Innovative approach successfully maps susceptibility to type 2 diabetes

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Research carried out at the Hebrew University of Jerusalem has provided the first proof of molecular risk factors leading to type 2 diabetes, providing an "early warning" sign that could lead to new approaches to treating this and other human disease conditions.

Despite extensive research on the molecular basis for the variance in susceptibility between individuals to common diseases, the subject is still poorly understood. A prime example of this is type 2 diabetes (T2D), a very widespread human disorder.

What is it that characterizes the susceptibility to this disease? Epigenetic variations – which are small molecular marks superimposed on the DNA structure – have been frequently hypothesized to modify predisposition, but direct evidence was missing.

Now, a research team led by Dr. Asaf Hellman of the Hebrew University's Institute of Medical Research Israel Canada has developed a novel, multistep, study design involving the analysis of disease-contributing epigenetic variations among hundreds of patients and control individuals. The research was presented in a scientific conference at the Cambridge University Genomic Center and was recently published in the scientific journal *Human Molecular Genetics*.

Taking an innovative research direction, the Hebrew University research team decided to map DNA methylation variations rather than DNA sequence variations, as was traditionally done. The team undertook a

proof-of-concept study among 1,169 type 2 diabetes patients and non-diabetic controls. The results demonstrated the unique abilities of this novel research approach by revealing a clear-cut, disease-predisposing DNA methylation signature. This is a first report in the scientific literature of epigenetic risk factor for T2D.

DNA methylation is a naturally occurring mechanism used to regulate genes and protect DNA from some types of cleavage. It is one of the regulatory processes that are referred to as epigenetic, in which an alteration in gene expression occurs without a change in the nucleotide sequence of the DNA. Defects in this process cause several types of disease that afflict humans.

The method used by Hellman was developed during postdoctoral training at the Harvard University Medical School. Later, his research students at the Hebrew University, Gidon Tperoff and Dvir Aran, further developed it into an efficient, genome-wide mapping method.

The mapping was carried out on the methylation sites in cooperation with Prof. Benjamin Glaser, head of the Endocrinology and Metabolism Department at the Hebrew University-Hadassah Medical School and a leading researcher of T2D genetics, and with additional key researchers including Professors Jeremy Kark and Yechiel Friedlander from the Braun Hebrew University-Hadassah School of Public Health and Community Medicine, Prof. Julio Wainstein from the Wolfson Medical Center, and Prof. Ephrat Levy-Lahad from the Shaare Zedek Medical Center.

This analysis not only revealed, for the first time, a clear-cut epigenetic signature in T2D, telltale methylation signature marks were also shown to appear on the DNA of young individuals who latter developed impaired glucose metabolism, even before the appearance of clinical diabetic manifestations.

These findings shed new light on the mechanism of individual predisposition to T2D and pave the way for the elucidating of similar mechanisms in a long list of common human diseases, including many metabolic, autoimmune and psychiatric disorders.

Given that epigenetic marks are sensitive to a wide range of environmental clues, including diets, chemical exposures, intrauterine environments, and also to therapeutic drugs, these finding may open the way for the development of new prevention and/or intervention epigenetic therapies.

More information: Genome-wide survey reveals predisposing diabetes type 2-related DNA methylation variations in human peripheral blood, *Human Molecular Genetics.*

Provided by Hebrew University of Jerusalem

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