Copy Number Analysis and Mutational Signature of Mature B-cell Neoplasms Using an in-house Custom Bioinformatic Pipeline

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BACKGROUND

Mature B-cell neoplasms are common hemopoietic malignancies but detailed molecular characteristics have not been fully understood. Next-generation sequencing (NGS) has become more widely used to characterize the molecular genetics of hemopoietic malignancies. Here we present a bioinformatic platform to integrate NGS assay data to characterize copy number alteration and mutational signatures of mature B-cell neoplasms.

METHODS

Fifty-five samples from 53 patients were sequenced by an NGS system (Illumina Inc., CA, USA). Thirty of 55 samples were chronic lymphocytic leukemia/small lymphocytic lymphoma, 8 diffuse large B-cell lymphoma, 5 mantle cell lymphoma and 5 plasma cell myeloma. The NGS data with 1425-gene assay capacity were processed and integrated by an in-house custom bioinformatic pipeline that combines eight genomic programs and allows visualization and analysis through cBioPortal platform (MSKCC, NY, USA). For each tumor, mutation spectrum was compared to copy number alteration if present. Thirty mutational signatures (data available in 45 samples), each of which represents a unique pattern of Watson-Crick base pair change and attributes to a specific biological origin, were analyzed by MuSiCa-R application (GPtoCRC Research Group, Spain).

RESULTS

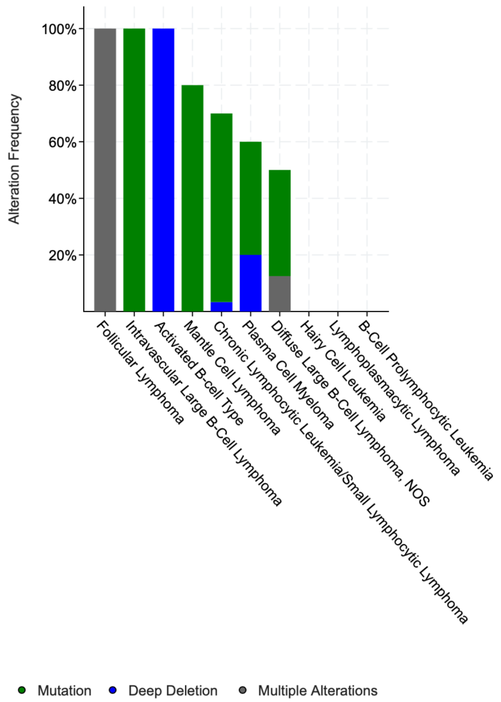


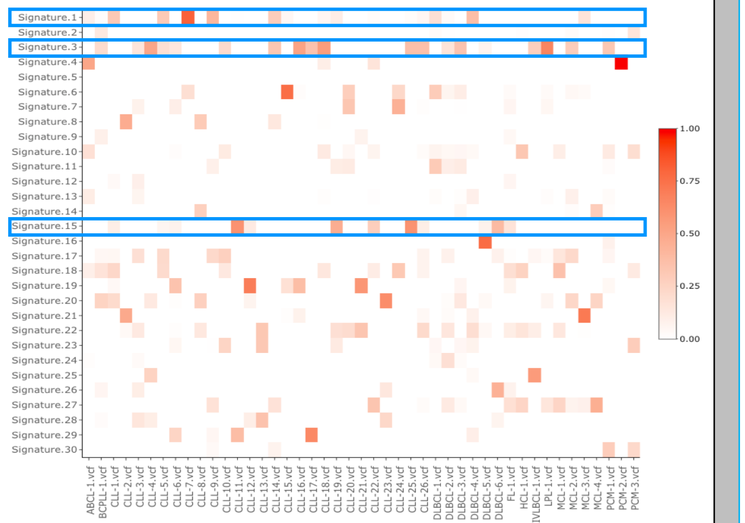
Figure 1. Distribution of genetic alteration types for varied mature B-cell neoplasm entities.

There were 226 significantly mutated genes identified in 32 of 55 samples (range: 1 – 75 per sample). Distribution of the three genetic alteration types is shown in Figure 1. The most common mutant genes included TP53 (14.6%), CHEK2 (12.7%), MDC1 (10.9%), ATM (9.1%), MSH3 (9.1%) and KMT2D (9.1%). Copy number gain was present in 182 genes while copy number loss was present in 155 genes. TP53 mutation was frequently associated with copy number alteration (6 of 8 mutant genes) while none of the 7 CHEK2 and 6 MDC1 mutant genes were accompanied with any copy number alteration. The most frequent mutational signatures included #3, #1 and #15, which were attributed to proposed etiologies of BRCA1/2, age and defective DNA mismatch repair respectively (Figure 2).

DISCLOSURE

LH, EV, GJ, DO, JG, BC: None

Figure 2. Mutational signature contribution for individual tumor.



CONCLUSIONS

- An in-house custom bioinformatics pipeline has been established to characterize genomic features of mature B-cell neoplasms and can be potentially applied to other tumor types.
- Mutational signatures of mature B-cell neoplasm have been found to be associated with BRCA pathway, suggesting B-cells may share similar pathogenesis of DNA double-strand break repair.