010).
[246] D. Corella, L. Qi, J. V. Sorli, D. Godoy, O. Portoles, O. Coltell, A. S. Greenberg, and J. M. Ordovas, The Journal of Clinical Endocrinology & Metabolism **90**, 5121 (2005).
[247] J. Ruiz, E. Larrarte, J. Margareto, R. Ares, P. Alkorta, and I. Labayen, British journal of nutrition **106**, 486 (2011).
[248] D. J. Liu, G. M. Peloso, H. Yu, A. S. Butterworth, X. Wang, A. Mahajan, D. Saleheen, C. Emdin, D. Alam, A. C. Alves, *et al.*, Nature genetics **49**, 1758 (2017).
[249] L. M. Delahanty, Q. Pan, K. A. Jablonski, K. E. Watson, J. M. McCaffery, A. Shuldiner, S. E. Kahn, W. C. Knowler, J. C. Florez, P. W. Franks, *et al.*, Diabetes Care **35**, 363 (2012).
[250] E. Goyenechea, M. D. Parra, and J. A. Martinez, British Journal of Nutrition **96**, 965 (2006).
[251] C. Galbete, J. Toledo, M. Martínez-González, J. A. Martínez, F. Guillén-Grima, and A. Marti, Genes & Nutrition **8**, 61 (2013).
[252] L. Goni, L. Qi, M. Cuervo, F. I. Milagro, W. H. Saris, I. A. MacDonald, D. Langin, A. Astrup, P. Arner, J.-M. Oppert, *et al.*, The American Journal of Clinical Nutrition **106**, 902 (2017).
[253] C. J. Lynch and S. H. Adams, Nature Reviews Endocrinology **10**, 723 (2014).
[254] M. Xu, Q. Qi, J. Liang, G. A. Bray, F. B. Hu, F. M. Sacks, and L. Qi, Circulation **127**, 1283 (2013).
[255] R. A. Scott, V. Lagou, R. P. Welch, E. Wheeler, M. E. Montasser, J. Luan, R. Mägi, R. J. Strawbridge, E. Rehnberg, S. Gustafsson, *et al.*, Nature Genetics **44**, 991 (2012).
[256] M. Mattila, I. Erlund, H.-S. Lee, S. Niinistö, U. Uusitalo, C. A. Aronsson, S. Hummel, H. Parikh, S. S. Rich, W. Hagopian, *et al.*, Diabetologia **63**, 278 (2020).
[257] A. J. Michels, T. M. Hagen, and B. Frei, Annual Review of Nutrition **33**, 45 (2013).
[258] N. J. Timpson, N. G. Forouhi, M.-J. Brion, R. M. Harbord, D. G. Cook, P. Johnson, A. McConnachie, R. W. Morris, S. Rodriguez, J. Luan, *et al.*, The American Journal of Clinical Nutrition **92**, 375 (2010).
[259] M. D. Glidden, K. Aldabbagh, N. B. Phillips, K. Carr, Y.-S. Chen, J. Whittaker, M. Phillips, N. P. Wickramasinghe, N. Rege, M. Swain, *et al.*, Journal of Biological Chemistry **293**, 47 (2018).
[260] A. Stančáková, T. Kuulasmaa, J. Paananen, A. U. Jackson, L. L. Bonnycastle, F. S. Collins, M. Boehnke, J. Kuusisto, and M. Laakso, Diabetes **58**, 2129 (2009).
[261] M. Fan, W. Li, L. Wang, S. Gu, S. Dong, M. Chen, H. Yin, J. Zheng, X. Wu, J. Jin, *et al.*, "Association of slc30a8 gene polymorphism with type 2 diabetes, evidence from 46 studies: a meta-analysis," (2016).
[262] Y. Jing, Q. Sun, Y. Bi, S. Shen, and D. Zhu, Nutrition, Metabolism and Cardiovascular Diseases **21**, 398 (2011).
[263] S. Cauchi, S. Del Guerra, H. Choquet, V. DAleo, C. J. Groves, R. Lupi, M. I. McCarthy, P. Froguel, and P. Marchetti, Molecular genetics and metabolism **100**, 77 (2010).
[264] A. Sutton, H. Khoury, C. Prip-Buus, C. Cepanec, D. Pessayre, and F. Degoul, Pharmacogenetics and Genomics **13**, 145 (2003).
[265] T. Algarve, F. Barbisan, E. Ribeiro, M. Duarte, M. Mânica-Cattani, C. Mostardeiro, A. Lenz, and I. da Cruz, Genetics and Molecular Research **12**, 5134 (2013).
[266] W. Stahl and H. Sies, Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease **1740**, 101 (2005).
[267] J. Tucker and D. Townsend, Biomedicine & Pharmacotherapy **59**, 380 (2005).
[268] S. B. Nimse and D. Pal, Rsc Advances **5**, 27986 (2015).
[269] J. A. Martinez, S. Navas-Carretero, W. H. Saris, and A. Astrup, Nature Reviews Endocrinology **10**, 749 (2014).
[270] M. Heni, S. Herzberg-Schäfer, F. Machicao, H.-U. Häring, and A. Fritsche, Diabetes Care **35**, e24 (2012).
[271] A. Haupt, C. Thamer, M. Heni, C. Ketterer, J. Machann, F. Schick, F. Machicao, N. Stefan, C. D. Claussen, H.-U. Häring, *et al.*, Diabetes **59**, 747 (2010).
[272] J. Kozlitina, E. Smagris, S. Stender, B. G. Nordestgaard, H. H. Zhou, A. Tybjærg-Hansen, T. F. Vogt, H. H. Hobbs, and J. C. Cohen, Nature genetics **46**, 352 (2014).
[273] Y. Lu, F. R. Day, S. Gustafsson, M. L. Buchkovich, J. Na, V. Bataille, D. L. Cousminer, Z. Dastani, A. W. Drong, T. Esko, *et al.*, Nature communications **7**, 1 (2016).
[274] C.-T. Liu, K. L. Young, J. A. Brody, M. Olden, M. K. Wojczynski, N. Heard-Costa, G. Li, A. C. Morrison, D. Muzny, R. A. Gibbs, *et al.*, Circulation: Cardiovascular Genetics **7**, 344 (2014).

[275] H. Mei, W. Chen, F. Jiang, J. He, S. Srinivasan, E. N. Smith, N. Schork, S. Murray, and G. S. Berenson, PloS one **7**, e31470 (2012).
[276] C. J. Willer, E. K. Speliotes, R. J. Loos, S. Li, C. M. Lindgren, I. M. Heid, S. I. Berndt, A. L. Elliott, A. U. Jackson, C. Lamina, *et al.*, Nature genetics **41**, 25 (2009).
[277] G. Thorleifsson, G. B. Walters, D. F. Gudbjartsson, V. Steinthorsdottir, P. Sulem, A. Helgadottir, U. Styrkarsdottir, S. Gretarsdottir, S. Thorlacius, I. Jonsdottir, *et al.*, Nature genetics **41**, 18 (2009).
[278] R. Larder, M. M. Sim, P. Gulati, R. Antrobus, Y. L. Tung, D. Rimmington, E. Ayuso, J. Polex-Wolf, B. Y. Lam, C. Dias, *et al.*, Proceedings of the National Academy of Sciences **114**, 9421 (2017).

10. Warnings

The Report IS PROVIDED AND USABLE IN THE CONDITION AND WITH THE CONTENTS SET FORTH THEREIN, OBJECTIVELY AS THEY ARE PRESENTED, WHICH REFLECT THE STATE OF THE ART AND KNOWLEDGE CURRENTLY AVAILABLE AT HEARTGENETICS.
HEARTGENETICS DOES NOT GUARANTEE IN ANY WAY THAT THE REPORT IS SUITABLE FOR ANY PURPOSE OR OBJECTIVE, INCLUDING its use as an auxiliary diagnostic tool, or any other that may be binding for healthcare professionals.
The degree of confidence in the information contained in the Report provided by HeartGenetics depends on the technical discretion and autonomy of the health professional responsible for requesting the Test and/or any other responsible for the clinical follow-up of the patient.
The use of this Report is entirely at the expense, risk and responsibility of the aforementioned patient and health professional and/or anyone responsible for the patient's clinical follow-up.
The genetic variants studied are responsible for only part of the complexity of the human being. There may be unknown genes, environmental factors or lifestyle options that are much more important for achieving a holistic understanding of the individual. All doubts and/or inconsistencies that the Report raises should be thoroughly assessed and discussed with the requesting health professional and/or whoever is responsible for the clinical follow-up of the patient. Whenever necessary or advisable, the information in the Report must be available for scrutiny and/or validation by other auxiliary means of investigation and/or diagnosis.
The content of the Reports may affect the patient and should be transmitted in due clinical context and recommended in particular for sensitive or impressionable individuals.
The patient can discover information contained in his genetic material (in the aspects analysed) that he did not anticipate and that may cause him to be emotional, disappointed or irritated or to have any other type of reactions that justifies psychological or psychiatric help.
The healthcare professional is particularly advised of the need to properly inform the patient of the content of the Report, clarifying it in a detailed and relevant way.
Healthcare professionals remain responsible for the correct reading, understanding and explanation of the contents of the Report to patients and are and remain exclusively responsible for its use in a clinical context, be it as an auxiliary means of diagnosis or otherwise.
THE REPORT DOES NOT ANALYSE ANY PROBABILITIES OF CONTRACTING ANY DISEASE NOR DOES IT MAP AND/OR CROSS OR DISMISS ANY PHYSICAL OR PSYCHOLOGICAL DISORDER BEYOND THE FACTORS IDENTIFIED IN THE REPORT.
THE CONTENT CONTAINED IN THE REPORT IS PROVIDED OBJECTIVELY IN ACCORDANCE WITH THE ANALYSED BIOLOGICAL SAMPLE, WITHOUT ANY PERSONAL INTERPRETATION DIRECTED TOWARDS A SPECIFIC INDIVIDUAL.
THE REPORT DOES NOT CONTAIN ANY MEDICAL ADVICE AND DOES NOT DISMISS OR INTEND TO SUBSTITUTE SAID ADVICE OR RECOMMENDATION.
HEARTGENETICS WILL NOT BE LIABLE FOR ANY KIND OF LOSS OR DAMAGE EVENTUALLY OR ALLEGEDLY ARISING FROM UNDUE ACCESS TO THE REPORT BY UNAUTHORISED PERSONS AFTER MAKING IT AVAILABLE TO THE REQUESTING PHYSICIAN IN THE CUSTOMER SUPPORT AREA ON THE HEARTGENETICS PORTAL. NOR WILL IT BE LIABLE FOR ANY EVENTUAL DAMAGE INCURRED FROM THE USE OF THE REPORT OUTSIDE THE CONTEXT AND FOR PURPOSES OTHER THAN THOSE SPECIFIED IN THE REQUEST BY THE REQUESTING PHYSICIAN.
LIMITATION OF LIABILITY
HeartGenetics does not exclude and/or limit its liability when prohibited by law. To the maximum extent permitted by law, HeartGenetics is liable for damages directly and exclusively arising from its own action or omission and / or that of the personnel in its service with regard to intent or gross negligence in carrying out the tests and correct reproduction of the results in the Report . Without prejudice to the foregoing and to the maximum extent permitted by law, HeartGenetics' cumulative and total liability will not exceed the full value of the Test (causing the liability) provided it has been invoiced and received by the former.
TO THE MAXIMUM EXTENT PERMITTED BY LAW, HEARTGENETICS AND ITS PARTNERS SHALL NOT BE LIABLE FOR ANY DIRECT DAMAGE OR LOSS OF PROFIT ARISING FROM MERE NEGLIGENCE, LACK OF ZEAL AND DILIGENCE.
TO THE MAXIMUM EXTENT PERMITTED BY LAW, HEARTGENETICS AND ITS PARTNERS SHALL NOT BE LIABLE FOR ANY DIRECT/INDIRECT DAMAGES, PROFIT LOSSES, COSTS, EXPENSES OR ANY CONSEQUENCES EMERGING FROM OR CORRELATED TO: (A) ANY INDIVIDUAL OR INSTITUTIONAL PURPOSES; (b) ANY ACTION OR OMISSION DETERMINED BY THIRD PARTIES OTHER THAN HEARTGENETICS AND AS A RESULT OF A CERTAIN READING AND/OR INTERPRETATION OF THE TEST REPORT OF WHICH THE LATTER IS UNAWARE, EVEN THOUGH SUCH INTERPRETATIONS, READINGS OR DECISIONS ARE SCIENTIFICALLY INCORRECT OR COVERED BY MANIFEST ERROR OF ASSESSMENT OR ANY OTHER; (c) UNAUTHORISED ACCESS, LOSS AND/OR ADULTERATION OF DATA, DISSEMINATION OR ABUSIVE USE, WHEN SUCH EVENTS OCCUR OUTSIDE THE AREA UNDER THE DIRECT CONTROL OF HEARTGENETICS' OPERATIONS; (d) EVENTS OF FORCE MAJEURE, UNFORESEEN CIRCUMSTANCES OR THIRD PARTY ACTIONS BEYOND THE CONTROL OF HEARTGENETICS OR ITS PARTNERS.
WHEN THE APPLICABLE LAW DETERMINES THAT LIABILITY CANNOT BE EXCLUDED OR LIMITED, THE ABOVE EXCLUSIONS AND LIMITATIONS MUST BE INTERPRETED AND APPLIED TO THE FULLEST EXTENT PERMITTED BY LAW.

In the development of its activity, HeartGenetics, Genetics and Biotechnology SA strictly complies with all the requirements set out in the legislation adopted by European Union authorities. The partners of HeartGenetics, Genetics and Biotechnology SA and Germano de Sousa Centro de Medicina Laboratorial are responsible for complying with the internal regulations of the respective legal systems. HeartGenetics, Genetics and Biotechnology SA and Germano de Sousa Centro de Medicina Laboratorial are not responsible for any violations of the regulations in force in the countries of origin of their partners.