The recently reported gain of function mutations in signal transduction molecules has remarkably increased our knowledge about the molecular genetics of myeloproliferative neoplasms (MPN) [1]. JAK2 mutations occur in most patients with polycythemia vera (PV) and in about half of the patients with essential thrombocytemia (ET) [2]. Missense mutations in the MPLgene, which encodes the thrombopoietin receptor MIM 159530 have also been reported in a small proportion (19%) of patients with ET and primary myelofibrosis [3–6]. MPL mutations usually affect the W515 residue in exon 10 [3, 7]. We investigated the frequency of MPLW515L/K mutations in a series of consecutive patients with ET and post-essential thrombocytemia myelofibrosis (post-ET MF). The study subjects were 63 patients diagnosed either with ET (N=59) or post-ET MF (N=4) at our institution between June 2006 and February 2010. Among them, 35 (55.6%) had the JAK2V617F mutation. MPLW515L/K mutations were detected by direct sequencing analyses of exon 10, and 2 patients were found to harbor the following MPL mutations: W515L in 1 patient with ET and W515K in 1 patient with post-ET MF. Neither of the patients had the JAK2V617F mutation. The frequencies of the MPLW515L/K and JAK2V617F-negative mutations in our subjects with ET/post-ET MF were 3.2% (2/63) and 7.1% (2/28), respectively. This is the first study to report the frequency of JAK2V617F and MPLW515L/K mutations in Korean patients with ET/post-ET MF. (Korean J Lab Med 2010;30:474-6)

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clinical and laboratory history of the 2 patients with the MPL W515L/K mutation was as follows.

Patient 1 was a 71-yr-old Korean woman and was admitted to our institution with a 5-month history of sustained thrombocytosis. Complete blood count (CBC) test performed on admission revealed the following results: Hb, 10.9 g/dL; white blood cells (WBC), 4.9×10⁹/L; and platelets, 580×10⁹/L. She did not have a family history of hematological disorders, including MPN. Clinically, she did not have a history of vascular events or other manifestations relevant to MPN. The bone marrow (BM) study showed hypercellular marrow with increased megakaryocytes with large and atypical morphology. Molecular genetic analyses were performed on the patient’s DNA samples from peripheral blood to detect JAK2 V617F and exon 12 mutations, both of which were negative. On suspicion of ET, we additionally performed direct sequencing of exon 10 of the MPL gene on the patient’s DNA samples from the BM aspirate. As a result, we detected the heterozygous MPL W515L mutation with a 50% mutant allele burden (Fig. 1). Finally, the patient was diagnosed with ET according to the WHO 2008 criteria [8]. She has been on routine follow-up for 3 months with aspirin medication.

Patient 2 was a 53-yr-old man with a history of ET for 12 yr. Due to progressive splenomegaly and anemia, a BM study was performed, which revealed extensive myelofibrosis and markedly decreased normal trilineage hematopoiesis. His CBC was as follows: Hb, 10.8 g/dL; WBC, 14.9×10⁹/L; and platelets, 170×10⁹/L. JAK2 V617F and exon 12 mutations were negative on direct sequencing using his BM aspirate sample. The subsequent test for MPL mutations revealed a homozygous W515K mutation with a mutant allele burden ~100% (Fig. 1). Considering the patient’s past medical history of ET and the BM findings of myelofibrosis by reticulin and Masson-Trichrome stains on the biopsy section, he was diagnosed with post-ET MF. He received unrelated allogeneic peripheral blood stem cell transplantation. He has been on routine outpatient follow-up for 2 yr post-transplant.

The data from this study showed that the frequency of the MPL W515L/K mutation in Korean patients with ET/post-ET MF was 3.2% (2/63) and that of JAK2 V617F-negative ET/post-ET MF was 7.1% (2/28). The MPL mutation observed in patient 1 was a G→T transversion at nucleotide 1544 (c.1544G>T) replacing tryptophan with leucine at codon 515 (p.W515L) with a ~50% allele burden. Patient 2 had c.1543_1544TG>AA replacing the TGG codon for tryptophan with AAG for lysine (p.W515K) with a ~100% allele burden (homozygous). W515L and W515K are the 2 most frequent MPL mutations in ET, each accounting for 60-75% and 16-40%, respectively [3, 6, 7]. Unlike MPN with JAK2 mutations, only limited studies have been reported on genotype-phenotype correlations in MPL mutations [3, 5, 6]. As for the type of the mutation, while the W515L mutation is consistently from c.1544G>T, 2 different mutations have been reported to cause W515K, c.1543_1544TG>AA and c.1543_1545TGG>AAA [3]. Interestingly, c.1543_1544TG>AA was reported in patients with both ET and idiopathic myelofibrosis (IMF), while c.1543_1545TGG>AAA was described only in IMF [3]. As for the mutant allele burden, W515K was reported more frequently to be homozygous than W515L, particularly in ET [3–6]. Lastly, a significantly younger age at onset was reported in W515K than in W515L, although controversies still exist on this correlation [3, 6]. In our 2 Kore-
an patients, patient 1 with W515L had early-phase ET at 71 yr of age with a ~50% mutant allele burden, while patient 2 with W515K from c.1543_1544TG>AA had been diagnosed with ET at the age of 41 and experienced progression into post-ET MF with a ~100% mutant burden (homozygous). Our findings, albeit only from 2 patients, are in line with the aforementioned genotype–phenotype correlations from previous studies. The relatively young age at onset, progression to myelofibrosis, and high mutant allele burden in patient 2 might suggest that W515K from 1543_1544TG>AA is more aggressive than W515L. It was unfortunate that we could not determine the MPL mutation status of patient 2 at his early manifestation of ET.

To the best of our knowledge, this is the first study to report the frequency of JAK2 V617F and MPL W515L/K mutations in Korean patients with ET/post-ET MF. In addition to the JAK2 mutations, the MPL gene mutation status should be determined in patients suspected of having MPN. Data from more patients and comprehensive analyses are required to reveal the frequency of MPL mutations and genotype–phenotype correlations in MPN in Korean patients.

REFERENCES