**Copy number variation analysis identifies distinct genomic features in adult Burkitt lymphoma**

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Introduction: Burkitt lymphoma (BL) is an aggressive B-cell non-Hodgkin lymphoma that disproportionately affects populations in malaria-endemic regions. Although BL is curable, age is associated with inferior clinical outcomes in most series, but the genetic basis of response is unknown. Recent large efforts in the characterization of pediatric BL (pBL) showed key genomic aberrations underlying disease progression. However, these studies have not focused on structural abnormalities of a large number of adult BL (aBL). In this study, we aimed to identify age-specific genomic landscapes of copy number variations (CNV) in BL.

Methods: Two cohorts comprising 124 pBL and 89 aBL patients, representing both EBV-positive and EBV-negative cases within BL Genomic Sequencing Project, were used in the study. Age cut-off between pBL and aBL was 20 years. In addition, genomes from 186 patients with diffuse large B-cell lymphomas (DLBCL) were included in our analysis for comparison. Somatic CNV were detected using Battenberg and ControlFREEC algorithms.

Results: In BL, the proportion of genome altered by CNV was significantly lower when compared with DLBCL. This difference can be attributed to the higher average length of CNV (P < 0.0001) and frequency of whole-genome duplication (P < 0.0001) in DLBCL. In aBL specifically, amplifications within long arms of chromosomes 7, 10, 11, 15, 16, 19, and 20, or deletions affecting the short arm of chromosome 9 were found at a higher frequency compared to pBL. The amplified regions uniquely altered among aBL included genes involved in the regulation of MYC function, such as *KAT5*, *COPS6*, *TRRAP*, and *PRMT1*, suggesting they contribute to the MYC transcriptional program. Importantly, aberrations within aBL-specific regions showed no difference when stratified on EBV status or patient sex. In contrast, when patients are stratified based on EBV status, EBV-negative BL samples are uniquely associated with recurrent amplifications within long arms on chromosomes 1 and 13, as well as deletions at 6q15 and 11q25. The recurrent CNVs specific to EBV-negative BL are resulting in deletion of *PRDM1* (identified in 6.9% EBV-negative aBL and not detected in EBV-positive aBL) and amplification of the locus containing *FCGR2B* (found in 24.1% EBV-negative aBL and not identified in EBV-positive aBL), a known contributor to rituximab resistance in DLBCL and chronic lymphocytic leukemia.

Conclusions: We show that aBL has a distinct CNV profile compared to pBL, suggesting either distinct mutational processes or selective pressures in this malignancy. These differences are not explained when samples are stratified on EBV status or sex. aBL-specific CNVs affect genes that regulate or cooperate with MYC-mediated transactivation. In addition, we show that chromosomal abnormalities affecting 1q, 6q, and 13q predominantly occur in EBV-negative BL.