Fagron genomics

Fagron NutriGen™ Introduction Document

12 December 2019

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Fagron BV
Lichtenauerlaan 182
3062 Rotterdam
The Netherlands

T +31 88 33 11 210
F +31 88 33 11 210

www.fagron.com

Introduction

The **Fagron NutriGen™ Introduction document** contains a general introduction about the test, genetic variations analyzed, involved pathways and information about the suggested treatment options.

A genetic test is used to:

- Diagnose and predict/prevent diseases;
- Analyze specific metabolic characteristics of the patient;
- Understand which APIs will be more effective in a specific patient;
- Optimize the dose of APIs to improve the effectiveness of treatments and reduce side effects.

Fagron Genomics is a (laboratory services) company, focused on providing specific pharmacogenetics and diagnostic molecular analysis. **Fagron NutriGen™** is a genetic test developed by Fagron Genomics for personalized weight loss planning.

Global weight loss services market size is expected to reach $21.1 billion by 2025 expanding at a CAGR of 8.4% (Source: Grand View Research, Inc). Therefore, even though Fagron NutriGen™ analyzes more than just genes directly related with weight loss, it is mainly focused on weight loss and slimming, as this is the biggest market within the nutritional landscape, being highly related with Fagron's API/DCIs portfolio

Fagron NutriGen™ will be available in two different versions sold via different types of healthcare professionals, **Fagron NutriGen™** and **Fagron NutriGen™ Medical**, offering different solutions based on the patient's genetic background and lifestyle.

For more information regarding Fagron NutriGen™ Medical please be referred to the **Fagron NutriGen™ Medical Introduction document**.

For more information about basic genetics, genetic variations, analysis of genetic variations and the genotyping process, please be referred to Fagron Genomics Introduction document. All available materials can be found online on the concept page within the Innovation Platform.

If information is missing, please contact info@fagrongenomics.com.

General information

All information needed to build a human is anchored in our DNA (deoxyribonucleic acid). DNA contains 4 building blocks known as bases: adenine (A), guanine (G), cytosine (C), and thymine (T). More than 99% of these bases is similar in each human and 1% is the responsible part for causing unique human variations.

Genes are parts of the DNA, containing the information needed to produce proteins in the human body (figure 1). The production of these proteins regulates every characteristic in the body: hair and eyes color, predisposition to diseases, activity of the enzymes.

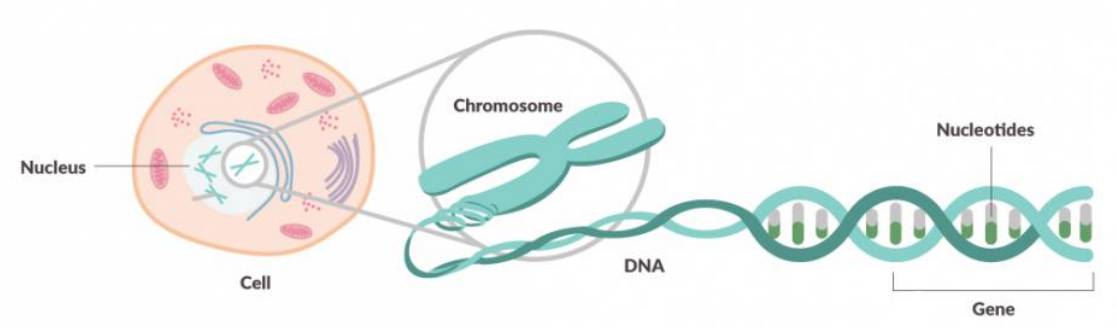

Figure 1 - Gene representation in the DNA strand.

In normal conditions, every person has two copies of each gene, one inherited from each parent. Most genes are the same in all people. As mentioned, less than 1% of the total DNA is slightly different between people. Alleles are variations of the same gene with small differences in their sequence of DNA bases. These small differences contribute to each person's unique physical features.

Genes are identified through a unique name and symbol that is usually related to the information that it codifies. For example, a gene that has been associated with cystic fibrosis is called the cystic fibrosis transmembrane conductance regulator and its symbol is CFTR.

The genome (the genetic material of an organism) contains inherited genetic variations. These genetic variations are caused by genetic mutations, by which the coding DNA was permanently changed.

Single nucleotide polymorphisms (SNPs) are the most frequent type of DNA variation found in humans. Each SNP represents a difference in a single nucleotide. For example, in a SNP variation the nucleotide adenine (A) might be replaced with the nucleotide guanine (G).

SNPs occur normally throughout a person's DNA. Most commonly, these variations are found in the DNA between genes. When a SNP occurs within a gene, it can have a more direct interference, affecting the gene's function.

Most SNPs have no effect on health or development. Some of these genetic differences, however, have proven to be of high importance in the study of human health. It has been reported that some SNPs may help to predict an individual's response to certain drugs, the susceptibility to environmental factors and the risk of developing particular diseases.

Genotyping searches for specific locations in the DNA and identify variations known as single-nucleotide polymorphisms (SNPs). By selecting these specific locations, it is possible to focus on the variations that are known to be associated with certain health conditions and drugs metabolism.

For more detailed information about genetics, please be referred to the Fagron Genomics Introduction document on the Innovation Platform.

Weight management

The regulation of body weight is complex and dependent on several factors: energy intake and expenditure, physiological parameters, hormones, stress, among others [1].

For body weight maintenance, a balanced energy homeostasis is necessary. Therefore, lifestyle factors leading to a positive or negative energy balance can result in weight gain or loss, respectively. Lifestyle changes based on increasing physical activity and reducing energy intake are the basic therapeutic approaches for weight loss and weight maintenance [1,2].

Individual metabolic responses

In the last few years, studies showed that individuals respond differently to predefined meal challenges [1].

In the Human Metabolome (HuMet) study, 15 males were investigated for metabolic responses to specific challenges [3]. After a fasting period of 36 hours, participants underwent an oral glucose and lipid test, liquid test meals, and exercises, and they were exposed to cold. Due to deep phenotyping and the healthy nature of the participants, Krug et al. could show large variability in metabolic responses between phenotypically similar individuals after challenges by test meals or exercise programs. Another study investigated the metabolic response to identical meals in 800 participants [4]. In this Israeli study, blood glucose levels of the participants, aged 18–70 years, were analyzed during a standardized meal resulting likewise in a large inter-individual variability. The average postprandial glycemic response (PPGR) differed largely between individuals (e.g., bread: 44 ± 31 mg/dL·h (mean ± standard deviation).

This inter-individual difference of glycemic response validated the fact that the same meal may lead to another or even the opposite metabolic response when comparing different individuals [1,4].

Personalized nutrition

Nizel et al. defined personalised nutrition with a personal consultation of patients in order to achieve an improvement in dietary habits [5]. In 2013, Stewart-Knox et al. described a personalised nutrition as a healthy dietary recommendation tailored to the health status, lifestyle, and/or the genetic information of an individual [6].

Furthermore, personalised nutrition is directly related to nutrigenetics [1]. However, direct translation from a genetic profile to the phenotypic characterisation of a person is of a complex nature. Therefore, the concept of personalised dietary recommendations has to follow a multi-dimensional approach considering, e.g., social, lifestyle, genetic, and metabolic parameters.

Nutrigenetics is an aspect of personalised nutrition that studies the different phenotypic responses (ie, weight, blood pressure, plasma cholesterol, or glucose levels) to a specific diet (ie, low fat or Mediterranean diets), depending on the genotype of the individual [22]. Nutrigenomics involves the characterisation of all gene products affected by nutrients and their metabolic consequences [22].

The major aim of a personalised nutrition should be a dietary recommendation adjusted to an individual's requirements by including dietary recommendations based on phenotype and genotype to maintain the health status and to counteract risks for diseases or their comorbidities [7]. In a double-blinded randomised controlled trial, shortand long-term effects on dietary intake of a gene-based personalised nutrition were investigated [8].

In this study, it was observed that there was no significant difference in dietary intake after three months of intervention between the intervention group receiving information on their genetic background and, additionally, a corresponding gene-based dietary recommendation and the control group. After 12 months, some significant improvements in dietary intake such as a reduced intake of sodium in the personalised nutrition group were observed, suggesting a long-term change in dietary habits [8].

Personalisation of dietary advice assisted and/or motivated consumers to eat a healthier diet and follow a healthier lifestyle (in comparison with "impersonal" (conventional) dietary advice). Personalisation based on analysis of current diet was more effective in assisting and/or motivating study participants to make, and to sustain, appropriate healthy changes to their usual (habitual) diet and lifestyle [8,22].

Fagron NutriGen™

Fagron NutriGen™ analyzes 3 polymorphisms within 128 DNA mutations (SNPs) resulting in 384 (3x128) genetic variations on the most relevant genes related to different metabolic pathways involved in weight loss and nutritional needs. All SNPs used in Fagron NutriGen™ have been scientifically validated from population studies, presenting a significative global incidence.

The genetic variations analyzed with Fagron NutriGen™ are associated with different main categories:

- Genetic causes of overweight and obesity.
- Macronutrients metabolism.
- Micronutrients metabolism.
- Hormonal genetic profile.
- Weight loss strategies.
- Inflammation genetic profile.
- Intolerances/sensitivities.
- Detoxification capacities.
- Nutritional supplements – only available in Fagron NutriGen™ medical.
- Obesity/overweight pharmacogenetics – only available in Fagron NutriGen™ Medical.

1. Genetic causes of overweight and obesity

The first category analyzed is related to key genetic predisposition genes linked to obesity and weight gain.

Obesity is influenced by the interplay between external factors and is highly linked to individual genetics. Genetics highly determines how the body processes and metabolizes fats and/or nutrients, and therefore, understanding our own genetics is a must in order to understand the best strategy for weight loss.

1.1. Morphological genetics in overweight predisposition

Overweight predisposition by morphological genetics is evaluated by analysing the patient's predisposition of reduced resting metabolic rate risk, increased BMI, genetic overweight risk and weight recovery after diet intervention.

Sub-categories	Genes analysed	Insights
Reduced resting metabolic rate risk	LEPR	Predisposition to burn more or less calories while resting
Increased BMI	MC4R SH2B1	Predisposition to increased BMI, waist circumference and insulin resistance
Genetic overweight risk	FTO MC4R SH2B1	Inherited genetic factors that lead to overweight and obesity
Weight recovery after diet intervention	ACSL5 ADIPOQ	Predisposition to regain weight after diet interventions (rebound effect)

1.2. Behavioural genetics in food intake

The behavioural genetics in food intake are related to the will of snacking, satiety dysregulation and the way anxiety can influence appetite.

Sub-categories	Genes analysed	Insights
Snacking	LEPR SH2B1	Body requirements of snacking between meals
Satiety dysregulation	LEP FTO COMT	Perception of feeling full and satisfied after food intake
Appetite and anxiety	MC4R FTO LEP SH2B1	Uncontrolled food intake behaviour that forces the body to eat more quantity and faster

2. Macronutrients metabolism

Macronutrients can be defined as the chemical compounds that humans consume in the largest quantities and provide bulk energy - carbohydrates, proteins, and fats [9].

The macronutrients metabolism differs among individuals. This category analyzes in depth how exactly the human body interact with the macronutrients.

2.1. Fat metabolism

Fat consist of a glycerin molecule with three fatty acids attached. Fats are needed for construction and maintenance of cell membranes, to maintain a stable body temperature and to sustain the health of skin and hair. Because the body does not manufacture certain fatty acids (termed essential fatty acids), they must be obtained through one's diet [9, 10].

Sub-categories	Genes analysed	Insights
Fat burning dysregulation	APOA5 PPAR-γ	Inherited modulators of the body capacity of burning fat.
Benefits from a high-MUFA diet	ADIPOQ	Capacity to metabolize monounsaturated fatty acids (MUFA).
Benefits from a high-PUFA diet	FADS1 PPAR-γ	Capacity to metabolize polyunsaturated fatty acids (PUFA) and improve the lipidic profile (decreased LDL-levels) with PUFA intake.

2.2. Carbohydrates metabolism

Carbohydrates are compounds made up of types of sugar, that are classified according to their number of sugar units: monosaccharides (such as glucose and fructose), disaccharides (such as sucrose and lactose), oligosaccharides, and polysaccharides (such as starch, glycogen and cellulose) [9, 10].

Sub-categories	Genes analysed	Insights
Carbohydrates and cholesterol dysregulation	NMAB KCTD10	Effect of carbohydrates intake in the cholesterol levels regulation.
Starch digestion	AMY1-AMY2 AMY1	Capacity to breakdown the starch from food.
Carbohydrate sensitivity	FABP2	Predisposition to increase weight by carbohydrates intake.

2.3. Lipid metabolism

Two types of lipoproteins carry cholesterol to and from cells: low-density lipoprotein (LDL) and high-density lipoprotein (HDL).

LDL cholesterol is considered the “bad” cholesterol, as it contributes to atherosclerosis, increasing the risk for heart attack and stroke.

HDL cholesterol can be thought of as the “good” cholesterol, meaning that higher levels can actually be better for the individual. A healthy HDL cholesterol level may protect against heart attack and stroke. Studies show that low levels of HDL cholesterol increase the risk of heart disease.

Triglycerides are the most common type of fat in the body and store excess energy from the diet. A high triglyceride level combined with high LDL (bad) cholesterol or low HDL (good) cholesterol is linked with fatty build-ups within the artery walls, which increases the risk of heart attack and stroke.

Sub-categories	Genes analysed	Insights
HDL levels	APOA5 CETP TCF7L2	Dysregulation of the HDL levels
LDL levels	ABCG8 APOB CELSR2 HNF1A LDLR PPAR-γ	Dysregulation of the LDL levels
LDL oxidation	APOB	Cardiovascular risk increases due to LDL oxidation levels
Triglycerides levels	CDKN2A/B PPAR-γ	Triglycerides levels increase
Triglycerides/HDL ratio	HMGCR	Triglycerides/HDL-C ratio imbalance

2.4. Glucose metabolism

Glucose is the major circulating sugar in mammals, being a primary energetic substrate. Certain tissues such as the brain, red blood cells, and kidney medulla rely predominately on glucose to meet their energetic needs, in different circumstances [11].

However, excess circulating glucose can damage cells and organ systems. Hyperglycemia, which defines type 2 diabetes, causes microvascular disease including retinopathy, nephropathy and ophthalmopathy [12].

Since the discovery that insulin deficiency causes diabetes mellitus, the pathogenesis of diabetes is commonly framed in terms of this hormone’s actions to regulate glycemia. Insulin potently stimulates glucose uptake in

skeletal muscle and adipose tissue while inhibiting adipose tissue lipolysis and stimulating adipose lipogenesis and fat deposition [13, 14]. In the liver, insulin suppresses glucose production and stimulates lipogenesis [11].

In the obese, the hyperinsulinemia condition that commonly precedes development of overt hyperglycemia and type 2 diabetes, lipogenesis is increased consistent with increased insulin signaling in the liver. However, glucose production is increased to the degree of hyperinsulinemia, with potential progression to type 2 diabetes [11-15].

Sub-categories	Genes analysed	Insights
Fasting blood sugar	GHSR PLIN1	Tendency to high or low glucose levels in plasma after fasting
Diabetes type 2 risk	CDKAL1 CDKN2A/B FTO KCNQ1 MC4R PLIN1 PPAR-γ TCF7L2	Inherited diabetes type 2 risk
Insulin resistance	ADIPOQ FTO PPAR-γ TCF7L2	Risk of inherited insulin resistance profile

3. Micronutrients metabolism

Micronutrients are essential elements required in small quantities, in order to orchestrate a range of physiological functions. Required micronutrients are vitamins and dietary minerals, in amounts generally less than 100 milligrams per day, whereas macronutrients are required in gram quantities daily [16].

Sub-categories	Genes analysed	Insights
Calcium levels	CASR CYP24A1 GCKR	Tendency for high/low calcium levels
Calcium absorption	CYP2R1 GC	Risk of calcium malabsorption by lack of Vitamin D
Iron levels	TF TMPRSS6	Risk of low iron transference into the body
Iron overload risk	HFE	Tendency to iron overload on high intake.
Magnesium levels	MUC1 TRPM6	Inherited risk of low magnesium plasma levels
Sodium sensitivity	ACE	Inherited risk of dietary salt-induced high blood pressure.
Selenium levels	AGA SLC39A11	Tendency to high/low selenium serum levels
Vitamin A deficiency risk	BCMO1	Tendency to vitamin A deficiency
Vitamin B6 deficiency risk	NBPF3	Inherited risk of vitamin B6 metabolism deficiency or low plasma levels.
Vitamin B12 deficiency risk	FUT2	Inherited risk of vitamin B12 metabolism deficiency or low plasma levels.
Vitamin B9 (folate) deficiency risk	MTHFR	Inherited risk of vitamin B9 (folate) metabolism deficiency or low plasma levels.
Vitamin C deficiency risk	SLC23A1 SLC23A2	Inherited risk of vitamin C metabolism deficiency or low plasma levels.
Vitamin D deficiency risk	CYP2R1 GC NADSYN1	Inherited risk of vitamin D metabolism deficiency or low plasma levels.
Vitamin E deficiency risk	APOA5 INTERGENIC TPPA	Inherited risk of vitamin E metabolism deficiency or low plasma levels.

4. Hormonal genetic profile

As mentioned on the beginning of this document, there are several hormones involved in weight management.

Among these, leptin is a satiety hormone released by the adipose tissue, that regulates the neuropeptide expression in the hypothalamus [2]. Leptin deficiency can lead to extreme obesity. Another hormone related to satiety is ghrelin, secreted in the gastrointestinal tract after energy intake, being involved in glucose and lipid metabolism[1,2].
A reduced level of adiponectin is associated with impaired fasting glucose, leading to type-2 diabetes development, metabolic abnormalities, coronary artery calcification, and stroke [1,2].

There are many other hormones involved in the regulation of hunger and satiety. Fagron NutriGen™ analyzes the following hormones: adiponectin, apelin, ghrelin, leptin, omentin, resistin, vaspin and visfatin.

Sub-categories	Genes analysed	Insights
Adiponectin	ADIPOQ	Inherited hormonal disbalance risk
Resistin	RETN	
Leptin	LEP LEP-R	
Visfatin	NAMPT	
Apelin	APLN APLNR	
Vaspin	SERPINA12	
Omentin	ITLN1	
Ghrelin	GHRL	

5. Weight loss strategies

Fagron NutriGen™ analyzes how efficient physical exercise will be on a weight loss plan, as well as which type of diet will work better for a specific individual, based on genetics.

5.1. Exercise efficacy

Sub-categories	Genes analysed	Insights
Slimming through exercise	FTO LEP LIPC MATK	Inherited genetics related to the expected efficacy of the exercise in the fat reduction
Aerobic exercise for HDL increasing	LIPC PPARD	Inherited genetics related to the expected efficacy of the exercise in the cholesterol regulation

5.2. Response to diet type

Sub-categories	Genes analysed	Insights
Low-fat diet	APOA2 APOA5 FTO GHSR PPAR-γ SH2B1 TCF7L2	Inherited genetics related to the expected efficacy of low-fat diets
Low-carbohydrates diet	AGTR2 CETP GAL GYS2 LIPF	Inherited genetics related to the expected efficacy of low-carbohydrates diets
Low-calories diet	AGTR2 CETP GAL GYS2 LIPF	Inherited genetics related to the expected efficacy of low-calories diets

6. Inflammation genetic profile

The excess of macronutrients in the adipose tissues stimulates them to release inflammatory mediators such as tumor necrosis factor α and interleukin 6, and reduces the production of adiponectin, predisposing to a pro-inflammatory state and oxidative stress [17].
As a risk factor, inflammation is an imbedded mechanism of developed cardiovascular diseases including coagulation, atherosclerosis, metabolic syndrome, insulin resistance, and diabetes mellitus. It is also associated with development of non-cardiovascular diseases such as psoriasis, depression, cancer, and renal diseases [17, 18].
Finally, managing obesity can help reduce the risks of cardiovascular diseases and poor outcome via inhibiting inflammatory mechanisms [17].

Sub-categories	Genes analysed	Insights
TNF-a levels	TNF	Inherited risk of increased TNF-a levels (pro-inflammatory)
IL6 levels	IL6	Inherited risk of increased IL6 levels (pro-inflammatory)
IL10 levels	IL10	Inherited risk of decreased IL10 levels (anti-inflammatory)

7. Intolerances and sensitivities

Food intolerance is a detrimental reaction, often delayed, to a food, beverage, food additive, or compound found in foods that produces symptoms in one or more body organs and systems, but generally refers to reactions other than food allergy. Food hypersensitivity is used to refer broadly to both food intolerances and food allergies [19].

Food intolerances can be classified according to their mechanism. Intolerance can result from the absence of specific chemicals or enzymes needed to digest a food substance, as in hereditary fructose intolerance. It may be a result of an abnormality in the body's ability to absorb nutrients, as occurs in fructose malabsorption. Food intolerance reactions can occur to naturally occurring chemicals in foods, as in salicylate sensitivity [19].

Sub-categories	Genes analysed	Insights
Fructose intolerance	ALDOB	Inherited status for fructose intolerance
Lactose intolerance	MCM6	Inherited status for lactose intolerance
Gluten intolerance	HLA	Inherited status for gluten intolerance
Salt sensitivity	ACE	Inherited status for salt as an inducer of high blood pressure
Caffeine metabolism	CYP1A2	Inherited status for caffeine metabolism (slow or fast metabolization)

8. Detox capacities

Detoxification (detox for short) is the physiological or medicinal removal of toxic substances from the human body, which is mainly carried out by the liver. Additionally, it can refer to the period of withdrawal during which an organism returns to homeostasis after long-term use of an addictive substance [20].

The liver plays a crucial role in protecting the organism from potentially toxic chemicals through its capacity to convert lipophiles into more water-soluble metabolites which can be efficiently eliminated from the body via the urine [21].

Sub-categories	Genes analysed	Insights
Phase I Detoxification	CYP1A1 CYP1B1	Inherited mutations in the first detoxification steps: toxin breakdown in liver
Phase II Detoxification	GSTP1	Inherited mutations in the first detoxification steps: toxin breakdown in liver
Antioxidant capacity	COMT GPx1P1 NQO1 SOD2 SULT1A1*1/2	Inherited mutations in the genes involved in the body antioxidant reactions

9. Food supplements

According to the analysis of the genetic characteristics and lifestyle, Fagron NutriGen™ provides a suggestion of food supplements that might be beneficial to the patient. The selection of the food supplements recommended is complex, being performed by the algorithm and depending on several factors.
The list of possible supplements that can be suggested on the report is present below. For further information please be referred to the Fagron NutriGen™ Literature Review – Supplements document, available on the Innovation Platform.

- Affron® (Crocus sativus L.)
- Allyl ABG™ (Aged Black Garlic extract)
- Astragalus
- CactiX® (Opuntia ficus-indica)
- Caffeine
- Carob Active™ (Ceratonia siliqua L. extract)
- Cinnamon
- Citrimax® (Garcinia cambogia-derived (-)-hydroxycitric acid)
- CitrusiM® (Citrus sinensis L. Osbeck)
- Conjugated Linoleic Acid
- Curcumin + Piperine
- DHA
- Ginger (Zingiber officinale)
- Green Tea
- GreenSelect®
- Korean Ginseng (Panax ginseng)
- Melatonin
- Olive leaf extract
- PomAge™ (Dry extract of Malus pumila - min 98% of phloretin)
- Resveratrol
- Slimaluma® (Caralluma fimbriata extract)

- Vitamin D3

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