CPG LOCI REPORT

TruDiagnostic™
The Epigenetic Company

IMPACT: Weight loss response to caloric restriction

GENES: PON3

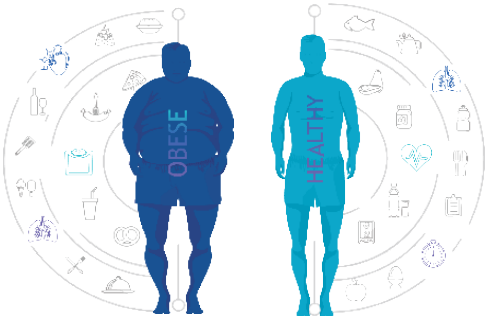
Weight Loss

Weight loss can be difficult, especially for individuals who have been overweight for years. There is not a one-size-fits-all approach to weight loss therapy. A hypocaloric (calorie-deficient) diet is typically considered one of the best approaches for weight loss, but not everyone responds to calorie deficit in the same way. Even with a strict regimen and no deviations, there are molecular and epigenetic components to how a body will respond to calorie deficit. Sometimes weight loss isn't a sure thing.

This report aims to help individuals identify their personal weight-loss response to caloric restriction.

YOUR EPITYPE:

Based on your methylation, you are a **Intermediate responder** for weightloss interventions using caloric restriction



What is Obesity?

Obesity can be defined as a disease in which excess body fat has accumulated such that health may be adversely affected.
The prevalence of obesity has increased dramatically over the past few decades. It presents major health obstacles because of its substantial increase in risk for diseases such as type 2 diabetes, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, and many types of cancer.

The rising incidence of obesity has caused the condition to be so common within the world's population that it is beginning to replace undernutrition and infectious diseases as the most significant contributor to ill health.

The global epidemic of obesity is fueled by a combination of genetic susceptibility, increased availability of high-calorie foods and decreased requirement for

Analyzing DNA Methylation

Our laboratory uses array-based DNA methylation testing to identify sites where methylation has occurred and measure the degree to which that location has been methylated. Advances in the field of epigenetics have found that we can use these variations in methylation can identify changes in specific biological responses.
For each gene, there is a range of methylation statuses that are considered normal, and methylation that falls outside that range.

Hypomethylation is when the methylation status is below a specific threshold. This threshold depends on the CpG loci it's on. Hypomethylation is also what we call the process of a gene losing methylation.

Hypermethylation, is when a gene's methylation status is over a specific threshold. It can also be the process of gaining more methylation.
A hypermethylated gene is usually being repressed or silenced.

What are CpG Loci?

CpG loci are specific locations on your DNA where methylation can occur. They are often near sites that begin transcribing a gene's instructions so those instructions can be carried out by the body.
When methylation occurs on the loci around a gene, the instructions can be changed from their original meaning or silenced entirely. A single gene can be influenced by the methylation on many nearby CpG loci.
In this report, we examine how much methylation has occurred on CpG loci around specific genes, and offer insights into how those changes affect you.

What affects DNA Methylation?

We have not yet uncovered the full list of everything that can influence DNA Methylation development. Known factors include nutrition, chronic or acute stress, sleep habits, activity levels, inflammation, oxidative stress, hypoxia, and much more.

Many patterns of methylation are not permanant, and studies have found they can be reversed by interventions like reducing stress, improving nutrition, and reducing exposure to pollutants or biological stressors. Neither of these lists are comprehensive.

What are Beta Values?

A beta value is essentially the percent-value that a specific CpG loci has been methylated. Depending on how many methyl molocules attached to that CpG, the loci could be anywhere from 0% to 100% methylated.
The more methylation a CpG has, the more it's working to silence nearby genes.
While a single CpG that is 100% methylated generally cannot silence an entire gene, groups of highly methylated CpG can work together to do so.

Your CpG Beta Values

	CpG site	Gene	ß-value Responders	Your Score	Response Status
1	cg15500865	PON3	0.072	0.09	Hypermethylated
2	cg25161512	PON3	0.115	0.14	Hypermethylated
3	cg11435506	PON3	0.165	0.06	Hypomethlyated
4	cg03301582	PON3	0.120	0.09	Hypomethlyated
5	cg08898155	PON3	0.163	0.04	Hypomethlyated
6	cg04080282	PON3	0.324	0.22	Hypomethlyated
7	cg26457160	PON3	0.490	0.52	Hypermethylated
8	cg10329418	PON3	0.252	0.29	Hypermethylated
9	cg27166921	PON3	0.253	0.33	Hypermethylated
10	cg24750391	PON3	0.355	0.39	Hypermethylated
11	cg08461772	PON3	0.418	0.40	Hypomethlyated

Possible Outcomes:

Non-Responder: CpG loci around your PON3 gene are generally under-methylated. Your response to caloric restriction alone is low, so it is not likely to be the most effective form of weight loss.

Intermediate Responder: CpG loci around your PON3 gene are in the normal range. Using a calorie deficit diet for weight loss may work, but it may not be as successsful as other therapies.

Full Responder: CpG loci around your PON3 gene have been hypermethylated, so calorie restriction as a method of weight loss should be very effective.

Learn About Your Genes

PON3

PON3 creates a protein that circulates in the blood stream. This protein binds to lipoproteins, which transport fat molecules through the blood.

The PON3 protein protects lipoproteins like HDL and LDL (also known as cholesterols) against oxidation. When LDL is oxidized, it can cause inflammation which leads to plaque in the arteries and possible damage to arterial walls.

Oxidized LDL is also believed to play a role in increasing the amount of fat your body deposits. It increases the production of triglycerides, which is the most common type of fat produced when your body has extra calories available.

Studies have found that the pattern of methylation on PON3 can predict how a person's weight and body fat will respond to caloric restriction.

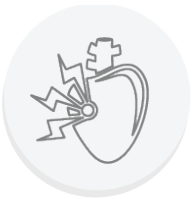


THE IMPACT ON YOU

CpG loci around your PON3 gene are in the normal range. Based on your methylation, you are an **Intermediate responder** for weight-loss interventions. Using a calorie deficit diet for weight loss may work, but adding other strategies has a greater chance of meeting weight loss goals

Knowing the impact your gene expression has on your ability to treat weight management can help you and your healthcare provider determine the best interventions for weight loss in the future.





REFERENCES

1. Blüher, M. (2019) Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol 15, 288–298. https://doi.org/10.1038/s41574-019-0176-8

2. Cawley, J., & Meyerhoefer, C. (2012). The medical care costs of obesity: an instrumental variables approach. Journal of health economics, 31(1), 219–230. https://doi.org/10.1016/j.jhealeco.2011.10.003

3. Edillor, C. R., Parks, B. W., Mehrabian, M., Lusis, A. J., & Pellegrini, M. (2019). DNA Methylation Changes More Slowly Than Physiological States in Response to Weight Loss in Genetically Diverse Mouse S https://doi.org/10.3389/fendo.2019.00882

4. Garcia-Lacarte, M., Milagro, F. I., Zulet, M. A., Martinez, J. A., & Mansego, M. L. (2016). LINE-1 methylation levels, a biomarker of weight loss in obese subjects, are influenced by dietary antioxidant capacity. Redox report : communications in free radical research, 21(2), 67–74. https://doi.org/10.1179/1351000215Y.0000000029

5. Hruby, A., & Hu, F. B. (2015). The Epidemiology of Obesity: A Big Picture. PharmacoEconomics, 33(7), 673–689. https://doi.org/10.1007/s40273-014-0243-x

6. Kopelman P. G. (2000). Obesity as a medical problem. Nature, 404(6778), 635–643. https://doi.org/10.1038/35007508

7. Milagro, F. I., Mansego, M. L., De Miguel, C., & Martínez, J. A. (2013). Dietary factors, epigenetic modifications and obesity outcomes: progresses and perspectives. Molecular aspects of medicine, 34(4), 782–812. https://doi.org/10.1016/j.mam.2012.06.010

8. Moleres, A., Campión, J., Milagro, F. I., Marcos, A., Campoy, C., Garagorri, J. M., Gómez-Martínez, S., Martínez, J. A., Azcona-Sanjulián, M. C., Martí, A., & EVASYON Study Group (2013). Differential DNA methylation patterns between high and low responders to a weight loss intervention in overweight or obese adolescents: the EVASYON study. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 27(6), 2504–2512. https://doi.org/10.1096/fj.12-215566

9. Salas-Pérez, F., Cuevas-Sierra, A., Cuervo, M., Goni, L., Milagro, F. I., Martínez, J. A., & Riezu-Boj, J. I. (2021). Differentially methylated regions (DMRs) in PON3 gene between responders and non-responders to a weight loss dietary intervention: a new tool for precision management of obesity. Epigenetics, 1–12. https://doi.org/10.1080/15592294.2021.1873629

10. van Dijk, S.J., Tellam, R.L., Morrison, J.L. et al. Recent developments on the role of epigenetics in obesity and metabolic disease. Clin Epigenet 7, 66 (2015). https://doi.org/10.1186/s13148-015-0101-5

11. Young, S., McEneny J., (2001) Lipoprotein oxidation and atherosclerosis.Biochem Soc Trans. 29 (2): 358–362. https://doi.org/10.1042/bst0290358