

STR Profiling Reveals Tumor Genome Instability in Primary Mediastinal B-Cell Lymphoma

Yana Mangasarova¹, Natalya Risinskaya¹, Elena Nikulina¹, Yana Kozhevnikova², Julia Chabaeva¹, Anna Yushkova¹, Sergey Kulikov¹, Hunan Julhakyan¹, Sergey Kravchenko¹, Andrey Sudarikov¹

¹National Research Center for Hematology, Moscow, Russia,
²School of Medicine, Lomonosov Moscow State University, Moscow, Russia



Background

Loss of heterozygosity (LOH) in Short Tandem Repeats (STR) loci, elevated microsatellite alteration at selected tetranucleotides (EMAST) and instability of mononucleotide tandem repeats (MSI - microsatellite instability) are intrinsic features of diverse tumor cells. MSI-high is associated with a good response to immunotherapy for many solid tumors [1]. For primary mediastinal B-cell lymphoma (PMBCL) these molecular features of the disease have not been proven yet to have prognostic value [2]. A standard MSI set of five mononucleotide microsatellite repeat markers BAT-25, BAT-26, NR-21, NR-24, and NR-27 might not be informative in aggressive lymphoma cases since low occurrence (up to 5%). Furthermore, in about half of the cases, the altered allele may also present in the control material, possibly characterizing not the tumor, but the genetic features of the patient [3]. According to the literature data, EMAST-high is associated with MSI-high in solid tumors[4]. Overlapping combinations of enzymes of the DNA repair complex are responsible for the repair of unpaired bases and the removal of oligonucleotide insertion loops. Therefore certain defects in the DNA repair complex (MMR) may lead to both MSI and EMAST. In this regard, LOH and EMAST in STR loci in the tumor genome are of interest (Fig.2). An appropriate analysis of these features might be used for the selection of patients for the checkpoint inhibitors immunotherapy.

Objective

To analyze the frequency of LOH and EMAST in tumor cells of PMBCL patients at diagnosis and to check possible association with disease features.

Figure 1. Diagram of LOH and EMAST distribution in STR-loci

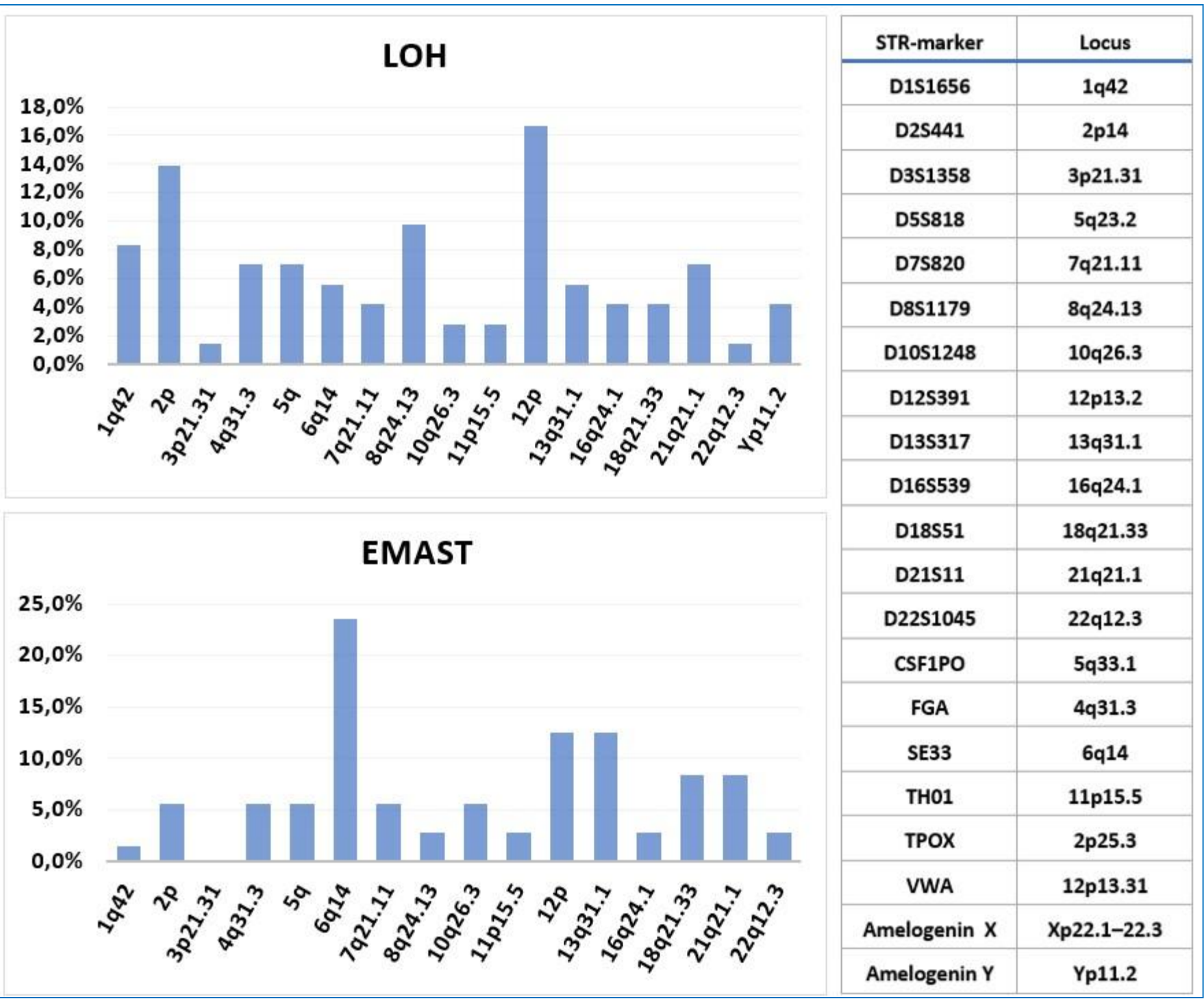
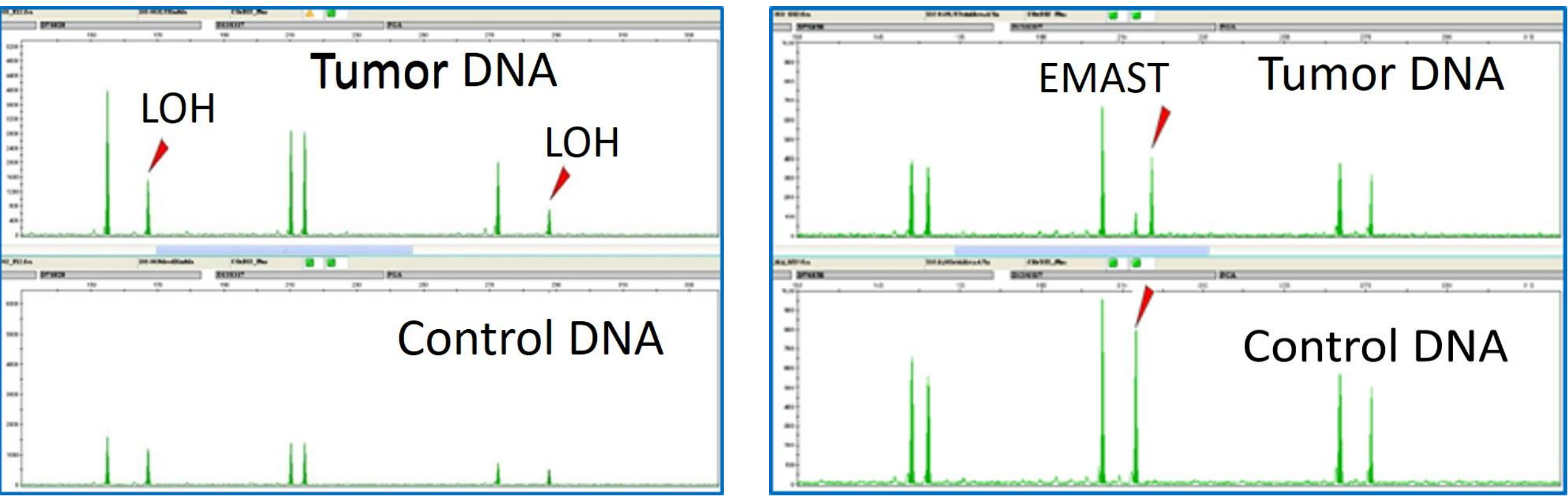


Figure 2. LOH and EMAST patterns in STR profile of PMBCL patient



Materials & Methods

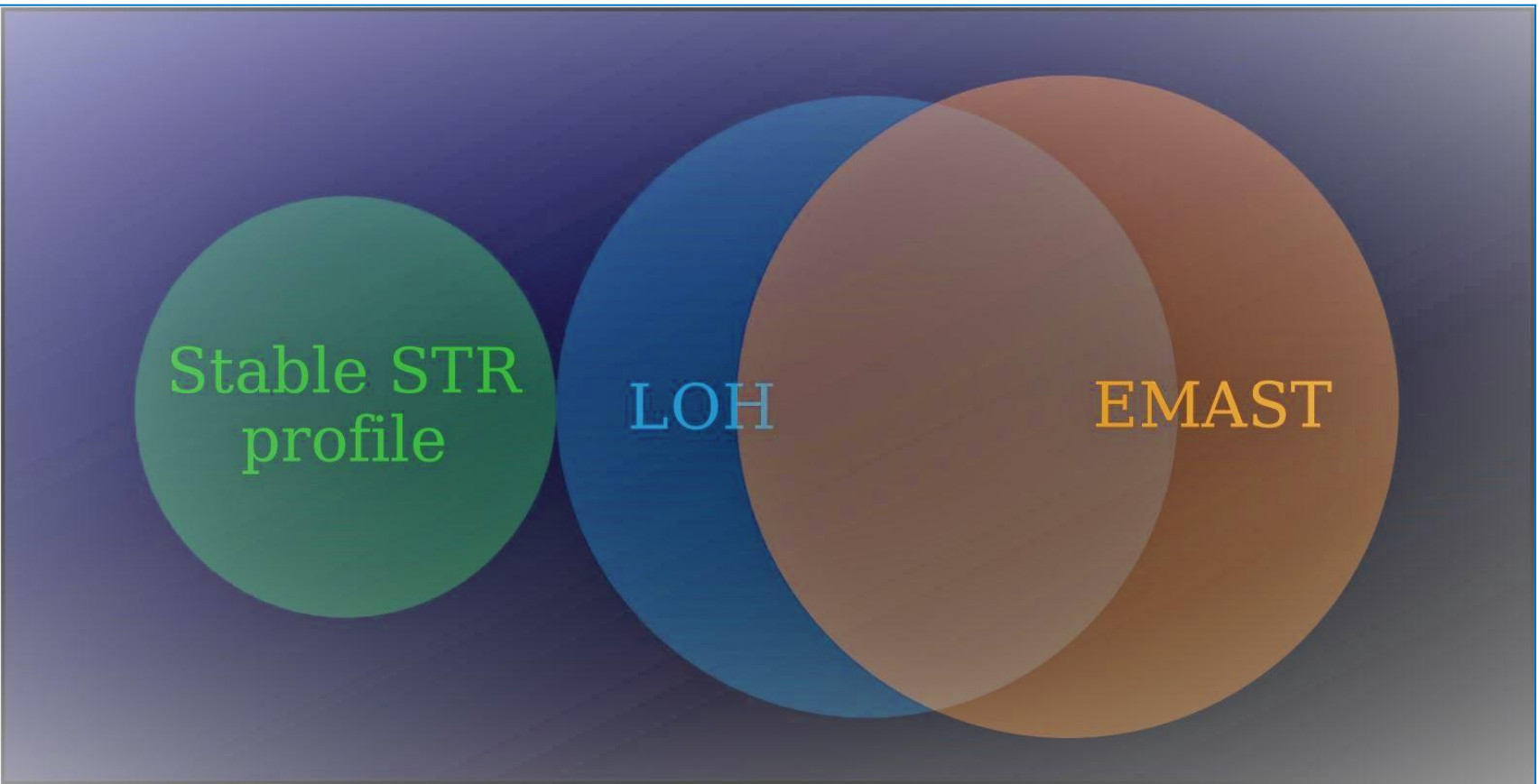
DESIGN: STR profiles of the DNA of tumor cells were analyzed on a cohort of 72 PMBCL patients undergoing EPOCH regimen treatment at the National Research Center for Hematology (Moscow, Russia).

SETTING: Tumor DNAs were isolated from the biopsy samples taken at diagnosis. Control DNAs were isolated from the blood samples taken in complete remission or from the buccal epithelium. STR-profiles for LOH and EMAST analysis were assessed by PCR with CORDIS Plus multiplex kit for amplification of 19 STR-markers (tetranucleotide repeats) and amelogenin loci (Gordiz Ltd, Russia). The fragment analysis was performed on the ABI3130 Genetic Analyzer.

PATIENTS: Inclusion criteria: de novo diagnosed PMBCL patients. Exclusion criteria: pretreatment.

MAIN OUTCOMES MEASURES: Progression-free survival (PFS) and overall survival (OS) at 24 months from diagnosis were used to assess the independent impact of the genetic instability as a risk factor.

Figure 3. Venn diagram indicating the distribution of PMBCL patients according to their LOH and EMAST status



Summary

LOH was detected in 37 of 72 patients (51.4%), LOH 2p and LOH 12p were most frequent. EMAST was found in 40 patients (55.5%), SE33 was the most unstable STR marker (Fig.1). 24 patients had a combination of EMAST with LOH (Fig.3). For all EMAST-positive patients, the number of involved loci was no more than 4 out of 19 (EMAST-low, less than a third of the panel of STR markers).

Conclusion

STR profiling of PMBCL tumor genome revealed LOHs associated with deletions or uniparental disomy and detected EMAST attributed to a failure of DNA mismatch repair. The high incidence of LOH and EMAST in PMBCL can be associated with standard therapy failure in a significant number of patients.

Funding

This study was supported by Rakfond grant 2/2020

References

- Luchini C et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. *Ann Oncol.* 2019
- Dai H et al. Genomic Landscape of Primary Mediastinal B-Cell Lymphoma Cell Lines. *PLoS ONE*, 2015
- Sychevskaya KA et al. Pitfalls in mononucleotide microsatellite repeats instability assessing (MSI) in the patients with B-cell lymphomas. *Klin Lab Diagn.*; 2021
- Watson MM et al. Prevalence of PD-L1 expression is associated with EMAST, density of peritumoral T-cells and recurrence-free survival in operable non-metastatic colorectal cancer. *Cancer Immunol Immunother*, 2020