RAPPORT **DIET • DNA**

HEALTHY • LAB®

Genetic Evaluation for Nutrition Traits

CASE INDEX	
Full name:	**N.A.**
Gender:	**Female**
Date of birth:	**1979-10-17**
Ethnicity:	**N.A.**
Referral reason:	**Nutritional plan adequacy**
Purpose:	**Wellness genetics**
Specimen type:	**Blood**

CUSTOMER INSTITUTION	
Referring physician:	**Dra. Isabel Mendes Gaspar**
Referral number:	**HGCTRL36**
Place of harvest:	**Heartgenetics**
Referring facility:	**HeartGenetics**
Sample collection date:	**N.A.**
Sample reception date:	**2019-06-27**
Report issue date:	**2024-02-06**

What is analysed in this genetic test?

This genetic test analyses your DNA with the objective of evaluating 26 genetic variants of 22 genes which are decisively associated with nutrition and weight management.

The associations identified between the genes and evaluated traits are corroborated by international standard scientific studies referred to in this report.

Polygenic computational model

The personal traits assessed in this genetic test are polygenic traits, i.e. several genes contribute to the same trait. In this context, it is necessary to use a computational model that considers all the individual contributions of each genetic variant. The result of the computational evaluation is a scoring model, which is illustrated in this report through a more or less filled bar. HeartGenetics' proprietary algorithm builds the scoring model based on a large set of variables, i.e. gene characteristics. The result of the scoring model is more relevant than the number of genes that may be marked as altered. The size of the scoring bar is proportional to the relevance of the risk or impact of the genetic variants identified for the trait under evaluation.
We raise your attention to the fact that the filling in the score bar, particularly in areas with few genetic variants, can be affected by small variations in the contribution of each genetic variant. Small changes can exist whenever computational models are updated according to the latest scientific studies.
Since most scientific studies are carried out in individuals of European ancestry, it is expected that the predictive power of the genetic panel for the traits under study is superior in these individuals. When European-derived polygenic scores are applied to individuals with other ancestries, the predictive power is lower and dependent on ancestry.

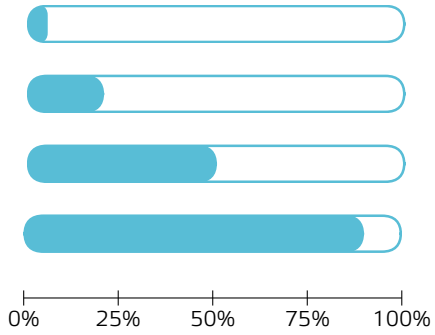
Important disclaimer

Wellness genetics is an area of genetics that investigates the association between genes and individual traits with an impact on the definition of a healthy lifestyle. The use of information on genetic predisposition to establish a nutritional plan should be integrated with information on physical characteristics (e.g. age, gender, etc.) and behavioural information (e.g. eating habits, physical activity, etc.).

Non-genetic factors have a strong impact on the physical manifestation of different traits. For this reason, there may be no physical manifestation of a trait for which a high genetic predisposition has been identified, and the reverse is also true.

How to read the report

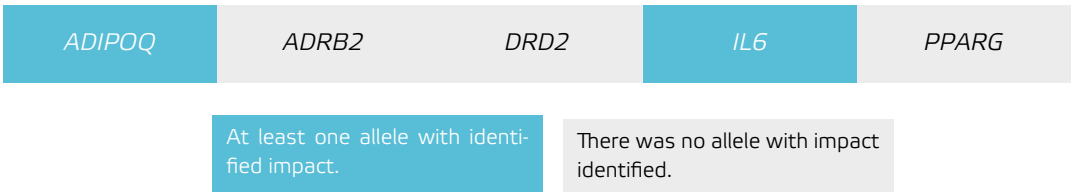
This test studies six traits, divided into two areas: **WEIGHT MANAGEMENT** and **POSITIVE IMPACT BEHAVIOURAL STRATEGIES**. For the study of the various traits, scoring models presented through bars are used. **Filling in the score bar is proportional to the relevance of the joint impact of the genetic variants identified for the trait under evaluation.** See the table below for how to interpret the results.



	Weight management	Positive impact behavioural strategies
	No risk alleles	No risk alleles
	Less favourable profile	Lower response
	Intermediate profile	Intermediate response
	More favourable profile	Higher response

The bars show examples of possible scores. Score bars can take different values than those shown in the examples.

In the detail sections of all areas of the test you can find genetic impact schemes.



The number of highlighted genes does not have to be proportional to the size of the corresponding bar.

All variants with an impact on the analysed parameter are presented in the respective subarea in tables as shown below.

1 Biological role	2 Gene	3 rsID	4 Nucleotidic change [1]	5 Aminoacidic change [1]	6 Result
Energy expenditure	*ADIPOQ*	rs17300539	c.-1138A>G	–	G
Inflammation	*IL6*	rs1800795	c.-237G>C	–	G

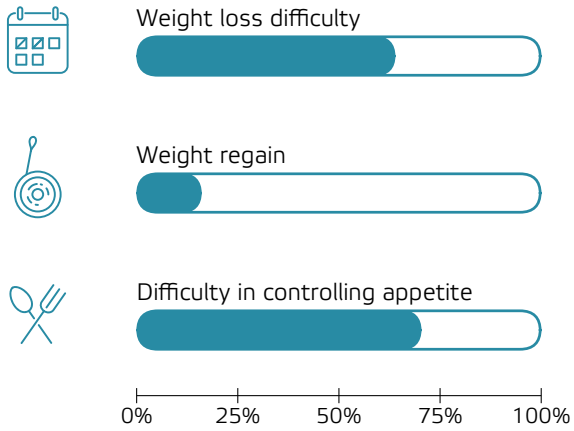
[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

1. Biological function of the corresponding gene.
2. Gene identification.
3. Variant identifier of the dbSNP (NCBI) database.
4. Change at the DNA level.
5. Change at the encoded protein level. In the absence of a change, a hyphen (-) is displayed. In these cases, the impact of the variant is not related to changes in the structure of the corresponding protein.
6. Alleles with impact identified. The presence of two characters indicates the presence of the variant in heterozygosity and that of a single character the presence in homozygosity.

Summary of your genetic profile

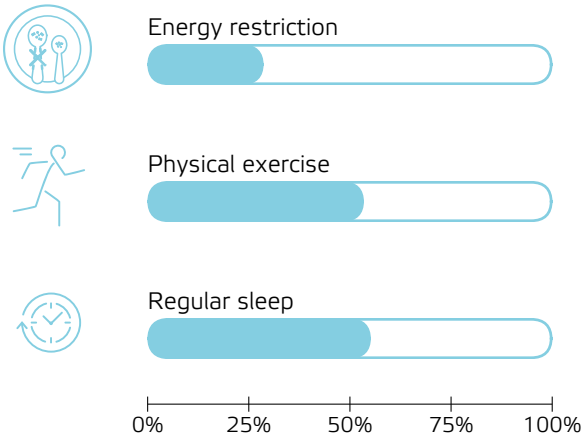
Weight management

The impact of genetics on weight loss and maintenance parameters is analysed in this area. By customizing the dietary plan to these genetic indicators, one can optimize the weight loss process to achieve more successful results.



Positive impact behavioural strategies

The findings presented here demonstrate the impact of the genetic profile under examination on the body's response to behaviour changes that positively impact weight reduction and improve overall metabolic health.

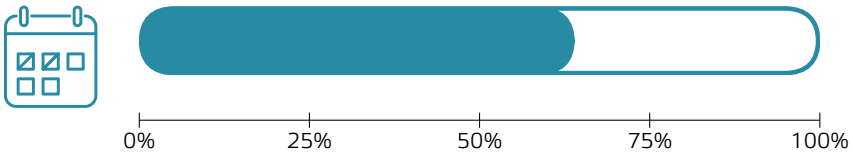


The advantages of nutritional and behavioural adequacy to the results presented above are outlined in the detailed information for each parameter in the subsequent pages of the report.

Your genetic profile details

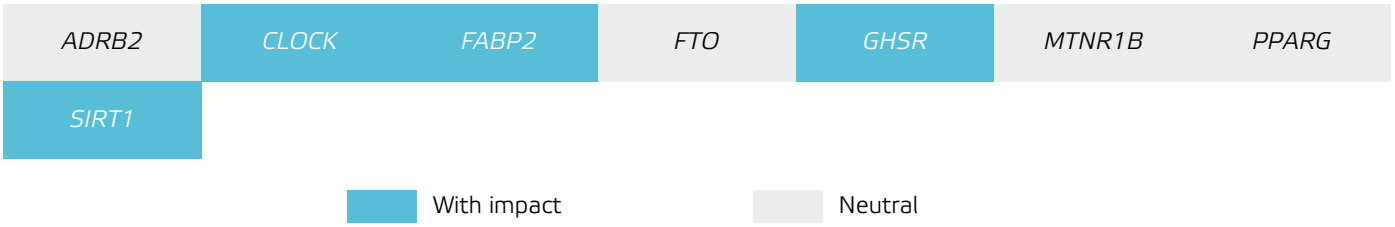
Weight loss difficulty

Difficulty in losing weight often results from eating errors associated with a sedentary lifestyle and less favourable genetic factors [1]. In order to optimize the weight loss strategy, it is important to consider our genetic profile [2]. 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 [3, 4].



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

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



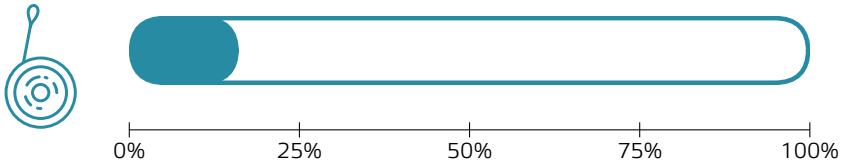
The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	rsID	Nucleotidic change	Aminoacidic change	Result
Circadian rhythm	*CLOCK*	rs1801260	c.*213T>C	–	C
Energy expenditure	*SIRT1*	rs1467568	c.1916-864A>G	–	AG
Lipid metabolism	*FABP2*	rs1799883	c.163G>A	p.Ala55Thr	AG
Orexigenic stimulus	*GHSR*	rs490683	g.172175074C>G	–	GC

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.

Weight regain

Maintenance of body weight is regulated by the interaction of several processes, encompassing genetic, environmental and behavioural factors [5, 6]. 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 [7, 8].



- Yours results suggest that you are not predisposed to easily recover lost weight.

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

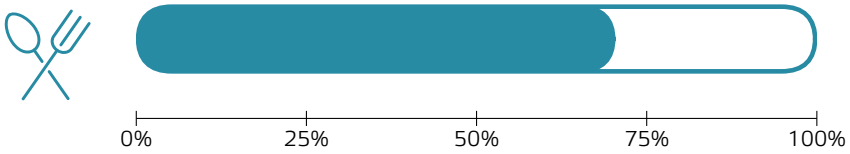
The following table lists all variants whose identified result is relevant for this parameter.

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

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.

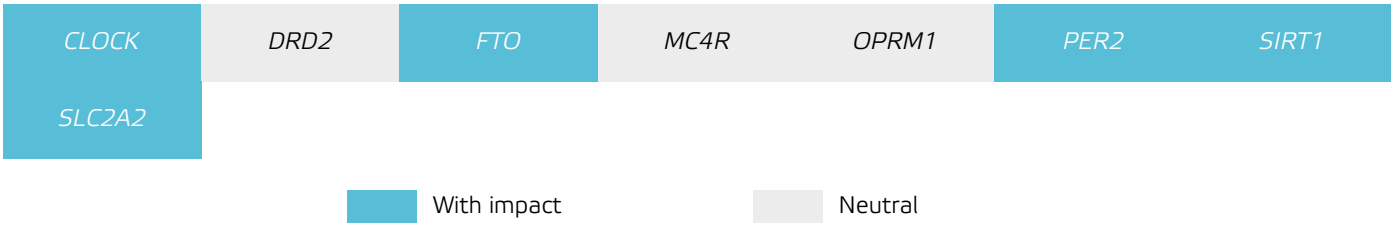
Difficulty in controlling appetite

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 [9]. In various areas of the brain, information on gustatory stimuli is integrated with signs of hunger, satiety, and appetite [10]. 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 [11], and several genetic variants are described in the scientific literature that affect the control of energy homeostasis and food intake [12, 13, 14].



- According to your genetic profile, you have a high predisposition to the deregulation of appetite control mechanisms.
- 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.
- Carriers of a specific variant of *PER2* gene have an increased predisposition for stress behaviours associated with the adaptation to a hypoenergetic diet, namely to give up the diet.
- Your genotype for the *SIRT1* gene is associated with the secretion of higher levels of ghrelin (the hunger hormone) and with higher intake of saturated fat.
- You carry a genetic variant of *SLC2A2* that is often associated with increased drive to eat sweet foods.
- You have sensitive gene variants in your genome that have been associated with predisposition to false hunger and/or difficulty in controlling appetite.

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

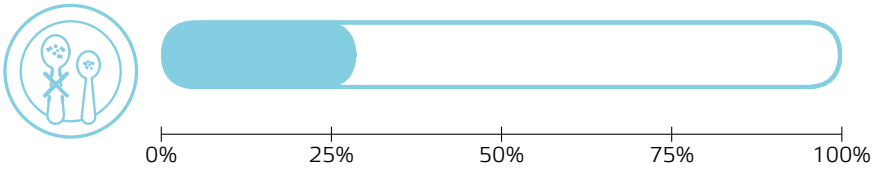


The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	rsID	Nucleotidic change	Aminoacidic change	Result
Circadian rhythm	*CLOCK*	rs1801260	c.*213T>C	–	C
	PER2	rs4663302	g.238295120C>T	–	T
Energy expenditure	*FTO*	rs9939609	c.46-23525T>A	–	TA
	SIRT1	rs1467568	c.1916-864A>G	–	AG
Glucose homeostasis	*SLC2A2*	rs5400	c.329C>T	p.Thr110Ile	CT

Energy restriction

Energy restriction (ER) is a methodology based on low daily calorie intake (low-calorie diet), with a reduction of 20-50 % of people's daily energy ingested [15]. It is commonly used in clinical practice for weight loss, improvement of metabolic biomarkers and in the treatment of non-alcoholic hepatic steatosis [16]. Scientific evidence has shown that ER is an intervention strategy that promotes healthy ageing and longevity, but its mechanisms are not well known yet [17]. ER, combined with intermittent fasting and liquid meals, is a successful strategy for weight loss in obese people and for cardiovascular risk reduction [18], but its adherence and maintenance in the medium and long term is difficult and sometimes leads to the recovery of lost weight [17]. 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 [19]. People with certain genetic variants have different responses to energy restriction programmes [7, 20, 21, 22, 23, 23, 24, 25].



Your genetic results suggest some benefits of adopting a hypoenergetic diet, should this be a goal to you.

- 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 energy restriction compared with people who do not carry these variants.

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

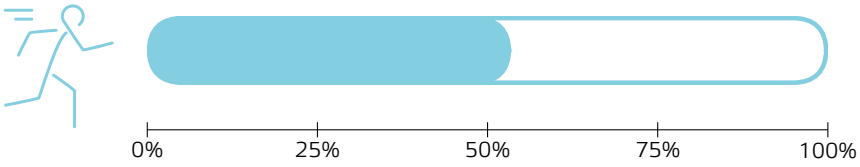
The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	rsID	Nucleotidic change	Aminoacidic change	Result
Adipogenesis, lipogenesis and glucose homeostasis	*PPARG*	rs1801282	c.34C>G	p.Pro12Ala	C
Lipid metabolism	*PLIN*	rs894160	c.772-799G>A	–	G

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.

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, endurance 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.

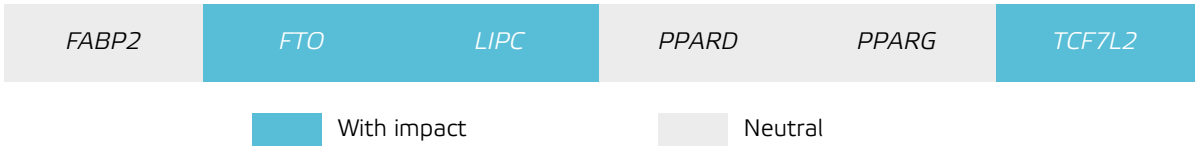


According to the World Health Organization (WHO), regular physical activity of moderate intensity, such as walking, cycling or playing sports, has significant health benefits at all ages.

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

- Your results indicate that you benefit from physical exercise 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 exercise is particularly beneficial to increase insulin sensitivity. This means that 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:

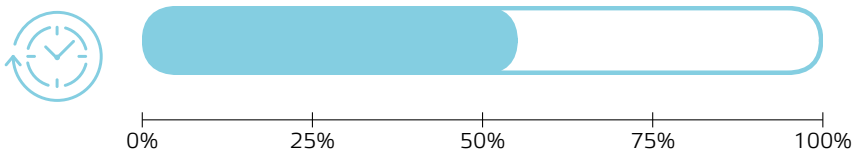


The following table lists all variants whose identified result is relevant for this parameter.

Biological role	Gene	rsID	Nucleotidic change	Aminoacidic change	Result
Energy expenditure	*FTO*	rs1121980	c.46-34805G>A	–	GA
		rs8050136	c.46-27777C>A	–	CA
Glucose metabolism	*TCF7L2*	rs7903146	c.382-41435C>T	–	C
Lipid metabolism	*LIPC*	rs1800588	c.-557C>T	–	C

Regular sleep

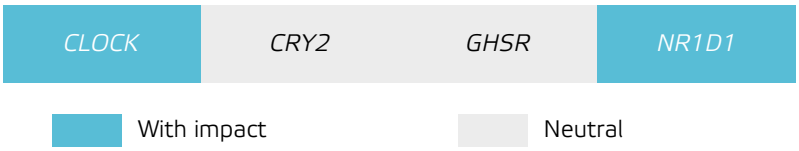
A regular sleep pattern is essential for maintaining a healthy weight. During sleep, the balance between the energy that resulted from the ingestion of nutrients, energy expenditure and the metabolism of fats and carbohydrates is regulated. Sleeping poorly or having little restful sleep decreases the 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.



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

- Your test indicates a genetic profile that is 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	rsID	Nucleotidic change	Aminoacidic change	Result
Circadian rhythm	*CLOCK*	rs1801260	c.*213T>C	–	C
	NR1D1	rs12941497	c.31+723C>T	–	T

Technical information

Methodology

1. When aplicable a commercial kit is used to perform DNA extraction and purification. DNA concentration and quality are evaluated with a spectrophotometer (HG_SOP.03).
2. Genotyping was made through the study of 26 genetic variants in 22 genes, described as nutrition and weight management-related.
3. Genotyping is 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 (HG_SOP.06, HG_SOP.08, HG_SOP.09, HG_SOP.18).
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).

Genetic panel

ADIPOQ	**Adiponectin, C1Q and collagen domain containing** | NM_004797.3
ADRB2	**Adrenoceptor Beta 2** | ENSG00000169252
BDNF	**Brain Derived Neurotrophic Factor** | NM_001143805.1
CLOCK	**Clock Circadian Regulator** | ENSG00000134852
CRY2	**Cryptochrome Circadian Clock 2** | ENSG00000121671
DRD2	**Dopamine Receptor D2** | NM_000795.3
FABP2	**Fatty Acid Binding Protein 2** | NM_000134.3
FTO	**Fat Mass And Obesity Associated** | NM_001080432.2
GHSR	**Growth Hormone Secretagogue Receptor** | NM_198407.2
IL6	**Interleukin 6** | NM_000600.3
LIPC	**Lipase C, Hepatic Type** | NM_000236.2
MC4R	**Melanocortin 4 Receptor** | NM_005912.2
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
PER2	**Period Circadian Clock 2** | NM_022817.2
PLIN	**Perilipin 1** | NM_001145311.1
PPARD	**Peroxisome Proliferator Activated Receptor Delta** | NM_006238.4
PPARG	**Peroxisome Proliferator Activated Receptor Gamma** | NM_015869.4
SIRT1	**Sirtuin 1** | NM_012238.4
SLC2A2	**Solute Carrier Family 2 Member 2** | NM_000340.1
TCF7L2	**Transcription Factor 7 Like 2** | NM_030756.4

Risks and limitations

HeartGenetics, Genetics and Biotechnology SA applies a rigorous quality control 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. The company guarantees the accuracy of the scientific knowledge presented in the report. It has been assumed as truthful all the above declarations about the individual and healthcare professional identity, the purpose of the study, index case and nature of analysed biological products.
The study allows for up to one genetic variant with an undetermined outcome. These variants are listed in the table in section Genetic information, alongside the others, but marked with a "-" in the "Result" column. According to the polygenic computational model, an undetermined outcome is equivalent to having no impact.

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, Reference Institute and IBBL. The laboratory that performs this genetic test complies, at all times, with all the applicable certifications and Law in its territory.

Terms and conditions

HeartGenetics, Genetics and Biotechnology SA will not be liable whether in contract, tort, warranty, or under any statute, or any other basis of special, incidental, indirect punitive, multiple, or consequential damages in connection with in arising from this document, or improper use of the product described herein or any use of such product outside the scope of the express written licenses or permissions granted by HeartGenetics, Genetics and Biotechnology SA, to the extent allowed by law.
The results presented in Section Genetic information, are the responsibility of the laboratory that performed the genetic test.

In the development of its work, HeartGenetics, Genetics and Biotechnology SA rigorously conforms to all the requirements set out in the legislation of the European Union institutions. It is the responsibility of partners of HeartGenetics, Genetics and Biotechnology SA to meet with the internal standards of the respective legal jurisdiction. HeartGenetics, Genetics and Biotechnology SA does not take responsibility for any eventual violations of existing regulations applicable in its partners' home countries.

Genetic information

This genetic test has identified 14 genetic variants, out of a total of 26 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 [1]	Result
	HGMD	rsID			
ADIPOQ	CR052432	rs17300539	c.-1138A>G	–	AG
ADRB2	CM950016	rs1042713	c.46A>G	p.Arg16Gly	G
BDNF	–	rs10767664	c.-22+16205A>T	–	AT
CLOCK	CR121503	rs3749474	c.*897G>A	–	G
CLOCK	CR984677	rs1801260	c.*213T>C	–	C
CRY2	–	rs11605924	c.32+4259A>C	–	C
DRD2	CM041241	rs1800497	c.2137G>A	p.Glu713Lys	G
FABP2	CM950433	rs1799883	c.163G>A	p.Ala55Thr	AG
FTO	–	rs1121980	c.46-34805G>A	–	GA
FTO	CS076623	rs9939609	c.46-23525T>A	–	TA
FTO	CS088104	rs8050136	c.46-27777C>A	–	CA
GHSR	CR084002	rs490683	g.172175074C>G	–	GC
IL6	CR983402	rs1800795	c.-237G>C	–	GC
LIPC	CR971949	rs1800588	c.-557C>T	–	C
MC4R	–	rs17782313	g.60183864T>C	–	T
MTNR1B	CR110512	rs10830963	c.223+5596C>G	–	C
NR1D1	–	rs12941497	c.31+723C>T	–	T
OPRM1	CM003770	rs1799971	c.118A>G	p.Asn40Asp	GA
PER2	–	rs2304672	c.-12C>G	–	C
PER2	–	rs4663302	g.238295120C>T	–	T
PLIN	CS045669	rs894160	c.772-799G>A	–	G
PPARD	CR035869	rs2016520	c.-87C>T	–	T
PPARG	CM981614	rs1801282	c.34C>G	p.Pro12Ala	C
SIRT1	–	rs1467568	c.1916-864A>G	–	AG
SLC2A2	CM941277	rs5400	c.329C>T	p.Thr110Ile	CT
TCF7L2	CS065626	rs7903146	c.382-41435C>T	–	C

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

HEARTGENETICS
GENETICS & BIOTECHNOLOGY

Technical direction
HeartGenetics, Genetics and Biotechnology SA
Cantanhede, Portugal, 2024-02-06

Lúcia Gonçalves
Technical Laboratory Coordinator
Molecular Biologist, MSc

Daniel Luís
Scientific director
Molecular Biologist, MSc

Appendix

Evidence 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.

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 [25, 26, 27]. This allele is also associated with short-time sleepers with increased levels of the hunger-inducing hormone ghrelin, and with increased saturated fat intake [25, 26, 27]. Sleeping an appropriate number of hours and having a regular sleep pattern is beneficial to decrease ghrelin levels in those carrying this allele [28].

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 show that A allele carriers have a predisposition to a higher absorption of fats by the intestine [29]. Carriers of this allele have a predisposition to higher LDL-cholesterol levels and greater difficulty in losing weight [24, 30, 31].

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 [32]. Carriers of the A allele have a predisposition to a higher BMI and accumulation of abdominal fat [33, 34, 35]. Physical exercise is recommended to attenuate this predisposition, which is exacerbated by a sedentary lifestyle [34].

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 [32]. 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 [36, 37, 38, 39, 40, 41, 42, 43]. However, there is evidence that a high protein diet is particularly beneficial for them as a strategy to decrease their appetites [44]. 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 [36, 38, 39, 40, 42, 45, 46].

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 [32]. Carriers of the A allele benefit from physical exercise in order to achieve better weight loss results [47, 48].

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 [49, 50].

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 [51].

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 [52].

PER2, – / rs4663302

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. Studies of genotype-phenotype association show that TT genotype carriers have a

predisposition to anxiety behaviours associated with the adaptation to a hypoenergetic diet, being this genotype more frequent among those giving up the diet [53].

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 [54] and reduction of the abdominal perimeter [55] following such restriction.

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 [23]. However, individuals with this genotype might recover lost weight more easily [56, 57].

SIRT1, – / rs1467568

The SIRT1 protein plays an important role in the regulation of energy metabolism. Studies of genotype-phenotype association show that the A allele is associated with a predisposition to higher levels of ghrelin, a hormone that plays an important role in regulating appetite by inducing the sensation of hunger. Carriers of this allele show a tendency towards the increase of saturated fat intake and are more resistant to lose weight. These predispositions have a greater impact in the presence of a combined genotype, that is, this variant together with the C allele of *CLOCK* RS1801260 [27].

SLC2A2, CM941277 / rs5400

The SLCA2 protein is a low-affinity glucose transporter, which functions as a glucose sensor in order to regulate its circulating levels. Studies of genotype-phenotype association indicate that T allele carriers are predisposed to consume excess sugars [58, 59].

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 exercise in order to achieve better weight loss results [60, 61, 62, 63].

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