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Gene linked to increasingly common type of blood cancer

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California and Arizona researchers have identified a gene variant that carries nearly twice the risk of developing an increasingly common type of blood cancer, according to a study published online today by the science journal *Nature Genetics*.

Investigators at the University of California, Berkeley (UC Berkeley) and at the Translational Genomics Research Institute (TGen) found that mutations in a gene called C6orf15, or STG, are associated with the risk of developing follicular lymphoma. This is a cancer of the body's disease-fighting network whose rates have nearly doubled in the past three decades.

In the first genome-wide association study of non-Hodgkin lymphoma, scientists at UC Berkeley and TGen identified a SNP - a single nucleotide polymorphism - that could determine susceptibility to follicular lymphoma. The SNP, a DNA variant within the more than 3-billion base pairs in the human genome, was identified as rs6457327.

The study was led by Dr. Christine Skibola, Associate Adjunct Professor of Environmental Health Sciences at UC Berkeley's School of Public Health, and by Dr. Kevin M. Brown, an Associate Investigator in the Integrated Cancer Genomics Division of TGen, a Phoenix-based, non-profit biomedical research institute.

"What's exciting about this study is that we found a target in the genome influencing the susceptibility to follicular lymphoma, which helps us

discern between three major types of lymphomas," said Skibola, the paper's co-lead author. "That had not been done before on a genome-wide scale. It is our hope that this research may some day be useful in helping develop prevention, early detection and treatment of this disease."

Follicular lymphoma accounts for as much as 30 percent of all non-Hodgkin lymphoma, a cancer of the lymphatic system involving the blood, bone marrow and lymph nodes. In NHL, tumors develop in lymphocytes, a type of white blood cell. Follicular lymphoma arises from B-cells, a specific type of white blood cell. NHL is the fifth most common type of cancer in the U.S., and is newly diagnosed in about 66,000 Americans each year, and annually kills nearly 20,000, according to the National Cancer Institute.

Researchers found that, for SNP rs6457327, the presence of the G allele - a DNA letter that varies within the genome - was protective against follicular lymphoma, while the presence of the A allele was predictive of an increased risk of developing follicular lymphoma. Dr. Brown said individuals who had the A variant were nearly twice as likely to develop follicular lymphoma.

"There's clearly a genetic component to the disease. The hope is to one day be able to take these results, combine them with other tests, and turn them into an individualized assessment of disease risk," said Dr. Brown, the study's other co-lead author. "This is a starting point."

Dr. Skibola said more studies would be needed to determine the biological importance of other STG SNPs linked to rs6457327 that might change the function of the gene. This could help determine how they might influence risk of the disease.

The scientists also want to know if genetic susceptibility to follicular

lymphoma is associated with:

- Environmental factors, such as exposure to the sun.
- Conditions such as psoriasis - a chronic, autoimmune skin disease closely associated with a similar region of the genome.
- Exposure to viruses. Follicular lymphoma is associated with HIV infection, occurring in as many as 10 percent of all HIV-positive patients, according to the Lymphoma Research Foundation.

The genome-wide association study was conducted using DNA from a population-based non-Hodgkin lymphoma case-control study in the San Francisco Bay Area led by UC San Francisco researchers. Follow-up validation studies were done using independent case-control studies from Canada and Germany.

To reduce the potential for complicating factors, the more than 3,000 samples in the UC Berkeley-TGen study were from individuals who were HIV negative. Dr. Brown said future studies could include HIV-positive individuals, if enough samples were made available.

This pooled genome-wide association study used by the UC Berkeley-TGen investigators allowed them to screen more than 500,000 SNPs. The nearly 90 most significant SNPs were then genotyped to more closely examine their association with lymphoma.

This same pooling technique has been pioneered by TGen to screen for genes in other studies. Additional collaborations between UC Berkeley and TGen are planned.

"This study paves the way for more in-depth research into this type of

cancer, which is increasingly affecting more people," said Dr. Jeffrey Trent, TGen's President and Research Director. "This study also builds an important collaborative relationship between TGen and UC Berkeley, one of the nation's top universities."

Source: The Translational Genomics Research Institute