

Study finds genetic link to human herpes susceptibility

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There's a high probability that people who are prone to herpes simplex virus (HSV) outbreaks can inherit that susceptibility through their genes, University of Utah researchers report in a new study.

In the Feb. 1 issue of *The Journal of Infectious Diseases*, the researchers identify a region on the long arm of human chromosome 21 with high odds—at least 1,000-to-1—of being linked to cold sore susceptibility. The researchers further say they pinpointed six specific genes in that chromosomal region as candidates for making people prone to outbreaks of cold sores (also called “fever blisters”). Cold sores occur when the herpes virus reactivates from its quiescent state within the nerve, infecting the lip, nose, or face.

Discovery of the probable link could lead to the development of new drugs that reduce the frequency of herpes outbreaks, according to John D. Kriesel, M.D., the study's corresponding author and research associate professor in the U School of Medicine's Division of Infectious Diseases.

“One or more of these genes might make excellent targets for new drugs to reduce the number of herpes outbreaks,” Kriesel said. Maurine R. Hobbs, Ph.D., research assistant professor in the Division of Endocrinology and Metabolism, is the study's first author.

There are two types of the herpes simplex virus. Type 1 (HSV-1) is responsible for the vast majority of cold sores, the most common recurring viral infection in humans, as well as herpes keratitis, an eye infection that can lead to corneal scarring and blindness. The majority of the U.S. population is infected with HSV-1, although millions of people manifest no symptoms. Nonetheless, at least 40 percent of the population will experience at least one cold sore at some point during their lives.

Herpes simplex virus type 2 (HSV-2) is the primary

cause of genital herpes, and infects an estimated 17 percent of the U.S. population or approximately 50 million people. Between 5 million and 10 million people in this group have recognized cases of genital herpes.

To search for cold sore susceptibility genes, the U researchers used linkage analysis, which traces genetic markers in families to identify regions on chromosomes that harbor disease genes. When genetic mutations are passed from parent to offspring, genetic markers near the disease gene are passed along as well. By identifying markers shared among family members, researchers can locate regions of chromosomes where genes responsible for disease may lie. The U of U study was the first whole-genome study of herpes simplex virus to use linkage analysis.

The researchers studied 421 people from 39 large Utah families. The families are part of a genomic study called the Utah Genetic Reference Project. Participants were grouped according to how often they experienced cold sore outbreaks:

- Frequently affected—HSV-1 infected and two or more outbreaks annually (89 participants)
- Mildly affected—HSV-1 infected and two or less outbreaks annually (111)
- Unaffected—HSV-1 infected but had never experienced an outbreak (85)
- Unknown or HSV uninfected—could not be categorized (146)

The researchers compared the “frequently affected” and “unaffected” groups (both proven to be HSV-1 infected) to allow the greatest possible distinction in the expression of outbreaks. Participants who couldn't be categorized were excluded from the linkage analysis, as were the 111 mildly affected people. When all the genetics data were collected, a mathematical analysis determined the odds of a link between cold sores and the long arm of chromosome 21 to be at least

1,000-to-1.

The probable genetic link is not the only component believed to trigger reactivation of HSV and cold sores. Environmental factors, such as fever, wind, and sunburn, also are believed to play a part. Viral factors, like strain and burden of latent infection, also probably influence the frequency of HSV outbreaks.

The researchers began the study with no preconceptions about which regions of the human genome might be linked to cold sore susceptibility, Kriesel said. Therefore, the linkage with the long arm of chromosome 21 came as a surprise. "We didn't start with the thought that particular genes were important in the search," he said. "That helped ensure an unbiased study and led to a completely unexpected result in chromosome 21."

Now Kriesel, Hobbs, and their colleagues are looking at the six candidate susceptibility genes to find out which are related to cold sores. Three of those genes look particularly promising to study.

"Finding a drug target to reduce the frequency of cold sores would be even more valuable if we could expand our study results to include genital herpes or herpes keratitis," Kriesel said, "and that's something I'd like to do."

Source: University of Utah Health Sciences

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