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BURKITT LYMPHOMA GENOME SEQUENCING PROJECT (BLGSP): INTRODUCTION

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Burkitt lymphoma (BL) is an aggressive B-cell non-Hodgkin lymphoma with a hallmark translocation involving *MYC* and an immunoglobulin enhancer. It is most common in children and has three clinical variants: endemic, sporadic, and HIV-associated. The Epstein–Barr virus–associated endemic subtype is highly prevalent in equatorial Africa, where it is the most common pediatric cancer. Previous genomic studies of smaller BL cohorts revealed that endemic BL harbors mutation patterns similar but not identical to sporadic cases from high-resource countries. The BLGSP aims at conducting an integrative molecular characterization of a large comprehensive BL cohort including an unprecedented representation of endemic cases. The objective is to define molecular features that drive lymphomagenesis, which can be translated to new therapeutic strategies deployable worldwide. The goal is to collect 160 BL cases, of which 50% will be endemic, 38% sporadic and 12% from HIV+ patients. For the discovery phase, each tumor requires case-matching constitutional DNA as well as treatment, outcome and other clinical information. The optimal source of tumor DNA and RNA is from frozen tissue with at least 50% tumor nuclei, but FFPE immobilization is also accepted. Accrual locations include Africa, Brazil, Europe and the United States. The BLGSP has developed extensive standard operating procedures for tissue collection, pathology review and tissue processing. Molecular characterization includes whole genome sequencing of tumor and constitutional DNA (80X and 40X coverage, respectively), RNA sequencing (RNA-seq) and microRNA sequencing. These data will enable the BLGSP to identify somatic mutations, human and viral expression signatures, and miRNA-mediated transcript regulation. We have accrued 167 cases of BL of which 75% passed diagnostic pathology review with a 25% attrition at the tissue processing stage. We have completed sequencing for 94 cases. We have identified recurrent mutations in *ID3*, *DDX3X*, *ARID1A*, *FOXO1*, *TP53*, *SMARCA4* and multiple novel genes that appear to be associated with BL. Most mutations are supported by the RNA-seq data. Some genes accumulated somatic mutations in a BL subtype-specific fashion, warranting further investigation. BLGSP is an ongoing international collaborative project aimed at providing a comprehensive molecular portrait of BL across all subtypes. In summary, this effort has the potential to reveal molecular targets for therapy that can lead to more effective treatments that are less toxic than the current regimens.

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