

Small protein changes may make big difference in natural HIV control

November 4 2010

Tiny variants in a protein that alerts the immune system to the presence of infection may underlie the rare ability of some individuals to control HIV infection without the need for medications. In a report that will appear in *Science* and is receiving early online release, an international research team led by investigators from the Ragon Institute of Massachusetts General Hospital (MGH), MIT and Harvard and from the Broad Institute of MIT and Harvard describe finding that differences in five amino acids in a protein called HLA-B are associated with whether or not HIV-infected individuals can control viral levels with their immune system only.

"We found that, of the three billion [nucleotides](#) in the human [genome](#), just a handful make the difference between those who can stay healthy in spite of HIV infection and those who, without treatment, will develop AIDS," says Bruce Walker, MD, director of the Ragon Institute and co-senior author of the *Science* article. "Understanding where this difference occurs allows us to sharpen the focus of our efforts to ultimately harness the immune system to defend against HIV."

"Earlier studies had showed that certain genes involved with the HLA system were important for HIV control," adds Paul de Bakker, PhD, of the Broad Institute and Brigham and Women's Hospital, co-senior author. "But they couldn't tell us exactly which genes were involved and how they produced this difference. Our findings take us not only to a specific protein, but to a part of that protein that is essential to its function."

It has been known for almost two decades that a small minority – about one in 300 – of individuals infected with HIV are naturally able to suppress viral replication with their immune system, keeping viral load at extremely low levels. To identify genetic differences that may underlie this rare ability, Florencia Pereyra, MD, at the Ragon Institute established the International HIV Controllers Study (<http://www.hivcontrollers.org/>) in 2006, with a goal of enrolling 1,000 HIV controllers from medical clinics and research institutes around the world. That goal was expanded to 2,000 controllers in 2008, and thus far over 1,500 controllers have been enrolled.

The current investigation began with a genome-wide association study (GWAS) of almost 1,000 controllers and 2,600 individuals with progressive [HIV infection](#), through a collaboration with the AIDS Clinical Trials Group. The GWAS, which tests variations at a million points in the human genome, identified some 300 sites that were statistically associated with immune control of HIV, all in regions of chromosome 6 that code for HLA proteins. Further analysis narrowed the number of gene sites to four but could not indicate whether those differences actually affected viral control or were just located near the causal variants. Fully sequencing that genome region in all participants was not feasible, but a process developed by Sherman Jia – a medical student in the Harvard-MIT Health Sciences and Technology program, working with de Bakker at the Broad – pinpointed specific [amino acids](#); and directly testing those sites associated five amino acids in the HLA-B protein with differences in viral control.

HLA-B is essential to the process by which the immune system recognizes and destroys virus-infected cells. Usually HLA-B grabs onto viral protein segments called peptides that are inside the cell and carries them to the cell membrane where they essentially flag the infected cell for destruction by CD8 "killer" T cells. The portion of the HLA-B protein that grabs and displays viral peptides is called the binding pocket,

and all of the five identified amino acid sites are in the lining of the binding pocket.

"Amino acid variation within the HLA-B binding pocket will impact its shape and structure, probably resulting in some peptides being presented effectively and others not," de Bakker says. "Our work demonstrates that these variants could make a crucial difference in the individual's ability to control HIV by changing how HLA-B presents peptides from this virus to the [immune system](#)."

Walker adds, "HIV is slowly revealing its secrets, and this is yet another. Knowing how an effective immune response against HIV is generated is an important step toward replicating that response with a vaccine. We have a long way to go before translating this into a treatment for infected patients and a vaccine to prevent infection, but we are an important step closer."

The investigators note that these findings would not have been possible without the participation of the hundreds of HIV controllers, many of whom traveled to Boston for testing, who have enrolled in the study. "The enthusiasm among the patients we have enrolled and the [HIV](#) providers who referred them has been amazing," says Pereyra. "They tell us that being part of this collaborative study means a lot to them."

Provided by Massachusetts General Hospital

Citation: Small protein changes may make big difference in natural HIV control (2010, November 4) retrieved 26 April 2024 from <https://medicalxpress.com/news/2010-11-small-protein-big-difference-natural.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.