Korean J Lab Med 2010;30:474-6
DOI 10.3343/kjlm.2010.30.5.474



# *JAK2* V617F and *MPL* W515L/K Mutations in Korean Patients with Essential Thrombocythemia

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*JAK2* V617F and *MPL* W515L/K mutations have been reported in approximately 50% and 5% of the patients with essential thrombocythemia (ET), respectively. We investigated the frequency of *MPL* W515L/K mutations in a series of consecutive patients with ET and post-essential thrombocythemia 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 *JAK2* V617F mutation. *MPL* W515L/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 *JAK2* V617F mutation. The frequencies of the *MPL* W515L/K and *JAK2* V617F-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 *JAK2* V617F and *MPL* W515L/K mutations in Korean patients with ET/post-ET MF. *(Korean J Lab Med 2010;30:474-6)*

Key Words : *Essential thrombocythemia, mutation, JAK2, MPL, Korea*

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 thrombocythemia (ET) [2]. Missense mutations in the *MPL* gene, 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 *MPL* W515L/K mutations in a series of consecutive patients with ET and post-essential thrombocythemia 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 patients (55.6%) had the *JAK2* V617F mutation, which was identified by allele-specific PCR and direct sequencing analyses. *MPL* W515L/K mutations were detected by direct sequencing analyses of exon 10. As a result, two patients were found to harbor the following *MPL* mutations: W515L mutation in 1 patient with ET (Patient 1) and W515K mutation, 1 patient with post-ET MF (Patient 2). Neither of the patients had the *JAK2* V617F mutation. The

Received : March 6, 2010 Manuscript No : KJLM10-043
Revision received : May 3, 2010
Accepted : July 12, 2010
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*This study was supported by the Samsung Medical Center Clinical Research Development Program grant, #CRS-106-56-2.

ISSN 1598-6535 

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), $4.9\times10^9$/L; and platelets, $580\times10^9$/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, $14.9\times10^9$/L; and platelets, $170\times10^9$/L. *JAK2* V617 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.

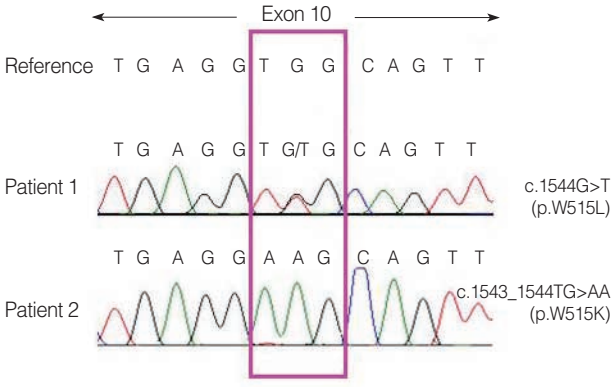


Fig. 1. *MPL* gene mutations in 2 Korean patients with myeloproliferative neoplasms. Patient 1 with essential thrombocythemia (ET) had the W515L mutation from c.1544G>T with an allele burden of approximately 50%. Patient 2 with post-ET myelofibrosis had W515K from c.1543_1544TG>AA with an allele burden of approximately 100% (homozygous).

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-to-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.

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