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Researchers identify genetic elements influencing the risk of type 2 diabetes

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A team led by researchers at the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health, has captured the most comprehensive snapshot to date of DNA regions that regulate genes in human pancreatic islet cells, a subset of which produces insulin.

The study highlights the importance of genome regulatory sequences in human health and disease, particularly type 2 diabetes, which affects more than 20 million people in the United States and 200 million people worldwide. The findings appear Nov. 3 in Cell Metabolism.

"This study applies the power of epigenomics to a common disease with both inherited and environmental causes," said NHGRI Scientific Director Daniel Kastner, M.D., Ph.D. "Epigenomic studies are exciting new avenues for genomic analysis, providing the opportunity to peer deeper into genome function, and giving rise to new insights about our genome's adaptability and potential."

Epigenomic research focuses on the mechanisms that regulate the expression of genes in the human genome. Genetic information is written in the chemical language of DNA, a long molecule of nucleic acid wound around specialized proteins called histones. Together, they constitute chromatin, the DNA-protein complex that forms chromosomes during cell division.

The researchers used DNA sequencing technology to search the chromatin of islet cells for specific histone modifications and other

signals marking regulatory DNA.

Computational analysis of the large amounts of DNA sequence data generated in this study identified different classes of regulatory DNA.

"This study gives us an encyclopedia of regulatory elements in islet cells of the human pancreas that may be important for normal function and whose potential dysfunction can contribute to disease," said senior author and NIH Director Francis S. Collins, M.D., Ph.D. "These elements represent an important component of the uncharted genetic underpinnings of type-2 diabetes that is outside of protein-coding genes."

Among the results, the researchers detected about 18,000 promoters, which are regulatory sequences immediately adjacent to the start of genes. Promoters are like molecular on-off switches and more than one switch can control a gene. Several hundred of these were previously unknown and found to be highly active in the islet cells.

"Along the way, we also hit upon some unexpected but fascinating findings," said co-lead author Praveen Sethupathy, Ph.D., NHGRI postdoctoral fellow. "For example, some of the most important regulatory DNA in the islet, involved in controlling hormones such as insulin, completely lacked typical histone modifications, suggesting an unconventional mode of gene regulation."

The researchers also identified at least 34,000 distal regulatory elements, so called because they are farther away from the genes. Many of these were bunched together, suggesting they may cooperate to form regulatory modules. These modules may be unique to islets and play an important role in the maintenance of blood glucose levels.

"Genome-wide association studies have told us there are genetic

differences between type 2 diabetic and non-diabetic individuals in specific regions of the genome, but substantial efforts are required to understand how these differences contribute to disease," said co-lead author Michael Stitzel, Ph.D., NHGRI postdoctoral fellow. "Defining regulatory elements in human islets is a critical first step to understanding the molecular and biological effects for some of the genetic variants statistically associated with type 2 diabetes."

The researchers also found that 50 single nucleotide polymorphisms, or genetic variants, associated with islet-related traits or diseases are located within or very close to non-promoter regulatory elements. Variants associated with type 2 diabetes are present in six such elements that function to boost gene activity. These results suggest that regulatory elements may be a key component to understanding the molecular defects that contribute to type 2 diabetes.

Genetic association data pertaining to diabetes or other measures of islet function continue to be generated. The catalog of islet regulatory elements generated in the study provides an openly accessible resource for anyone to reference and ask whether newly emerging, statistically-associated variants are falling within these regulatory elements. The raw data can be found at the National Center for Biotechnology Information's Gene Expression Omnibus using accession number GSE23784.

"These findings represent important strides that were not possible just five years ago, but that are now realized with advances in genome sequencing technologies," said NHGRI Director Eric D. Green, M.D., Ph.D. "The power of DNA sequencing is allowing us to go from studies of a few genes at a time to profiling the entire genome. The scale is tremendously expanded. "

In addition to the NHGRI and the NIH Intramural Sequencing Center,

researchers from Duke University, Durham, N.C. and the University of Michigan, Ann Arbor, contributed to the study.

Previously known as adult-onset, or non-insulin dependent diabetes mellitus, type 2 diabetes usually appears after age 40, often in overweight, sedentary people. However, a growing number of younger people — and even children — are developing the disease.

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