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GENETICS

CLUES FOR TARGETING LEUKEMIA

By sequencing the genome of tumors from patients with chronic lymphocytic leukemia (CLL) researchers have identified four recurrent oncogenic mutations that contribute to the course of the disease. "Our data confirm the value of whole-genome sequence strategies to identify new mutations in cancer with clinical relevance," says Elías Campo, who is one of the coordinators of the study.

CLL is a clinically and biologically heterogeneous disease, and its molecular pathogenesis is poorly understood. Two major subtypes of CLL are distinguished by the number of mutations in immunoglobulin (*IGHV*) genes.

The Spanish Chronic Lymphocytic Leukemia Genome Consortium fully sequenced the genome of tumor samples from four patients with CLL (two of each subtype). The team identified 46 mutations in leukemic cells with a potentially disruptive effect on gene function. Validating these leads in DNA samples from a further 363 patients with CLL, Campo and colleagues found four genes that were recurrently mutated in leukemic cells. Interestingly, the prevalence of these mutations varied between the two CLL subtypes: mutations in *NOTCH1* and *XPO1* were more frequent in *IGHV*-unmutated CLL, and *MYD88* and *KLHL6* mutations were more prevalent in *IGHV*-mutated CLL. Findings from functional studies indicated that mutations in these genes are likely to contribute to the clinical evolution of the disease.

This work might lead to the classification of patients with CLL on the basis of genomic driver mutations, and highlights these genes as potential therapeutic targets. For Campo, however, this study is just the beginning. "The main aim of the Consortium is to complete the whole-genome sequence of 500 CLL patients," he says.

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