BEN'S OBESITY RISK METHYLATION REPORT

FGFRL1 (cg25932599), NCAPH2 (cg25152348),
PNKD (cg22712983), SMAD3 (cg0757622) Genes

TruDiagnostic™

Are You at Greater Risk for Becoming Obese and Developing Obesity-Related Disorders?

Epigenetic Biomarkers for Obesity and Metabolic Disorders

The prevalence of obesity is increasing rapidly worldwide, the number of obese individuals has tripled between 1975 and 2016. With 650 million obese people all over the world, this condition is responsible for 3 million deaths each year [11]. The current status of obesity and its associated disorders have reached global pandemic status and are a major challenge for the healthcare system.

Metabolic alterations, such as obesity, are due to the interplay between environmental, lifestyle, and genetic factors [1]. Obesity originates from a failure of the body-weight control systems, which may be affected by changing environmental influences. Basically, obesity risk depends on two important mutually-interacting factors: genetic variants (inheritance, epigenetic mechanisms, etc.) and exposure to environmental risks (diet, physical activity, etc.). DNA methylation at specific gene loci for obesity may act as effect modifiers for environmental factors [5].

Fat tissue, frequently the largest organ in humans, is central to mechanisms involved in longevity, the origin of age-related disease, inflammation, and metabolic dysfunction. Fat distribution and function change dramatically throughout life. Obesity is associated with accelerated onset of diseases common in old age, including diabetes, hypertension, cancers, cognitive dysfunction, and atherosclerosis leading to heart attacks and strokes [7].

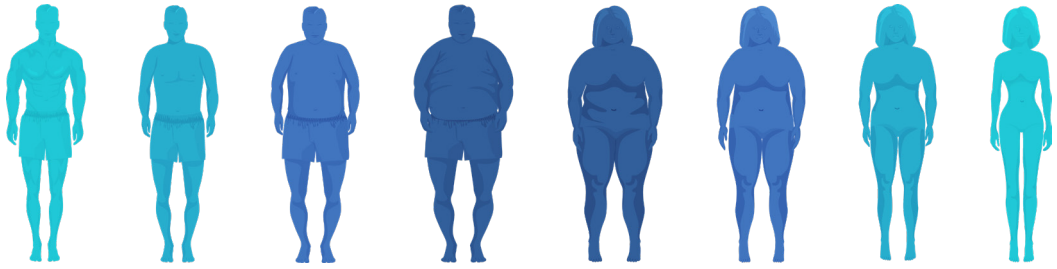
Epigenetic Mechanisms Influence the Process of Becoming Obese

It is well known that physical inactivity and unhealthy dietary patterns exert major influences on metabolic syndrome, diabetes, and obesity. However, despite intensive genetic research into these alterations, the basic mechanisms and pathogenesis of obesity are still poorly understood. In this regard, emerging evidence suggests that epigenetics represents one link between environmental factors and the greater predisposition to develop obesity and its associated conditions.

Therefore, there is great interest in the use of epigenetic biomarkers such as DNA methylation, which, unlike the DNA sequence, can be influenced by the environment, and has the potential to improve how healthcare officials treat those with obesity and those who are at higher risk for the onset of obesity. The characterization of the epigenetic changes within obesity-related adipose tissue provides new insights into understanding toward metabolic disorders.

Researchers discovered a test that uses blood cells to reflect whether an individual is more or less susceptible to becoming obese based on their DNA methylation status. This is huge because now we can measure your personal obesity risk by using blood as the one collection method to rule them all [1].

Analysis of DNA samples shows us what your specific level of risk is for developing obesity. ***Therefore your EpiType for the methylation levels of FGFRL1, NCAPH2, PNKD, and SMAD3 provides valuable insight regarding your overall susceptibility to becoming obese and your risk for diseases associated with obesity.***



What Is Your Epitype:

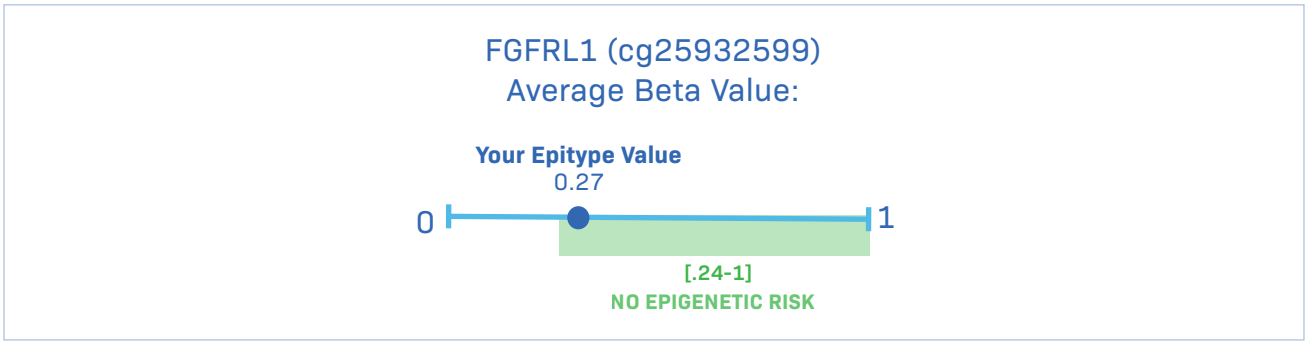
Your EpiType is your methylation status at these particular locations. The research mentioned on the first page shows that DNA methylation at 4 gene loci are linked to gene expression and your risk of becoming obese, we will define these particular sites and your ß-values for each of these.

What is FGFRL1?

FGFRL1 (fibroblast growth factor receptor-like 1) is a gene that is involved in metabolism signaling and insulin processing. This gene is an early indicator of adipogenesis which is known to increase fat tissue mass concerning obesity.

This gene was found to have increased methylation in fat tissue of twins that have different BMIs. FGFRL1 activity shows changes in glucose-stimulating and insulin secretion. FGFRL1 induced signaling regulates cells and is associated with the onset and progression of metabolic disorders such as diabetes [5].

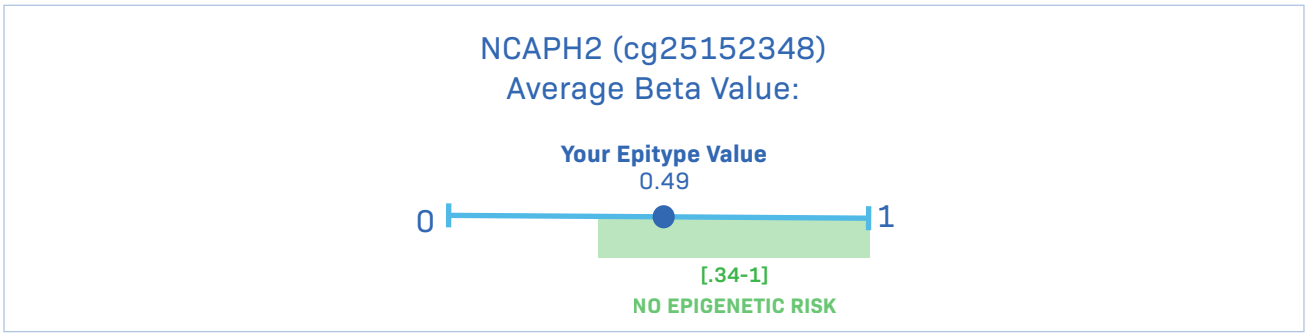
Having a beta value of 0.24 or less puts you at higher risk for disturbed metabolism signaling and insulin processing which increases the chance accumulating excess body fat.



What is NCAPH2?

The condensin II gene (NCAPH2) does non-structural maintenance of chromosomes by providing chromosomes with additional organization and rigidity. This chromosome-associated gene is involved in senescence by driving senescence through genomic reorganization. Cellular senescence is characterized by cell cycle arrest and is a process that is increased in dysfunctional obese fat tissue and is related to the development of metabolic disturbances [10].

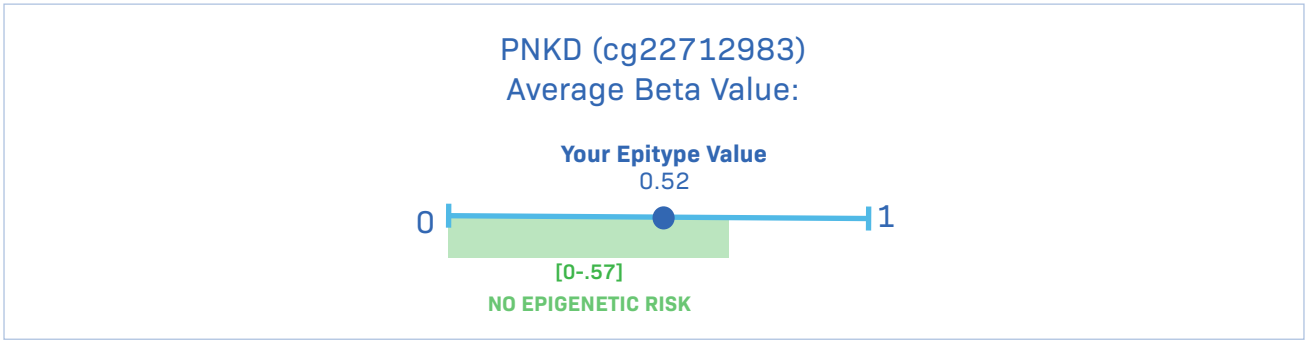
Having a beta value of 0.34 or less means that you are at higher risk for developing a metabolic disorder. This contributes to excess fat tissue accumulation that can lead to the development of obesity.



What is PNKD?

Regarding mitochondrial function, mutations of the identified paroxysmal nonkinesigenic dyskinesia (PNKD) gene are involved in the development of a rare motor disease induced by mitochondrial dysfunction. Research suggests that the PNKD gene mutations alter the structure of the PNKD protein and interfere with its ability to function. The methylation levels observed in the blood of the obese patients compared with the non-obese patients establishes this gene's loci role in the onset of accumulating too much fat tissue [2].

Having a beta value of 0.57 or greater suggests that you have an increased chance for developing the obese phenotype.

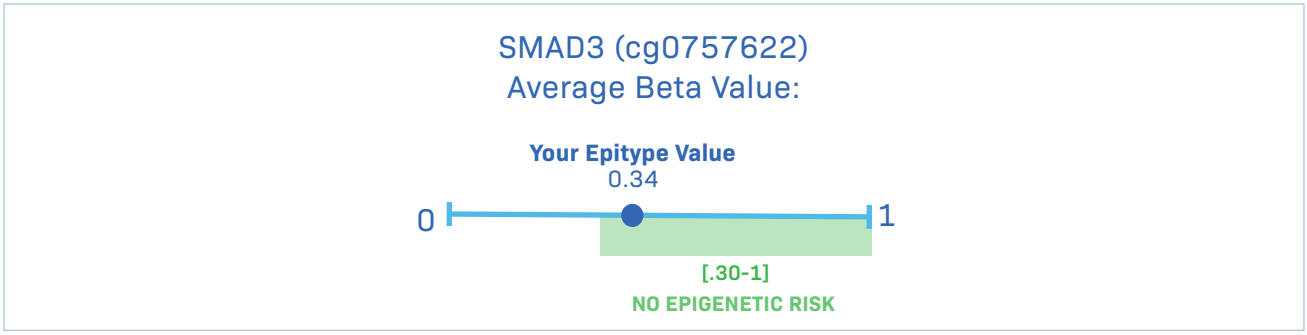


What is SMAD3?

This relevant, methylated gene identified was SMAD family member 3 (SMAD3). Our bodies' have an energy imbalance when energy intake exceeds energy expenditure, leading to the net storage of excess calories in the form of fat in the adipose tissue. The excess-accumulation of fat in adipose tissue is what leads to obesity. Mammalian adipose tissue is broadly classified as either white adipose tissue (WAT) or brown adipose tissue (BAT)

The loss of SMAD3 results in the transformation of white adipose tissue (WAT) to brown adipose tissue (BAT) which increases the minimal level of energy expenditure for the body to function properly. SMAD3 signaling protects against high-fat diet-induced obesity and Type 2 diabetes. Therefore, the blockage of SMAD3 contributes to a higher risk of obesity and type 2 diabetes mellitus [9].

Having a beta value of 0.30 or less means you are at greater risk for adipogenesis, this is the formation of adipocytes (fat cells) and is known to contribute to the excessive increase of fat tissue mass. These fat cells produce an accumulation of fat stores which can trigger cellular stress and cause the onset of obesity.



The Science

The area under the receiver operating characteristic (ROC) curves further analyzed the diagnostic power of this report's findings. Relevantly, the areas under the ROC curves (AUCs) measures how well the parameters of FGFRL1, NCAPH2, PNKD, and SMAD3 can be distinguished from obese and non-obese groups (figure 1). There is a great correlation in the DNA methylation between the subcutaneous adipose tissue and leukocytes for FGFRL1 ($r = 0.77$; $p < 0.001$), NCAPH2 ($r = 0.68$; $p < 0.001$), and SMAD3 ($r = 0.74$; $p < 0.001$) [1].

FGFRL1, NCAPH2, PNKD, and SMAD3 are target genes that could reflect the obesity state in leukocytes because they exhibited the greatest differences between the obese and non-obese samples. These genes are involved in important processes associated with adipose tissue balance. It is evident that the methylation levels of these gene loci suggest epigenetic regulation associated with obesity.

DNA methylation at the FGFRL1 locus cg25932599 in DNA is statistically correlated with metabolism signaling and insulin processing [6]. DNA methylation at the FGFRL1 locus cg25932599 in blood DNA displays statistical significance in the differentiation of having either obesity status or non-obesity status (AUC > 0.80; p < 0.05). Also, the level of DNA methylation at the FGFRL1 locus cg25932599 is statistically correlated with Body Mass Index indicating its role in the increase of excess fat [1].

Strong evidence that complex diseases, such as metabolic disorders, are under the influence of epigenetic modifications even in early life. This is opening up new avenues for the identification of DNA methylation biomarkers associated with these disorders and the estimation of future disease risk.

The characterization of the epigenetic changes associated with obesity will provide new insights about the pathophysiological processes and environmental influences (figure 2) involved with this metabolic disorder to help us develop better approaches for prevention and disease management [1].

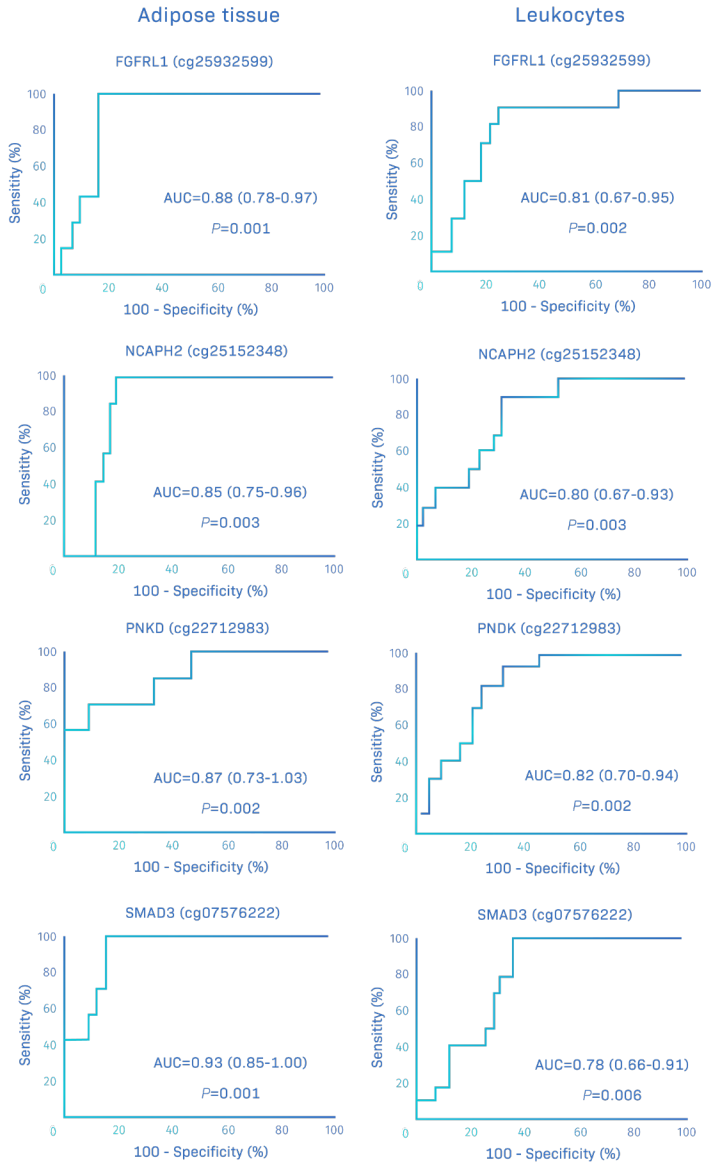


Fig 2 Receiver operating characteristic (ROC) curves for the methylation levels of the obesity-related differentially methylated CpGs. The abilities to discriminate the obese from the non-obese samples of adipose tissue (a) and leukocytes (b).

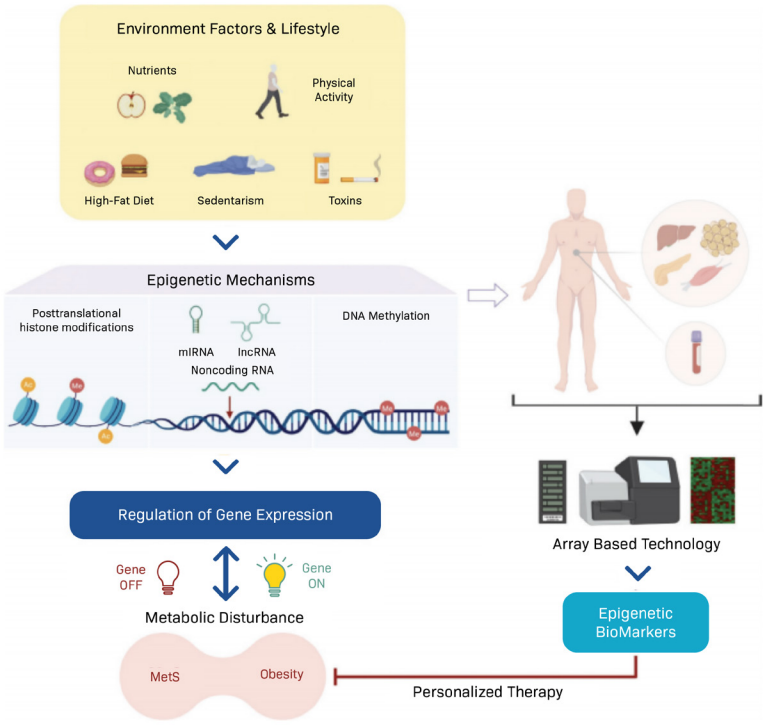


Fig. 2 The interplay between environment/lifestyle factors and metabolic diseases via epigenetic machinery and epigenetic biomarkers. Environment and lifestyle may contribute to metabolic disorders through the dysregulation of the epigenetic machinery. The alteration of the epigenetic mechanisms can modify the activity of genes related to the metabolism that trigger metabolic disorders such as insulin resistance and, consequently, diabetes mellitus and metabolic syndrome. These epigenetic modifications can be used as clinical biomarkers for metabolic diseases since these can be reversed by epigenetic drugs or functional foods and thus restore the right metabolic state of the gene in patients [3]

THE IMPACT TO YOU

The impact your genes' have on you is based on your level of methylation at these gene loci compared with the level of risk for the development of obesity.

Your DNA methylation score was _A__ at the FGFRL1 locus, __B_ at the NCAPH2 locus, __C__ at the PNKD locus, and __D__ at the SMAD3 locus.

Based on your DNA methylation scores at these four gene loci means that you are at __E_ for developing obesity according to the referenced study [1].

Some studies on this particular CpG loci have suggested that fasting and low carb diets can reduce methylation at these loci to lower your risk. Please consult your doctor to discuss this and more treatment options.

Summary

Many metabolic alterations, such as obesity, are due to the interplay between environmental, lifestyle, and genetic factors. ***Recent studies have found 4 DNA methylation loci, FGFRL1, NCAPH2, PNKD, and SMAD3, that are able to predict your risk of becoming obese. By altering these loci's levels of methylation you have the power to change risk factors for obesity. TruDiagnostic™ is continuing to uncover interventions that will change these risk factors in order for you to make appropriate adjustments to reduce your risk.*** The alteration of epigenetic mechanisms can modify the activity of genes related to metabolism that triggers metabolic disorders. These genes' epigenetic modifications can be used as clinical biomarkers for obesity-related metabolic diseases, by predicting disease onset and determining a patient's response to therapy.

REFERENCES

1. Crujeiras, A. B., Diaz-Lagares, A., Sandoval, J., Milagro, F. I., Navas-Carretero, S., Carreira, M. C., Gomez, A., Hervas, D., Monteiro, M. P., Casanueva, F. F., Esteller, M., & Martinez, J. A. (2017). DNA methylation map in circulating leukocytes mirrors subcutaneous adipose tissue methylation pattern: a genome-wide analysis from non-obese and obese patients. Scientific reports, 7, 41903. https://doi.org/10.1038/srep41903

2. Ghezzi, D., Canavese, C., Kovacevic, G., Zamurovic, D., Barzaghi, C., Giorgi, C., Zorzi, G., Zeviani, M., Pinton, P., Garavaglia, B., & Nardocci, N. (2015). A family with paroxysmal nonkinesigenic dyskinesias (PNKD): evidence of mitochondrial dysfunction. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society, 19(1), 64–68. https://doi.org/10.1016/j.ejpn.2014.10.003

3. Izquierdo, A. G., & Crujeiras, A. B. (2019). Chapter 10 - Epigenetic biomarkers in metabolic syndrome and obesity. In S. B. T.-P. E. Sharma (Ed.), Translational Epigenetics (Vol. 15, pp. 269–287). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-814259-2.00011-X

4. Pietiläinen, K. H., Ismail, K., Järvinen, E., Heinonen, S., Tummers, M., Bollepalli, S., Lyle, R., Muniandy, M., Moilanen, E., Hakkarainen, A., Lundbom, J., Lundbom, N., Rissanen, A., Kaprio, J., & Ollikainen, M. (2016). DNA methylation and gene expression patterns in adipose tissue differ significantly within young adult monozygotic BMI-discordant twin pairs. International journal of obesity (2005), 40(4), 654–661. https://doi.org/10.1038/ijo.2015.221

5. Silva, P. N., Altamentova, S. M., Kilkenny, D. M., & Rocheleau, J. V. (2013). Fibroblast growth factor receptor like-1 (FGFRL1) interacts with SHP-1 phosphatase at insulin secretory granules and induces beta-cell ERK1/2 protein activation. The Journal of biological chemistry, 288(24), 17859–17870. https://doi.org/10.1074/jbc.M112.440677

6. Tchkonia, T., Morbeck, D. E., Von Zglinicki, T., Van Deursen, J., Lustgarten, J., Scrable, H., Khosla, S., Jensen, M. D., & Kirkland, J. L. (2010). Fat tissue, aging, and cellular senescence. Aging cell, 9(5), 667–684. https://doi.org/10.1111/j.1474-9726.2010.00608.x

7. Trueb B. (2011). Biology of FGFRL1, the fifth fibroblast growth factor receptor. Cellular and molecular life sciences : CMLS, 68(6), 951–964. https://doi.org/10.1007/s00018-010-0576-3

8. Yadav, H., Quijano, C., Kamaraju, A. K., Gavrilova, O., Malek, R., Chen, W., Zerfas, P., Zhigang, D., Wright, E. C., Stuelten, C., Sun, P., Lonning, S., Skarulis, M., Sumner, A. E., Finkel, T., & Rane, S. G. (2011). Protection from obesity and diabetes by blockade of TGF-β/Smad3 signaling. Cell metabolism, 14(1), 67–79. https://doi.org/10.1016/j.cmet.2011.04.013

9. Yokoyama, Y., Zhu, H., Zhang, R., & Noma, K. (2015). A novel role for the condensin II complex in cellular senescence. Cell cycle (Georgetown, Tex.), 14(13), 2160–2170. https://doi.org/10.1080/15384101.2015.1049778