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More doubt on virus, chronic fatigue connection

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A study supported by the U.S. Department of Health and Human Services could not validate or confirm previous research findings that suggested the presence of one of several viruses in blood samples of people living with chronic fatigue syndrome. The new study also could not find the viruses in blood samples of healthy donors who were previously known to not have the viruses.

The HHS-supported study examined the validity of testing techniques intended to detect the presence of several viruses, xenotropic murine leukemia virus-related virus (XMRV) or related polytropic murine leukemia viruses (P-MLVs). Such follow-up studies are standard in science to determine whether earlier findings are accurate. The new findings suggest earlier results may have resulted from laboratory error, either contamination or false positive test results.

The initial reports of a link between XMRV and chronic fatigue syndrome prompted HHS to investigate how well tests detect XMRV/P-MLVs, and the prevalence and potential transmission of these viruses in the blood supply. If the viruses had been proven to be present in patients with chronic fatigue syndrome or healthy donors, concerns were raised that these viruses could put the blood supply at risk. The new results were published online on Thursday, Sept. 22, 2011 in *Science Express*.

"The results of this study, along with other recent findings, reassure us that these viruses do not pose a threat to the safety of the nation's blood supply," said Susan B. Shurin, M.D., acting director of the National

Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. "These data add to the mounting evidence that there is no need to screen blood donors for them at the present time."

In the new study, blood samples were taken from healthy donors and from 14 patients with chronic fatigue syndrome who had previously tested positive for XMRV or P-MLV, and samples from another person who had tested positive for XMRV but who did not have chronic fatigue syndrome. The study also used blood samples from healthy volunteers whose blood tests previously had shown no signs of XMRV/P-MLV.

The samples were blinded with no indication as to their source, and sent to nine laboratories. The study involved laboratories supported by several HHS agencies along with Abbott Laboratories, Abbott Park, Ill., GenProbe Inc., San Diego, and the Whittemore Peterson Institute (WPI), Reno, Nev.

The nine laboratories tested identical sets of the new blood samples for the XMRV/P-MLV nucleic acid, for replication of the virus (whether it reproduced itself in cells), and for antibodies to the viruses. Two labs, which previously had reported the association of XMRV with chronic fatigue syndrome, reported the presence of XMRV for some samples. However, the labs reported similar rates of finding XMRV in samples from patients with chronic fatigue syndrome and from healthy donors who were known to not have XMRV. Additional tests run in the same and other laboratories on the same samples did not find XMRV, strongly suggesting that these persons were negative for XMRV/ P-MLVs. This would be a sign that the few observed positive results represented false positives – that is, the results indicated the condition was present when it actually was not.

To investigate the validity of testing techniques and to determine XMRV's potential impact on the blood supply, HHS formed the Blood

XMRV Scientific Research Working Group in December 2009. The NHLBI leads the working group, which includes other HHS agencies including the Office of the Assistant Secretary for Health, NIH's National Cancer Institute (NCI) and the NIH Clinical Center, as well as the Centers for Disease Control and Prevention and the Food and Drug Administration. The current study is based on the working group's efforts to determine the best way to test blood samples for the virus. Researchers used 11 nucleic acid, five antibody, and three culture assays to determine the assays' abilities to detect XMRV/P-MLVs. The study also checked for evidence of contamination with mouse DNA, because XMRV or its predecessors may be present in some mouse strains and cell lines.

In 2009, WPI researchers had reported a possible link between XMRV and chronic fatigue syndrome. In June 2010, the AABB, a nonprofit U.S. blood banking association, recommended that collection centers discourage people with chronic fatigue syndrome from donating blood.

However, within the last year, evidence emerged suggesting that contamination in the laboratory was potentially responsible for detection of XMRV in some blood samples from patients with chronic fatigue syndrome. To ensure that this did not compromise results in the new study, extensive efforts were undertaken to avoid laboratory contamination and contamination of samples.

The Blood Systems Research Institute, San Francisco, including Graham Simmons, Ph. D., the paper's lead author, compiled the blood samples and distributed them to participating laboratories. The following labs and investigators were responsible for testing the sample panels:

- Abbott (Two labs: Molecular Laboratory and Diagnostic Laboratory) -- John Hackett Jr., Ning Tang

- CDC -- William M. Switzer, Walid Heneine
- FDA -- Indira K. Hewlett, Jiangqin Zhao
- FDA -- Shyh-Ching Lo/ Harvey Alter, NIH Clinical Center, Bethesda, Md.
- Gen-Probe, Inc. -- Jeffrey M. Linnen, Kui Gao
- NCI -- Mary F. Kearney/John M. Coffin, Tufts University, Boston
- NCI -- Francis W. Ruscetti
- WPI -- Judy A. Mikovits, Max A. Pfost

W. Ian Lipkin, M.D., of Columbia University's Mailman School of Public Health, is currently leading a separate study that is testing fresh blood samples from 150 people living with chronic fatigue syndrome and 150 similar but healthy people. Through this effort, organizers will process, blind, and send samples to laboratories at the FDA, the CDC, and the WPI for testing for the presence of XMRV, MLV or related viruses.

If one of the participating laboratories finds that a sample is virus positive, further tests will be conducted to determine the validity of the result. If one participating laboratory finds a positive sample but another laboratory does not, the same samples can be shipped again, with a new blinded code, to be retested. It is hoped that the results from this study will be available by the end of 2011.

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