High-speed genetic analysis looks deep inside primate immune system

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This system, called the "major histocompatibility complex" or MHC, is found in all mammalian immune systems. Although MHC genes are complicated, variable and difficult to read, a good "map" of the genes would help biologists understand why individuals have different responses to viruses.

Variations in the MHC genes could be key to some of medicine's best-kept secrets: why some rare "non-progressors" do not get AIDS despite long-term infection with HIV, why some people respond poorly to vaccines, and how best to harness the immune response to defeat viruses.

Now, in a study published today (Oct. 11) in Nature Medicine, a team of researchers at the Wisconsin National Primate Research Center at the University of Wisconsin-Madison have shown a high-speed method for analyzing the stubbornly complex MHC genes in three species of

monkeys. "We have an abiding interest in the genes that are involved in immunity to pathogens," says David O'Connor, the study's senior author and deputy director of the primate center. "People around the world, like other mammals, have encountered pathogens that have shaped the genes that control their immune systems. These genes are highly variable, and have been very difficult to study with conventional methods."

The new study used "454 parallel sequencing," which is typically used to create a highly detailed, "deep" genome sequence of individual organisms. The Wisconsin team tweaked this technology. Instead of attaining the greatest detail on a small number of individuals, they sacrificed a bit of accuracy to look at hundreds of samples from macaque monkeys, animals that are widely used in immunology research. They found that each monkey expresses more than two dozen MHC genes, at least four times the number in humans. The genes varied greatly, reflecting each individual's geographic origin and the history of infection among its ancestors.

The sequencing was performed in collaboration with researchers at the University of Illinois at Urbana-Champaign, and the instrument maker, 454 Life Sciences, a division of Roche. "This study shows the tremendous potential of 454 sequencing to fundamentally change the way we study MHC genetics in human disease research," says Michael Egholm, chief technology officer and vice president of research and development at 454 Life Sciences.

Because variations in MHC plays such a key role in immunity, the new ability to "read" the structure of MHC genes should improve the efficiency of animal research, says Roger Wiseman, a geneticist and the study's lead author. "This will allow us to select better groups of animals for vaccine trials, perhaps allowing for fewer animals to be used in each study."

The high-speed sequencing technology "can be used to look at any highly variable gene in large numbers of samples simultaneously," adds O'Connor, whose laboratory has started using the technology to study immune responses and drug resistance in HIV/AIDS patients, correlating genetics with different responses to the virus. "We think this will help us understand why some people do much better than others. The global diversity of HIV and the MHC genes of infected people are complex and expensive to study."

"This idea of looking for drug-resistant mutations has already been applied to single patients," adds Wiseman, who is also in UW-Madison's Department of Pathology and Laboratory Medicine. "We can now do this more economically on much larger groups of patients, which would be particularly useful in developing countries, where drug-resistance tests are seldom affordable." The United Nations just reported that about 4 million people in the developing world are taking anti-retroviral medicines for HIV.

Another application for rapid sequencing could be to screen potential donors for bone-marrow transplants, says Wiseman. "It's a bit down the road, but this could be used to tissue-type hundreds or thousands of individuals, maybe even an entire donor registry, in one fell swoop, and it could be faster, more thorough and less expensive than conventional techniques. This could produce better treatment outcomes by ensuring better tissue matches."

Provided by University of Wisconsin-Madison (news : web)