**Key genetic and molecular aberrations identified in both adult and EBV-positive Burkitt lymphoma patients**

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**Introduction:** Burkitt lymphoma (BL) is the most common B-cell non-Hodgkin lymphoma (NHL) in children accounting for ~50% of pediatric NHLs, while accounting for only 1-2% of adult NHLs. The genetic hallmark of BL is a translocation that places *MYC* under the regulation of an immunoglobulin (*IG)* heavy or light chain enhancer. Recently, we described molecular differences between EBV-positive (EBV+) and EBV-negative (EBV-) pediatric BLs. Specifically, EBV+ BLs are characterized by elevated expression of activation-induced cytidine deaminase, higher genome-wide mutation burden due to aberrant somatic hypermutation, and fewer driver mutations per tumor. The limited available studies comparing pediatric BL (pBL) to adult BL (aBL) have revealed the latter more frequently harbor *MYC*-*IG* light chain rearrangements and possibly display some distinct driver mutation profiles. The inferior survival rates of aBL patients necessitates the need for a better understanding of the full suite of genetic and molecular features of aBL to enable more effective treatments and prognostication within this population. Further, important differences that distinguish EBV+ BL tumors from EBV- tumors have only recently been elucidated and the multi-faceted role EBV plays in BL pathogenesis remains incompletely understood.

**Methods:** We performed whole genome sequencing and RNA-seq on 205 BL tumors: 124(91 EBV+) pBL and 81(26 EBV+) aBL cases. We analyzed mutation patterns to identify significantly mutated genes (SMGs) and compared their frequencies between EBV+/- BL and aBL/pBL.

**Results:** We identified 4 SMGs not previously associated with BL: *TET2, HNRNPU, BRAF*, and *EZH2*. Three of these are commonly mutated in other cancers and at variable rates in diffuse large B-cell lymphoma. We specifically associate *TET2* mutations with aBL versus pBL (11% vs 1.6%, Q=0. 0.09)(Fig. 1A). *TP53* mutations were associated with significantly inferior progression free survival (PFS) in aBL at 2yr follow up (Fig. 1B). *HNRNPU* mutations have not previously been linked to any cancer. These were mostly truncating variants that track with EBV-positivity (Fig. 1A), with mutant cases having significantly reduced expression of *HNRNPU* mRNA.

**Conclusion:** This work highlights key mechanisms underlying BL pathogenesis and key genetic differences based on age and EBV status. We show the first evidence of mutations in *TET2, HNRNPU, BRAF,* and *EZH2* being associated with BL, with *TET2* mutations specifically associated with aBL. Among the SMGs, *TP53* mutations were associated with inferior PFS in aBL, presenting a subset of patients to be considered for novel treatment approaches. These findings further elucidate differences between adult and pediatric BL and highlight model systems for the further development of novel therapeutics exploiting these differences.

