MyNutriGenes®

FOOD IS FUEL

Are you eating right?
Ask your genes.

HEARTGENETICS
GENETICS & BIOTECHNOLOGY

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Nutrigenetic Report

INDEX CASE	
Name:	**N.A.**
Gender:	**N.A.**
Date of birth:	**N.A.**
Age:	**N.A.**
Ethnicity:	**N.A.**
Consultancy referral number:	**N.A.**
Reason:	**Nutritional plan adequacy**
Purpose:	**Nutrigenetics**
Specimen type:	**Saliva**

CUSTOMER INSTITUTION	
Referring physician:	**N.A.**
Reference:	**N.A.**
Institution:	**N.A.**
Requisition date:	**N.A.**
Fulfillment date:	**2017-12-11**

1. WHAT IS ANALYZED IN THIS GENETIC TEST?

- In this genetic test, the Laboratory of HeartGenetics has analysed the DNA collected from a sample of saliva in order to evaluate 54 genes (from a total of 80 genetic variants) which are decisively associated with nutrition and weight management.
- The result achieved, called the genetic profile, is unique for each individual and could play a key role in preparing a personalized nutritional plan.
- This genetic test needs to be performed only once in a lifetime.
- The associations identified between the genes studied and the body's response to food intake are corroborated by international standard scientific studies with an impact on 5 areas of intervention.

AREAS OF INTERVENTION

	Predisposition to weight gain
Impact:	Weight, recovery of lost weight, waist-hip ratio, body mass index (BMI)
	Influence of diet on body fat
Impact:	Body mass index (BMI) associated with diet, distribution of body fat, response to fat intake, response to the intake of carbohydrates
	Nutritional metabolism
Impact:	Response to a hypoenergetic diet, fat metabolism, carbohydrate metabolism, insulin response to exercise and diet
	Nutritional sensitivities, needs, and detox
Impact:	Sensitivity to caffeine and salt, need for vitamins B6, B12, A, C, D, and E, omega 3 and antioxidants
	Appetite control, satiety, and emotional eating
Impact:	Sensation of hunger or false hunger, appetite control, circadian rhythm/biological clock, sleep rhythm regulation

DISCLAIMER

- **Nutrigenetics is a science that investigates the association between genes and each individual's response to nutrient intake. The use of information on genetic predisposition to establish a nutritional plan should be integrated with information on physical characteristics (e.g. age, gender, muscle mass index, etc.) and behavioural information (e.g. eating habits, physical activity, etc.).**
- **The results of this genetic test cannot be used for clinical diagnostics, disease prevention or to identify a clinical condition.**
- **The results of the genetic test do not depend on the physical or clinical condition or on the therapeutic management of the individual tested.**

2. RESULTS – GENETIC PROFILE

2.1. ANALYSIS OF GENETIC PREDISPOSITION

This genetic test identified 36 genetic variants (out of 80 analysed), with a significant impact for the design of a personalized nutritional plan.

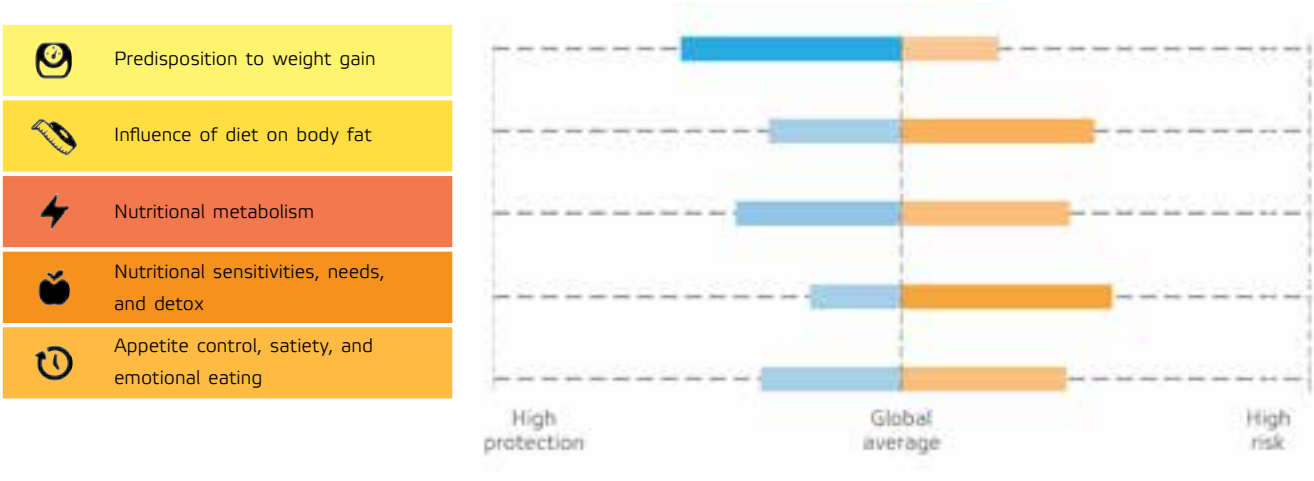

Figure 1: Relevance of the identified genetic variants, in the context of the global population.

2.2. INDICATIONS FOR A PERSONALIZED NUTRITIONAL PLAN

ACTION PLAN – Summary of protective actions for the following areas: Nutritional metabolism; Nutritional sensitivities, needs, and detox; Appetite control, satiety, and emotional eating

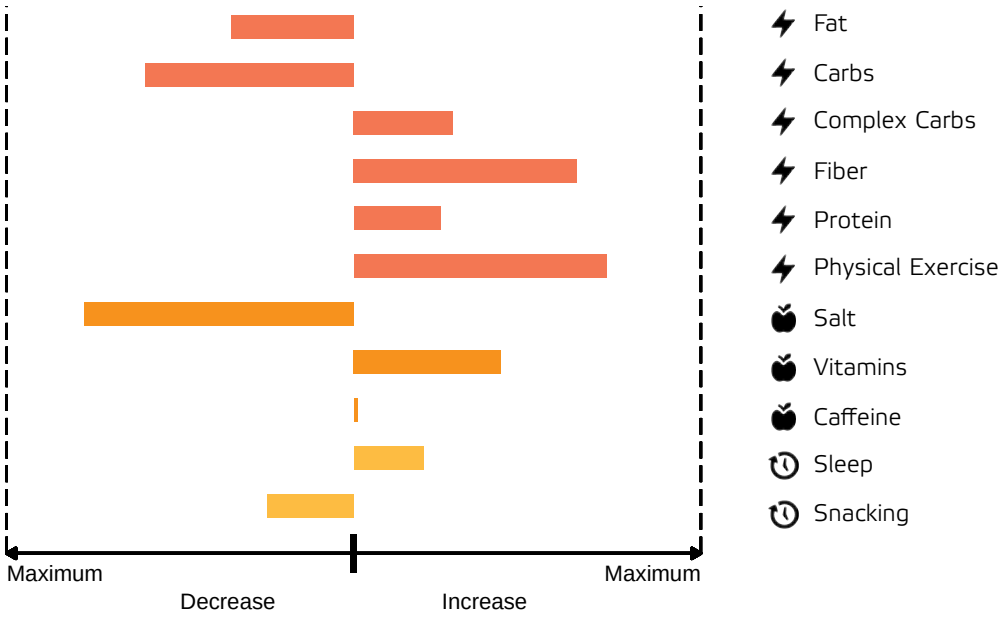

Figure 2: Action plan summary

DETAILED ACTION PLAN

Each indication, classified as predisposition, protection or benefit, is associated with one or more genetic variants assessed. There may be similar indications resulting from different genetic variants which contribute to the same type of risk or protection. The existence of similar indications reinforces the importance of the risk or protection for the parameter under analysis.

The information identified as benefits should be perceived as protective actions and has contributed to the action plan (figure 2.2).

PREDISPOSITION TO WEIGHT GAIN		
	IMPACT	**INFORMATION**
Body mass index (BMI)	Moderate risk	• Predisposition to a high body mass index (BMI).
Waist-to-hip ratio	Moderate risk	• Predisposition to a high waist-hip ratio.
Weight	Moderate risk	• Predisposition to overweight. • Predisposition to weight loss difficulty. This is a common variant in the population which contributes to a cumulative effect.
Weight loss regain	Moderate risk	• Predisposition to recovering lost weight. • Predisposition to recovering lost weight. This is a common variant in the population which contributes to a cumulative effect.

INFLUENCE OF DIET ON BODY FAT		
	IMPACT	**INFORMATION**
Distribution of body fat	Moderate risk	• Predisposition to building up abdominal fat and/or fat around the organs. • Predisposition to building up abdominal fat. • **Protection**: Lower predisposition to building up abdominal fat.
Response to carbohydrates intake	Moderate risk	• Predisposition to fat accumulation around the organs.Strong impact from the intake of carbohydrates.
Response to fat intake	Moderate risk	• Predisposition to building up body fat. This is a common variant in the population which contributes to a cumulative effect. • Predisposition to building up fat around the organs. Strong impact from the intake of fat.

NUTRITIONAL METABOLISM		
	IMPACT	**INFORMATION**
Carbohydrate metabolism	Protective action	• **Benefits** from decreased intake of carbohydrates, since decreases LDL levels. • **Benefits** from decreased intake of carbohydrates, since reduces BMI.
Fat metabolism	High risk	• Predisposition to a decreased fat metabolism. Greater resistance to weight loss. • Predisposition to higher LDL cholesterol levels (bad cholesterol). • Predisposition to higher triglycerides levels. • Predisposition to lower HDL levels (good cholesterol).
	Protective action	• **Benefits** from a carbohydrate-enriched and low-fat nutritional plan,since decreases insulin resistance. • **Benefits** from decreased intake of saturated, hydrogenated and trans-fats, since reduces triglycerides levels and BMI. • **Benefits** from decreased intake of saturated, hydrogenated and trans-fats. • **Benefits** from the practice of physical exercise, since increases HDL cholesterol levels (good cholesterol). • **Benefits** from the practice of physical exercise, since increases weight loss. This is a common variant in the population and it contributes to a cumulative effect.
Insulin response	Protective action	• **Benefits** from a fibre-enriched nutritional plan, since decreases insulin resistance. • **Benefits** from regular physical exercise, since decreases insulin resistance and reduces LDL cholesterol levels and BMI.
Reaction to the hypoenergetic diet	Protective action	• **Benefits** from a hypoenergetic diet associated with a suitable sleep rhythm, since enhances weight loss. Teens aged 13-18 years, 8-10 hours a day. Adults aged 18 years or older, 7-8 hours a day [1, 2]. • **Benefits** from a hypoenergetic diet associated with physical exercise, since enhances weight loss. • **Benefits** from a hypoenergetic diet with decreased fat intake, since enhances weight loss. • **Benefits** from a low fat, fibre-enriched nutritional plan. • **Benefits** from a protein-enriched hypoenergetic diet, since decreases insulin resistance.

NUTRITIONAL SENSITIVITIES, NEEDS, AND DETOX		
	IMPACT	**INFORMATION**
Antioxidant capability	Protective action	• **Benefits** from a diet plan enriched in foods with vitamin A (of animal origin to obtain the active component retinol).
Omega 3	Moderate risk	• Predisposition to lower levels of omega-3.
	Protective action	• **Benefits** from a nutritional plan enriched in foods with omega-3.
Sensitivity to salt	Moderate risk	• Predisposition to sodium sensitivity and higher fluid retention. • Predisposition to sodium sensitivity and higher fluid retention. This is a common variant in the population which contributes to a cumulative effect.
	Protective action	• **Benefits** from a low sodium diet. For an healthy adult: up to 5 g of daily consumption [3].
Vitamin A	Moderate risk	• Predisposition to lower levels of vitamin A.
Vitamin B6	Moderate risk	• Predisposition to lower levels of vitamin B6.
Vitamin D	Moderate risk	• Predisposition to lower levels of circulating vitamin D. There may be a need to adjust the diet plan with food rich in this vitamin, with vitamin supplements or even greater exposure to the sun.
Vitamins B6 and B12	Moderate risk	• Predisposition to higher homocysteine levels.
	Protective action	• **Benefits** from a nutritional plan enriched in foods with vitamins B6, B12 and B9

APPETITE CONTROL, SATIETY, AND EMOTIONAL EATING		
	IMPACT	**INFORMATION**
Sensation of hunger and/or appetite control	Moderate risk	• Predisposition to false hunger and/or difficulty in controlling appetite. • Predisposition to stress behaviours associated with the adaptation to a hypoenergetic diet, namely to snack frequently and even to give up the diet.

	Protective action	• **Benefits** from eating at regular times to avoid snacking or to get a feeling of false hunger. The nutritional plan may be adapted with foods that allow longer satiety (for example rich in fiber).

TECHNICAL DIRECTION
HeartGenetics, Genetics and Biotechnology SA
Cantanhede, 2017-12-11
Portugal

Helena Vazão
Molecular Biologist, PhD
Associate Laboratory Director
(Operation responsibility)

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(Validation responsibility)

3. TECHNICAL INFORMATION

3.1. 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 via the study of 80 genetic variants in 54 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).

3.2. GENETIC PANEL

ADD1	**Adducin 1 (alpha)** | ENSG00000087274
ADIPOQ	**Adiponectin, C1Q and collagen domain containing** | NM_004797.3
ADRB2	**adrenoceptor beta 2** | NM_000024
AHR	**Aryl Hydrocarbon Receptor** | NM_001621.4
ALPL	**Alkaline Phosphatase, Liver Bone Kidney** | NM_000478.4
APOA1	**Apolipoprotein A1** | ENSG00000118137
APOA2	**Apolipoprotein A2** | ENSG00000158874
APOA5	**Apolipoprotein A5** | ENSG00000110243
APOB	**Apolipoprotein B** | ENSG00000084674
APOE	**Apolipoprotein E** | ENSG00000130203
BCMO1	**Beta-Carotene Oxygenase 1** | NM_017429.2
CLCNKA	**Chloride voltage-gated channel Ka** | ENSG00000186510
CLOCK	**Clock Circadian Regulator** | ENSG00000134852
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
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** | NC_000011
FTO	**alpha-ketoglutarate dependent dioxygenase** | NM_001080432
FUT2	**Fucosyltransferase 2** | NM_000511.5
GC	**GC, Vitamin D Binding Protein** | NM_000583.3
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
GSTM1	**Glutathione S-Transferase Mu 1** | NM_000561.3
IL6	**interleukin 6** | NM_000600
IRS1	**Insulin Receptor Substrate 1** | NM_005544.2
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
MMAB	**Methylmalonic Aciduria (Cobalamin Deficiency) CblB Type** | NM_052845.3
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
PER2	**Period Circadian Clock 2** | NM_022817.2
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
RS12272004	**Intergenic marker** | NC_000011.10
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
SOD2	**superoxide dismutase 2** | NM_000636
TCF7L2	**Transcription Factor 7 Like 2** | NM_030756.4
TFAP2B	**Transcription Factor AP-2 Beta** | NM_003221.3

3.3. RISKS AND LIMITATIONS

HeartGenetics 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 patient and medical identity, the purpose of the study, index case and nature of analysed biological products.

3.4. QUALITY ASSURANCE

HeartGenetics, Genetics and Biotechnology SA is an ISO 9001 and ISO 13485 certified company for Quality Management System and applies an External Quality Assessment program from UK NEQAS. The laboratory that performs this genetic test undertakes to, at all times, comply with the all applicable certifications and Law in its territory.

3.5. 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 4.1, Genetic Information, are the responsability 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

4. APPENDIX

4.1. GENETIC INFORMATION

The table below presents the genetic variants that have been identified as relevant for the design of a personalized nutritional plan. The results are described according to the HGVS nomenclature (`http:www.hgvs.org`), accessed on October 2016.

No other genetic variants from MyNutriGenes panel were identified, than those shown in the table.

Gene	Genetic variant references		Nucleotidic change [1]	Aminoacidic change	Observation [2]
	HGMD	Ensembl			
ADRB2	–	rs1042713	c.46A>G	p.Arg16Gly	hmz
AHR	–	rs6968865	g.17287269A>T	–	hmz
AHR	–	rs4410790	g.17284577T>C	–	hmz
ALPL	–	rs4654748	c.134-9113T>C	–	htz
APOA1	CR900263	rs670	c.-113A>G	–	hmz
APOA5	CR033141	rs662799	c.-620C>T	–	hmz
APOE	CM860003	rs7412	c.526C>T	p.Arg176Cys	wt
APOE	CM900020	rs429358	c.388T>C	p.Cys130Arg	wt
BCMO1	CM091857	rs12934922	c.801A>T	p.Arg267Ser	htz
BCMO1	CM091858	rs7501331	c.1136C>T	p.Ala379Val	htz
CLCNKA	–	rs848307	n.530+427C>T	–	htz
CLOCK	CR121503	rs3749474	c.*897G>A	–	htz
DHCR7	–	rs12785878	c.146+1233T>G	–	wt
DRD2	CM041241	rs1800497	c.2137G>A	p.Glu713Lys	htz
FADS1	CR1510437	rs174546	c.*53A>G	–	htz
FTO	–	rs9939609	c.46-23525T>A	–	htz
GC	–	rs2282679	c.*26-796A>C	–	htz
GRK4	CM025430	rs1024323	c.425C>T	p.Ala142Val	hmz
GRK4	CM025429	rs2960306	c.194G>T	p.Arg65Leu	hmz
IRS1	CR096329	rs2943641	g.227093745TC>T	–	wt
LIPC	CR971949	rs1800588	c.-557C>T	–	htz
LIPC	CR002154	rs2070895	c.-293G>A	–	htz
LPL	CS931395	rs320	c.1322+483G>T	–	hmz
LPL	CS890131	rs285	c.1019-1582C>T	–	hmz
LYPLAL1	–	rs2605100	g.219470882A>G	–	htz
MC4R	–	rs11152221	g.60350016C>T	–	htz
MMAB	–	rs2241201	c.*2701C>G	–	hmz
MTHFR	CM950819	rs1801133	c.665C>T	p.Ala222Val	htz
NR1D1	–	rs2314339	c.370+106A>G	–	hmz
PCSK1	CM132638	rs6234	c.1993C>G	p.Gln665Glu	htz
PCSK1	CM1311914	rs6235	c.2069C>G	p.Thr690Ser	htz
PER2	–	rs2304672	c.-12C>G	–	htz
PPARD	CR035869	rs2016520	c.-87C>T	–	htz
PPARG	CM981614	rs1801282	c.34C>G	p.Pro12Ala	htz
SIRT1	–	rs1467568	c.1916-864A>G	–	hmz
TCF7L2	CS065626	rs7903146	c.382-41435C>T	–	wt

[1] The numeric identification associated with each variant is indexed to a reference sequence obtained from Ensembl database (`http://www.ensembl.org/index.html`).
[2] hmz – Homozygosity; htz – Heterozygosity; wt – Wild type

4.2. 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`) and HGMD Professional database 2015.4 database (`http://www.hgmd.org`), accessed in October 2016.

ADRB2, – / rs1042713

The ADRB2 protein is involved in regulating catecholamines (e.g. adrenaline, dopamine) which are important for lipolysis and energy consumption by mobilising energy from adipocytes. The ADRB2 gene mutations are associated with the predisposition to overweight. Studies on the phenotype-genotype association show that GG genotype carriers have a higher predisposition to overweight, greater ease in recovering lost weight and greater difficulty in weight loss. These individuals benefits from reduced fats. This is a common variant in the population which contributes to a cumulative effect [4, 5, 6, 7].
The ADRB2 protein is involved in regulating vasodilation insofar as it induces sodium reabsorption by the kidneys. Studies on the phenotype-genotype association show that GG genotype carriers present an increased sensitivity to sodium, which induces fluid retention. The retention of fluids, mostly water, within fat cells causes swelling and the attendant weight gain. This is a common variant in the population which contributes to a cumulative effect [4, 5, 6, 7].

AHR, – / rs4410790

The AHR enzyme regulates the activity of the CYP1A1-CYP1A2 genes associated with caffeine metabolism. Meta-analysis studies indicate that genetic mutations that increase the activity of the AHR gene are likely to be associated with increased levels of caffeine metabolism. C allele carriers tend to consume more caffeine [8, 9, 10, 11, 12, 13].

AHR, – / rs6968865

The AHR enzyme regulates the activity of the CYP1A1-CYP1A2 genes associated with caffeine metabolism. Meta-analysis studies indicate that genetic mutations that increase the activity of the AHR gene are likely to be associated with increased levels of caffeine metabolism. T allele carriers tend to consume more caffeine [8, 9, 10, 11, 12, 13].

ALPL, – / rs4654748

The ALPL protein regulates the vitamin B6 catabolism process. Meta-analysis studies indicate that C allele carriers have lower levels of vitamin B6. Vitamin B6 is involved in the synthesis of tryptophan and its conversion into niacin, in the production of epinephrine and serotonin, among other neurotransmitters, and in glycogen breakdown [13].

APOA1, CR900263 / rs670

The APOA1 apolipoprotein is the main protein component of the high-density lipoprotein (HDL) in the plasma. The APOA1 protein is synthesised in the liver and 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. Studies on the phenotype-genotype association show that genetic mutations in this gene induce abdominal fat build-up and the resistance to insulin, with the most significant impact deriving from saturated fat intake [14, 15, 16].

APOA5, CR033141 / rs662799

The APOA5 protein regulates lipid metabolism and plasma triglycerides levels. Genotype-phenotype association studies indicate that individuals harbouring the TT allele have a predisposition to body fat accumulation, overweight and weight loss difficulty, being the impact more significant with saturated fats intake [17, 18, 19, 20].

APOE, CM860003 / rs7412 + APOE, CM900020 / rs429358

The apolipoprotein APOE plays a role in cholesterol absorption at the intestinal mucosa in response to fat intake. Overall the $\varepsilon 2$ allele is associated with lower values of LDL cholesterol and the $\varepsilon 4$ allele to higher levels of plasma cholesterol. Insofar as a high-fat diet often provides for higher LDL cholesterol levels for $\varepsilon 2$ allele carriers, a nutritional plan with a lower fat content and a higher carbohydrate and fibre content is beneficial. In turn, for $\varepsilon 4$ allele carriers a low-fat nutritional plan is beneficial to reduce LDL cholesterol levels. For $\varepsilon 3$ allele carriers, a fibre-enriched nutritional plan is beneficial [21, 22, 23].

BCMO1, CM091858 / rs7501331 + BCMO1, CM091857 / rs12934922

The BCM01 enzyme converts beta-carotene into vitamin A. This vitamin can be found in two sources: i) in food of animal origin in the form of retinoids (retinol being the active component), and ii) in foods of plant origin as pro-vitamin in the form of carotenoids (e.g. beta-carotene). Studies on the genotype-phenotype association in women have shown that T allele carriers for the rs7501331 variation show a catalytic activity of the BCM01 enzyme reduced by about 32%. In turn, in association with the rs12934922 variation of the same gene, the catalytic activity of the enzyme is reduced by about 69%. These individuals benefit from vitamin A-supplemented foods or from foods of animal origin with retinol. This is fundamental for various functions of the body, particularly vision, bone development, cell growth and repair while maintaining the integrity of the skin and mucous membranes and is very important for the immune system by preventing cellular oxidation [24, 25, 26, 27].

CLCNKA, – / rs848307

The ClC-Ka chloride channel is involved in regulating water homoeostasis and controlling sodium levels in the kidneys. Studies on the phenotype-genotype association show that T allele carriers have the ClC-Ka channel with an increased function, which contributes to increased sensitivity to

sodium and the consequent retention of fluids. The retention of fluids, mostly water, within fat cells causes swelling and the attendant weight gain [28, 29].

CLOCK, CR121503 / rs3749474

The CLOCK protein participatesin the regulation of the circadian rhythm to the extent that it regulates the balance between energy output and fat, carbohydrate and protein metabolism. Studies on the phenotype-genotype association show that there is a change in this balance in T allele carriers. These individuals have a predisposition to changes in sleep rhythm and to higher levels of ghrelin, a hormone which plays an important role in regulating appetite, inducing the sensation of hunger. Compared to CC genotype carriers, they have a predisposition to weight gain, a higher BMI and increased difficulty in losing weight. They benefit from a hypoenergetic diet with decreased fat intake, and a regular sleep rhythm to lose weight [30, 31, 32, 33, 34].

DHCR7, – / rs12785878

The DHCR7 enzyme is involved in the production of cholesterol, a precursor of vitamin D. The GG genotype is associated with increased activity of the DHCR7 enzyme, inhibiting the activation process of vitamin D and making it a mandatory external source nutrient. In turn, clinical studies show that a protein-rich nutritional plan could modulate the function of the DHCR7 gene and, consequently, influence both vitamin D levels and resistance to insulin. Therefore, in a nutritional plan for losing weight, T allele carriers benefit from a protein-enriched diet so as to induce decreased resistance to insulin and the consequent loss of weight [35, 36].

DRD2, CM041241 / rs1800497

The DRD2 protein plays a role in regulating dopamine in the brain, a neurotransmitter involved in food reward and satiety related to food intake. Studies on the phenotype-genotype association show that overweight individuals have a lower ability to signal dopamine and a decreased availability of the D2 receptor of this hormone. A allele carriers have a predisposition to high-palatability food intake (often with high caloric content) in order to activate the brain's reward system. In this context, the likelihood of gaining weight increases [37, 38].

FADS1, CR1510437 / rs174546

The FADS1 protein is involved in the processing of omega-3 and omega-6 polyunsaturated fats. These fats regulate the body's inflammatory response, stimulate brain function and play a key role in the body's growth, development, and repair. They regulate the levels of total cholesterol and LDL (bad cholesterol) promoting their recycling and they promote increased levels of HDL (good cholesterol). The omega-3 and omega-6 fats can be subdivided into the short chain and long chain. Short-chain omega-3 fats, alpha-linoleic acid (ALA), and short-chain omega-6 fats, linoleic acid (LA), are essential to the body and are only acquired from food. Studies on the phenotype-genotype association indicate that T allele carriers have decreased omega-3 and omega-6 levels, benefiting from the intake of foods rich in these fats to raise HDL cholesterol levels.
The main sources of ALA include foods like flaxseed, walnuts, fish oils and fish like salmon. LA is the most common omega-6 fat in plant foods and is found in most vegetable oils. It should be noted that processed foods often contain high levels of long-chain omega-6 fat, arachidonic acid (AA), which may be harmful to the body [13, 39, 40].

FTO, – / rs9939609

The FTO protein plays an important role in regulating body weight, energy consumption, insulin resistance, appetite and the feeling of satiety. Appetite is defined as the need for eating while satiety refers to the state of feeling fully gratified after a meal. Meta-analysis studies indicate that A allele carriers have a predisposition to a higher BMI and waist-hip ratio, especially individuals with sedentary lifestyles. There is a resistance to insulin as well, particularly in individuals who eat excessive fats. For these individuals physical exercise and reducing fat intake are beneficial for losing weight [41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54].

GC, – / rs2282679

The GC protein is the vitamin D receptor. Studies on the genotype-phenotype association indicate that C allele carriers have a lower concentration of circulating vitamin D. 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 is 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 [36, 55].

GRK4, CM025430 / rs1024323 + GRK4, CM025429 / rs2960306

The GRK4 protein plays a role in the desensitization of type I (DI) dopamine receptors. Studies on the phenotype-genotype association show that T allele carriers present decreased activity of DI receptors in the proximal renal tubule cells, which results in lower sodium elimination, and this, in turn, contributes to increased sensitivity to salt and the consequent retention of fluids. The retention of fluids, mostly water, within fat cells causes swelling and the attendant weight gain [56, 57, 58, 59].

IRS1, CR096329 / rs2943641

The IRS1 protein contributes to regulating to insulin resistance. Studies on the phenotype-genotype association show that CC genotype carriers benefit from a carbohydrate-enriched and low-fat nutritional plan insofar as it decreases resistance to insulin, with the consequent loss of weight. This is a common variant in the population which contributes to a cumulative effect [60, 61].

LIPC, CR002154 / rs2070895
The LIPC protein is involved in the regulation of triglyceride and LDL and HDL cholesterol levels circulating in the plasma. A allele carriers are advised to reduce the intake of saturated fat and carbohydrates to avoid increased triglyceride levels [62, 63].

LIPC, CR971949 / rs1800588
The LIPC protein is involved in the regulation of triglyceride and LDL and HDL cholesterol levels circulating in the plasma. Meta-analysis studies indicate that T allele carriers have a predisposition to higher triglyceride and LDL cholesterol (bad cholesterol) levels and lower HDL (good cholesterol) levels. TT genotype carriers benefit from a reduced fat and carbohydrates intake and from physical exercise in reducing LDL cholesterol and BMI and decreasing insulin resistance [63, 64, 65].

LPL, CS890131 / rs285
The LPL protein regulates the metabolism and transport of lipids hence regulating the triglycerides level in the blood plasma. The genotypes causing a lower activity of this protein are associated with higher triglyceride and LDL cholesterol (bad cholesterol) levels. Studies on the phenotype-genotype association show that TT genotype carriers have a predisposition to higher triglyceride and LDL cholesterol (bad cholesterol) levels and lower HDL (good cholesterol) levels. These individuals benefit from a decreased intake of saturated, hydrogenated and trans-fats in reducing triglyceride levels [63, 64, 66, 67, 68, 69].

LPL, CS931395 / rs320
The LPL protein regulates fat metabolism and transport and also the level of triglycerides circulating in the plasma. The genotypes causing a lower activity of this protein are associated with higher triglyceride and LDL cholesterol (bad cholesterol) levels. Studies on the phenotype-genotype association show that T allele carriers have a predisposition to higher triglyceride and LDL cholesterol (bad cholesterol) levels and lower HDL (good cholesterol) levels. These individuals benefit from a decreased intake of saturated, hydrogenated and trans-fats in reducing triglyceride levels [63, 64, 66, 67, 68, 69].

LYPLAL1, – / rs2605100
The LYPAL1 protein promotes the metabolism of fatty acids. Meta-analysis studies indicate that G allele carriers have a predisposition to weight gain, abdominal fat build-up and high BMI and waist-hip ratio values. Since this is a common variant in the Caucasian population, several studies have been conducted on how genetics can be compensated, and it has been demonstrated that they benefit from physical exercise for losing weight [70, 71, 72, 73, 74, 75].

MC4R, – / rs12970134 + MC4R, – / rs11152221 + MC4R, – / rs17782313 + MC4R, – / rs17700633
The MC4R protein plays an important role in regulating body weight, energy consumption, appetite and the feeling of satiety. Meta-analysis studies indicate that loss-of-function genetic mutations are associated with the predisposition to weight gain. GT genotype carriers tend to display a behaviour geared towards high-palatability food intake (often with high caloric content), and eating larger portions and more frequently. They also show effects on the regulation of energy homoeostasis. Consequently, a predisposition to overweight and a higher BMI are observed. These individuals benefit from a low-calorie nutritional plan for losing weigh [76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88].

MMAB, – / rs2241201
The MMAB protein is involved in the regulation of circulating cholesterol levels. Studies on the phenotype-genotype association show that GG genotype carriers have increased levels of LDL (bad cholesterol) and decreased levels of HDL (good cholesterol) mainly due to excess carbohydrate intake [89].

MTHFR, CM981315 / rs1801131 + MTHFR, CM950819 / rs1801133
The MTHFR enzyme is involved in the metabolism of the homocysteine amino acid into methionine. Meta-analysis studies suggest that a decreased activity of this enzyme is observed in carriers of the C677T or 677TT genotypes of the MTHFR gene, with a consequent increase in homocysteine levels, which could have an adverse effect on the body's toxicity. Moreover, the combination of the 677CT or 677TT genotypes with the 1298CC genotype of the same gene has a cumulative effect on the levels of homocysteine. In turn, the build-up of homocysteine is exacerbated by a diet low in vitamins B12 and B6. Therefore, for carriers of these genotypes, it is beneficial to include foods that are rich in these vitamins in their diet plans. Vitamin B12 is essential to cellular metabolism, especially of the gastrointestinal tract, bone marrow and nerve tissue, as well as for the synthesis of nucleic acids. It is also involved in the metabolism of carbohydrates and fats. Vitamin B6 is involved in the synthesis of tryptophan and its conversion into niacin, in the production of epinephrine and serotonin, among other neurotransmitters, and in the breakdown of glycogen [90, 91, 92].

NR1D1, – / rs2314339
The NR1D1 protein is involved in the regulation of the circadian rhythm controlling the expression of the CLOCK and CRY1 proteins that regulate the balance between energy output and fat, carbohydrate and protein metabolism. Studies on the phenotype-genotype association show that in A allele carriers there is a lower predisposition to building up abdominal fat [93, 94, 95, 96].

PCSK1, CM083013 / rs6232 + PCSK1, CM132638 / rs6234 + PCSK1, CM1311914 / rs6235
The PCSK1 enzyme regulates the homoeostasis of hormones involved in appetite control, namely insulin (glucose metabolism) and proopiomelanocortin (satiety control). Studies on the phenotype-genotype association show that GG genotype carriers present an enzyme loss of function

which could be associated with excess weight and a higher BMI [97, 98, 99, 100, 101].

PER2, – / rs2304672
The PER2 protein is involved in the regulation of the circadian rhythm to the extent that it regulates the balance between energy output and fat, carbohydrate and protein metabolism. Studies on the phenotype-genotype association show that G allele carriers have a predisposition to building up abdominal fat and to higher circulating fatty acids in the plasma. There is also a predisposition to stress behaviours associated with the adaptation to a hypoenergetic diet, namely to snack frequently and even to give up the diet [93, 102, 103, 104].

PPARD, CR035869 / rs2016520
The PPARD protein participates in the metabolism and absorption of fats. Meta-analysis studies indicate that G allele carriers have a predisposition to losing weight more easily and benefit from physical exercise [105, 106, 107, 108].

PPARG, CM981614 / rs1801282
The PPARG protein participates in fat metabolism and adipogenesis, hence in regulating fat storage. Meta-analysis studies indicate that GG genotype carriers benefit from a hypoenergetic diet associated with physical exercise for losing weight. [107, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118].

TCF7L2, CS065626 / rs7903146
The TCF7L2 protein participates in regulating glucose levels and fat metabolism. Studies on the phenotype-genotype association show that CC genotype carriers benefit from a fibre-enriched nutritional plan for maintaining lost weight [99, 119, 120, 121, 122].

4.3. KEYWORDS AND CONCEPTS

DNA: Molecule which determines each individual's genetic profile.
Gene: DNA segment which encodes information on a characteristic (e.g. weight) or a specific function (e.g. fat metabolism).
Fat metabolism: Fat processing along the digestive system, from ingestion, digestion, absorption, storage and use.
Carbohydrates metabolism: Carbohydrate processing along the digestive system, from ingestion, digestion, absorption, storage and use
Genetic profile: Genetic information on each individual obtained from the analysis of DNA and its genetic variants.
Genetic variant: Variation of a DNA segment which could cause a change in the gene's function.

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