Sean Goes Hetero

A new genetic test raises more questions than it answers about HIV and risks

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Laboratory analyses of blood and other medical measurements, which help health practitioners make diagnoses and detect toxic effects of medication, can also help people with HIV track their health. ***Jerome E. Groopman, MD****, heads the Division of Experimental Medicine at Beth Israel Deaconess Medical Center in Boston and is a professor of medicine at Harvard Medical School. He has researched genetic aspects of HIV infection for many years. Groopman analyzes the genetic test results of* POZ *founder Sean O. Strub.*

Last year, the world of AIDS research was riveted by findings suggesting that the presence or absence of certain genetic mutations might determine whether an HIV negative person would be immune to HIV and whether an HIV positive person would become a slow or a fast progressor to full-blown AIDS. A study that tested the blood of people who were repeatedly exposed to HIV but remained HIV negative -- including intravenous drug-users, gay men who participated in unsafe sex and recipients of contaminated blood products -- found that some (although not all) such individuals had a genetic mutation or deletion in both of the genes responsible for a protein called CCR5 (or CKR5). (Remember: You inherit two copies of each of your genes, one from your father and one from your mother.) CCR5 normally occurs on the surface of certain immune cells, acting as a receptor for immune proteins called chemokines. The double mutation rendered these people's CCR5 protein nonfunctional.

Other studies revealed that CCR5 is a "fusion coreceptor" used by the HIV strains that most frequently cause initial infection to enter cells after the virus attaches to the other better-known receptor, CD4. People who have inherited two mutated copies of the gene (called "homozygotes") completely lack functional CCR5 receptors and seem to be infected by HIV only rarely. The latest studies estimate that only about one percent of the white population has this double gene mutation. (Note: In most of the research to date, only white [Caucasian] people have been studied. Researchers believe that people of other races have the same coreceptors but that there may be different mutations. It is also important to realize that the HIV strains generally present in people with advanced AIDS include other forms of the virus that are able to bind to T-cells via a different receptor called CXCR4.)

People who have one mutated copy of the CCR5 gene and one normal copy (who are called "heterozygotes") can definitely be infected but may, at least in some cases, have a tendency

toward slower disease progression. In studies to date, it appears that some (although not all) so-called long-term nonprogressors -- people who have had HIV for years without significant immune deterioration -- are heterozygotes for CCR5. This suggests that a reduced number of CCR5 receptors may slow HIV replication in some people.

Sean's blood was analyzed using the commercial version of the CCR5 test now available. But before discussing his results we must ask: Is there any practical value to knowing one's CCR5 genetic status? It's important to emphasize that our understanding of CCR5 and other chemokine receptors -- and their role in both susceptibility to infection and disease progression -- is limited and likely to change as ongoing laboratory and clinical studies add to our base of knowledge.

For example, Australian researchers have recently reported finding a Caucasian man who had no CCR5 receptors due to the double genetic mutation but nonetheless became HIV positive. Other recent findings indicate that as the virus mutates it may develop the ability to attach to chemokine receptors other than CCR5 or CXCR4. It also appears that HIV-2, the type of virus that is prevalent in West Africa and has been diagnosed sporadically in Europe, is capable of attaching via several different chemokine receptors.

In addition, many people who have been repeatedly exposed to the virus without becoming HIV positive turn out to have perfectly normal CCR5 receptors on the surface of their cells. And researchers have also found individuals who are heterozygotes for CCR5 who have shown significant progression of HIV disease. Thus, we do not have a simple or fixed picture of how HIV enters susceptible cells, how this may change over time or the ultimate effect of any of this on disease progression -- and the story on all of this is likely to be far more complex than we currently understand.

So it would be premature, inaccurate and potentially dangerous to assume that a CCR5 homozygote is not susceptible to HIV infection, or that a CCR5 heterozygote will have slow or no disease progression. And therein lie the dangers in using this test. The first is that an HIV negative person who is told that he or she is a CCR5 homozygote (listed on the test as "2 Gene Deletion") might throw caution to the wind and participate in unsafe sex based on the assumption that it's not possible to become HIV infected. That would be a very grave mistake -- somewhat like playing Russian roulette thinking the gun is empty when it might really be loaded.

And the second danger is the false sense of security that some HIV positive people might feel if they find out they are CCR5 heterozygotes and, based on that, then believe that they are unlikely to progress. In the extreme, such people might decide not to consider antiretroviral treatments that have proven to be helpful or, in general, might pay little attention to issues affecting their health and wellness.

Sean's results are a good example, in this regard. The test shows that he's a heterozygote with one mutated gene and one normal one (reported as "1 Gene Deletion"). However, although compared to statistical averages he might be said to have progressed more slowly than the norm, he did ultimately progress to full-blown AIDS -- and has experienced a number of serious complications including Mycobacterium avium complex (MAC) and Kaposi's sarcoma that extended

into his lungs, as well as numerous symptoms such as fatigue, swollen lymph glands and multiple skin problems, such as fungal infections. Luckily, he has used all the best available treatments and is currently in remarkably good shape. Someone who, learning his or her heterozygote status, had made less wise decisions about medical therapies might not have been so fortunate.

A number of HIV negative gay men have asked me to administer the CCR5 test, clearly seeking a green light to throw away their condoms and return to unprotected sex. I always direct them to research studies, where there is behavioral counseling and ongoing discussion about each person's results and their medical implications. With the current version of individual testing, there is no such communication -- a great disservice, since accurate information is our strongest weapon in making intelligent decisions.

The only good reason I can see to be tested would be to participate in such research studies aimed at improving our understanding of the genetic differences that may be relevant to HIV susceptibility, and of how genetic differences, as well as behavioral cofactors (such as drug use and nutrition) or infectious cofactors (such as herpes viruses), may influence the course of HIV disease. These studies may provide an improved understanding of the role of genes in HIV disease and, thus, lead to the development of antibodies or drugs that can protect healthy immune cells from HIV. Such receptor-blocking agents would be an important addition to the currently available antiretroviral drugs. And new gene information might also assist in the currently stalled efforts to create an effective vaccine against HIV.

People curious about their chemokine receptor genetics would best be served, and would best serve others, through participation in such research. It is this joining of the forces of science with the at-risk and HIV positive communities that will allow us to ultimately triumph over the common enemy, HIV.

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