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Next-Generation Sequencing Uncovers Genetic Variation Linking Type 1 Diabetes with Enterovirus Infection

Science study discovers rare mutations in a disease-associated antiviral response gene that reduce the risk developing type 1 diabetes.

A study by Nejentsev et al. published online today in Science reports that researchers have discovered a group of rare variants in a disease-associated gene that appear to lower the risk of developing type 1 diabetes (T1D). The study, conducted by scientists at the Wellcome Trust/JDRF Diabetes and Inflammation Laboratory at the University of Cambridge, used deep sequencing with the Genome Sequencer FLX system from 454 Life Sciences to re-sequence ten candidate genes including those previously identified by genome-wide association studies (GWAS) of T1D. The study presents a novel insight into the genetic basis of type 1 diabetes, a common autoimmune disorder that results in the destruction of insulin-producing pancreatic cells. Also, the study marks one of the first of its kind in discovering a number of protective T1D alleles directly from the results of a previously conducted GWAS. The findings and pioneering scientific method will ultimately provide the knowledge to develop better strategies to detect, treat and prevent T1D and other genetic-based diseases in the future.

Type 1 diabetes is a highly complex, multifactorial disease, meaning that more than one genetic factor, combined with environmental conditions, participates in causation of the condition. To date, genome-wide association studies have identified 15 loci linked to T1D. While GWAS are widely used to map genomic regions contributing to common human diseases, they often do not identify the precise causative genes and sequence variants which are essential to clinical applications. To further elucidate these T1D loci, the researchers in the study selected ten genes for ultra-deep sequencing from the DNA of 480 T1D patients and 480 healthy controls from Great Britain. From the results they identified 179 rare single-nucleotide polymorphisms (SNPs) and then tested the SNPs' association with the disease by comparing allele frequency in the

DNA of over 30,000 T1D patients, controls and family members. The final results found four rare SNPs in the IFIH1 gene with strong statistical evidence of association with the disease. Surprisingly, the results suggest that the rare variants have strong protective effects on T1D risk, meaning that rare alleles of all associated IFIH1 polymorphisms consistently reduce the risk of T1D while IFIH1 alleles carried by the majority of the population predispose to the disease. “These new results pinpoint the IFIH1-MDA5 gene as being causal and actively participating in type 1 diabetes development, and indicate a route to identifying more genes specifically acting in the disease, from currently a very large list of possible candidate genes,” explained Dr. John Todd, senior author of the study. “While these results only accounts a very small piece of the whole picture, it is an important principal finding.”

Interestingly, the researchers found that the protective effects of the rare variants make sense in light of the biological role of the IFIH1 protein. The protein, also known as MDA5, recognizes RNA of picornaviruses and mediates immune activation within the body. Infection with enteroviruses such as coxsackie, polioviruses and echoviruses, all members of the picornavirus family, are more common among newly diagnosed T1D and pre-diabetic patients than in the general population. Although details of the underlying mechanism for the IFIH1 gene’s contribution to disease state would still have to be studied, these variants are predicted to alter transcript splicing or result in truncation of the gene product. This suggests that the variants, which would be expected to reduce function of the IFIH1 protein, decrease the risk of T1D while normal gene function is positively associated with disease. “Finding several new rare disease variants with clear biological functions was crucial. Not only has this proved that IFIH1 is involved in T1D, it also gave us clues to understand the mechanism,” said Dr. Sergey Nejentsev, the first author of the study.

The use of deep 454 Sequencing of amplicons, which enables highly sensitive detection of rare mutations, to even as low as 1% of the allele population, has applications to similar studies in a wide variety of complex diseases. “We are pleased to see 454 Sequencing being used for this type of translational research,” said Michael Egholm, Chief Technology Officer at 454 Life Sciences. “The method outlined in this study pushes the information obtained in GWAS to the next level by identifying actual causative and protective mutations which will potentially serve as targets for detecting, treating and preventing type 1 diabetes and other diseases in the future.”

454 Life Sciences, a center of excellence of Roche Applied Science, develops and commercializes the innovative 454 Sequencing System for ultra-high-throughput DNA sequencing. Specific applications include de novo sequencing and re-sequencing of genomes, metagenomics, RNA analysis, and targeted sequencing of DNA regions of interest. The hallmarks of the 454 Sequencing System are its simple, unbiased sample preparation and long, highly accurate sequence reads, including paired-end reads. The technology of the 454 Sequencing System has enabled hundreds of peer-reviewed studies in diverse research fields, such as cancer and infectious disease research, drug discovery, marine biology, anthropology, paleontology and many more.

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