Team discovers new gene that affects clearance of hepatitis C virus

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(Medical Xpress)—Scientists have discovered a gene that interferes with the clearance of hepatitis C virus infection. They also identified an inherited variant within this gene, Interferon Lambda 4 (IFNL4), that predicts how people respond to treatment for hepatitis C infection. The results of this study, by investigators at the National Cancer Institute (NCI), part of the NIH, and their collaborators at NIH and other institutions, were published online in *Nature Genetics* on Jan. 6, 2013.

Chronic infection with hepatitis C virus is a cause of liver cirrhosis and liver cancer. Up to 80 percent of people who are acutely infected with hepatitis C fail to clear the virus and develop chronic hepatitis C infection, and of these, approximately 5 percent develop liver cancer. Individuals of African ancestry do not respond as well to current treatments of hepatitis C infection compared to patients of European or Asian ancestry.

Previously, results from genome-wide association studies (GWAS) identified common inherited genetic markers that were associated with response to hepatitis C virus treatment and spontaneous clearance of the infection. Those markers are located on chromosome 19 near a known interferon gene, IFNL3. However, molecular investigations into IFNL3 did not explain the GWAS association with spontaneous virus clearance or treatment response. To find the new gene, the investigators used a technology involving RNA sequencing on human liver cells treated to mimic hepatitis C virus infection.

"By using RNA sequencing we looked outside the box to search for something beyond what was already known in this region. We hit the jackpot with the discovery of a new gene. It is possible that other important genes may be discovered using this approach," said co-lead investigator Ludmila Prokunina-Olsson, Ph.D., of the Laboratory of Translational Genomics in NCI's Division of Cancer Epidemiology and Genetics (DCEG).

The researchers found that the IFNL4 region harbors a variant that is found in two alternative forms. One form, called deltaG, results in a deletion in one of the four bases that comprise DNA. The change creates an alteration known as a frameshift, which produces the IFNL4 protein, while the form without the deletion does not produce IFNL4. By analyzing data from hepatitis C-infected African-Americans and European-Americans participating in clinical studies, the authors found that the presence of the IFNL4 protein is associated with poorer clearance and response to treatment than the form that does not produce IFNL4. The deletion variant is more common in people of African ancestry, which helps partially explain why African-Americans have a lower response to current hepatitis C treatments than patients of Asian and European ancestry.

"Our work fulfills several promises of the genomic era," said NCI's Thomas R. O'Brien, M.D., Infections and Immunoepidemiology Branch, DCEG. "One, a better understanding of biology; two, personalized medicine; and three, new potential treatments. We deliver immediately on the first two. We've identified a new gene that may help us better understand response to viral infection and the new genetic marker may transition to clinical practice because it predicts treatment outcome for African-American patients better than the current genetic test. For the third, the INFL4 protein may be used as a novel therapeutic target for hepatitis C virus infection, and possibly other diseases."

The new gene belongs to what is now a family of four interferon-lambda protein-encoding genes, three of which were discovered more than ten years ago (IFNL1, IFNL2 and IFNL3) The mechanism by which the IFNL 4 protein impairs hepatitis C virus clearance remains unknown. Further studies will explore molecular function of this novel protein in normal and disease conditions.

More information: Prokunina-Olsson, at al. A variant upstream of IFNL3 (IL28B) creating a novel interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. Jan. 6, 2013. *Nature Genetics.* DOI: 10.1038/ng.2521.