DETOXgenes

Xenobiotics detoxification

Surname:	Ejemplo	**Reception date:**	DD/MM/YYYY
Name:	Paciente Modelo	**Validation date:**	DD/MM/YYYY
Birth Date:	DD/MM/YYYY	**Sample Type:**	–
ID nr:	–	**Physician:**	–
Gender: Male		**Physician:**	–
Order:	–	**Validation by:**	–

Hepatic detoxification

The processes of hepatic metabolism and elimination are mechanisms by which the body gets rid of substances that could potentially interfere with the proper function of the body, and impair long-term health.

Xenobiotics

It is any chemical substance that is not produced by our body, that is, that comes from outside. We get rid of these xenobiotics through urine, bile, feces, etc. However, it is often necessary for the body to previously carry out chemical transformations in these substances.

Hepatic metabolism

The aim of these chemical reactions is to inactivate the molecules and make them less harmful and more easily eliminated. Although detoxification can take place in different organs, the main organ responsable for this process is the liver. Hepatic metabolism reactions can be classified between those of Phase I and Phase II.

Phase I detoxification

Phase I consists of reactions that add a functional group to the molecule. That can make it more hydrosoluble, and easier to eliminate, but it can also form compounds even more reactive than the original molecule, and therefore more dangerous. However, these groups are quickly neutralized in Phase II reactions.

Phase II detoxification

Phase II is catalyzed by different families of enzymes, each of them specialized in conjugating a small molecule, usually polar, to the functional groups of the xenobiotic, either preexisting or generated during the Phase I metabolism. This union tends to neutralize the xenobiotic and facilitate its elimination.

Impact on health

Having a deficient elimination capacity, due to a lack of activity or an imbalance between Phase I and Phase II metabolism (that is, activated compounds are generated faster than they can be eliminated), may facilitate the accumulation of these xenobiotics in the body that can have, in the long term, a negative impact on health.

Detoxification and genetics

These detoxification processes can be affected by the person's genetics. There are genetic variants in the genes that encode metabolism enzymes, and that make their activity higher or lower than normal. These differences may indicate a worse capacity to detoxify certain substances.

Selected genetic polymorphisms

The genetic variants studied for this report are shown below.

According to the obtained results in the analysis, nutritional and lifestyle recommendations will be adapted to your profile. Also, in *Complementary informtation* you will find additional information about them.

Before taking any **nutritional supplement along with medication**, you must **discuss it with your health care professional**, in order to avoid adverse drug events.

Gene	Rs identifier	Polymorphism	Results
ADH1B	rs1229984	His48Arg	CC
ALDH2	rs671	42076G›A	GG
APOE	rs7412	Cys158Arg	CC
APOE	rs429358	Cys112Arg	TT
CAT	rs1001179	-262C›T	CC
COMT	rs4680	Val158Met	Val/Met
CYP1A1	rs4646903	*2	wt/*2
CYP1A2	rs2069514	*1C	wt/wt
CYP1A2	rs762551	*1F	*1F/*1F
CYP1B1	rs1056836	*3	wt/*3
EPHX1	rs1051740	Tyr113His	CC
EPHX1	rs2234922	His139Arg	AA
GPX	rs1050450	599C›T	CC
GSTM1	GSTM1_CNV	*0	1/1
GSTM3	rs7483	3209G›A	CT
GSTP1	rs1695	Ile105Val	Ile/Ile
GSTT1	GSTT1_CNV	*0	1/1
MTHFR	rs1801133	677C›T	GA
MTHFR	rs1801131	1298A›C	TT
NAT2	rs1801280	*5A	wt/wt
NAT2	rs1799931	*7A/B	wt/wt
NAT2	rs1799930	*6A	wt/wt
NFE2L2	rs6721961	-617T›G	GG
NQO1	rs1800566	C609T	GA

Gene	Rs identifier	Polymorphism	Results
SOD2	rs4880	Ala16Val	AG
SULT1A1	rs9282861	*2	wt/wt

| Risk	Normal	Protector

Hepatic detoxification pathways

Hepatic metabolism is a process by which the body facilitates the **clearance of substances** such as **drugs** or other **xenobiotics**. In general terms the process consists of making the **molecules more soluble in water** to improve their excretion. There is a small group of enzymes responsible for the metabolism of these substances.

The process of liver detoxification takes place in **two phases**. The first aims to modify the xenobiotics by creating **polar groups** to which, in the second, **certain molecules are added** in order to promote their elimination.

Phase I involves oxidation reactions mediated by enzymes of the **cytochrome P450 superfamily (CYP)**. In the next phase, thanks to different enzymes, there are **conjugation** reactions using the polar groups present in the intermediary molecules. The molecules that are conjugated in **phase II** can be **glutathione** or **methyl** groups, for example.

Although on many occasions the liver metabolism inactivates xenobiotics, **not in all cases the product is inactive**. It can generate molecules with **toxic activity** that cause **damage in the body**. For this reason, a **correct balance** between the different detoxification reactions is essential.
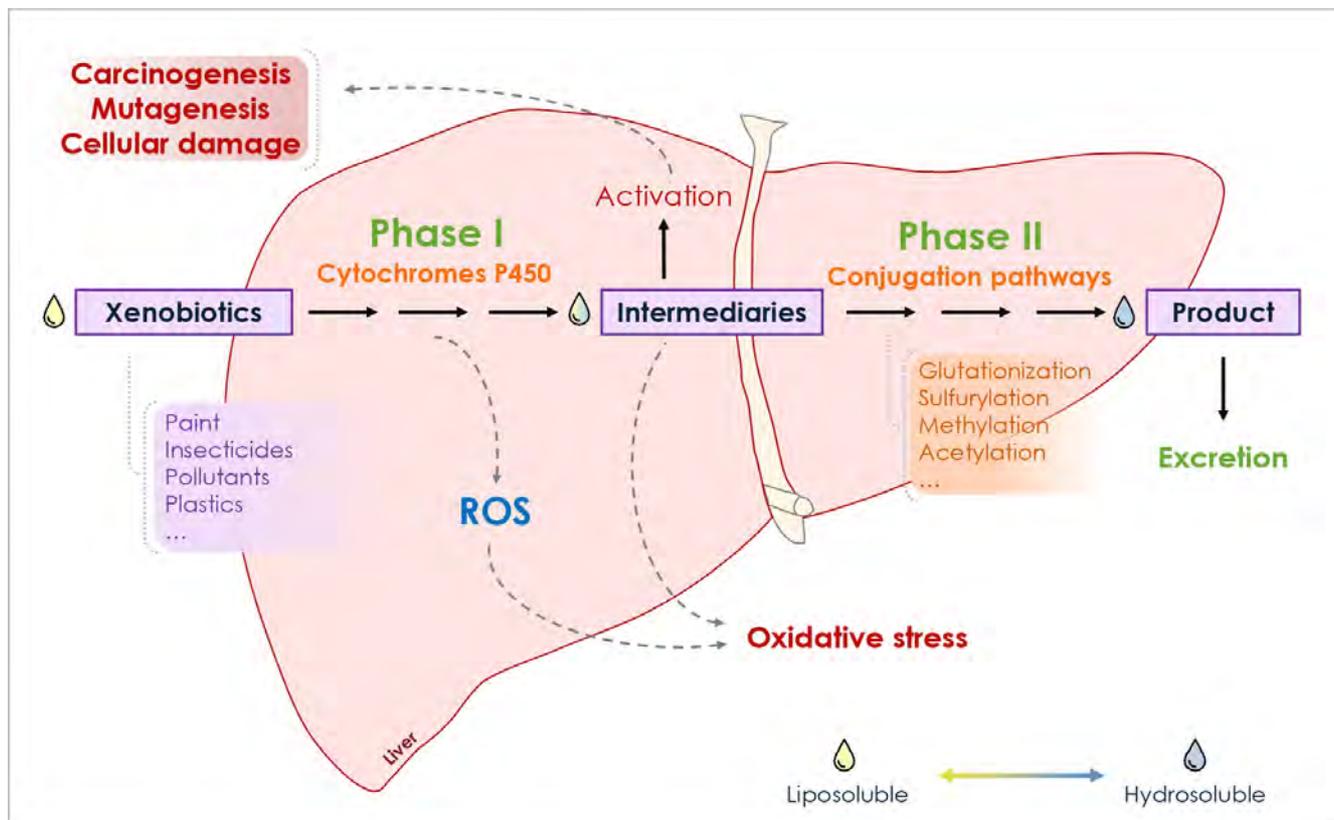
Phase I hepatic detoxification

The detoxification of xenobiotics is carried out in two phases: Phase I and Phase II. **Phase I**, is characterized by oxidation, reduction or hydrolysis reactions. This process can make a substance less aggressive or, that an inert substance becomes a toxic one.

These reactions are catalyzed by the **cytochrome P450 (CYP) family**. CYP1A1, CYP1A2 and CYP1B1 can present polymorphisms that result in an alteration of their activity.

• **CYP1A1** is an enzyme responsible for metabolizing environmental toxins, such as benzopyrenes generated during chemical synthesis processes and polycyclic aromatic compounds contained in tobacco smoke.
•**CYP1A2** is an enzyme involved in the metabolic activation of environmental toxins such as heterocyclic amines or nitroaromatic compounds of tobacco smoke.
•**CYP1B1** is an important enzyme in the metabolism of various xenobiotics and in the synthesis of cholesterol, steroids and other lipids. It also metabolizes estrogens.

Gene	Rs identifier	Polymorphism	Results
CYP1A1	rs4646903	*2	wt/*2
CYP1A2	rs2069514	*1C	wt/wt
CYP1A2	rs762551	*1F	*1F/*1F
CYP1B1	rs1056836	*3	wt/*3

Consequences

The detected genotype for the studied genes is related to an increased hepatic Phase I detoxification enzyme activity.

Recommendations

The most important thing in Phase I is to avoid its substrates and especially any inductors that activate it. Therefore it is recommended to:

• **Avoid benzopyrenes** and **Polycyclic Aromatic Hydrocarbons** (PAH), as well as **heterocyclic aromatic amines** (HAA).

• **Avoid acrylamides**, **furans**, **nitrosamines** and also **aflatoxins**.

• **Avoid** industry-derived **chemicals**, **heavy metals** such as mercury, lead, arsenic, nickel, aluminum, tungsten, beryllium, platinum, copper, uranium ... and **PVC plastics**.

•**Moderate** the **consumption** of **glucosinolates** such as sulforaphane and isothiocyanates present in **cruciferous vegetables** (broccoli, watercress, brussels sprouts, radishes, turnips, cabbage, cauliflower...). Maximum 100 gr of broccoli 2-3 times / week. It is convenient to eat them raw or to use gentle ways of cooking and for a short time.

•**Increase** the intake of **organic fruits, vegetables** and **spices** (without pesticides), rich in antioxidants capable of neutralizing excess free radicals.

•**Increase** the consumption of foods rich in **resveratrol**.

• It is **recommended** the use of **resveratrol supplements** because they inhibit the expression of dioxin-induced Phase I and at the same time acts as a protector of the proactivation of carcinogens.

•**Avoid** the use of **supplements** with **high doses** of **glucosinolates** (cruciferous), **indoles** (IP6), **Salvia miltiorrhiza** (Danshen), or **St. John's Wort** as they increase the activity of Phase I metabolism.

Antioxidant defense

Oxidative stress occurs through the generation of **reactive oxygen species** (ROS) that can damage cells, DNA and proteins, influencing the development of **degenerative, cardiovascular diseases** or various types of **cancer**. **ROS** are **generated** in particular metabolic processes, such as **inflammation**, but also from the simple act of **breathing oxygen**.

These harmful substances are neutralized thanks to the action of various enzymes. Among them, **SOD2** constitutes the **first step** in this **antioxidant pathway**. It transforms **superoxide radicals** (a type of ROS) that are produced by many redox reactions into **hydrogen peroxide** (H_2O_2), which is then converted to **water** (H_2O) by the **CAT** and **GPX** enzymes. These three form the **first line** in the antioxidant defense.

Furthermore, the **NQO1** enzyme is involved in the **reduction of quinones** to hydroquinones. This prevents these quinones from producing more ROS from hydrogen peroxide and therefore results in a **protection of cells from oxidative stress** .

Finally, the activation of these and many other enzymes is **modulated** by the **NRF2 factor**, which is considered a **master regulator** of the antioxidant system. This allows increasing the production of enzymes in the face of **oxidative overload** by activating their genes. Polymorphisms in the NRF2 gene (NFE2L) decrease its regulatory capacity and, thus, the response under **high oxidative stress.**
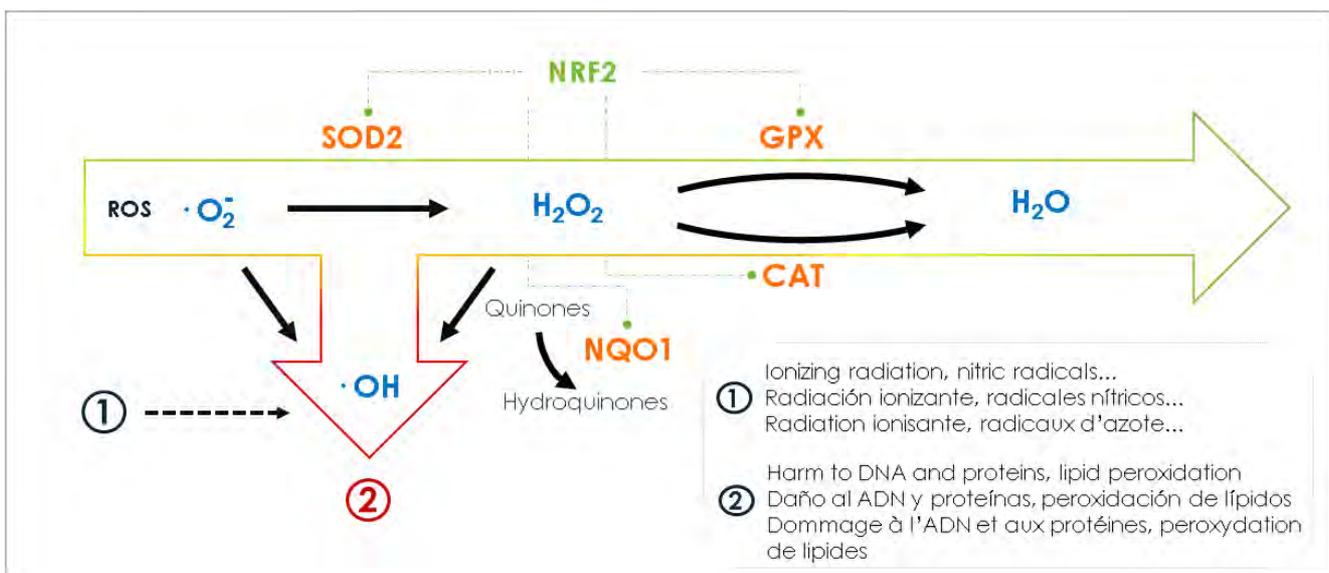
Gene	Rs identifier	Polymorphism	Results
CAT	rs1001179	-262C›T	CC
GPX	rs1050450	599C›T	CC
NFE2L2	rs6721961	-617T›G	GG
NQO1	rs1800566	C609T	GA
SOD2	rs4880	Ala16Val	AG

Consequences

The detected genotype for the enzyme genes is related to a slightly reduced antioxidant defense compared to non-variant homozygotes.

Recommendations

To increase the antioxidant activity:

• **Avoid** the **induction of Phase I detoxification** produced by **benzopyrenes**, **polycyclic aromatic hydrocarbons** (PAH), **heterocyclic aromatic amines** (AAH), **acrylamides**, **furans**, **nitrosamines**, **insecticides**, **herbicides**, **pesticides**, **heavy metals**, **PVC plastics**, **aflatoxins**... because they generate a lot of oxidative and nitrosative stress.

• **Follow** a diet rich in **micronutrients** and **antioxidants**, increasing the consumption of **group B vitamins:** B6, B9, B12, B2, B3, **vitamins C and E and resveratrol**.

• **Avoid foods rich in trans fats** present in industrially produced foods with vegetable oils such as chips, salted snacks, pastries, cookies...

• **Avoid excessive physical activity** in time and intensity (marathon, triathlon, etc.), as it increases oxidative stress. However, **moderate physical activity** (walking, swimming, jogging), is **beneficial** to health.

• **Avoid alcohol consumption** because it is one of the main factors affecting the redox mechanism (oxidation and reduction reactions) that generates high production of free radicals derived from oxygen and nitrogen and that affects the respiratory chain of the mitochondria.

Supplementation
Although the risk model with the results obtained does not indicate a need for the use of supplements, they may be useful in case of insufficient intake through the diet.

• Betacarotenes
• Lycopene
• Resveratrol
• Vitamin E

• Tumeric
• Fermented Papaya
• Vitamin C

Phase II hepatic detoxification – Glutathione conjugation

The bioactive substances of Phase I detoxification are transformed into more soluble substances through the addition of polar molecules by reactions of: sulfation, glutathione conjugation, amino acids, methylation, acetylation and glucoronidation. Once transformed, they can be easily eliminated by the liver or kidneys.

In this chapter we study **glutathione S-transferases (GSTs)**, enzymes involved in the addition of a glutathione group to Phase I molecules. GSTs may present polymorphisms that may reduce or even null their activity and this leads to a reduction in the Phase II detoxification capacity.

GSTs play an important role in susceptibility to environmental diseases, have also been linked to different types of cancer (lungs, bladder, colon, skin, ovaries, etc.) and can be considered as risk modifiers for various diseases, induced by the environment.

Gene	Rs identifier	Polymorphism	Results
GSTM1	GSTM1_CNV	*0	1/1
GSTM3	rs7483	3209G›A	CT
GSTP1	rs1695	Ile105Val	Ile/Ile
GSTT1	GSTT1_CNV	*0	1/1

Consequences

The genotype detected for the studied genes, is related to an enzymatic activity without alterations, that is, a normal conjugation with glutathione, despite not being very frequent in the population.

Recommendations

• **Avoid** exposure to **benzenes** and **ethylbenzenes**, **epoxies**, **herbicides** and **pesticides**, **polycyclic aromatic hydrocarbons** (PAH), **quinones**, **tobacco smoke**...

• **Avoid** consuming **roasted products**, as well as **acrolein**, which is generated by grilled, barbecued or fried foods.

• **Avoid** the use of **mercury amalgams**.

Phase II hepatic detoxification - Sulfation

Phase II detoxification also involves **sulphotransferase 1A1 (SULT1A1)** which belongs to the sulphotransferase family. This enzyme catalyzes the conjugation of a sulfonate group to hydroxyl or amine groups previously added in Phase I.

The enzyme **SULT1A1** is involved in the detoxification of many endogenous and exogenous substances such as steroids, catecholamines, iodothyronine and some drugs.

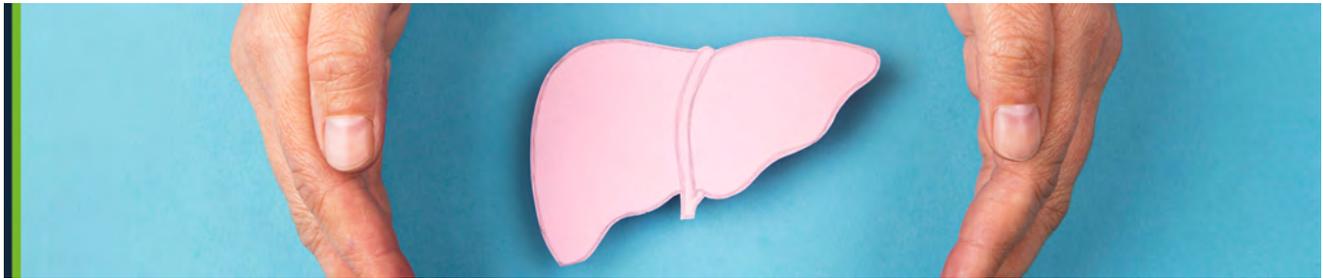| Gene	Rs identifier	Polymorphism	Results
SULT1A1	rs9282861	*2	wt/wt

Consequences

The detected genotype in the **SULT1A1** gene is related to normal enzymatic activity.

Recommendations

No specific recommendations.

Phase II hepatic detoxification - Methylation

The **Methylation Cycle** is a biochemical pathway that contributes to a wide range of crucial biochemical functions: **detoxification, immune function, energy production, mood balance and inflammation control.** All these processes help the body respond to environmental xenobiotics, detoxify, adapt and rebuild. Thus, a reduction in the function of methylation can contribute to many chronic diseases. Methylation is involved in almost all biochemical reactions of the body, and occurs constantly in cells.

Gene	Rs identifier	Polymorphism	Results
COMT	rs4680	Val158Met	Val/Met
MTHFR	rs1801133	677C›T	GA
MTHFR	rs1801131	1298A›C	TT

Consequences

The genotype detected for **COMT** gene is associated with a normal enzymatic activity.

The detected genotype for **MTHFR** is related to a slightly reduced enzymatic activity with respect to non-variant homozygotes, with no clinically relevant consequences.

Recommendations

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• It is recommended to take supplements with, specifically, **methylated group B vitamins** due to the reduced capacity of methylation. Also, it is recommended to carry out **relaxing activities**.

Phase II hepatic detoxification - Acetylation

The enzyme **N-acetyltransferase 2 (NAT2)** is related to Phase II hepatic detoxification. It is involved in the detoxification of a variety of substances to which the body is constantly exposed, such as industrial pollution, nutrition, smoking and drugs.

NAT2 may present polymorphisms that result in a reduction in its activity, which leads to a lower efficiency of elimination of substrates of this enzyme, which may accumulate and cause side effects and even promote various forms of cancer.

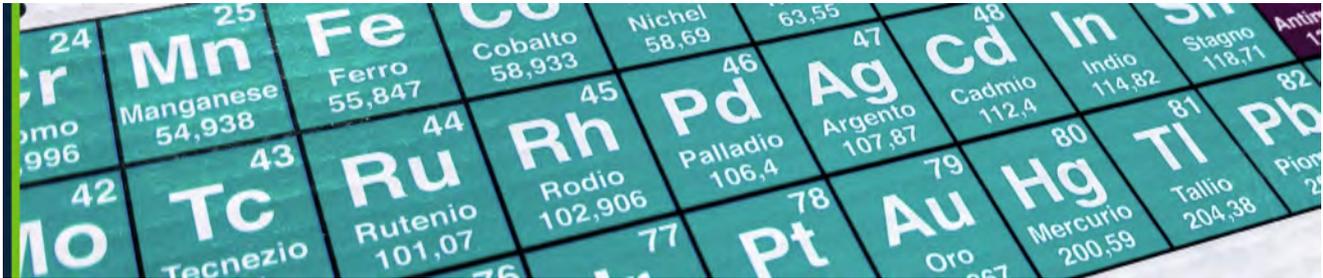| Gene	Rs identifier	Polymorphism	Results
NAT2	rs1801280	*5A	wt/wt
NAT2	rs1799931	*7A/B	wt/wt
NAT2	rs1799930	*6A	wt/wt

Consequences

The genotype detected for **NAT2** (*4/*4) gene is related to a normal enzymatic activity.

Recommendations

The elimination of substances by acetylation is normal, and no specific measures are necessary.

Heavy metal detoxification

Apolipoprotein E (ApoE) is a glycoprotein involved in **lipoprotein transport**. ApoE is involved in the process of **capturing cholesterol** in cells. It plays an important role in **coagulation**, **immunitary** defense and protection against **oxidation** processes.

It is an enzyme that has a very important role in the detoxification of **heavy metals**, especially mercury and lead.

Gene	Rs identifier	Polymorphism	Results
APOE	rs7412	Cys158Arg	CC
APOE	rs429358	Cys112Arg	TT

Consequences

The genotype for **APOE** corresponds to the **E3/E3** isoform, which is considered normal for the population.

Recommendations

• **Avoid** exposure to **mercury (Hg)**.

• **Avoid refined oils**: soybean oil, canola oil, cottonseed oil and others.

• **Avoid** comsuming **highly processed foods**: labeled "low fat" or "diet" or industrial processing.

• **Consume fruits** and **vegetables**, **eggs**,**fish**, **seafood**,**legumes**,**nuts** and **seeds**.

• **Prefer healthy fats**: virgin olive oil, olives, avocados, and increase the use of herbs and spices such as garlic, basil, mint..

Supplementation
• Aged garlic
• Vitamin C
• Algae (Chlorella, Spirulina, kelp, sweet)

• Marian thistle
• Zinc

Epoxide metabolism

Epoxides are **highly reactive** chemical compounds, as they have an unstable functional group to perform a wide variety of reactions. They can be found as **plastics** for structures, coatings and adhesives. These epoxides are metabolized by **microsomal epoxide hydrolase (EPHX1)** enzyme.

EPHX1 belongs to the family of **hydrolases**, which are a group of enzymes that catalyze the reaction of epoxides to diols, preventing or reducing their reaction with proteins or DNA. EPHX1 is able to **detoxify** or **bioactivate** a wide range of substrates and plays an important role in the **hepatic metabolism of xenobiotics.**

There are **genetic variants** that can **modify** the **activity of EPXH1** modulating the elimination of epoxides.

| Gene	Rs identifier	Polymorphism	Results
EPHX1	rs1051740	Tyr113His	CC
EPHX1	rs2234922	His139Arg	AA

Consequences

The detected genotype for **EPHX1** is related to a **reduced enzymatic activity**.

Recommendations

Due to the reduced activity of EPHX1, it is recommended to:
• **Avoid** substances that are metabolized to epoxides in phase I detoxification such as **tobacco smoke** and **car exhaust gases**. They contain **polycyclic aromatic hydrocarbons** (PAHs) that are transformed into harmful epoxides during the first step of detoxification.

• Special care should be taken with the consumption of **nuts**, **cereals** or **spices** stored in damp places as **aflatoxin B1** can be found. It is an extremely **harmful** and **carcinogenic** substance produced by fungi and metabolized by EPHX1.

• **Avoid** EPHX1 enzyme substrates: **ethylene oxide**, used in the production of adhesives or the plastics industry, and excessive **alcohol** consumption.

Alcohol metabolism
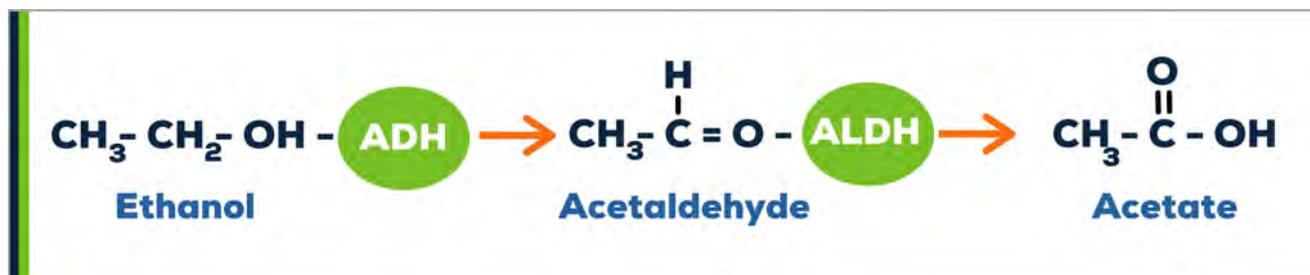
Alcohol is metabolized mainly in the **liver**. By the enzyme **alcohol dehydrogenase** (ADH) it is transformed into **acetaldehyde**, and this, thanks to the enzyme **aldehyde dehydrogenase** (ALDH) is transformed into **acetate**.

There are **genetic variants** in these enzymes (ADH and ALDH) that **modulates their activity** and facilitate in the short term the appearance of symptoms such as skin flushing, nausea and headache. Also, in the long term, exposure to acetaldehyde facilitates the development of liver pathologies linked to alcohol consumption. It has been reported that **higher ADH activity** and **lower ALDH activity** may confer risk in some population for the **accumulation of acetaldehyde**, which is toxic for the body.

In addition to genetic factors, **age** and **gender** may **affect** the **alcohol metabolism.**

Gene	Rs identifier	Polymorphism	Results
ADH1B	rs1229984	His48Arg	CC
ALDH2	rs671	42076G›A	GG

Consequences

The genotypes detected are related to normal enzyme activity, leading to **normal alcohol metabolism**, being the most frequent in the general population.

Complementary information

Nutritional supplements in natural products

• **Antioxidants**: such as vitamin C, selenium, polyphenols, flavonoids, lutein, lycopene …

• **Copper**: present in hazelnuts, almonds, dark chocolate 40% cocoa, dried vegetables, raw mushrooms, lentils…

• **Glutathione precursors and cofactors**: L-cysteine, L-glycine, L-glutamic acid, methionine, -lipoic acid.

• **Glutathione**: raw broccoli, carrots, avocados, asparagus, nuts and watermelons.

• **L-cysteine**: present in garlic, whole rice and grain, broccoli, onion …

• **Manganese**: present in wheat germ, hazelnuts, almonds, dried vegetables, raw mushrooms, cooked lentils, soya shoots, dark chocolate 40% cocoa …

• **Resveratrol**: present in the seeds and skin of red grapes also in nuts, red fruits or dark chocolate.

• **Vitamin B1**: present in brewer's yeast, whole grains, oats, dehydrated seeds, sunflower seeds, red and black beans, peas, asparagus, pumpkin, watermelon

• **Vitamin B2**: present in beer yeast, brown rice, wheat germ …

• **Vitamin B3**: present inrice, whole grain and legumes, green apple…

• **Vitamin B5**: present in shiitake mushrooms, 100% bran cereals, sunflower seeds…

• **Vitamin B6**: present in dry beans, whole grains, apple with skin, pistachios, banana…

• **Vitamin B7**: present in green molasses, brewer's yeast, whole grains, lecithin, all vegetables, citrus fruits and especially oranges, nuts…

• **Vitamin B9**: present in legumes, flax seeds, boiled or fried soybeans, broccoli, romaine lettuce.

• **Vitamin B12**: present in beet, carrots, cabbage, celery, ginger, ginseng, turnip, parsley, radish, Jerusalem artichoke .

• **Vitamin C**: present in açai, guava, papaya, kiwi, orange, mango, broccoli, Brussels sprouts, beet...

• **Vitamin E**: present in wheat germ oil, almonds, sunflower seeds, hazelnuts, sunflower oil, cereals 100% bran, peanuts, wheat bran, peanut oil, olive oil, avocado...

• **Zinc**: present in cashew, almond, oats, wheat germ...

Sources of xenobiotics

• **Acrylamides** and **furans**: present in French fries and toast.

• **Aflatoxins**: present in peanuts, dried fruits, corn, rice, soybeans ... that have been subjected to poor storage conditions.

• **Benzopyrenes** and **Polycyclic Aromatic Hydrocarbons** (PAH): are generated in the environment during the combustion of wood, oil (diesel and gasoline), oils, coal, tobacco. And in culinary preparations such as smoking, grilling, roasting, grilling, frying, baking, roasting and roasting.

• **Heavy metals**: **cadmium** present in ceramics, tobacco, paints, foundries, shellfish ...

• **Heavy metals**: **mercury** present in dental amalgams, old thermometers, laxatives, paints, pesticides, crustaceans, large blue fish ...

• **Heavy metals**: **lead** present in paints, ceramics, pesticides, solders, tobacco smoke ...

• **Heterocyclic aromatic amines** (HAA): generated in the process of cooking proteins at high temperatures, such as grilled fish, fried meat ...

• **Nitrosamines**: they come from the additives E250-sodium nitrite, E251-sodium nitrate, E252-potassium nitrate ...

• **PVC plastics**: present in hot water bottles, plastics heated in microwaves ...

• **Industrial chemicals**: such as insecticides, herbicides, pesticides, paints and industrial pollutants ...

Selection of revised bibliography

To create this report, we have been reviewed contrasted scientific publications, are available upon request. A selection of the most relevant ones is shown below.

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• Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138(1):103-141.

Additional information

The genetic polymorphisms included in this report have been selected on the basis of scientific publications that endorse their interpretative value for predicting individual health risks.

There are changes in genes, which do not directly cause disease, but which alter the activity of an enzyme, a transport protein or a receptor, which may themselves condition metabolic dysfunction, or in association with other variants. Therefore, they can predispose to diseases or health alterations, if life habits are not implemented and if appropriate nutritional or pharmacological supplements are not used.

Its objective is to make a risk prediction, i.e. Predictive Medicine, in order to implement a Personalized Preventive Medicine.

The genetic polymorphisms that appear in this report are not directly a specific diagnosis, but a complementary help for the health professional who has requested them. Consequently, it is solely responsible for the conclusions and recommendations to the patient that it deems appropriate in each case, regardless of what can be stated in general terms in this report.

It is the responsibility of the health care professional to incorporate the data in this report and any recommendations that may arise from the interpretation of these polymorphisms into the patient's medical record, along with other results from conventional analyses or other complementary explorations.

This report may contain lists of suggested foods based on their nutrient content that may be beneficial to the patient. However, such foods may not be indicated for food intolerances, allergies, specific diets, or medications that the patient may be taking. Therefore, this report and its contents should be reviewed together with the prescribing physician and decide within the suggested foods which to take. If not, establish other food supplements.

The processing laboratory is responsible for the accuracy of the results obtained, but the interpretation of the results is the responsibility of the health professional who requested them.

The genetic results presented do not allow us to conclude with certainty about the development of a disease or its susceptibility, because the tests carried out do not allow us to consider all the factors that contribute to the relative risk of a given susceptibility or of the possible evolution of a disease. Complex variables such as the degree of risk to develop adverse effects to drugs, or to suffer from multifactorial diseases in which genetic factors are not totally determinant are also relevant.