infection, it has been speculated that other viruses are involved in EBV+ cases, but our analysis did not reveal any new viruses.

**Conclusions:** Transcriptome sequencing of HRS cells provided new insights into cHL pathogenesis, potentially individualized approaches to cHL therapy.

**Keywords:** classical Hodgkin lymphoma (cHL); gene expression profile (GEP); Reed-Sternberg cells.

**95 PROFILING OF DNA METHYLATION IN EPIDEMIOLOGICAL AND CLINICAL SUBGROUPS OF BURKITT LYMPHOMA IN THE FRAMEWORK OF THE MMML: ICGC AND BLUEPRINT CONSORTIA**


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Introduction: Burkitt lymphoma (BL) is the most common pediatric mature aggressive B-cell lymphoma. The genetic hallmark of BL is a chromosomal translocation involving the MYC oncogene and one of the immunoglobulin loci leading to MYC deregulation. Three epidemiologic variants of BL are differentiated: endemic BL (eBL), predominantly occurring in Equatorial Africa and associated with EBV infection, sporadic BL (sBL), occurring in Western countries, and immunodeficiency-associated BL. We studied eBL as well as clinical presentations of sBL encompassing solid BL (solBL) and leukemic BL (leukBL) samples, and MYC-positive precursor B-cell acute lymphoblastic leukemia (TdT + BL). Furthermore, we included Burkitt-like lymphoma with 11q aberration (nmBL). The aim of the present study was to examine the DNA methyleme of these BL variants.

Methods: We analyzed the DNA methylation of 116 BL (60 solBL, 10 leukBL, 29 eBL, 15 mBL, 2 TdT + BL) using the HumanMethylation450 BeadChip (HM450k) in comparison to 24 diffuse-large B-cell lymphomas (DLBCL) and 30 follicular lymphomas (FL). Most of the cases were recruited in the ICGC MMML-Seq and MMML projects. The eBL were obtained from the NCI Ghana BL project. We included publicly available HM450k data from 93 B-cell populations of various differential stages. Furthermore, we analyzed whole-genome bisulfite sequencing (WGBS) data of 12 solBL and 6 leukBL and compared them to 4 germinal center B-cell populations from healthy donors.

Results: Unsupervised DNA methylation analysis of BL, FL and DLBCL revealed that all BL variants cluster apart from non-BL cases supporting on methylation level all BL samples to be BL variants. Unsupervised comparison of the BL variants separated them in EBV positive and EBV-negative BL which was mainly driven by a massive hypermethylation of EBV-positive eBL. Applying a newly developed DNA-methylation-based EBV classifier, we were able to predict correctly the EBV status in 12 of 13 cases (92%) with initially unknown status. Comparison of the DNA methylation using HM450k data of solBL and leukBL revealed 218 CpGs to be differentially methylated (σ/σ_max = 0.4, p < 0.0025). Using WGBS data of the same samples, 1697 differentially methylated regions (DMR) were identified, most of them being hypomethylated in leukBL. The latter were mostly located in enhancer and polycomb target regions which were enriched for transcription factor binding sites including AP-1/JUND.

Conclusion: In conclusion, we show that all BL variants can be separated from the non-BL based on their DNA methylene. Interestingly, DMRs between solBL and leukBL were mainly located in enhancer and polycomb regions. EBV-positive BL showed a hypermethylated epigenotype in comparison to the other BL variants. Thus, the differences identified by DNA methylation analysis can add to the understanding of the biological differences of the BL variants.

Keywords: Burkitt lymphoma (BL); epigenetics; Epstein-Barr virus (EBV).

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Introduction: The ICGC MMML-Seq consortium aims at a precise characterization of germinal center derived B-cell lymphomas (gBCL). Mutational signatures are patterns of single nucleotide variants (SNVs) taking into account the motif context. 30 mutational signatures had previously been extracted from a cross-entity data set, half of which could be attributed to mutational mechanisms. The goal of this work was to identify mutational mechanisms active in gBCL and link these to B-cell biology.

Methods: Matched tumor normal control pairs of gBCL (76 diffuse large B-cell lymphomas (DLBCL), 85 follicular lymphomas (FL), 16 FL/DLBCLs, two double hit lymphomas, and one B-cell lymphoma not otherwise specified (B-NOS)) from adult patients were analyzed by whole genome sequencing. SNVs were called with the DKFZ inhouse pipeline. An unsupervised analysis of mutational signatures was performed with non-negative matrix factorization. This analysis was complemented by a supervised analysis of mutational signatures using non-negative least squares and thereby enabling the extraction of enrichment and depletion patterns of the mutational signatures. Clusters at different mutation density were extracted based on intermutation distance.

Results: Clusters of mutations at different mutation density were extracted: Kataegis (rainfalls, high mutation density at single sample level) and Psichales (intermediate mutation density at single sample level). Genomic regions affected by the respective processes recurrently across the cohort were called regions of interest (ROIs).