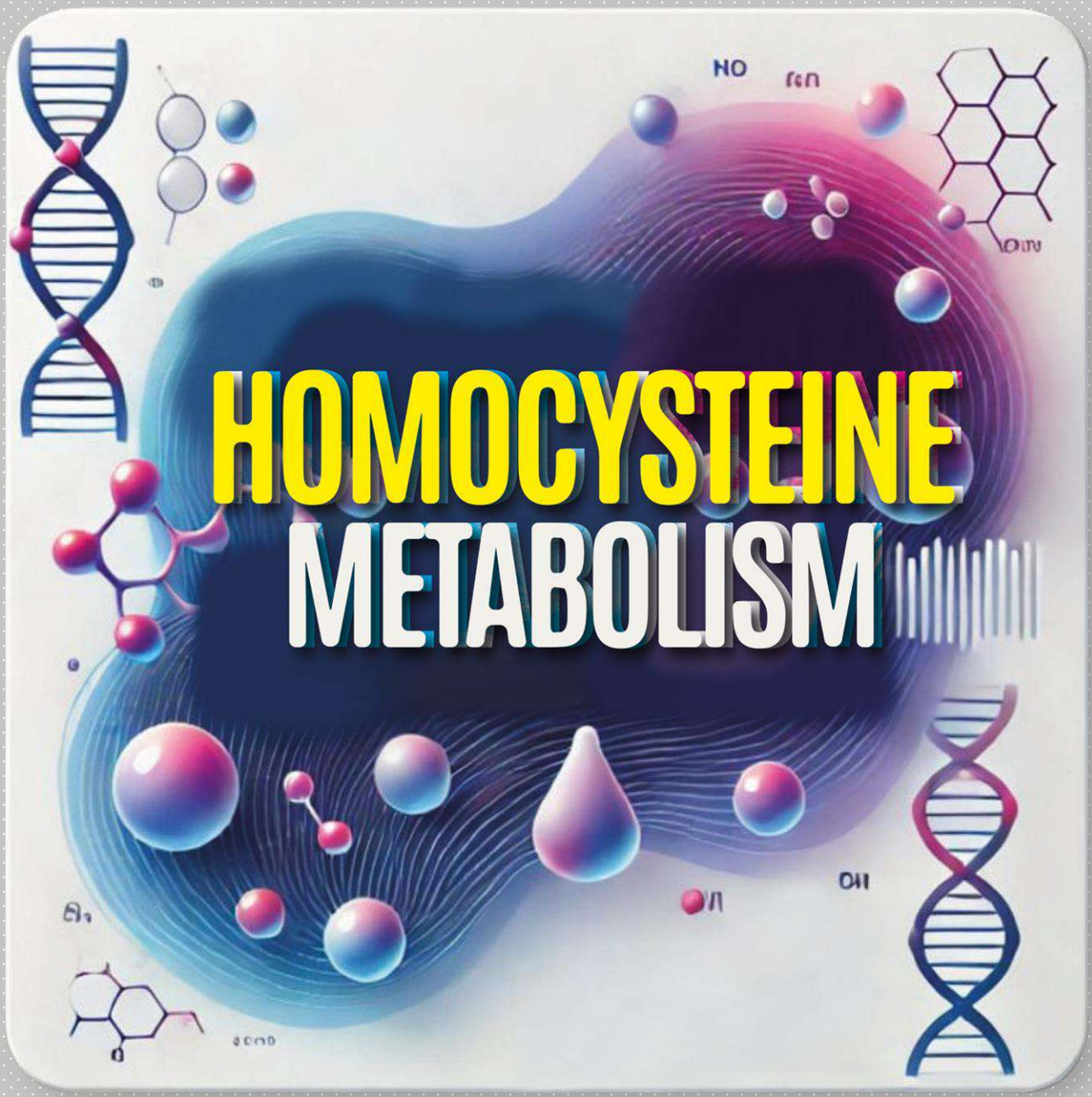
HOMOCYSTEINE
METABOLISM

WHAT THE REPORT INCLUDES

- Detailed EXPLANATION of the test performed and recommendations to be followed;
- SUMMARY TABLE showing the metabolic areas investigated and the results obtained from the DNA analysis, in order to have a quick overview of one's general situation and to check for compromised situations;
- BIBLIOGRAPHY providing scientific references for the test.

COLOURS USED

Green indicates that the variants identified in the analysis do not unfavourably alter the enzymatic activity of the proteins they encode and/or the risk associated with certain diseases.

Orange indicates that the variants identified in the analysis slightly unfavourably alter enzyme activity and/or the risk associated with certain disorders or diseases.

Red indicates that the variants identified in the analysis alter enzyme activity in a particularly unfavourable way, resulting in an increased risk of developing certain disorders or associated diseases.

The results shown, as well as the considerations and explanations contained in the following pages of this booklet, should not be regarded as a medical diagnosis. It is important to bear in mind that the genetic information is only a part of the total information required to gain a complete picture of a person's state of health, and the data reported here is therefore a tool available to the treating physician to formulate a correct assessment of the patient's physiological state and suggest an appropriate personalised treatment.

Test result:

ID laboratory	Gene	Allelic variants	Genotype		Predisposition
GTS003	MTHFR	C	T	T	HIGH
(methylene tetrahydrofolate reductase)		T			

Laboratory ID	Gene	Allelic variants	Genotype		Predisposition
GTS016	MTHFR-2	A	A	C	INTERMEDIATE
(methylen tetrahydrofolate reductase)		C			

WHAT YOUR GENETICS SAY	
	
*The **MTHFR** gene profile is present with HIGH SUSTAINABILITY indicating reduced folate metabolism.*	**MTHFR-2** *There is a genetic profile of INTERMEDIATE SUSTAINABILITY that indicates the likelihood of skin disorders.*

Explanation of genetic analysis:

Two variable gene sites were evaluated: C677T and A1298C on the MTHFR gene.

C677T is indicative of the body's ability to metabolise folate because it influences the functionality of a key enzyme in this metabolism, methylen tetrahydrofolate reductase (MTHFR), and is a measure of blood folic acid deficiency. MTHFR is an enzyme that affects the efficiency of folic acid metabolism.

While the A1298C site has been correlated with certain skin disorders. In the presence of the unfavourable variant, there is a potential reduction in MTHFR enzyme activity, which may affect folate and homocysteine metabolism.

Homocysteine

Homocysteine is a sulphur amino acid (i.e. containing a sulphur atom) normally present in very small amounts in the body's cells. In the blood, homocysteinemia values considered physiological are in the range of **5-13 micromoles per litre (µmol/L)**. It derives from the metabolism of methionine, an essential amino acid that we take in with food.

Poor DNA methylation (methylation is a fundamental process for DNA formation and repair, for regulating cell growth and for correct gene expression) leads to excessive homocysteine levels, a condition considered to be a cardiovascular risk factor, and not only that, it can in fact underlie miscarriages, infertility, neurological disorders, chronic fatigue, immune and gastrointestinal system disorders, and ageing.

Homocysteine metabolism

Homocysteine and folic acid are interrelated. Low folic acid corresponds to high homocysteine and vice versa. For homocysteine metabolism, two mutations in the same MTHFR gene are specifically evaluated. The presence of the unfavourable variants correlates with high homocysteine levels in the blood.

What are Folates

Folate is a form of vitamin B9, a vitamin essential for many biological functions. They occur naturally in various foods, such as green leafy vegetables (spinach, broccoli, asparagus), pulses, fruits (oranges, avocados), and whole grains.
They play a crucial role in DNA synthesis, cell division and growth, and red blood cell formation. For this reason, they are particularly important during pregnancy, as adequate intake can prevent neural tube defects in the foetus.
Another form of vitamin B9 is folic acid, which is the synthetic version used in food supplements and some fortified foods.

Folate metabolism

Folate metabolism is the process by which our body uses folate (vitamin B9) to perform several essential functions:

- Absorption: When we eat folate-rich foods (such as green leafy vegetables), folates are absorbed in the small intestine.
- Conversion: Once absorbed, folates are converted into an active form called tetrahydrofolate (THF). This is the form that the body can use for its functions.
- DNA synthesis: THF is involved in the production of DNA, which is essential for cell division and growth.
- Red blood cell formation: It also serves to create red blood cells, which carry oxygen in the blood.
- Amino acid metabolism: THF helps transform certain amino acids, which are the building blocks of proteins.
- Methylation: Folate plays a role in a process called methylation, which is like 'switching on' or 'switching off' certain genes, contributing to the proper functioning of cells.

In the presence of low folate levels, problems such as anaemia (few healthy red blood cells) and, during pregnancy, foetal malformations can occur.
The MTHFR (methylenetetrahydrofolate reductase) variant is a genetic mutation that can affect folate metabolism. This mutation can reduce the efficiency with which the body converts folic acid (the synthetic form of vitamin B9) and dietary folates into 5-MTHF (5-methylenetetrahydrofolate), the active form used.
If a person has an unfavourable variant of the MTHFR gene, he or she may be at greater risk of problems such as elevated homocysteine, which is linked to an increased risk of cardiovascular disease, and may not metabolise folic acid well.

Countermeasures to be considered if the MTHFR variant is unfavourable

Here are the recommended countermeasures:

- Supplementation with 5-MTHF: Instead of taking folic acid, it is recommended to take 5-methyltetrahydrofolate (5-MTHF), which is already the active form of vitamin B9, directly. This bypasses the need for efficient conversion by the MTHFR gene.
- Natural folate intake: Consuming foods rich in natural folates, such as green leafy vegetables, pulses and citrus fruits, can be helpful. Folate found in natural foods tends to be better assimilated by the body than synthetic folic acid.
- Monitor homocysteine levels: People with an MTHFR variant may have elevated homocysteine levels in their blood. Monitoring these levels regularly with a doctor is important to manage cardiovascular risk.
- B vitamins: It is often helpful to take other B vitamins (B6 and B12), which work together with folate to lower homocysteine levels.
- Healthy lifestyle: Maintaining a balanced diet, regular physical activity and reducing stress can help improve cardiovascular health and offset any negative effects of the MTHFR variant.

Consulting a doctor or nutritionist is essential for a customised supplementation plan.

Countermeasures to consider if the MTHFR2 variant is unfavourable

If you also have an unfavourable variant of the MTHFR A1298C gene (commonly called MTHFR-2), you may be at risk of skin disorders due to problems with folate and homocysteine metabolism. Inefficient metabolism can cause a number of problems related to inflammation and skin health, such as acne, rosacea, eczema or dry skin. Here are some countermeasures to avoid these skin disorders:

- Taking 5-MTHF supplements (active folates)

The MTHFR-2 variant can reduce the body's ability to convert folic acid into 5-MTHF (5-methyltetrahydrofolate), which is the active form of folate required for numerous cellular functions, including skin health. Instead of using folic acid, it is recommended to take 5-MTHF as a supplement, which is already in its active form and easily utilised by the body.

- Increase consumption of foods rich in natural folates

Supplementing the diet with foods that naturally contain folate can help compensate for the reduced ability to process synthetic folic acid. Some of the foods richest in folate are: -Green leafy vegetables (spinach, kale, Swiss chard).

- Asparagus, broccoli and avocado .
- Legumes (lentils, beans, chickpeas).

These foods can improve skin health due to their content of folate, antioxidants and anti-inflammatory substances.

- Vitamin B12 intake

Vitamin B12 is essential for working together with folate in homocysteine metabolism. A vitamin B12 deficiency can worsen skin problems, especially if there is an unfavourable variant of MTHFR-2. It may be helpful to take vitamin B12 supplements or include foods such as meat, fish, eggs and dairy products in the diet.

- Vitamin B6 for skin metabolism

Vitamin B6 helps reduce homocysteine levels and supports skin health. It is involved in the synthesis of collagen, the protein that keeps the skin elastic and strong. Foods rich in B6 include bananas, sweet potatoes, fish and whole grains.

- Antioxidants and skin-supporting supplements

Antioxidants such as vitamin C, vitamin E and glutathione can help counteract oxidative stress that can damage the skin, especially if folate metabolism is inefficient. Antioxidants protect skin cells from damage and promote skin regeneration.

- Hydration and skin care

Maintaining good hydration is essential to prevent dryness and inflammation of the skin. In addition to drinking plenty of water, using moisturising creams with natural ingredients such as aloe vera or shea butter can help keep the skin healthy and protected.

- Avoiding synthetic folic acid

If you have an unfavourable variant of MTHFR-2, it is best to avoid supplements and foods fortified with synthetic folic acid, as the body may not metabolise it properly. This can lead to an accumulation of unmetabolised folic acid, which may interfere with cellular processes and cause inflammation, worsening skin problems.

- Managing stress levels

Stress can negatively affect metabolism and skin health. Stress management techniques such as yoga, meditation and deep breathing can help reduce levels of the stress hormone cortisol, which can contribute to skin disorders such as acne and rosacea.

- Avoiding irritating substances

Harsh chemicals in some cosmetics or skin care products can worsen skin problems if you have a genetic sensitivity such as that caused by an unfavourable MTHFR-2 variant. Use products that are gentle, hypoallergenic and free of parabens or perfumes.

- Consult a dermatologist or a doctor with expertise in genetics

A doctor specialising in genetics or a dermatologist can help you monitor homocysteine levels and suggest personalised treatments for your skin. In some cases, genetic tests may be recommended to better understand your metabolic status and treat possible vitamin deficiencies.

BIBLIOGRAPHY

1. Marini NJ, Gin J, Ziegle J, Keho KH, Ginzinger D, Gilbert DA, Rine J (2008) The prevalence of folate-remedial MTHFR enzyme variants in humans. *Proc Natl Acad Sci U S A* 105: 8055-8060.

2. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, Kiel DP, Streeten EA, Ohlsson C, Koller DL, Peltonen L, Cooper JD, O'Reilly PF, Houston DK, Glazer NL, Vandenput L, Peacock M, S (2010) Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet* 376: 180-188.

3. Ahn J, Yu K, Stolzenberg-Solomon R, Simon KC, McCullough ML, Gallicchio L, Jacobs EJ, Ascherio A, Helzlsouer K, Jacobs KB, Li Q, Weinstein SJ, Purdue M, Virtamo J, Horst R, Wheeler W, Chanock S, Hunter D (2010) Genome-wide association study of circulating vitamin D levels. Hum Mol Genet 19: 2739-2745.

4. Zhi Luo, Zhan Lu, Irfan Muhammad, Yun Chen, Qiuhong Chen, Jiaojiao Zhang, Yongyan Song. Lipids Health Dis (2018). Associations of the MTHFR rs1801133 polymorphism with coronary artery disease and lipid levels: a systematic review and updated meta-analysis.

5. Wei Zhang, Ye Wang, Guorong Bi. Cell Biochem Biophys (2015). Quantitative assessment of association between rs1801133 polymorphism and susceptibility to stroke.

6. Yingchao Fan, Liting Wu, Wenfang Zhuang. Cardiovasc Ther (2022). Methylenetetrahydrofolate Reductase Gene rs1801133 and rs1801131 Polymorphisms and Essential Hypertension Risk: A Comprehensive Analysis.

7. Laura Dean, Victoria M. Pratt, Stuart A. Scott, Munir Pirmohamed, Bernard Esquivel, Brandi L. Kattman, Adriana J. Malheiro. Medical Genetics Summaries (2012). Methylenetetrahydrofolate Reductase Deficiency.