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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Whole Exome Sequencing Analysis of Diffuse Large B-Cell Lymphoma That Progressed to Central Nervous System

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Background: Recent sequencing analyses have identified distinct genetic subtypes of diffuse large B-cell lymphoma (DLBCL). The MCD subtype, characterized by *MYD88* L265P and *CD79B* gene mutations, is frequently found in DLBCL that progresses to the central nervous system (CNS), known as secondary CNS lymphoma (sCNSL) (Ollila, Blood 2021). In addition, the MCD subtype is also frequently found in primary CNS lymphoma (PCNSL) (Radke, Nat commun 2022). Therefore, we hypothesized that specific genetic alterations that are present in the initial DLBCL tumors are associated with their progression to the CNS. We aimed to investigate i) the clinical impact of genetic subtypes of DLBCL and ii) genomic mutations that may be associated with sCNSL. To this end, genetic alterations in DLBCL samples at diagnosis that later developed into sCNSL were evaluated using whole-exome sequencing (WES).
Methods: A total of 44 patients with DLBCL who developed sCNSL after receiving standard rituximab-containing chemotherapy between 2009 and 2020 were identified from five institutions. sCNSL was diagnosed on the basis of imaging and/or pathological findings. Genomic DNA (gDNA) was extracted from formalin-fixed, paraffin-embedded tumor samples obtained at the initial diagnosis of DLBCL. Finally, 26 of the 44 samples with sufficient gDNA were subjected to WES at BGI Genomic Co. Ltd. Single-nucleotide variants and short indels were detected using Mutect2 and filtered as described in Figure 1. Genetic subtypes were determined using the LymphGen algorithm (https://llmpp.nih.gov/lymphgen/index.php). The association between the clinicopathological features and genetic subtypes was also evaluated. In addition, recurrently mutated genes (>10% in our cohort) were identified and their alteration frequencies were compared with those in a representative general DLBCL cohort (N=574, available in the article by Schmitz, NEJM 2018) and PCNSL cohort (N=30, whole genome sequencing performed, available in the article by Radke, Nat Commun 2022) (Figure 1a).
Results: The median age of the 26 patients was 69 years (range, 34-87). At the time of CNS progression, 54, 27, and 19% of the patients had parenchymal CNS disease, extraparenchymal CNS disease, and both, respectively. Immunohistological analysis showed that the non-germinal center B-cell-like (GCB) type, as defined using the Hans algorithm, and dual expression of MYC and BCL2 (DEL) were identified in 65% and 69% of patients, respectively. The median overall survival (OS) from CNS relapse was 16 months (95% confidence interval, 2-30).
WES analysis showed that the median mean coverage depth of the 26 samples was 140 (range, 53-299). The median mapping rate was 94% (range, 80-99). As expected, the most frequently mutated genes in our cohort were *MYD88* (50%), *PIM1* (50%), *BTG2* (31%), and *CD79B* (31%), corresponding to the MCD subtype. The LymphGen algorithm classified the 26 samples into MCD (n=12, 46%), EZB (n=5, 19%, including one with a composite feature of ST2), BN2 (n=1, 4%) and "not classified" (n=8, 31%) (Figure 1b). The CNS-IPI risk, DEL status, and CNS relapse sites did not differ among the genetic subgroups. In addition, univariate analysis showed that non-GCB status, DEL status, and genetic subtype at initial diagnosis did not influence OS.

Next, we shortlisted 38 genes whose mutations were identified in three or more samples (>10%) of our cohort as well as in >10% of the PCNSL cohort (by Radke, Nat Commun 2022). We further selected genes that were less frequent (<3%) in the general DLBCL cohort and identified several genes, such as *MUC16* and *FAT4*, that were more enriched in PCNSL and our sCNSL cases (Figure 1a). Metascape analysis (https://metascape.org/gp/index.html#/main/step1) revealed that the top three enriched processes associated with these genes were sensory organ development, cell adhesion via plasma membrane adhesion molecules, and morphogenesis of epithelium.
Conclusion: Our study confirmed that MCD was a major genetic subtype of DLBCL that developed sCNSL. We identified recurrently mutated genes that were common in both sCSNL and PCNSL but not in the general DLBCL cohort; these genes may be associated with CNS progression. Validation of our results and investigation of the functions of these genes will help to understand the mechanisms of CNS relapse and develop more accurate markers to predict sCNSL.
*Suzuki T and Yokomori R equally contributed to this study.

Disclosures Suzuki: *Chugai Pharmaceutical:* Honoraria; *SymBio:* Honoraria; *Janssen Pharmaceutical:* Honoraria; *Sanofi:* Honoraria; *Bristol Myers Squibb:* Honoraria; *Astellas:* Honoraria. **Sasaki:** *Chugai Pharmaceutical:* Honoraria; *Ono Pharmaceutical:* Honoraria. **Narita:** *Shionogi:* Research Funding; *Janssen Pharmaceutical:* Honoraria; *Asahi Kasei:* Honoraria; *Novartis:* Honoraria; *Eisai:* Honoraria; *Daiichi Sankyo:* Honoraria; *Abbvie:* Honoraria. **Ri:** *Bristol-Myers Squibb:* Research Funding; *Daiichi Sankyo:* Research Funding; *Chugai Pharmaceutical:* Research Funding; *Kyowa Kirin:* Research Funding; *Ono Pharmaceutical:* Research Funding; *Takeda:* Research Funding; *Janssen:* Honoraria. **Kusumoto:** *Meiji-Seika:* Honoraria; *Mundipharma:* Honoraria; *Nippon-Shinyaku:* Honoraria; *AbbVie:* Honoraria; *SymBio:* Honoraria; *Astellas:* Honoraria; *Bristol Myers Squibb:* Research Funding; *Kyowa-Kirin:* Honoraria; *Ono:* Honoraria; *Janssen:* Honoraria, Research Funding; *Eisai:* Honoraria; *Chugai:* Honoraria, Research Funding; *Takeda:* Honoraria; *Shionogi:* Research Funding; *Eil Lilly:* Honoraria; *AstraZeneca:* Honoraria; *Daiichi-Sankyo:* Honoraria, Research Funding. **Iida:** *Otsuka:* Consultancy; *Shionogi:* Research Funding; *Pfizer:* Consultancy, Research Funding; *Alexion:* Research Funding; *GlaxoSmithKlein:* Consultancy, Research Funding; *Amgen:* Research Funding; *Otsuka:* Research Funding; *Novartis:* Consultancy, Research Funding; *Chugai:* Research Funding; *Abbvie:* Consultancy, Research Funding; *Ono:* Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Daiichi Sankyo:* Research Funding; *Sanofi:* Consultancy, Honoraria, Research Funding; *Regeneron:* Consultancy; *Takeda:* Consultancy, Honoraria, Research Funding; *Bristol-Myers Scuibb:* Consultancy, Honoraria, Research Funding.

Figure 1a. Overview of genetic analyses

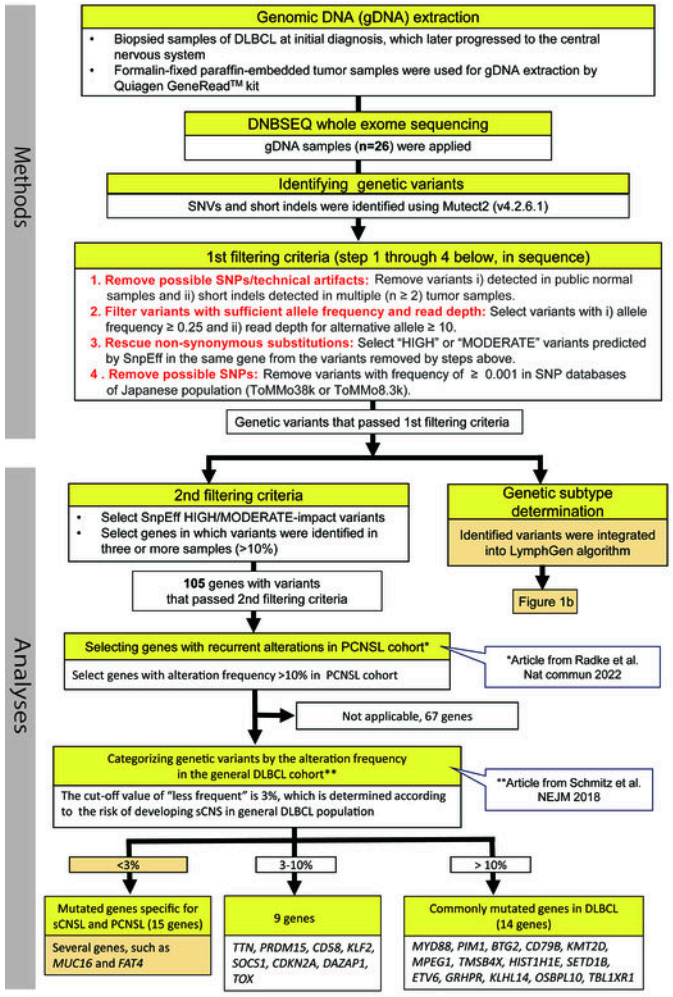

Figure 1b. Results of WES, limited to the representative genes for DLBCL genetic subtype

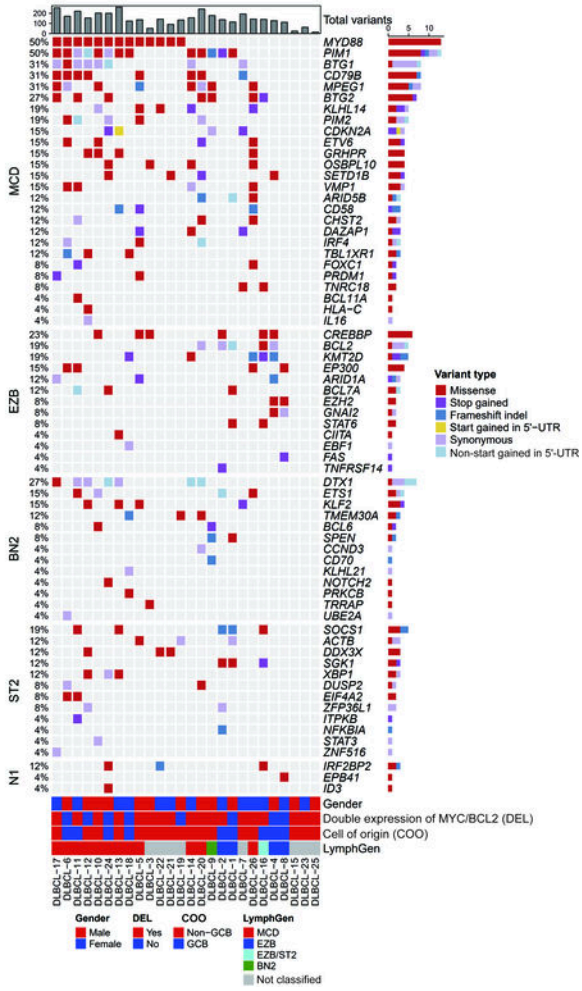

Figure 1

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