

Fever after smallpox vaccination tied to individual genetic variations

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St. Louis researchers have identified common DNA variations that underlie susceptibility to fever after smallpox vaccination. Their finding is the first to link individual differences written into the genetic code with a vaccine-related complication – albeit a mild one.

Most of the eight genetic alterations the scientists identified increased the likelihood of fever after smallpox vaccination. A few, however, reduced fever risk. The research, led by scientists at Washington University School of Medicine in St. Louis, will be published in the July 15 issue of *The Journal of Infectious Diseases*.

The study's results raise the possibility the same genetic variations linked to fever following smallpox vaccination may also influence fever risk after other live-virus vaccines, including the one for measles, mumps and rubella. This so-called MMR vaccine is routinely administered to small children, and fever is a bothersome and common side effect.

Eventually, the authors say, it may be possible to develop a test that predicts which patients are at risk for vaccine-related fevers. Such a test also may help doctors anticipate and prevent more serious complications linked to the vaccines.

“Vaccines are extraordinarily safe and effective, but that doesn't mean we can't try to make them even more acceptable by discovering ways to further reduce the chance of adverse events, including minor ones like fever,” says the study's lead author, Samuel Stanley Jr., M.D., vice

chancellor of research at Washington University and a professor of medicine and microbiology. The research was funded by the National Institutes of Health through a grant to the Midwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Research (MRCE), which Stanley directs.

Routine smallpox vaccinations in the United States were halted in 1972, when the disease was considered eradicated in this country, but the U.S. military and other high-risk groups, including some healthcare workers, continue to get the vaccine. It is made with a live but weakened vaccinia virus that provides immunity against smallpox but which can cause complications ranging from fever and fatigue to more serious illness. About 15 percent of those being vaccinated for smallpox for the first time develop a fever over 99 degrees.

Fevers related to vaccines are not considered a serious medical issue, but in rare cases they can lead to more severe complications. Individuals who get a fever after the smallpox vaccine occasionally develop myopericarditis, a potentially life-threatening inflammation of the heart muscle or sac surrounding the heart. And a small percentage of children who get fevers after the MMR vaccine will develop seizures.

“We don’t know whether the same genetic variations we identified in our study are also linked to more serious vaccine complications, but our study raises that possibility,” Stanley says. “I think this study will point us in that direction in terms of looking for genetic alterations that predict more serious complications.”

The Washington University scientists, working in collaboration with MRCE colleagues Robert Belshe, M.D., and Sharon Frey, M.D., at St. Louis University, studied the occurrence of fever in 346 individuals who had participated in previous smallpox vaccination clinical trials evaluating Dryvax®, the vaccine given to U.S. military personnel. About

95 percent of study participants were white.

Records showed that 94 developed fever after vaccination – 61 who received the vaccine for the first time and 33 who had been vaccinated before. The 252 individuals who did not develop fevers after vaccination served as the control group.

Using blood samples donated by study participants, the scientists analyzed SNPs, sites of common genetic variation, in 19 genes linked to immune response, viral replication or inflammation. They found eight alterations associated with fever in four of the genes.

Not surprisingly, those who received the vaccine for the first time were more likely to develop fever, but Stanley says, “We were able to identify specific genetic alterations that contribute to fever even in people who had already received the vaccine before.”

The research team found that variations in the IL-1 gene complex on chromosome 2 were most closely linked to an increased risk of fever. This complex of genes produces a molecule that stimulates fever and is involved in inflammation. Additionally, several variations in the IL-18 gene on chromosome 11 increased fever risk, while one decreased the likelihood of fever. That gene is involved in revving up the immune system. One variation in IL-4, a gene that dampens down the inflammatory response, also reduced fever risk.

Interestingly, studies in mice have shown that immune system molecules produced by the IL-1 and IL-18 genes are linked to tissue damage in viral myocarditis, raising the question of whether a more severe complication of smallpox vaccination might be associated with variations in these genes. Although none of the study participants developed this rare complication, it has been documented in 59 of the more than 492,000 military personnel who were vaccinated between

December 2002 and September 2003.

Stanley hopes further studies will delineate whether genetic alterations linked to fever also play a role in more serious vaccine complications. About 12 percent of children who receive the MMR vaccine develop fevers over 103 degrees, and about 4 percent of them go on to develop seizures in the weeks that follow vaccination.

“There might be a real benefit if we could use this kind of screening to identify children who may be more susceptible to febrile seizures after MMR,” Stanley says. “If we can find ways to identify people at risk and medicate them to reduce the possibility of fever, we might be able to reduce the incidence of seizures.”

Source: Washington University School of Medicine

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