Leukemia Research Reports 23 (2025) 100512

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Characteristics of *BCR::ABL1* kinase domain mutations in Vietnamese chronic myeloid leukemia patients

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ARTICLE INFO

Keywords:
BCR::ABL1
Kinase domain mutation
Chronic myeloid leukemia
Imatinib resistance
Vietnamese patients

ABSTRACT

Background: BCR::ABL1 kinase domain (KD) mutations represent a common cause of resistance to tyrosine kinase inhibitors in chronic myeloid leukemia (CML) patients. The frequency and pattern of KD mutations differ among populations worldwide. However, the characteristics of KD mutations in Vietnamese patients remain unclear.
Methods: A retrospective cohort study of CML patients at Blood Transfusion Hematology Hospital who were resistant to frontline imatinib between Oct 2010 and Oct 2018. Direct sequencing technique was performed to detect KD mutations.
Results: 488 imatinib-resistant CML patients were included in our study. The median age of the patients was 39, with the majority (82.1 %) diagnosed with chronic phase at the time of resistance. KD mutations were identified in 173 (35.5 %) patients, with 8 cases involving novel variants. The KD mutations predominantly localized within the P-loop of BCR::ABL1 (36.7 %). G250E was the most common mutation, followed by Y253H, M351T, and M244V. In particular, Y253H, T315I, F359V, F317L, E355G, and Q252H were frequently observed in accelerated phase and blast crisis patients. In addition, M244V, T315I, E459K, E255K, F317L, Q252H and E355G were all observed in primary resistant patients.
Conclusion: The emergence of certain specific mutations may serve as the early indicators of leukemic progression, necessitating prompt intervention for better disease control.

1. Introduction

Chronic myeloid leukemia (CML) was reported a dramatic improvement in the outcome with imatinib [1]. However, approximately 26.5 % of patients had imatinib resistance or intolerance [1]. *BCR::ABL1* kinase domain (KD) mutations have been considered to be a major cause of drug resistance [2]. >60 *BCR::ABL1* KD mutations have been reported. Several mutations, such as T315I or P-loop, may impact the risk of blastic transformation or long-term survival [3].

Interestingly, the frequencies and types of *BCR::ABL1* KD mutation markedly vary among populations worldwide. The study of Kim H showed that Asian patients tended to have a higher incidence of T315I and P-loop mutations, as well as a greater possibility of acquiring a single mutation that could be highly resistant to second-generation TKIs [4]. However, data on *BCR::ABL1* kinase mutations in Vietnamese patients remains limited. Therefore, we conducted a study to describe the clinical features and mutation patterns of *BCR::ABL1* KD in Vietnamese CML patients who failed imatinib therapy.

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https://doi.org/10.1016/j.lrr.2025.100512
Received 2 January 2025; Received in revised form 16 February 2025; Accepted 23 April 2025
Available online 23 April 2025

2. Materials and methods

2.1. Patients

A total of 488 imatinib-resistant CML patients recruited at Blood Transfusion Hematology Hospital in Ho Chi Minh City from October 2010 to October 2018 were enrolled in our study. All cases were only imatinib-resistant. Response assessment was performed based on European Leukemia Net (ELN) 2009 criteria [5]. Disease phases at the time of resistance, including chronic phase (CP), accelerated phase (AP), and blast phase (BP) were classified following the ELN 2009 [5]. Fluorescence in situ hybridization (FISH) using *BCR::ABL1* plus Translocation Dual Fusion Probe (Cytocell, UK) and a multiplex reverse transcription polymerase chain reaction (RT-PCR) was performed at diagnosed.

2.2. BCR::ABL1 kinase domain mutation analysis

At the time of resistance, RT-PCR reaction was performed using a primer pair designed to cover from BCR exon 12 (forward primer: F1 - 5′-CGGGAGCAGCAGAAGAAGTTGTTC-3′) to ABL exon 10 (reverse primer: R1 - 5′-CAGGCACGTCAGTGGTGTCTCTGTG-3′). The PCR products were purified using Exosap-IT (USB, USA) according to the manufacturer's protocol. Cycle sequencing was performed with primers including F2 (5′-CTGGCCGAGTTGGTTCATCA-3′), F3 (5′-ACTGAGTTCATGACCTACGGGAAC-3′), R2 (5′-CAGGCACGTCAGTGGTGTCTCTGTG-3′), R3 (5′-TCCACTGCCAACATGCTCGC-3′) using BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, USA). Mutations and variants were analyzed on SeqScape Software version 2.6 (Thermo Fisher Scientific, USA) and compared with the reference sequence of *ABL* (NM_007313.3).

3. Results

There were 488 (35.8 %) out of 1363 cases diagnosed with imatinib resistance and analyzed for *BCR::ABL1* mutations. The majority of the patients were males (308/180). The median age was 39 years (range, 1–75 years). Eleven patients were younger than 15 years at the time of resistance. The phases at the time of resistance were CP (82.1 %), AP (9.5 %), and BP (8.4 %). The percentage of primary resistance (77.7 %) was three times more than secondary resistance (22.3 %). Of the 262 patients who underwent RT-PCR analysis, the *BCR::ABL1* transcripts were b3a2 (60.3 %), b2a2 (39.3 %), and e1a2 (1.5 %). Most of patients (258/262) carried only one transcript type, and the remaining four had two types, which were b3a2 and e1a2.

3.1. Characteristics of BCR::ABL1 KD mutations in CML patients

We detected 173 patients (35.5 %) carrying TKI resistance mutations and 8 patients (1,6 %) acquiring 8 novel variants. Among 173 patients carrying mutation, 139 patients (80.3 %) had one mutation, and 34 patients (19.7 %) had two or more well-known mutations. Of the 215 mutations identified, 63 types were found along *BCR::ABL1* KD from c.550 to c.1423 (Fig. 1A). Most of the mutations (84.6 %) were located in the P-loop, C-loop, IM binding site, c-terminal lobe, and A-loop, with corresponding ratios of 36.7 %, 19.1 %, 10.2 %, 9.8 %, and 8.8 %, respectively (Fig. 1B). The remaining mutations, which accounted for 15.4 %, were in the C-helix region, SH2, SH3, and other regions including N231D, K234R, insertions, and deletions.

The most frequent mutation was G250E (8.8 %), followed by Y253H, M351T, M244V, c.1423_1424ins35bp, and H396R, which accounted for 7.4 %, 7 %, 6.5 %, 5.6 % and 5.1 %, respectively (Fig. 1C). Of the 63 mutation types, 90.7 % were point mutations, and 9.3 % were alternatively spliced mutations, including deletions (c.1086_1270del185bp, c.742_822del81bp and c.550_822del273bp) and insertion (c.1423_1424ins35bp). Regarding the alternatively spliced mutations, c.1423_1424ins35bp was found in the highest percentage (5.6 %).

Eight novel variants of *BCR::ABL1* KD in 8 subjects were detailed in Table 3. Two patients carried point variants including L354Q (C-loop) and W405G (C-terminal lobe). One patient had mutations at compound heterozygous status, including the well-known mutant E279K (C-helix region) in combination with the novel variant E292A (SH3 domain). The remaining five patients solely carried novel alternatively spliced variants, including c.334_335delins47bp, p.Asn414del, c.906_907ins4bp, c.1086_1157del72bp, and c.1270ins84bp.

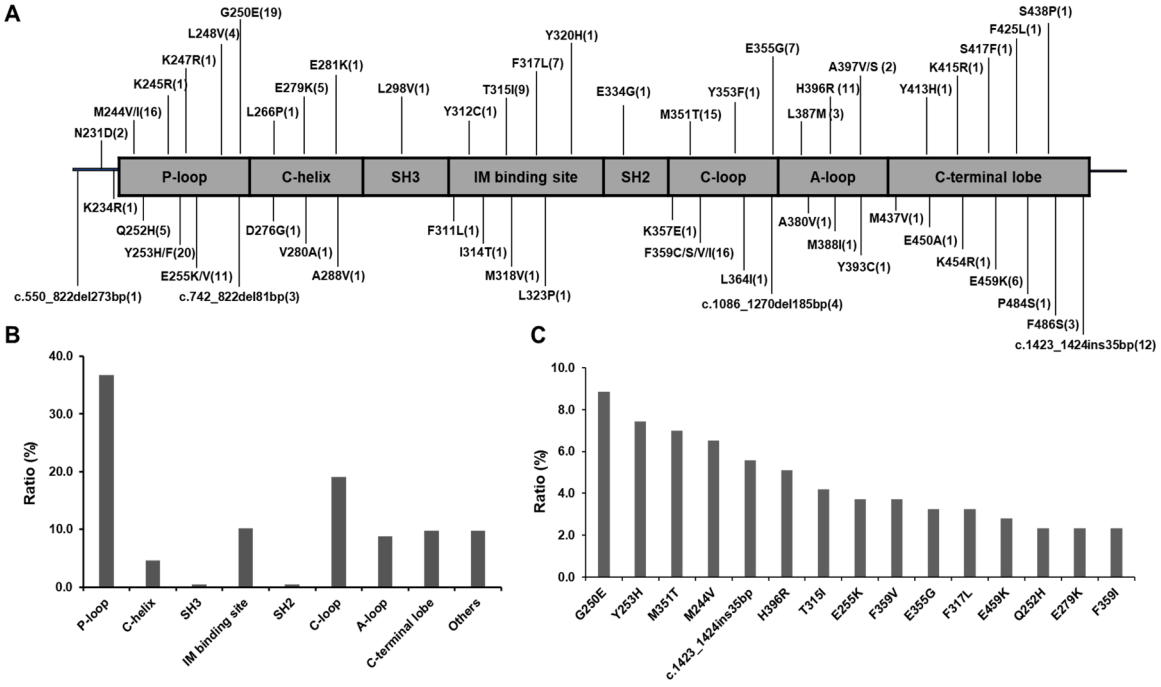

Fig. 1. Characteristics of *BCR::ABL1* kinase domain mutations in Vietnamese CML patients with imatinib resistance. (a) Distribution of *BCR::ABL1* kinase domain mutations. (b) Distribution of mutations by different regions of *BCR::ABL1* kinase domain. (c) Distribution of 15 most frequent *BCR::ABL1* kinase domain mutations.

3.2. Correlation between characteristics of CML patient and BCR::ABL1 kinase domain mutations

We conducted an analysis to compare 173 patients carrying mutations with 308 other patients without mutations. Seven patients with only novel *BCR::ABL1* KD variants were excluded from this analysis. Although there were no significant differences in terms of age, gender, resistance pattern, and transcript type between the two groups, patients in AP and BP had a significantly higher frequency of *BCR::ABL1* KD mutations as compared to those in CP (CP group: 31.7 %; AP group: 57.8 %; and BP group: 52.5 %) (Table 1).

The highest proportion of mutations in 129 CP patients was found in the P-loop region with 53 cases (41.1 %), followed by the C-loop with 26 cases (20.2 %) (Table 2). The prevalence of mutations in the P-loop region also predominated in AP patients (48 %), followed by C-loop and IM binding sites (20 % and 16 %, respectively) (Table 2). Meanwhile, a more even distribution was found in BP patients: P-loop (30 %), C-loop (20 %), C-terminal lobe (20 %), and IM binding site (20 %) (Table 2). In the perspective of resistance patterns, 128 primary resistant patients showed the highest occurrence of P-loop mutations (58 cases, 45.3 %) and C-loop mutations (23 cases, 18 %) (Table 2). Likewise, among 25 mutations recorded in patients with secondary resistance, the P-loop mutations were also the most common, with 8 cases (32 %), followed by C-loop mutations with 5 cases (20 %) (Table 2).

The total number of 15 common mutations were in 147 cases, however, the data about disease stage and resistance pattern were collected in 142 and 119 cases, respectively. The majority of patients carrying 15 common mutations were still in CP (100/142 = 70.4 %), with the following rates reported for each mutation: G250E (14/19 = 73.7 %), M244V (10/14 = 71.4 %), M351T (11/14 = 78.6 %), c.1423_1424ins35bp (9/11 = 81.8 %), H396R (9/11 = 81.8 %), E255K (7/8 = 87.5 %), E459K (4/6 = 66.7 %), E279K (5/5 = 100 %), and F359I (5/5 = 100 %) (Fig. 2A). On the other hand, there was a significant increase in the proportion of cases in AP and BP with mutations such as Y253H (8/16 = 50 %), T315I (4/9 = 44.4 %), F359V (3/7 = 42.9 %), F317L (3/7 = 42.9 %), Q252H (3/5 = 60 %), and E355G (2/5 = 40 %) (Fig. 2A). Mutations in primary resistance were found in 85.7 % (102/119). Among 15 common mutation types, primary resistance was highly associated with mutations such as G250E (15/17 = 88.2 %), Y253H (13/15 = 86.7 %), M351T (10/12 = 83.3 %), c.1423_1424ins35bp (8/12 = 66.7 %), H396R (6/9 = 66.7 %), and F359V (4/5 = 80 %) (Fig. 2B). Interestingly, only primary resistant patients were found to have M244V, Q252H, E255K, T315I, F317L, E355G, and E459K (Fig. 2B).

Table 1
Correlation of CML patient characteristics between *BCR::ABL1* kinase domain mutation and wild type groups.

Characteristic	*BCR::ABL1* kinase domain wild type (308)	*BCR::ABL1* kinase domain mutation (173)	p-value
Age/median (range)	39 (1–75)	39 (5–74)	0.9
Sex/cases (%)			0.6
Male	192 (63 %)	113 (37 %)	
Female	116 (65.9 %)	60 (34.1 %)	
Phase at time of resistance/cases (%)			<0.001
Chronic phase	261(68.3 %)	121 (31.7 %)	
Accelerated phase	19 (42.2 %)	26 (57.8 %)	
Blast phase	19 (47.5 %)	21 (52.5 %)	
Resistant pattern/cases (%)			0.4
Primary	217 (64.8 %)	118 (35.2 %)	
Secondary	68 (70.1 %)	29 (29.9 %)	
Transcript type/cases (%)			0.3
b2a2	68 (66.7 %)	34 (33.3 %)	
b3a2	107 (69.5 %)	47 (30.5 %)	
e1a2	3 (60 %)	2 (40 %)	

P-value < 0.05 was considered statistically significant.

4. Discussion

Our study demonstrated the similarity with others in terms of *BCR::ABL1* transcript type [6,7] but differed in disease phase and resistance pattern [8,9]. The frequency of *BCR::ABL* KD mutation was 35.5 %, which was higher than reported in other studies conducted in Jordan (11.3 %) [10], Saudi Arabia (20 %) [11], and China (30.9 %) [7]. The proportion of patients carrying more than one mutation was also higher (19.7 %) than in other reports by Qin [12] (6.7 %), McCarron [13] (9.5 %).

Analyzing the distribution of mutations by *BCR::ABL* KD showed that mutations in P-loop (Fig. 1B) were found in 36.7 %, similar to the result of Liu (36.1 %)[7], but lower than McCarron's findings (43.5 %) [13]. The second highest rate of mutations was located in the C-loop in this study but in the imatinib binding site in other reports [7,13]. The most frequent point mutation was G250E (8.8 %), and other common point mutations included Y253H (7.4 %), M351T (7 %), M244V (6.5 %), and H396R (5.1 %), similar to studies of Cortes [14] and Qin [12]. In addition to point mutations, c.1423_1424ins35bp, was also frequently found in our study and others [15]. According to a study by Yuda, this alternatively spliced *BCR::ABL1* mutation was induced by TKI treatment and persisted at a low level [15]. Therefore, c.1423_1424ins35bp mutation has value in evaluating minimal residual disease more accurately and making decisions to switch to next-generation TKI or change to another treatment [15]. In contrast, the frequency of T315I (4.2 %) and E255K (3.7 %) (Fig. 1A) in our study was lower than those reported in other studies, such as Cortes [14] and Abalkhail [11]. Interestingly, we identified 8 novel variants in 8 patients and all were in CP. Among 8 patients with novel variants, only one case with c.906_907ins4bp was secondary resistant to imatinib, the remaining 7 cases were primary resistant.

Disease phases at the time of imatinib resistance was the only factor significantly associated *BCR::ABL1* KD mutations (Table 1), aligning with those of Soverini [3], and Kim [4]. However, the study of Qin [12] could not establish a significant correlation. The P-loop region was the most common mutation site in our study, including CP (41.1 %), AP (48 %), and BP (30 %). This result was in line with the findings of Qin [12] and Kim [4]. Regarding the C-loop, our study identified an even distribution of mutations across disease stages (20 %–20.2 %) (Table 2), similar to Qin's study [12]. Notably, our population had a higher proportion of mutations in the IM binding site in AP and BP compared to CP (CP 10.9 %; AP 16 %; BP 20 %). Kim's study reported similar results [4]; however, it was opposite to Qin's findings [12]. In addition, our study showed a uniform distribution of mutations in the A-loop region across all disease stages (CP 10 %; AP 8 % and BP 10.2 %), whereas mutations in the A-loop region in Qin's study [12] were mainly found in AP patients.

The analysis of mutation distribution according to resistance pattern demonstrated that the highest proportion of mutations occurred in the P-loop region (primary resistance: 45.3 % and secondary resistance: 32.0 %) (Table 2), which was comparable to the findings of Qin [12] and Soverini [3]. Mutations in the IM binding site region mainly belonged to the primary resistance group (15/16), while Qin's study [12] reported the opposite result with the predominance of secondary resistance (7/8). Mutations in the A-loop region accounted for similar proportions in primary and secondary resistance groups in our study. On the contrary, Qin's results [12] revealed that A-loop mutations were more common in the primary resistance group (12.1 %) compared to the secondary resistance group (4.3 %), while Soverini's study [3] identified more common in the secondary resistance group. The majority of CML patients carrying common mutations were in CP at the time of resistance (70.4 %) (Fig. 2A), which was similar to Qin's results (54.1 %) [12]; while Soverini reported only 39.5 % in CP [3]. The distribution of mutations according to disease phase also varied greatly between studies,

Table 2
Distribution of *BCR::ABL1* kinase domain mutations according to disease phase and resistance pattern.

	P-loop	C-helix	IM binding site	C-loop	A-loop	C-terminal lobe	Total
CP (n/%)	53 (41.1 %)	7 (5.4 %)	14 (10.9 %)	26 (20.2 %)	13 (10.1 %)	16 (12.4 %)	129 (100 %)
AP (n/%)	12 (48.0 %)	1 (4.0 %)	4 (16.0 %)	5 (20.0 %)	2 (8.0 %)	1 (4.0 %)	25 (100 %)
BP (n/%)	3 (30.0 %)	0 (0.0 %)	2 (20.0 %)	2 (20.0 %)	1 (10.0 %)	2 (20.0 %)	10 (100 %)
Primary (n/%)	58 (45.3 %)	4 (3.1 %)	15 (11.7 %)	23 (18.0 %)	13 (10.2 %)	15 (11.7 %)	128 (100 %)
Secondary (n/%)	8 (32.0 %)	4 (16.0 %)	1 (4.0 %)	5 (20.0 %)	3 (12.0 %)	4 (16.0 %)	25 (100 %)

CP: chronic phase, AP: accelerated phase, BP: blast phase, IM: imatinib.

Table 3
The novel variants of *BCR::ABL1* kinase domain.

Variant type	$n = 8$
E292A*	1
L354Q	1
W405G	1
c.334_335delins47bp	1
p.N414del	1
c.906_907ins4bp	1
c.1086_1157del72bp	1
c.1270ins84bp	1

* Patient had E292A in combination with E279K.

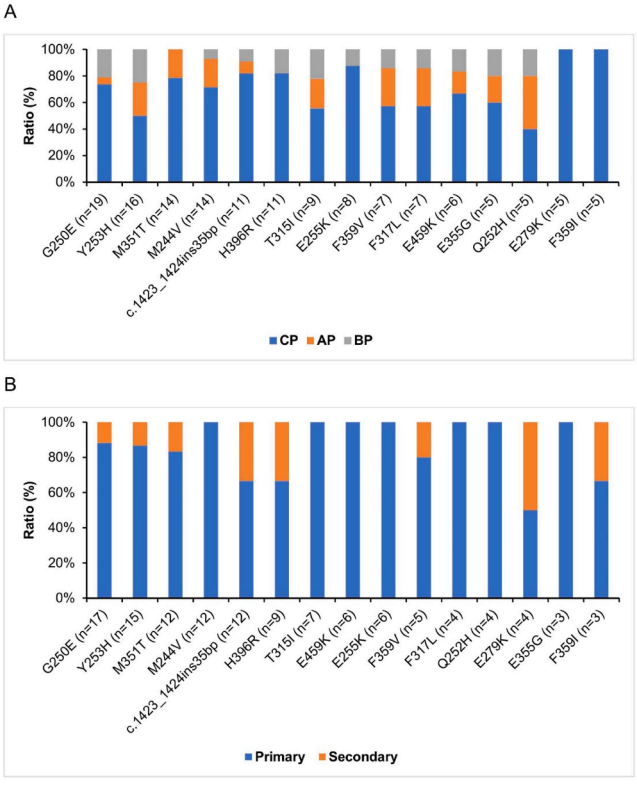

Fig. 2. Correlation between disease phase and resistance pattern of CML patient with *BCR::ABL1* kinase domain mutations. (a) Frequency of 15 common mutations according to disease phase. (b) Frequency of 15 common mutations according to resistance pattern.
CP: chronic phase (blue), AP: accelerated phase (orange), BP: blast phase (grey).

indicating the diversity of mutation spectrums in each population. In our study, 50 % of cases with Y253H were in AP and BP, a lower frequency than in Qin's (90 %) and Soverini's studies (82.4 %) [3,12]. Likewise, for patients with Q252H mutation, AP and BP accounted for 60 %, which was also lower than the result of Soverini (100 %) [3]. There were 44.4 % of cases carrying T315I mutation in AP and BP, significantly higher than Qin's study [12] (14.3 %) but much lower than Soverini's study [3] (86.7 %). Our study also found that the percentage of F359V mutation in AP and BP was 42.9 %, higher than that of Soverini [3] (21.4 %) and Qin [12] (28.6 %). Conversely, 73.7 % of G250E and 71.4 % of M244V cases were found in CP, resembling Qin's results [12] (62.5 % and 66.7 %, respectively). Meanwhile, Soverini [3] noted that 69.2 % of patients with M244V but only 23.1 % of patients with G250E were in CP. Most of the patients with H396R were in CP (81.8 %), similar to Soverini's study (100 %) but much higher than Qin's study (25 %) [3,12]. Notably, the E255K mutation was observed (87.5 %) in CP, in contrast to the findings of Qin (39.7 %) and Soverini (47.6 %) [3,12]. All patients with the M244V mutation in our study exhibited primary resistance, whereas the frequency was considerably lower in the studies by Qin (41.7 %) and Soverini (46.2 %) [3,12]. Similarly, all patients carrying the T315I mutation in our study displayed primary resistance, while Qin and Soverini reported the predominance of secondary resistance at rates of 100 % and 66.7 %, respectively [3,12] The proportion of primary resistance in patients carrying mutations G250E (88.2 %) and Y253H (86.7 %) was also significantly higher than that reported by Qin and Soverini [3,12]. Two potential explanations for the observed disparity mentioned above may be attributed to the racial heterogeneity and delayed initiation of therapy among the Vietnamese CML population. Furthermore, due to the limited availability of second-generation TKIs in Vietnam, high-dose imatinib remains a favored therapeutic approach which may promote genetic instability and facilitate the emergence of resistant mutations. Nowadays, the standard of care for CML patients in Vietnam has changed with increased accessibility to second-generation TKI (specifically nilotinib), especially for patients with KD mutations.

Ethics approval

This study was approved by the Ethics Committees of the University of Medicine and Pharmacy at Ho Chi Minh City (number 977/ ĐHYD-HĐĐĐ). Written informed consents were obtained from the patients or their parents.

Funding

This study was financially supported in part by the Department of Science and Technology at Ho Chi Minh City (grant number 222/HĐ-SKHCN).

CRediT authorship contribution statement

Phu Chi Dung: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Huynh Duc Vinh Phu:** Writing – original draft, Investigation, Data curation, Conceptualization. **Cao Van Dong:** Software, Investigation, Data curation. **Chau Thuy Ha:** Software, Investigation, Data curation. **Nguyen Thi Thanh Ha:** Software, Investigation, Data curation. **Tran Ngoc Xuan Thy:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Le Vu Ha Thanh:** Visualization, Resources, Project administration. **Huynh Nghia:** Visualization, Supervision, Project administration, Funding acquisition. **Nguyen Tan Binh:** Validation, Supervision, Project administration, Funding

acquisition. **Hoang Anh Vu:** Visualization, Validation, Project administration, Methodology, Conceptualization. **Phan Thi Xinh:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Cao Sy Luan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

The authors would like to thank the Department of Molecular Cytogenetics, Ho Chi Minh City Blood Transfusion Hematology Hospital and Department of Molecular Biology, Dai Phuoc Clinic, Ho Chi Minh City, Vietnam for assisstance in mutation analysis.

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