Genomic analysis uncovers new targets for HIV vaccine

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An international team of researchers has identified three gene variants in the DNA of 486 people infected with HIV that appear to have helped some of the patients fight off the virus and delay the onset of full-blown AIDS.

The researchers expect the new findings to aid the search for an HIV vaccine that would work by boosting the protective effects of one or more of these genes, and help the body's own immune system overcome an infection. One of the genes looks particularly attractive as a vaccine target.

The study, published early online by the journal Science July 19, was directed by David Goldstein at Duke University and is the first large cooperative study with major findings arising from the Center for HIV/AIDS Vaccine Immunology, (CHAVI) a seven-year project funded by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, in 2005, led by Duke's Barton Haynes, M.D.

It took the international genetics team, called EuroCHAVI, pooling their cohorts of carefully selected patients and using the latest in genome-wide screening technology, 18 months to discover the three genes, that together greatly increase our knowledge of why patients differ in how well they can control the virus that causes AIDS.

These findings represent only the first of what investigators said will be a

series of future genome-wide studies to pinpoint additional targets for HIV vaccines. In the new analysis, patients with specific gene variants in key immune system cells appear to be much better at controlling the proliferation of the virus after infection. These gene variants are known as polymorphisms.

“These results not only approximately double our understanding of the factors that influence variation amongst individuals in how they control HIV-1, but also point torward new mechanisms of control,” said David Goldstein, Ph.D., director of the Center for Population Genomics and Pharmacogenetics at Duke’s Institute for Genome Sciences & Policy. Goldstein is the senior author of the paper.

“As we expand the number of patients in future studies conducted by CHAVI researchers, we aim to discover even more polymorphisms that could provide additional clues how some patients are better able to control the virus than others,” Goldstein. “This should ultimately lead to novel targets for vaccines, the primary goal of CHAVI.”

Two of the polymorphisms found were in genes controlling the human leukocyte antigen (HLA) system, which plays a major role in the immune system by identifying foreign invaders and “tagging” them for destruction.

Two of the HLA genes, known as HLA-A and B, are turned off by HIV when it enters the body, which keeps the immune system from recognizing the virus as foreign. HLA-C however is not thought to be turned off by HIV-1. The new results suggest that for some individuals at least HLA-C is involved in controlling HIV-1. Since HIV-1 appears unable to shut off HLA-C, unlike A and B, HLA-C may represent an Achilles heel of HIV, according to Goldstein, who said that a vaccine could be designed to elicit an HLA-C mediated response which HIV-1 might be unable to defuse.

“This study was the first time a genome-wide approach has been used for an infectious disease,” Goldstein said. “Past studies have looked at individual candidate genes. Since different people respond differently to infections, a better understanding of how immune system genes control responses to infections should help us to design better treatments and more effective vaccines.”

Added Haynes: “CHAVI was designed to do big science, and the results of this analysis represent just the first of what should be many advances. The technology used and collaborative efforts involved were truly remarkable: together as a group we were able to do something that none of us individually could accomplish. The results of this and future CHAVI studies should help individual laboratories across the world perform research to better understand the virus.”

When someone becomes infected with HIV, the amount of virus in the blood spikes as the virus multiplies. After this peak, the amount of virus in the blood, known as the viral load, gradually decreases and then levels off, a period during which patients do not exhibit symptoms of their disease. The viral load during this leveling out is an indication of how well the patients’ own immune system is battling the virus, and this is the point in the infection’s natural history that the researchers studied.

The CHAVI investigators wanted to study those patients who had many sequential blood samples taken during this plateau in viral load. Before their analyses began collaborators in the EuroChavi consortium, coordinated by Amalio Telenti at the University of Lausanne, sifted through data collected from more than 30,000 patients who had blood samples taken as a part of nine studies in Europe and Australia. They arrived at 486 patients who had had multiple blood tests documenting viral loads after infection and before they started receiving antiretroviral treatment.

The three polymorphisms were identified after all the blood samples of the selected patients were screened for more than 555,000.

Additionally, the researchers discovered many other genetic variants that may confer protection for patients but whose effects did not reach statistical significance in the study. However, some of these polymorphisms could ultimately be shown to play a major role when future analyses involving more patients are performed, the researchers said.

Source: Duke University Medical Center