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Protein important in diabetes may also play a key role in heart disease, other disorders

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Studying a protein already known to play an important role in type 2 diabetes and cancer, genomics researchers have discovered that it may have an even broader role in disease, particularly in other metabolic disorders and heart disease. In finding unsuspected links to other disease-related genes, the scientists may have identified future targets for drug treatments.

The paper appeared online July 17 in the British journal *Diabetologia*.

"This protein could be a central player in many different diseases and traits," said study leader Struan F.A. Grant, Ph.D., a geneticist at The Children's Hospital of Philadelphia and a faculty member of the University of Pennsylvania School of Medicine. The current finding builds on Grant's 2006 discovery, now widely replicated, that a gene called TCF7L2 is strongly linked to type 2 diabetes.

Type 2 diabetes results either when the pancreas produces insufficient insulin or when the body's insulin-processing cells develop resistance to insulin, causing blood sugar to rise to unhealthy levels.

The TCF7L2 gene carries the code for a transcription factor--also called TCF7L2--a protein that binds to genes and regulates their activity. Exactly how this protein acts to affect diabetes is still unknown. However, Grant noted that there is great scientific interest in identifying which genes the transcription factor regulates. "It may be more feasible to develop drugs aimed at proteins encoded by specific gene classes

regulated by TCF7L2 that are more amenable to targeted interventions, rather than aiming at a more ubiquitous transcription factor," he said.

Because variants in the TCF7L2 gene are also associated with risk for different cancers, including colorectal cancers, there was even greater reason to learn details of its biological activity. "Our goal," said Grant, "was to simply uncover the repertoire of genes that this transcription factor controls."

Collaborating with investigators at the University of Pennsylvania, Grant used a technique called ChIP-sequencing, which locates and compiles the DNA sequences of genes to which proteins bind. "This uses the latest-generation sequencing technology that has only recently become feasible, allowing investigators to rapidly sequence at the scale of whole genomes," said Grant. In human cell lines, this ChIP approach identified and mapped DNA sequences of TCF7L2 binding sites at over 1,000 gene locations.

"What was unexpected and striking about our results was that this transcription factor binds to a large number of gene locations already implicated in disease from previous GWAS research," said Grant. In the last five years, GWAS, or genome-wide association studies, have proven to be highly successful in scouring the genome to locate gene sites associated with particular diseases.

"We found an over-representation of genes associated with metabolic disorders, such as diabetes, but also with cardiovascular disorders, such as coronary artery disease and atherosclerosis," Grant added. "We expect to follow up these initial observations with functional research to investigate how these genes operate in these diseases, and whether these genes may become candidates for better therapies. For now, our work suggests that this transcription factor may be a central node in a network of genes associated not only with type 2 diabetes, but also exerting its

influence much further in contributing to other genetic diseases."

Provided by Children's Hospital of Philadelphia