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Genetic mutations identified that suggest link between type 1 diabetes and common viral infection

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Scientists from Cambridge University have discovered four rare mutations of a gene associated with type 1 diabetes (T1D) that reduce the risk of developing the disease. Their findings, published today in the journal *Science* Express, suggest a link between T1D and the enterovirus (a common virus that enters via the gastrointestinal tract but is often non-symptomatic).

Everyone carries the IFIH1 gene, which plays a role in the body's antiviral responses. Importantly, it is also located in the region of the human genome associated with T1D, an autoimmune disorder which results in the body attacking its own insulin-producing pancreatic cells. The IFIH1 gene codes for a protein that recognizes the presence of viruses in the cell and controls immune activation. It is within this gene that scientists have identified four gene variants that protect against T1D.

Enteroviruses are well known to be associated with T1D: enterovirus infections are more common among newly diagnosed T1D patients and pre-diabetic subjects than in the general population and often precede the appearance of biological markers for pre-diabetes. However, no one knows if these infections are a cause of type 1 diabetes.

The study by Nejentsev et al., which was conducted at the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and

Inflammation Laboratory, establishes that the IFIH1 protein is involved in T1D, highlighting a molecular pathway by which enterovirus infections may contribute to the development of the disease. The four rare variants they identified, which are predicted to reduce function of the IFIH1 protein, consistently decrease the risk of T1D, rather than predispose to it. This suggests a model where normal immune activation caused by enterovirus infection and mediated by IFIH1 protein stimulates autoimmunity that eventually leads to T1D.

Professor John Todd, senior author on the study, said: "We have been able to pin-point one particular gene among a long list of candidates. Now we and others can begin to study the biology of IFIH1 in the context of type 1 diabetes knowing that it is part of the cause of the disease."

In the past three years genome-wide association studies have been a major success, revealing dozens of regions in the human genome that harbour genes which predispose individuals to various diseases, such as diabetes or cancers. Nevertheless, as disease-associated regions may contain several genes with different functions, scientists rarely know which gene or gene variant (mutations of the gene) in these regions cause the disease.

In order to overcome this limitation, the scientists searched for variants that had obvious biological effects, e.g. those affecting gene expression or protein function. They hypothesized that if a gene harbors several such variants, then it is likely to be causative. Most of such variants are rare in the population and are not tested in genome-wide association studies. Nevertheless, they could be discovered by sequencing (examining the sequence of the pairs of nucleotides which make up a gene).

The researchers studied 10 candidate genes associated with T1D. Using a

novel technique (high throughput sequencing of DNA pools) in collaboration with 454 Life Sciences, a Roche company, they examined the DNA of 480 T1D patients and 480 healthy controls. This approach allowed them to not only discover several rare variants associated with T1D, but also to accurately measure their frequency in the pools of patients and controls.

The researchers then genotyped approximately 30,000 individuals who were either T1D patients, controls or family members and proved that four rare variants or versions that reside in the gene IFIH1 reduce the risk of developing T1D.

The study demonstrates that re-sequencing genes associated with diseases can help pinpoint the specific gene or genes that lead to the disease.

"Finding several new rare disease variants with clear biological functions was crucial. Not only has this proved that IFIH1 is involved in type 1 diabetes, it also gave us clues to understand the mechanism" said Dr. Sergey Nejentsev, Royal Society Research Fellow at the Department of Medicine, the first author of the study. He added: "This experiment shows the way to identify causative genes contributing to various common diseases."

More information: The article 'Rare Variants of IFIH1, a Gene Implicated in Antiviral Responses, Protect Against Type 1 Diabetes' will appear online in Science Express on 05 March 2009.

Source: University of Cambridge

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