Mutational Spectra of the Korean Patients with Germline Predisposition in Hematologic Malignancies

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INTRODUCTION

• An expanding number of genes predisposing to hematologic malignancies are being discovered by nextgeneration sequencing (NGS) technology.
• The 5th edition of the World Health Organization (WHO) Classification of Hematolymphoid Tumors and International Consensus Classification of Myeloid Neoplasms and Acute Leukemias revised the previous WHO classification on hematologic neoplasms with germline predisposition acknowledging this development.
• We aimed to identify the mutational spectrum of germline predisposition in hematologic malignancies from Korean patients by retrospective analysis of somatic NGS panel for hematologic malignancies data.

METHODS

Study population and samples

• The study included 437 tests of 408 patients tested for hematologic malignancy NGS panel at Pusan National University Yangsan Hospital from 2019 to 2022. NGS was performed on the genomic DNA extracted from bone marrow samples obtained from patients at initial presentation or relapse. Twenty-nine patients were tested twice due to relapse.

Targeted gene sequencing

• The NGS panel comprised 200 genes related to hematologic malignancies, including 48 well-known germline predisposition genes.
• We identified potential germline variants by retrospective analysis of NGS results. Variant allele frequency > 0.3 of variants in a known germline predisposition gene was considered potential germline variants. However, due to the absence of germline tissues and the retrospective nature of the study, we could not confirm each variant’s germline status.

RESULTS

Table 1. Clinical characteristics of 36 patients harboring potential germline variants. Thirty-six (8.8%) among 408 patients harbored potential germline variants. Their ages ranged from 1 to 72 years (median 50 years).

| N of Patients | 36 |
| Age (range) | 50 (1–72) |
| ≤ 18 (%) | 8 (22.2) |
| > 18 (%) | 28 (77.8) |
| Sex | Male (%) 20 (55.6)
 Female (%) 16 (44.4) |
| Diagnosis | B-ALL (%) 9 (25.0)
 T-ALL (%) 4 (11.1) AML (%) 20 (55.6)
 MDS (%) 2 (5.6) MDS/MPN (%) 1 (2.8) |

CONCLUSION

• This study aimed to establish the general frequency and distribution of potential germline variants in Korean patients with hematologic malignancy and found that DD4X, RUNXI, GATA2, and PAX5 were the most common genes.
• 8.8% of patients carried potential germline variants, with the median age being 50. The American Society of Clinical Oncology recommends germline testing when a positive result is anticipated in at least 5% of the tested population. The study population in this study already exceeds this number. Therefore, regardless of age, universal germline testing for all patients with a hematologic malignancy may be beneficial.
• This study provides insight into the pathophysiology of germline predisposition in hematologic malignancies.

COI DISCLOSURE

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