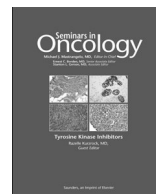




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## Gene mutations in chronic lymphocytic leukemia

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## ABSTRACT

The recent discovery of genes mutated in chronic lymphocytic leukemia (CLL) has stimulated new research into the role of these genes in CLL pathogenesis. CLL cases carry approximately 5–20 mutated genes per exome, a lower number than detected in many human tumors. Of the recurrently mutated genes in CLL, all are mutated in 10% or less of patients when assayed in unselected CLL cohorts at diagnosis. Mutations in *TP53* are of major clinical relevance, are often associated with del17p and gain in frequency over time. *TP53* mutated and associated del17p states substantially lower response rates, remission duration, and survival in CLL. Mutations in *NOTCH1* and *SF3B1* are recurrent, often associated with progressive CLL that is also IgV<sub>H</sub> unmutated and ZAP70-positive and are under investigation as targets for novel therapies and as factors influencing CLL outcome. There are an estimated 20–50 additional mutated genes with frequencies of 1%–5% in CLL; more work is needed to identify these and to study their significance. Finally, of the major biological aberration categories influencing CLL as a disease, gene mutations will need to be placed into context with regard to their ultimate role and importance. Such calibrated appreciation necessitates studies incorporating multiple CLL driver aberrations into biological and clinical analyses.

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## 1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world. It has a varied clinical course and multiple biological and clinical parameters influence the disease. Major biological phenomena driving the disease are CLL cell-intrinsic (eg, genomic aberrations, aberrant BCR signaling, epigenetic aberrations, or stable expression changes) or CLL cell-extrinsic (eg, a dependency on antigen-stimulated BCR signaling, cell to CLL cell interaction, or cytokine to CLL cell interaction, collectively referred to as the microenvironment). Of the genomic changes underlying CLL pathogenesis, acquired genomic copy number changes (aCNAs) are well described [1–4]. With regard to gene mutations in CLL, our knowledge is undergoing rapid expansion and definitive answers regarding the role of recurrent gene mutations or mutated functional pathways in CLL are available for only a few genes [5,6].

The recent advent of massively parallel sequencing technologies combined with advances in targeted DNA enrichment (exon capture reagents) and bioinformatics analysis tools has allowed for the identification of multiple recurrently mutated genes in CLL.

These mutated genes lay the foundation for studies into the biological and clinical consequences of such mutations and complement overall studies of factors influencing CLL disease behavior. Most of our current knowledge of gene mutations in CLL is the result of sequencing of CLL exomes using whole-exome sequencing or WES (exome: the sum of all coding exons of all genes); very few CLL cases subjected to whole genome sequencing have been reported and more work in this area is needed to derive meaningful conclusions [5–7]. The reagents used to capture and enrich exonic DNA from sheared total genomic DNA isolated from CLL cells are evolving and in addition to exons may also contain capture probes for genomic DNA encoding for microRNAs or other non-protein-coding RNAs. The depth of sequencing (the number of times any particular nucleotide is part of a sequencing trace or tag) determines the sensitivity of mutation detection, and in general the higher the depth of coverage the better the quality characteristics of the study. Due to multiple technical reasons, gaps in sequencing coverage nonetheless still exist, which are complicated further by the inability of modern software pipelines to call all true mutations (especially insertion/deletion mutations or indels) with high confidence. Therefore, WES studies do not detect all true exome mutations in CLL.

CLL exomes carry approximately 5–20 somatically acquired mutated genes per individual CLL case, much fewer than many other solid cancers [5–7]. Importantly, the somatically acquired mutation status of sequence variants in genes, similar to other

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