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Smallpox In Europe Selected For Genetic Mutation That Confers Resistance To HIV Infection

Berkeley -- People with a genetic mutation that makes them more resistant to the AIDS virus probably have smallpox to thank, according to two population geneticists at the University of California, Berkeley.

About 10 percent of Europeans have a mutation that disables a protein the Human Immunodeficiency Virus (HIV-1) uses to slip into immune system cells. HIV-1 has a harder time infecting people who have a mutation in one of the two genes that code for this receptor protein, and if these people become infected, their disease progresses more slowly. Those with mutations in both copies of the gene are almost completely resistant to the virus

This genetic mutation arose as recently as 700 years ago, and some researchers have suggested that the bubonic plague that devastated Europe periodically over the past 1,000 years may have selected for the mutation by sparing those who lacked one or both copies of the gene.

In a paper appearing this week in the online Early Edition of The Proceedings of the National Academy of Sciences, the two UC Berkeley researchers argue that smallpox, not bubonic plague, is the most likely cause of the spread of this mutation throughout the European population in such a short time.

That is, the same genetic mutation that confers resistance to HIV-1 protects against death from smallpox.

"Our population genetic model finds that genetic selection from plague wouldn't have been sufficient to drive the frequency of this genetic mutation to its current level," said Alison P. Galvani, a Miller Postdoctoral Fellow at UC Berkeley. "It was sufficient for smallpox."

Bubonic plague hasn't been a major source of death in Europe or elsewhere for the last 250 years, while smallpox was only eradicated in 1978, at the same time AIDS (acquired immune deficiency syndrome) appeared. The survival advantage this genetic mutation provided against smallpox has thus been transferred to AIDS, the authors noted.

Following a 1998 paper that linked the gene deletion with bubonic plague, "bubonic plague had been cited as a classical example of a historical selection pressure acting on a clinically important locus," she said. That classic example now changes, with smallpox replacing the plague.

The gene produces a receptor, called CCR5, that is the main entry port for HIV-1 into T cells and macrophages. While most people around the world have two CCR5 genes or alleles, about 10 percent of Europeans, on average, lack one of the alleles. They thus produce fewer CCR5 receptors, which hinders initial infection by HIV-1 and slows spread within the body once an immune cell has been infected.

Those lacking both alleles produce no CCR5 receptor.

Based on a population genetics model, Galvani and Montgomery Slatkin, a UC Berkeley professor of integrative biology, argue that bubonic plague could not have caused such a rapid spread of this genetic mutation throughout Europe. Even though the Black Death pandemic killed off 25-40 percent of all Europeans during its run through the continent between 1346 and 1352, bubonic plague was historically a sporadic disease with an average annual death rate of only a few percent during the 400-year period it afflicted Europe. Transmitted by fleas infesting rats, it killed people of all ages.

Smallpox, on the other hand, was a continuous presence in Europe for 2,000 years, and almost everyone was exposed by direct person-to-person contact. Most people were infected before the age of 10, with the disease's 30 percent mortality rate killing off a large part of the population before reproductive age.

"When you remove children from a population, you remove more of the reproductive potential for the species, compared to losing older people, who are not reproducing," Galvani said.

Other diseases common at the time, including measles, polio, whooping cough, rubella, scarlet fever, chicken pox and influenza, also targeted children, but fatalities were typically only a few percent and could not have exerted strong influence on the frequency of this genetic mutation.

The smallpox virus also has more biological similarities to HIV-1 than does bubonic plague, the authors point out. Plague is a bacterial disease, and there is no evidence that the bacterium, *Yersinia pestis*, uses the CCR5 receptor in infection. The bacteria actually reproduce outside immune cells.

Smallpox, on the other hand, is a virus based on RNA, just like HIV, she said. And there is some evidence that smallpox, *Variola major*, uses chemokine receptors like CCR5 to enter cells.

The researchers said the geographic distribution of smallpox also correlates better with the frequencies of the CCR5 deletion in Europe.

"The Scandinavian countries in particular have very high frequencies of this deletion allele - 14 to 16 percent - which some people have taken to mean that Vikings dispersed the deletion," Galvani said. "But it could also be due to smallpox hitting Scandinavian countries harder. There were certainly some big smallpox epidemics in Scandinavia, whereas plague affected the continent more, in particular Italy and France."

Polymorphisms, the technical term for small differences in peoples' genomes, are probably often the result of disease, Galvani said. Sometimes they even lead to other diseases, such as the documented case of sickle cell anemia resulting from selection for resistance to malaria.

"There are probably other alleles that have been selected by disease, but we just haven't found them," she said. "Diseases have the potential to exert strong selection. There is an arms race between the host to resist and clear infection and the pathogen to evade the resistance. That leads hosts to develop polymorphisms, and then the pathogen to respond by evolving its own polymorphisms, and so on - there is a constant battle."

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This story has been adapted from a news release issued by University Of California - Berkeley.