BEN'S TRIGLYCERIDES AND DIABETES RISK METHYLATION REPORT

ABCG1 (cg06500161), PHOSPHO1 (cg02650017), SOCS3, SREBF1, and TXNIP Genes

TruDiagnostic™

Are You At Increased Risk For Developing Type 2 Diabetes?

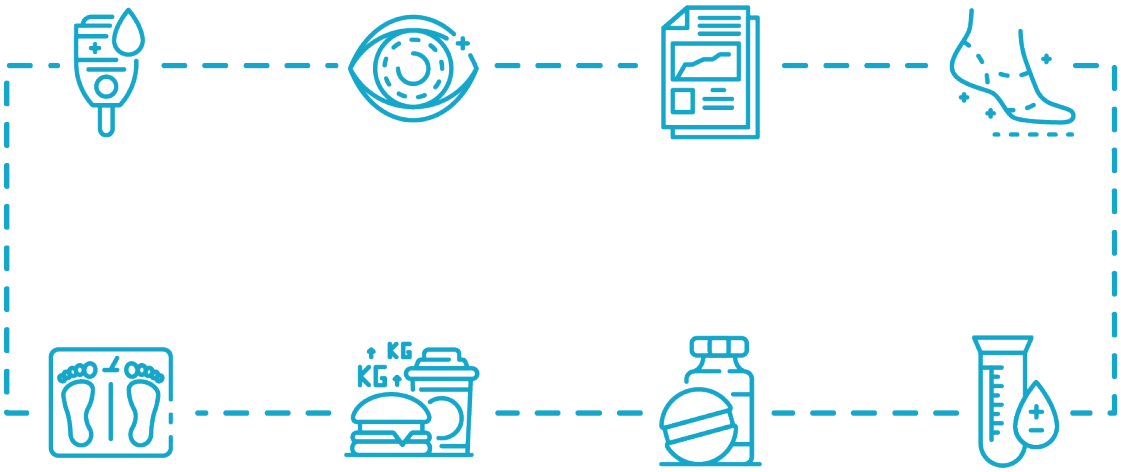
Epigenetic biomarkers for Type 2 Diabetes

Type 2 diabetes (T2D) is a complex disease that results from genetic and environmental interactions that can be modified and/or mediated by epigenetic changes. A number of genetic and non-genetic factors have been identified that increase the risk of T2D. However, a healthier lifestyle, including proper diet and exercise, can potentially reduce the risk of T2D by almost 50 percent in high-risk groups [3].

Therefore, there is great interest and need to identify individuals that have a high risk of developing T2D. By postponing and/or preventing T2D and its complications, it may be possible to reduce T2D-associated mortality and the financial cost of treating the disease and its complications.

To date, more than 65 genetic variants have been identified that increase the risk of T2D by almost 10 percent [8]. However, genetic screening for T2D risk variants has not been implemented in clinics. Despite the potential value of such screening tests, a number of limitations have hindered their use. These limitations include small effect size, their low discriminative ability, a small added value compared with the clinical risk factors, and a lack of models that take into account gene-gene and gene-environment interactions [3]. Failure to understand the pathophysiology of T2D hinders the efforts to develop improved therapeutic strategies [7].

There is great interest in epigenetic biomarkers such as DNA methylation, which, unlike the DNA sequence, can be influenced by the environment, and has the potential to improve T2D prediction [3]. Recently, an epigenome-wide association study identified 5 DNA methylation loci ***(ABCG1, PHOSPHO1, SOCS3, SREBF1, and TXNIP)*** in the blood that were associated with T2D. Furthermore, the study showed that a methylation score that combined the results from these 5 methylation loci found an association with prospective T2D occurrence [1].

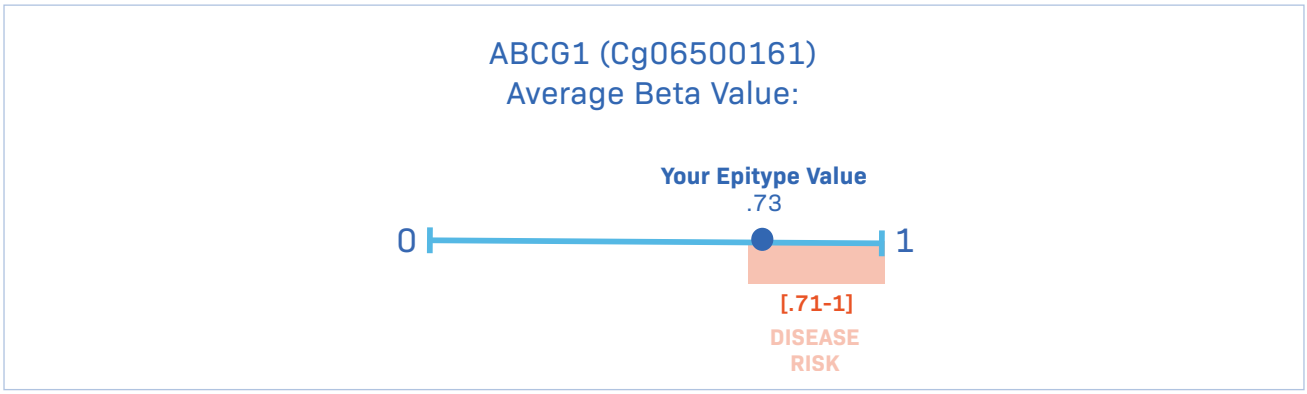


What is ABCG1?

ABCG1 is a gene that encodes a member of the ATP-binding cassette (ABC) protein family, which plays a role in the homeostasis of glucose and lipids. These proteins do so by removing excess cholesterol from peripheral tissues and transporting it to the liver. The HDL-mediated increase in insulin secretion is dependent on ABCG1 [2]. Loss of both the ABCA1 and ABCG1 genes results in sterol accumulation, impaired glucose-stimulated insulin secretion, and inflammation of pancreatic ß-cells which can all lead to diabetes [6].

The ABCG1 marker has been replicated across different tissues in more than 10,000 individuals representing different ethnicities. Altered DNA methylation in ABCG1 is associated with the downregulation of mRNA levels from T2D individuals [2]. DNA methylation at this site in blood DNA has demonstrated to be functionally correlated with a number of T2D risk factors, such as BMI, triglycerides, and HbA1c [3].

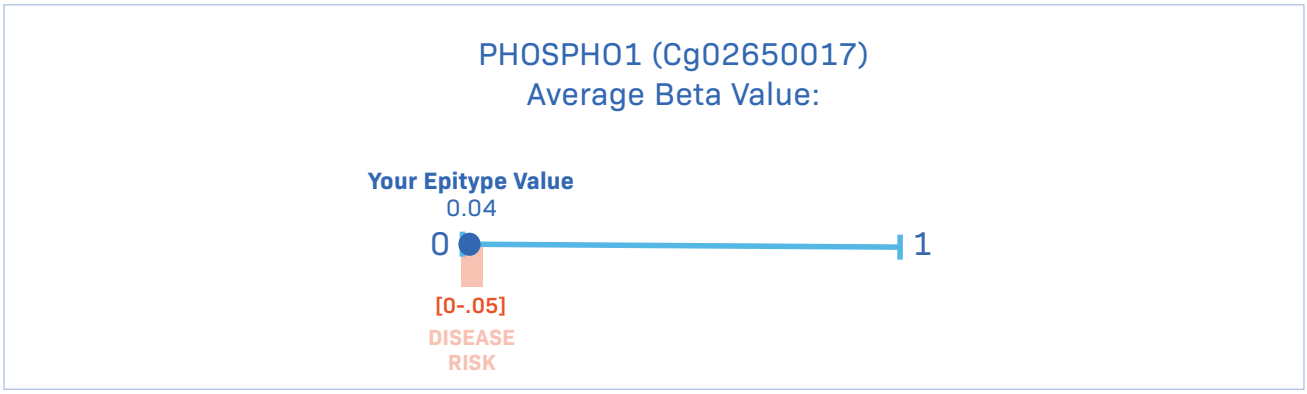
Your DNA methylation score at ABCG1 locus cg06500161 gives an indication of your level of risk for type 2 diabetes; if your score is 70.1% or greater it is associated with a 9% increased risk for future type 2 diabetes occurrence.



What is PHOSPHO1?

PHOSPHO1 encodes a phosphatase that is highly expressed in skeletal muscle and plays a role in skeletal mineralization. Under certain circumstances, it may also cause vascular mineralization. Cardiovascular calcification is a common consequence of aging, diabetes, and hypercholesterolemia. PHOSPHO1, is also considered to be an attractive target for cardiovascular therapy. Interestingly, it has been found that DNA methylation at the PHOSPHO1 locus cg02650017 in blood correlated positively with HDL levels. DNA methylation at the PHOSPHO1 locus cg02650017 is associated with future T2D risk [3].

A DNA methylation score of 5.0% or greater at the PHOSPHO1 locus cg02650017 in blood DNA was associated with a 15% decreased risk for future type 2 diabetes occurrence.



The Science

DNA methylation at the ABCG1 locus cg06500161 in blood DNA was associated with a 9% increased risk for future T2D (OR = 1.09, 95% CI = 1.02–1.16, P-value = 0.007, Q-value = 0.018), while DNA methylation at the PHOSPHO1 locus cg02650017 in blood DNA was associated with a decreased risk for future T2D (OR = 0.85, 95% CI = 0.75–0.95, P-value = 0.006, Q-value = 0.018) after adjustment for age, gender, fasting glucose, and family relation.

Furthermore, the level of DNA methylation at the ABCG1 locus cg06500161 in blood DNA correlated positively with BMI, HbA1c, fasting insulin, and triglyceride levels, and was increased in adipose tissue and blood from the diabetic twin among monozygotic twin pairs discordant for T2D. DNA methylation at the PHOSPHO1 locus cg02650017 in blood correlated positively with HDL levels [3].

THE IMPACT TO YOU

The impact to you is based on your level of methylation at these gene loci compared with the risk categories determined and assessed in the cited papers in regards to T2D risk.

Your DNA methylation score was _A__ at the ABCG1 locus and __B_ at the PHOSPHO1 locus.

Your DNA methylation scores at these gene loci would reflect __C__ according to the referenced study. [3]

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

Type 2 diabetes can be modified and/or mediated by epigenetic changes, and a number of genetic and non-genetic factors have been identified that increase the risk of T2D. Recent studies have found 5 DNA methylation loci associated with T2D occurrence. ABCG1 is a gene that insulin secretion is dependent on. Altered DNA methylation in ABCG1 is associated with the locus downregulation of mRNA levels from T2D individuals. DNA methylation at the ABCG1 locus cg06500161 in blood DNA was associated with an increased risk for future T2D and DNA methylation at the PHOSPHO1 locus cg02650017 in blood DNA was associated with a decreased risk for future T2D. DNA methylation at these loci is associated with cholesterol levels, triglyceride levels, ischemic stroke, and risk of T2D. Identifying T2D risk factors is fundamental for the prevention of

REFERENCES

1. Chambers, J. C., Loh, M., Lehne, B., Drong, A., Kriebel, J., Motta, V., Wahl, S., Elliott, H. R., Rota, F., Scott, W. R., Zhang, W., Tan, S.-T., Campanella, G., Chadeau-Hyam, M., Yengo, L., Richmond, R. C., Adamowicz-Brice, M., Afzal, U., Bozaoglu, K., … Kooner, J. S. (2015). Epigenome-wide association of DNA methylation markers in peripheral blood from Indian Asians and Europeans with incident type 2 diabetes: a nested case-control study. The Lancet. Diabetes & Endocrinology, 3(7), 526–534. https://doi.org/10.1016/s2213-8587(15)00127-8

2. Cheng, Z., Zheng, L., & Almeida, F. A. (2018). Epigenetic reprogramming in metabolic disorders: nutritional factors and beyond. The Journal of nutritional biochemistry, 54, 1–10. https://doi.org/10.1016/j.jnutbio.2017.10.004

3. Dayeh, T., Tuomi, T., Almgren, P., Perfilyev, A., Jansson, P.-A., de Mello, V. D., Pihlajamäki, J., Vaag, A., Groop, L., Nilsson, E., & Ling, C. (2016). DNA methylation of loci within ABCG1 and PHOSPHO1 in blood DNA is associated with future type 2 diabetes risk. Epigenetics, 11(7), 482–488. https://doi.org/10.1080/15592294.2016.1178418

4. Dedeurwaerder, S., Defrance, M., Bizet, M., Calonne, E., Bontempi, G., & Fuks, F. (2014). A comprehensive overview of Infinium Human-Methylation450 data processing. Briefings in bioinformatics, 15(6), 929–941. https://doi.org/10.1093/bib/bbt054

5. Dolzhenko, E., & Smith, A. D. (2014). Using beta-binomial regression for high-precision differential methylation analysis in multifactor whole-genome bisulfite sequencing experiments. BMC bioinformatics, 15, 215. https://doi.org/10.1186/1471-2105-15-215

6. Kruit, J. K., Wijesekara, N., Westwell-Roper, C., Vanmierlo, T., de Haan, W., Bhattacharjee, A., Tang, R., Wellington, C. L., LütJohann, D., Johnson, J. D., Brunham, L. R., Verchere, C. B., & Hayden, M. R. (2012). Loss of both ABCA1 and ABCG1 results in increased disturbances in islet sterol homeostasis, inflammation, and impaired β-cell function. Diabetes, 61(3), 659–664. https://doi.org/10.2337/db11-1341

7. Lyssenko, V., & Laakso, M. (2013). Genetic Screening for the Risk of Type 2 Diabetes. Diabetes Care, 36(Supplement 2), S120 LP-S126. https://doi.org/10.2337/dcS13-2009

8. McCarthy, M. I. (2010). Genomics, Type 2 Diabetes, and Obesity. New England Journal of Medicine, 363(24), 2339–2350. https://doi.org/10.1056/NEJMra0906948

9. Pfeiffer, L., Wahl, S., Pilling, L. C., Reischl, E., Sandling, J. K., Kunze, S., Holdt, L. M., Kretschmer, A., Schramm, K., Adamski, J., Klopp, N., Illig, T., Hedman, Å. K., Roden, M., Hernandez, D. G., Singleton, A. B., Thasler, W. E., Grallert, H., Gieger, C., Herder, C., … Waldenberger, M. (2015). DNA methylation of lipid-related genes affects blood lipid levels. Circulation. Cardiovascular genetics, 8(2), 334–342. https://doi.org/10.1161/CIRCGENETICS.114.000804

10. Sun, Z., Chai, H. S., Wu, Y., White, W. M., Donkena, K. V, Klein, C. J., Garovic, V. D., Therneau, T. M., & Kocher, J.-P. A. (2011). Batch effect correction for genome-wide methylation data with Illumina Infinium platform. BMC Medical Genomics, 4(1), 84. https://doi.org/10.1186/1755-8794-4-84

11. Qin, X., Li, J., Wu, T., Wu, Y., Tang, X., Gao, P., Li, L., Wang, M., Wu, Y., Wang, X., Chen, D., & Hu, Y. (2019). Overall and sex-specific associations between methylation of the ABCG1 and APOE genes and ischemic stroke or other atherosclerosis-related traits in a sibling study of Chinese population. Clinical epigenetics, 11(1), 189. https://doi.org/10.1186/s13148-019-0784-0

12. Weinhold, L., Wahl, S., Pechlivanis, S., Hoffmann, P., & Schmid, M. (2016). A statistical model for the analysis of beta values in DNA methylation studies. BMC bioinformatics, 17(1), 480. https://doi.org/10.1186/s12859-016-1347-4