Massive DNA search uncovers new mutations driving blood cancer

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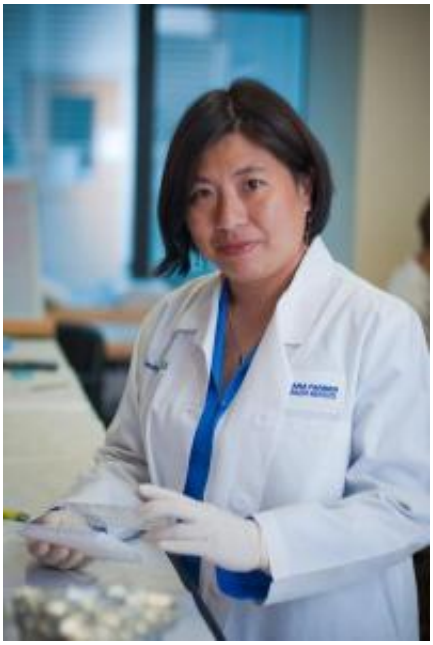

This is a researcher working on massive DNA search uncovers new mutations driving blood cancer. Results may aid treatment decisions in chronic lymphocytic leukemia. Credit: Dana-Farber Cancer Institute

The most comprehensive search to date of DNA abnormalities in chronic lymphocytic leukemia (CLL) has unearthed several new altered genes that drive this common blood cancer, a finding that could potentially help doctors predict whether an individual patient's disease will progress rapidly or remain indolent for years, say scientists from Dana-Farber Cancer Institute and the Broad Institute.

Using powerful "next-generation" DNA sequencing, the teams identified nine frequently mutated genes across 91 patients. Catherine J. Wu, MD, of Dana-Farber, a co-senior author of the report, says five of the mutated genes are implicated in CLL for the first time.

Wu says that mutations in one of the new genes, SF3B1, interfere with gene splicing, or "editing" of RNA messages that form a genetic template the cell uses to build a specified protein. "We have identified a new cancer pathway – aberrant RNA splicing – that has been underappreciated," says Wu, a researcher in Dana-Farber's Cancer Vaccine Center.

An advanced online publication has been scheduled for Dec. 12 by the *New England Journal of Medicine*, to coincide with a presentation of the results (abstract 463) at the American Society of Hematology's 2011 annual meeting on Monday, Dec. 12 at 10:30 a.m. PST.

The study's other two co-senior authors are Jennifer Brown, MD, PhD, of Dana-Farber and Brigham and Women's Hospital, and Gad Getz, PhD, of the Broad Institute, where the sequencing search was carried out.

CLL is the most common form of leukemia. The American Cancer Society expects it will be diagnosed in 14,570 patients in 2011, and projects 4,380 deaths. The behavior of the disease differs widely among patients. About half the time, CLL is aggressive, worsening steadily and rapidly, often with fatal outcomes. In many other patients, the leukemia is said to be "indolent," causing few symptoms for years or even decades. Doctors often choose not to treat the indolent form until symptoms become life-threatening.

Physicians have only a limited set of markers to predict the course of CLL in an individual, such as the presence of certain types of

chromosome damage in the cancer cells, which are associated with more aggressive disease. Previous searches for predictive genetic clues spotted only a small number of "driver" mutations, but those hunts were limited in their power by the small number of tumor samples in the study.

The latest search harnessed Illumina sequencing technology at the Broad Institute to sequence leukemia and matched normal DNA samples from 91 patients with CLL, looking for frequently mutated genes in the tumors. They sequenced the entire genome in three patient samples, and only the protein-coding genes, collectively termed the "exome," in the other 88 patients.

The search turned up nine genes frequently mutated in the CLL samples, and these fell into five pathways regulating DNA damage repair, cell-cycle control, Notch signaling, inflammation, and RNA splicing/processing. Two had previously been associated with CLL and cancer in general. Another two mutations – MYD88 and NOTCH1 – were implicated in leukemia this year (2011). The remaining five, now identified for the first time as culprits in CLL, are SF3B1, FBXW7, DDX3X, MAPK1, and ZMYM3.

The SF3B1 gene was the second most commonly mutated gene, being found abnormal in 14 of the 91 leukemia DNA samples. The gene's full name is Splicing Factor 3b, subunit 1, and the protein it makes is part of the "spliceosome" – a collection of proteins that govern the splicing out of extraneous RNA molecules ("introns") to create the RNA message ("exons"), or molecular recipe, from which the cell manufactures proteins for the body. "Defects in splicing have not previously been implicated in the biology of CLL," the researchers wrote.

The researchers checked to see whether CLL samples that contained the mutated genes also had specific deletions in chromosomes (the DNA structures that carry genes) previously known to signal a poor outlook in

patients. They found that, indeed, the SF3B1 gene was often found in tandem with a particular chromosomal abnormality, consistent with a more aggressive form of CLL.

However, independent of the presence of the chromosomal deletion, the study revealed that a mutated SF3B1 gene by itself was a red flag for an aggressive case of CLL; patients harboring the mutant SF3B1 gene were more likely to need treatment sooner than individuals lacking the gene. Wu said that that the gene alteration might serve as a biomarker. Since these patients have more aggressive disease, knowledge of the presence of the gene alteration might prompt physicians early on to consider alternatives to conventional chemotherapy, such as earlier use of stem cell transplants to quell the disease.

The researchers said the study findings show the value of large-scale genome searches in elucidating cancers. The numerous genetic flaws uncovered by the search could not only aid in the prediction of disease course, they said, but also offer clues to the biological underpinnings of CLL, paving the way for novel targeted treatments.

Provided by Dana-Farber Cancer Institute