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Mutational Analysis of *SH2B3* in Korean Patients With *BCR-ABL1* Negative Myeloproliferative Neoplasm

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Dear Editor,

Src homology 2 B3 (*SH2B3*), previously named *LNK*, has been reported as a new genetic abnormality in *BCR-ABL* negative myeloproliferative neoplasms (MPN) [1-3]. In western patients, the mutational hot spot of *SH2B3* is located in exon 2, within a pleckstrin homology (PH) domain. However, *SH2B3* mutations in Korean MPN patients can occur in several other regions of the *SH2B3* gene, including exons 7 and 8 [4]. In this study, we performed sequencing analyses of *SH2B3* in Korean patients with *BCR-ABL1* negative MPN and compared the results with previous studies.

In total, 75 patients were enrolled in the study, comprising 32 patients with essential thrombocytosis (ET), 25 patients with polycythemia vera (PV), 10 patients with primary myelofibrosis (PMF), and eight patients with unclassifiable MPN. All patients were diagnosed between June 2007 and March 2012 at Pusan National University Hospital in Busan, Korea. The patients comprised 40 males and 35 females with a median age of 57.3 yr. This research was reviewed and approved by full committee review of the Institutional Review Board at Pusan National University Yangsan Hospital (No. 05-2014-058).

We designed the primers and performed the mutation analyses by direct sequencing of the following loci: *SH2B3* exons 2, 7, and 8; *Janus kinase 2* (*JAK2*) exon 12 and V617F mutation; and *casitas B-lineage lymphoma proto-oncogene* (*CBL*) exons 8 and 9. Alterations in the *CBL* gene have been identified in AML, MPN, and chronic myelomonocytic leukemia patients [5].

We identified two different *SH2B3* mutations (2.7%) in exon 8 (Fig. 1 and Table 1). A novel p.Q571* (c.1711C>T) mutation which results in a premature stop codon and the known p.I568T (c.1703T>C) missense mutation were identified. In addition, two patients have a known polymorphism, p.A356T (c.1606G>A) [4]. The *JAK2* V617F mutation was detected in 48 of 75 patients (64.0%); however, no mutation of *JAK2* exon 12 or *CBL* exons 8 or 9 was identified. One of the two patients with a *SH2B3* mutation also harbored a *JAK2* V617F mutation (Table 1).

The mutations in *SH2B3* were described in approximately

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Table 1. The characteristics of two patients with *SH2B3* mutations

No.	Patient sex/onset age	Diagnosis	Disease state	Disease progression	*SH2B3* mutation	*JAK2* V617F mutation	*CBL* gene mutation
1	F/51	ET	chronic	No significant progression	c.1703T>C (p.I568T), exon 8 in C-terminal region	Detected	Not detected
2	F/59	PMF	chronic	No significant progression	c.1711C>T (p.Q571*) exon 8 in C-terminal region	Not detected	Not detected

Abbreviations: ET, essential thrombocythemia; PMF, primary myelofibrosis; *JAK2*, *Janus kinase 2*; *CBL*, *casitas B-lineage lymphoma proto-oncogene*.

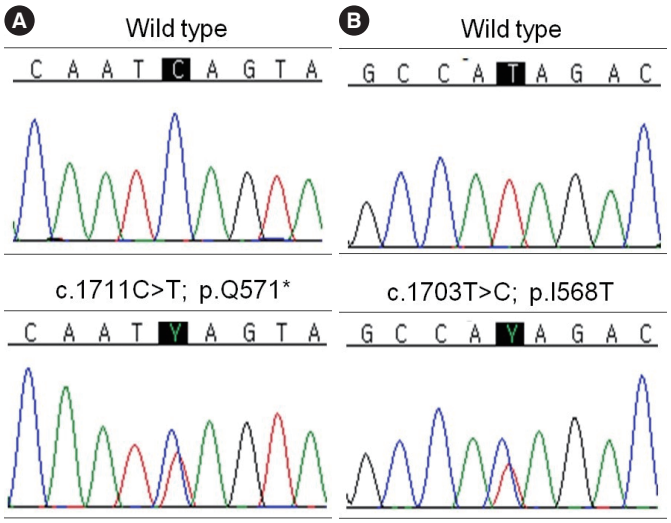

Fig. 1. Nucleotide sequence and chromatogram of *SH2B3* mutations in Korean patients with *BCR-ABL1* negative myeloproliferative neoplasm. (A) Nonsense mutation (c.1711C>T; p.Q571*), (B) missense mutation (c.1703T>C; p.I568T).

6.1-25.0% of patients with chronic phase MPN in western countries [1-3, 6]. In this study, the frequency of *SH2B3* mutation was 2.7%, and the mutations were found only in exon 8. Recently, Ha *et al*. [4] demonstrated that mutational frequency of the *SH2B3* gene was 7.1% in exons 7 and 8 in 42 Korean patients with chronic phase MPNs. They reported that three types of *SH2B3* mutation accompanied by *JAK2* V617F mutation, including p.Q423* located on exon 7, and p.R551W and p.I568T located on exon 8; the p.I568T mutation was also detected in this study. Including this data, mutations of *SH2B3* are discovered in exon 7 and 8 in the Korean population, and no mutation was identified in exon 2 of *SH2B3* gene.

The *SH2B3* is known to bind *JAK2* and perform a critical role in negative regulation of downstream signal transduction [7]. Pardanani *et al*. reported the co-occurrence frequency of *SH2B3* mutations and the *JAK2* V617F mutation and found that *SH2B3* mutations occur at similar frequencies in both *JAK2* V617F negative and positive patients [6]. The effect of co-occurrence of *SH2B3* and *JAK2* V671F is still unknown, but an animal model study suggested that a more severe phenotype may result in cases with both mutations [8]. In this study, there were no significant differences in prognosis in patients with *SH2B3* mutation according to the presence of *JAK2* V617F mutation (Table 1). Therefore, the clinical significance might be investigated in a large-scale study.

This study has some limitations, such as the small investigation size and the low detection sensitivity of the direct sequencing method. In addition, since we did not search the entire coding region, there is a possibility of *SH2B3* mutations in other regions outside exons 2, 7, and 8. For further study of *SH2B3*, mutational analysis of either the entire coding region or additional exons needs to be considered.

In conclusion, racial differences can cause variances not only in the prevalence but also in the mutational hot spot region of *SH2B3*. Our study suggests that *SH2B3* mutations occur infrequently, and exon 8 in *SH2B3* may be the most frequent mutational area in *BCR-ABL* negative MPN patients in Korea.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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