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...
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 V617F 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.

**Acknowledgments**

This work was supported by the year clinical research grant from Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital.

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