Small genetic variant can predict response to hepatitis C treatment

EurekAlert

Gothenburg, Sweden: A small genetic change can predict how people infected with hepatitis C react to treatment, paving the way to personalised therapy for this difficult to treat disease, the annual conference of the European Society of Human Genetics will hear today (Sunday 13 June). Dr. Zoltan Kutalik, from the Department of Medical Genetics, University of Lausanne, Switzerland, will tell delegates that individuals with this change, in a gene encoding for the antiviral cytokine (cell-signalling molecule) interferon lamda, reacts less well to treatment. This knowledge could spare them the unpleasant side effects of a therapy which most likely would have little benefit for them, he says.

Hepatitis C is a serious liver disease, normally contracted through drug use, blood transfusion or sexual transmission. About 10% of all patients have no identifiable source of infection. The virus produces chronic infection in around 80% of infected individuals, and half of these do not respond to existing therapies. Current treatment involves a combination of an interferon and the antiviral medication ribavirin. Side effects are common and can be serious to the extent that some people are unable to continue to work.

The fact that people respond so differently to the same treatment is usually because a genetic variation in the non-responders is, via complex genetic pathways, inhibiting the effects of therapy. "The Lausanne University Hospital (CHUV) has a large cohort of Hepatitis C patients seen at the hospital over many years", said Dr. Kutalik, "so this provided the opportunity for us to do a genome-wide association study on 1362 of them to see if we could track down any differences relating to patients' failure to respond to therapy."

Genome-wide association studies look at variations across the entire genome of individuals to look for genetic associations with well-defined traits, including why some people get a particular disease and condition as well as why they might react or not to therapy for it. In this case, approximately half of the patients studied had responded successfully to therapy, giving the scientists the opportunity to compare their genomes with those from patients who had not responded.

"Using a gene-chip technology, a team of clinicians, geneticists and statisticians looked at over one million polymorphic nucleotides, the letters A, C, G and T of the DNA sequence", said Dr. Kutalik. "Our analysis revealed that a single nucleotide polymorphism, or SNP, was present in a gene called IL28B, which encodes for interferon lambda. This was significantly associated with both natural and drug-induced clearance of the hepatitis C virus from the body. This polymorphism may exert its influence by modulating the expression level of the interferon lambda gene."

Individuals who carry the protective allele (letter) at this genetic locus are twice as likely to clear the virus and, even if they do not, they will respond to therapy in a sustained manner; the scientists say. "Individuals infected with the less malignant subtype of the virus and carrying no risk allele were five times more likely to respond than those who were infected with other subtypes and who carried at least one copy of the risk allele. Based on our results we can speculate that the interferon lamda gene is key to increasing the success of therapy, as such therapy could, in theory, compensate for the effect of the polymorphism. Phase 1B trials of interferon lamda therapy in patients with hepatitis C have already shown promising results", Dr. Kutalik said.

The scientists intend to follow up their work by focusing on a better understanding of the more complex characteristics of hepatitis C, including finding the genetic variants that are responsible for hepatitis C liver fibrosis. "This disease affects up to 300 million people worldwide. It is insidious, and often individuals are not aware that they are infected until serious liver damage has taken place", said Dr. Kutalik. "Finding better treatments is vital. As well as sparing those who would not react well to current treatment from side effects, we hope that our work may provide pointers to the development of effective therapies for the future."

SOURCE [1]

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