The Janus kinase 2 (*JAK2*) V617F mutation in Chinese patients with chronic myeloproliferative disorders

A single, valineto-phenylalanine somatic mutation at position 617 (V617F) in the JAK2 kinase in patients with chronic myeloproliferative diseases (cMPDs) were reported.[1-4] In the present study, the JAK2 V617F mutation was detected in a larger cohort of Chinese cMPDs patients, to evaluate the incidence of JAK2 V617F mutation in Asian populations. The relation between the JAK2 mutation load and the clinical features of cMPDs were also investigated.

This study was approved by the ethical committee of the Institute of Hematology, CAMS and PUMC according to the guidelines of the Declaration of Helsinki. A total of 523 patients with cMPDs enrolled between December 1987 to December 2006 (278 males, 245 females) were retrospective analyzed. Median age was 50 years old (7-83 years). According to the WHO diagnostic criteria,[5] among the 523 patients were 88 cases of chronic myeloid leukemia (CML) at the chronic phase (59 males, 29 females; median age of 40 years), 25 cases of CML complicated with myelofibrosis (MF), 116 cases of polycythemia vera (PV) (64 males, 52 females; median age 53 years including 6 cases of PV with secondary myelofibrosis), 153 cases of essential thrombocythemia (ET) (63 males, 91 females; median age 50 years including 15 cases of ET with secondary myelofibrosis), 142 cases of idiopathic myelofibrosis (IMF) (71 males, 71 females; median age 53.5 years), 4 cases of unclassified CMPD (CMPD-U) (2 males, 2 females; median age 60 years), 7 cases of hypereosinophilic syndromes (HES) (6 males, 1 female; median age 32 years), and 13 cases of chronic eosinophilic leukemia (CEL) (13 males; median age 34 years). In addition, 140 healthy adults were included as control.

Three hundred and forty-six (66%) had the JAK2 V 617F mutation as determined by the ASP method combined with DNA sequencing.[1-4] The positive rates for the PV, ET, MF, CMPD-U and HES patients were 94%, 79%, 78%, 75% and 14%, respectively (Table 1). The JAK2 V617F mutation could not be detected in the CML and CEL patients or in the 140 healthy adults. Most (98%, 341/346) of the 345 JAK2 V617F-positive cases had the heterozygous mutation and only the remaining 5 cases had the homozygous mutation; among these 5 cases were 4 PV patients and one ET patient, indicating that the mutation is mostly closely related to the PV, in agreement with previous studies.[1-4]

Three peak types were found by DNA sequencing of JAK2 V617F mutation, the samples with the different peak types were subjected to cloning detection, and the subsequent comparison of the percentages of mutant clone in the different peak-types of samples showed that the number of the mutant clone increased together with the T/G ratios, and that the T/G ratio was therefore able to reflect the JAK2 V617F mutation load. According to the ratios (T/G) of peak values at the point mutation sites, the JAK V617F-positive patients could be assigned into three groups: the JAK V617F-A group with a T/G ratio less than l, the JAK V617F-B group with a T/G ratio larger than 0.5, and the JAK V617F-C group with a T/G ratio less than 0.5. Of the 345 JAK2 V617F-positive patients, 246 (71.5%) had a T/G ratio <0.5 (low load group), 86 (25%) 1>T/G >0.5 (medium load group), and 13 (3.5%) T/G>1 (high load group). The proportion of high mutation load in the PV patients was significantly higher than those in the ET and IMF patients (p=0.003) (Table 1).

According to the size of the JAK2 V617F mutation load, the 109 JAK2 V617F-positive PV patients were divided into two groups: the medium/high load group (PV-AB, T/G>0.5) and the low load group (PV-C, T/G <0.5). The clinical features, including hypertension, thrombus event, splenomegaly, peripheral white blood cell count, red blood cell count, hemoglobin level, hematocrit, platelet count, degree of bone marrow hyperplasia, neutrophil alkaline phosphatase (N-ALP), secondary myelofibrosis, bone marrow EEC and serum EPO level, were compared between these two groups. The results showed that the positive rates of hemoglobin and N-ALP of the patients in the PV-AB group was significantly higher than those in the PV-C group (p=0.039 and 0.041 respectively). The correlation analysis showed that, for the PV patients, the hemoglobin levels were significantly correlated positively with the mutation loads (p=0.033; r=0.203). Similarly, the 122 JAK2 V617F-positive ET patients were

Table 1. The clinical futures and the incidences of JAK2 V617F mutation of patients with chronic myeloproliferative diseases.

Diagnosis	*N. of cases*	*Sex (M/F)*	*Median age (range)*	*V617F + cases (%)*	*V617F - cases (%)*	*N. cases of V617F homozygote (%)*	*V617F-A cases (%)*	*V617F-B cases (%)*	*V617F-C cases (%)*
PV	116	64/52	53 (17~79)	109 (94%)	7 (6%)	4 (3.6%)	7 (6.5%)	34 (31%)	68 (62.5%)
Complicated with MF	6	0/6	46.5 (38~61)	3 (50%)	3 (50%)	0	0	0	3 (100%)
ET	153	63/90	50 (7~83)	122 (79%)	31 (21%)	1 (0.6%)	3 (1.5%)	35 (28.5%)	84 (70%)
Complicated with MF	15	5/10	55 (32~81)	12 (80%)	3 (20%)	0	0	1 (8.5%)	11 (91.5%)
PMF	142	71/71	53.5 (17~79)	111 (78%)	31 (22%)	0	3 (2.5%)	16 (14.5%)	92 (83%)
CML	88	73/15	40 (12~75)	0	88 (100%)	0	-	-	-
Complicated with MF	25	14/11	40 (12~61)	0	25 (100%)	0	-	-	-
HES	7	6/1	32 (20~45)	1 (14%)	6 (86%)	0	-	-	1 (100%)
CEL	13	13/0	34 (20~57)	0	13 (100%)	0	-	-	-

assigned into two groups, the ET-AB and ET-C groups. The megakaryocyte counts of the patients in the ET-AB group were significantly higher than those in the ET-C group (p=0.024). The correlation analysis showed that the megakaryocyte counts were significantly correlated positively with the mutation loads (p=0.024; r=0.205). For all other indices of the clinical features, no statistically significant difference was found between the two groups. The JAK2 V617F-positive IMF patients were also assigned into two groups, the MF-AB and MF-C groups. The incidence rates of splenohepatomegaly of the patients in the MF-AB group were significantly higher than those in the MF-C group (47.5% *vs.* 14%; p=0.003), as well as the degree of hepatosplenomegaly (p=0.001). The correlation analysis showed that the incidence rates of hepatosplenomegaly were significantly correlated positively with the mutation loads (p=0.001; r=0.315). For all other indices of the clinical features, no statistically significant difference was found between the two groups. Our observations differed somewhat from the heterogeneity model of the JAK2 V617F-positive cMPDs developed by Villeval *et al.*;[6] in particular, with regard to the mutation load of MF. Villeval *et al.*[6] thought that the low kinase activity usually involved the generation of megakaryocytes as well as the ET phenotype, while the high kinase activity appeared to involve the generation of erythroid cells as well as the PV phenotype; different activities and duration times of the kinase would eventually lead to MF.

To summarize, different subtypes of cMPD have different rates and loads of the JAK2 V617F mutation, and the mutation loads are closely related to specific features of cMPDs. Therefore, the detection of JAK2 V617F mutation in the cMPDs patients contributes not only to the diagnosis of cMPDs, but also the analysis of mutation load as well as the prediction of the extent of cMPDs.

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