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Chronic lymphocytic leukemia and Chronic Lymphoproliferative Disorders

OPTICAL GENOME MAPPING IDENTIFIES MULTIPLE STRUCTURAL VARIATION AND CATASTROPHIC REARRANGEMENTS IN B-CELL PROLYMPHOCYTIC LEUKEMIA

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Introduction: B-cell prolymphocytic leukemia (B-PLL) is an extremely rare condition, accounting for less than 1% of all lymphoid leukemias. The identification of more than 55% of lymphocytes in the blood or bone marrow with prolymphocytic morphology is the hallmark feature of B-PLL. Conventional cytogenetic and molecular testing can detect MYC and TP53 abnormalities and mutations, identifying 3 distinct B-PLL groups with different clinical outcomes.

Methods: Optical genome mapping (OGM) is a new genome-wide technology that can detect structural genomic variations (SVs) including translocations, inversions, deletions, duplications etc., copy number variations (CNVs) and whole-chromosome aneuploidies with high resolution. In the present study, cryopreserved mononuclear cells obtained from 3 patients with B-PLL were processed to obtain Ultra-high molecular weight (UHMW) DNA samples useful to perform OGM analyses by Bionano Saphyr instrumentation.

Results: OGM detected an extremely complex genome with extensive copy number alterations and chromosomal rearrangements in all patients (Figure 1). OGM analyses found in case#1 the deletion of TNFRSF10A/B/C/D (alias DR4, DR5, BcR1 and DcR2) cluster and IKBKB gene in 8p loss, deletion of FAS and PTEN in loss of chromosome 10 and deletion of TP53 gene in 17p loss, implying that both intrinsic and extrinsic apoptotic pathways may be affected in this patient. Of interest, in case #1, the 1.25Mb loss at 13q22.2q22.3 comprised FBXL3 and MYCBP2 genes involved in MYC regulation. In case#2, deletion of BCL2L11 (alias BIM) in 2q loss, deletion of TP53 in chromosome 17p loss, together with amplification of BCL2 gene in 18q gain and MDM2 in chromosome 12 gain were observed, implying multifactorial alterations that can affect the intrinsic apoptotic pathway in case#2. Additionally, OGM detected gains of CDK2, CDK4 on chromosome 12, and gain of BCL6 and KLHL6 genes on chromosome 3, implicated in cell cycle regulation and germinal center formation. Interestingly, in case#2 chromosomes 12,17, and 21 were involved in multiple chained translocations, a typical pattern of complex genomic rearrangements that fall under the category of chromoanagenesis (Figure 1). In case#3, 11p15p11 CNV gain comprised WT1 and CD44 gene, whereas TP53 and BCOR were present in CNV losses identified by OGM analyses.

Conclusions: OGM revealed that, in addition to the frequent TP53 dysfunction (deletions and mutations) and MYC alterations, multiple concomitant genomic changes affect other genes and pathways involved in apoptosis and cell-cycle regulation. These findings highlight the intricate genomic landscape of B-PLL, indicating that further pathogenetic mechanisms may contribute to disease, and underscores the ability of OGM to comprehensively capture this genomic complexity, including catastrophic rearrangements and multiple structural variations.

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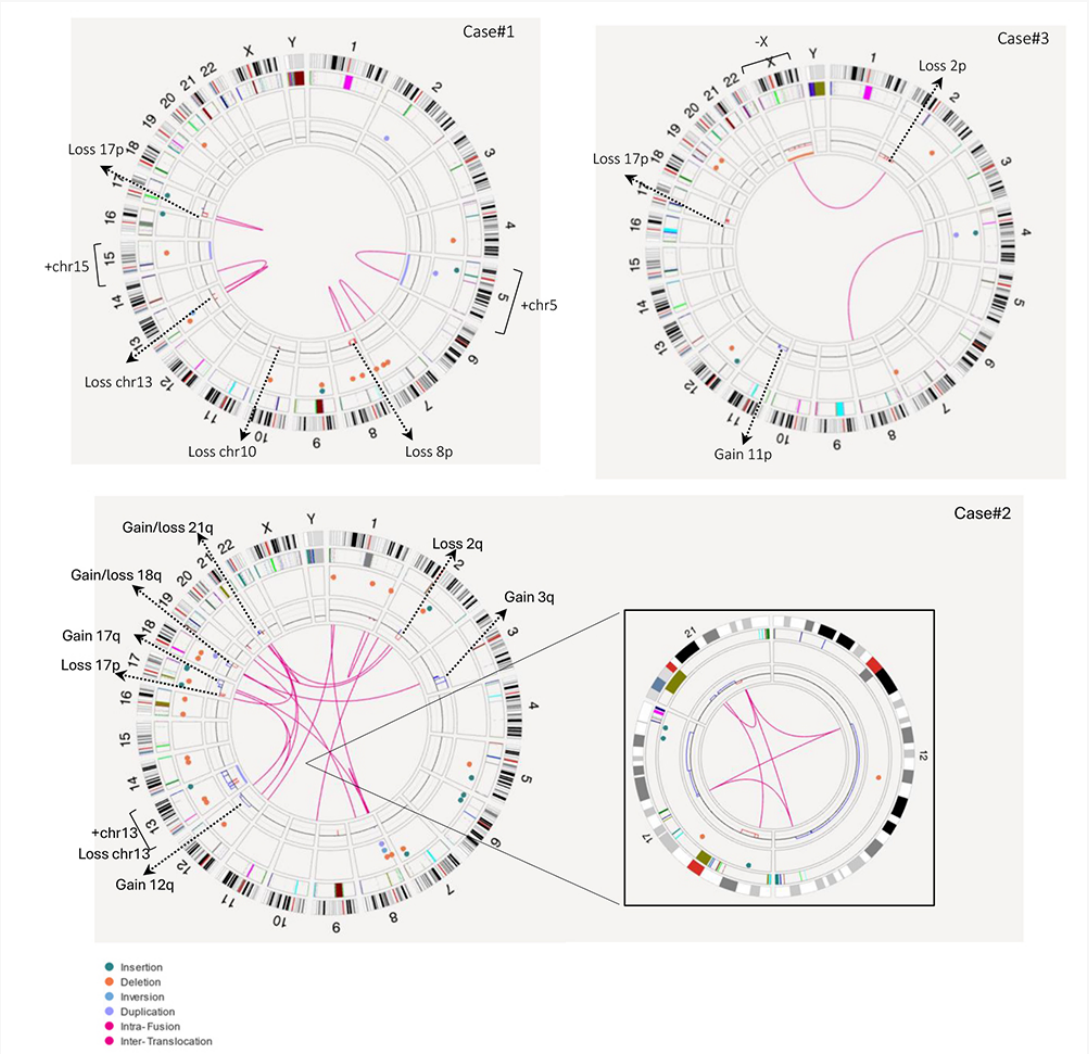

Figure 1. OGM detects multiple genomic alterations in 3 patients with B-PLL. Circos plots showing for cases #1, #2 and #3 from the outer to the inner: the chromosome number; the chromosomal ideogram; the masked regions; chromosomal regions of structural variants (SVs) as indicated in the legend; copy number variations (CNV) and intra and interchromosomal translocations and inversions. Genomic alterations are also showed by arrows and square brackets. A typical pattern of complex genomic rearrangements that fall under the category of chromoanagenesis was shown in enlarged panel for case 2.