RESEARCH ARTICLE

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The First Molecular Profiling of *JAK2* Exon 12 and Flanking Intronic Sequences in Indonesia

Farmaditya Eka Putra Mundhofir[1,2]*, Nani Maharani[1,3], Raisa Tahira[4], Amelia Syabani[4], Nydia Rena Benita Sihombing[1,2], Ferdy Kurniawan Cayami[1,2], Endang Mahati[1,3], Tri Indah Winarni[1,2]

Abstract

Objective: Data on *JAK2* Exon 12 mutations in Indonesia are not available. This study aimed to explore the presence of known *JAK2* exon 12 coding mutations in *V617F*-negative myeloproliferative neoplasm (MPN) patients in Indonesia and to describe any novel intronic changes downstream of exon 12. **Methods:** A total of 198 *V617F*-negative MPN samples were screened using allele-specific polymerase chain reaction (AS-PCR) for four commonly reported canonical exon 12 mutations. Of these, 57 cases were selected at random or for atypical PCR band patterns and underwent bidirectional Sanger sequencing of a 496-bp fragment covering exon 12 plus ~250 bp of the adjacent region. Variants were cross-referenced with gnomAD v4.1.0. Furthermore, SpliceAI was used to predict splice site gain or loss. **Results:** No coding mutations were identified in exon 12. However, two intronic variants were detected adjacently downstream: NC_000009.12:g.5070231_5070235delTCTTA in 29 of 57 cases (50.9%), which was not present in the gnomAD database, and NC_000009.12:g.5070319C>T in 1 of 57 cases (1.8%), corresponding to a rare gnomAD entry. The SpliceAI Δ scores remained below 0.2, a high-sensitivity threshold, indicating no predicted impact on canonical splicing. **Conclusion:** Classic exon 12 coding mutations are apparently absent in Indonesian *V617F*-negative MPNs. We report a highly frequent downstream intronic deletion not recorded in global databases, as well as a rare single nucleotide variant (SNV) that aligns with gnomAD data. Although in silico tools suggest minimal splice disruption, RNA-level assays are needed to rule out the subtle effects of the variant. Our workflow, which combines allele-specific PCR and targeted sequencing, may be suitable for laboratories facing resource constraints.

Keywords: Myeloproliferative neoplasm, *JAK2* exon 12, *V617F*-negative, intronic variation, allele-specific PCR

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Introduction

Myeloproliferative neoplasms (MPNs) are clonal disorders of hematopoietic progenitors, a concept that was first proposed by Dameshek (1951) and has since been formalized in contemporary diagnostic guidelines by the World Health Organization (WHO) [1, 2]. In practice, the main types of Philadelphia chromosome-negative syndromes, as described in the common forms observed, are primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET). A common feature of these disorders is the tendency of the bone marrow to produce excessive numbers of myeloid cells [2]. The incidence of MPNs varies between Western and Asian populations. Between 2004 and 2013, a Korean long-term registry tracked the frequency of different myeloproliferative disorders. It suggested that ET is seen in approximately 4.1–9.0 people per 100,000, PV in roughly 2.8–5.4 per 100,000, and PMF in approximately 0.5–0.9 per 100,000; however, rates may vary depending on the diagnostic criteria and case ascertainment [3]. The Korean study provided data representative of the Asian population. On the contrary, the prevalence of these myeloproliferative disorders may be higher in the Western world [4]. For example, health databases show that ET and PV occur more often than in the Asian population. The exact data may differ because of differences in healthcare systems, diagnostic methods, and data collection methods [4].

Genetic alterations are critical for understanding and diagnosing MPNs. The Janus kinase 2 (*JAK2*) *V617F* mutation is particularly significant, affecting numerous

[1]*Center for Biomedical Research (CEBIOR) Faculty of Medicine, Universitas Diponegoro, Semarang, Central Java, Indonesia.*
[2]*Department of Anatomy and Histology, Faculty of Medicine, Universitas Diponegoro, Semarang, Central Java, Indonesia.*
[3]*Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Diponegoro, Semarang, Central Java, Indonesia.*
[4]*Department of Biology, Faculty of Science and Mathematics, Universitas Diponegoro, Semarang, Central Java, Indonesia.*
**For Correspondence: farmaditya@fk.undip.ac.id*

patients with PMF, PV, and ET by causing persistent activation of the *JAK-STAT* pathway [5, 6]. Changes in other genes, such as Myeloproliferative leukemia (MPL), and Calreticulin (CALR), as well as Additional sex combs like 1 (ASXL1), Serine/arginine-rich splicing factor 2 (SRSF2), and DNA cytosine-5 methyltransferase 3 alpha (DNMT3A) also influence the progression of a disease and the effectiveness of treatments [7, 8]. Although the *JAK2 V617F* mutation is prevalent, additional mutations in the *JAK2* gene, particularly within exon 12, have been discovered to be associated with classic and atypical chronic myeloproliferative disorders. Furthermore, mutations in associated signalling pathways have been observed [9, 10]. These genetic discoveries have enabled the diagnosis and development of personalized therapeutic approaches, particularly with the use of JAK inhibitors [11].

The *JAK2 V617F* mutation is prevalent in most *JAK2*-related haematological disorders. However, some cases lack this mutation (*V617F*-negative) and may instead exhibit other *JAK2* exon 12 changes or mutations in CALR or MPL [12–15]. In patients with *JAK2 V617F*-negative PV, gain-of-function mutations in *JAK2* exon 12 define distinct molecular subgroups. These exon 12 mutations, such as *K539L, N542–E543del, F537–K539delinsL*, and *H538QK539L*, were first identified in 2007 [12, 14]. The reported prevalence of *JAK2* exon 12 mutations within these populations in Western cohorts ranges from 12% to 16% [16]. As mentioned previously, the prevalence of *JAK2* exon 12 mutations in MPNs, particularly among patients with PV, shows diverse rates across different East Asian studies. In Taiwan, approximately 23% of patients of *JAK2 V617F*-negative PV patients exhibit alterations in *JAK2* exon 12 [17]. In Korea, the prevalence of this condition is approximately 12% [18]. In Vietnam, approximately 17% of patients are affected [19]. However, no mutations in *JAK2* exon 12 have been observed in Pakistan [20]. Differences among ethnic groups may be ascribed to genetic composition, environmental influences, and research methodologies, underscoring the necessity for studies specifically tailored to distinct regions [21].

Sequence changes outside the coding exons may also be important. Intronic variants near exon 12 may alter auxiliary splicing elements, such as enhancers, silencers, or branch points. Furthermore, they may affect transcript processing, even when canonical GT–AG splice motifs are intact [22, 23]. Problems in these sequences can cause incorrect splicing, such as skipping parts, keeping parts that should be removed, or using the wrong splice sites. Even if sequence changes do not affect normal splice sites, they may still activate false splice sites, highlighting the complexity of intron modulation during splicing [22]. These changes can have significant effects on biology. They can disrupt mRNA processing, reduce mRNA stability, and produce defective proteins, potentially leading to diseases such as cancer [24].

Indonesia is a lower-middle-income nation. It faces problems with research funding and infrastructure issues. This is especially true for advanced genomic platforms. These issues make it difficult to conduct detailed molecular studies [25]. In this situation, cost-effective methods, such as allele-specific PCR and targeted Sanger sequencing, are good choices for laboratories with limited resources. Despite these challenges, using local genetic data is important for planning national health tests and improving patient care. The MPN rate in Indonesia has increased to 1.35 per 100,000 individuals [26]. This increase suggests a growing burden of hematological disorders in the Indonesian population. A study conducted in Indonesia investigated patients potentially diagnosed with MPN and found that the majority of these patients exhibited the *JAK2 V617F* mutation [27]. This shows the importance of this mutation in local MPN cases. Nevertheless, the analysis of *JAK2* exon 12 has never been conducted, resulting in a subset of *V617F*-negative patients lacking further genetic characterization. We conducted the first detailed study of specific exon 12 mutations and nearby intron changes in an Indonesian group without the *V617F* mutation for MPN. Our study aimed to evaluate the prevalence of established exon 12 mutations, discover novel downstream intronic variants, determine their population frequencies using gnomAD, and predict potential splice-site effects using SpliceAI.

Materials and Methods

Patients and samples

Between January 2012 and December 2024, peripheral blood samples were collected from 198 consecutive *V617F*-negative MPN patients who were referred to Dr. Kariadi Hospital and its associated centers in Central Java. PV, ET, and PMF were classified according to the WHO 2016 criteria. Samples were collected for diagnostic purposes; no additional samples were collected for the sole purpose of this study. Ethical approval was granted by the Ethical Committee of the Faculty of Medicine Universitas Diponegoro (No. 430/EC/KEP/FK-UNDIP/VIII/2024).

DNA Extraction

Genomic DNA was isolated from blood samples using the salting-out method. Purity was confirmed using a NanodropTM 2000C Spectrophotometer (Thermo Fisher Scientific, USA) by measuring the absorbance ratio A260/A280.

Allele-specific PCR screening

We screened four canonical exon 12 commonly reported mutations of the *JAK2* gene: *K539L, N542-E543del, F537-K539delinsL*, and *H538QK539L*, using allele-specific PCR with primers from published protocols [12]. Each 25 µL reaction contained ~100 ng of DNA, GoTaq® Green Master Mix (Promega), and mutation-specific primers. Cycling: 94 °C for 3 min; 35 cycles of (94 °C for 30 s, 55 °C for 45 s, and 72 °C for 45 s); final extension at 72 °C for 7 min. A 496 bp internal control was used to verify PCR efficiency. The products were visualized on 2 % agarose gels.

Sanger Sequencing and Variant Annotation

Owing to financial constraints, 57 of the 198 *V617F*-negative samples were selected for Sanger sequencing. Selection combined a random subset (n =

40) to provide an unbiased sample and an enrichment subset (n = 17) chosen because their allele-specific PCR banding patterns were atypical or ambiguous. Random selection was performed using a computer-generated list from the 198 *V617F*-negative samples. 'Atypical' banding was defined as deviation from the expected single internal control band or faint/extra bands suggestive of non-specific amplification; these were flagged by two independent laboratory staff and prioritized for sequencing. These 57 samples were amplified for a 496 bp fragment spanning exon 12 and ~250 bp of the downstream intron (chr9:5069857–5070352) using the following primers:

Forward: 5′-CTCCTCTTTGGAGCAATTCA-3′
Reverse: 5′-GAGAACTTGGGAGTTGCGATA-3′

Amplicons were purified using ExoSAP-IT and sequenced bidirectionally on an ABI 3730 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Chromatograms were aligned to NC_000009.12, using the ABI Variant Reporter v3.

Variant Annotation and In Silico Prediction

All sequence changes were described according to the HGVS nomenclature. We retrieved population-level allele frequencies from gnomAD v4.1.0 to assess the novelty or rarity of variants [28].

For each intronic variant, SpliceAI v1.3 was run against the GRCh38 reference to predict the effects on canonical splice donor and acceptor sites within a ±500 bp window. We recorded Δ scores for splice-site gain or loss, considering values ≥ 0.2 as indicative of a potential splice-altering effect [29].

Results

Exon 12 Coding Region Variant Screening

All 198 *V617F*-negative samples yielded the expected 496 bp internal control band using allele-specific PCR. As our analytical cut-off, a sample was classified as negative for a targeted mutation if the internal control band was clearly visible with no variant-specific amplification on the agarose gel. We did not observe any variant-specific bands for the four exon 12 commonly reported mutations. Although this confirms the absence of these specific targeted changes, we acknowledge that this cost-effective screening approach cannot detect all possible exon 12 mutations (Table 1).

Identification of Intronic Variants

Sanger sequencing of a 57-case subset, selected owing to funding constraints, as detailed in the Methods section, confirmed the presence of wild-type exon 12 in all 57 cases. However, two downstream intronic variants emerged (Table 1).

• NC_000009.12:g.5070231_5070235delTCTTA (GRCh38; 5 bp deletion) was observed in 29/57 (50.9 %) samples and was absent from gnomAD v4.1.0 [28]. Figure 1 shows an electropherogram of this deletion, with the missing segment indicated by two red arrows compared with the wild-type sequence.

• NC_000009.12:g.5070319C>T (GRCh38) was observed in 1/57 (1.8 %) individuals and was present in gnomAD at an allele frequency of 0.003572 in nine homozygotes [30]. Figure 2 illustrates the variant peak

Table 1. AS-PCR and Sanger Sequencing Outcomes

Method	Region	Variant	n	Frequency (%)
AS-PCR	Exon 12 coding	Wild-type	198	100.0
Sequencing	Exon 12 coding	Wild-type	57	100.0
Sequencing	Intron 12 downstream	Wild-type	27	47.4
Sequencing	Intron 12 downstream	NC_000009.12: g.5070231_5070235delTCTTA (5 bp del)	29	50.9
Sequencing	Intron 12 downstream	NC_000009.12: g.5070319C>T	1	1.8

Note: AS-PCR, allele-specific polymerase chain reaction; bp, base pair; del, deletion.

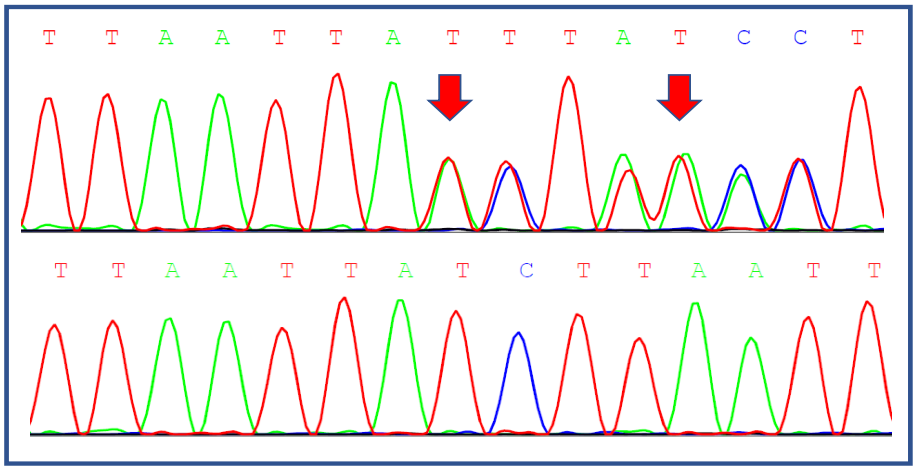

Figure 1. Variant of NC_000009.12:g.5070231_5070235delTCTTA (between two red arrows) vs. Wildtype

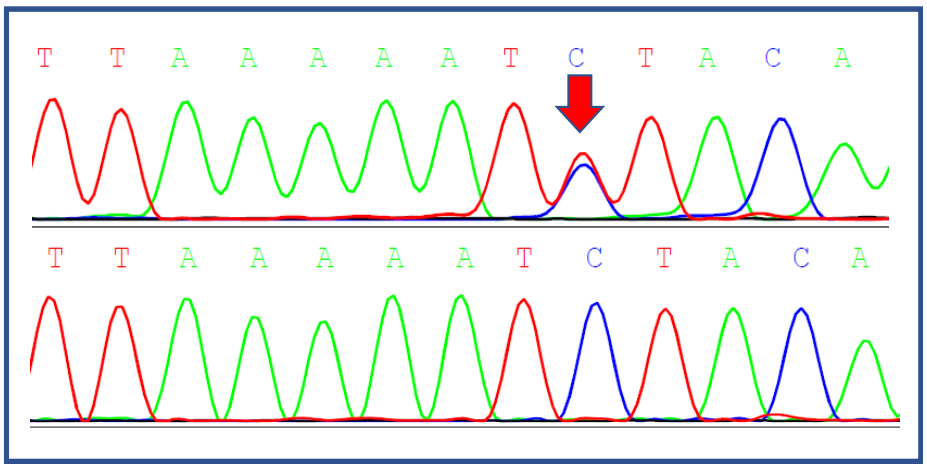

Figure 2. Variant of NC_000009.12:g.5070319C>T (red arrow) vs. Wildtype

(red arrow) relative to the wild-type trace.

In Silico Predictions

Neither variant reached the high-sensitivity threshold (SpliceAI Δ score ≥ 0.2) for acceptor or donor gain/loss, implying no predicted effect on canonical splice sites. Furthermore, Pangolin yielded separate low probabilities for splice loss (≤ 0.05) and splice gain (0.00). For NC_000009.12:g.5070319C>T (GRCh38), CADD PHRED = 0.333 and PhyloP = –0.021, suggesting little predicted deleteriousness or conservation of the variant. CADD/PhyloP data were unavailable for the 5-bp deletion (Table 2).

Discussion

In this study, 198 *V617F*-negative MPN patients in Indonesia were screened for canonical *JAK2* exon 12 mutations, and none were found. Sanger sequencing of a subset (n = 57) confirmed wild-type exon 12 in all cases. Rather than coding changes, two intronic variants were identified. A 5-bp deletion (NC_000009.12:g.5070231_5070235delTCTTA; GRCh38) was highly frequent within our cohort, despite being unrepresented in gnomAD, indicating a potentially population-specific allele or possible founder effect [28]. In contrast, the identified SNV (NC_000009.12:g.5070319C>T; GRCh38) is a rare variant, which is concordant with its low allele frequency (0.35%) reported in the gnomAD database. Furthermore, the absence of the 5 bp intronic deletion in global datasets should be interpreted cautiously, as noncoding regions and indels are historically underreported in many large-scale sequencing databases. Although we detected no canonical exon 12 coding mutations, we cannot rule out the possibility that rare, non-canonical, or low-level mosaic exon 12 mutations were missed due to the inherent detection limits of our assays. The reported prevalence of *JAK2* exon 12 varies widely across studies and populations, reflecting differences in cohort selection, assay sensitivity, and regional genetic backgrounds. Early molecular work by Scott et al. [14] recognized exon 12 as marking a distinct subgroup of *V617F*-negative patients with erythrocytosis and described several commonly reported mutations in small case series. Furthermore, four distinct mutation types were found in 10 *V617F*-negative patients [14]. Small, selected cohorts sometimes report surprisingly high yield rates. A study by Yeh et al. [17] found exon 12 mutations in all *V617F*-negative PV cases in their Taiwanese series (5/22; 23%). Nevertheless, fewer selected studies reported lower frequencies. Several multi-center or pooled analyses have reported exon 12 mutation rates among *V617F*-negative PV patients in the low single digits (commonly ~2–5%) [31]. A review of Asian reports helps illustrate this heterogeneity, even within specific populations. For instance, while one Korean study reported an unusually high exon 12 mutation frequency of approximately 12% among all PV patients [18], another Korean cohort found a complete absence (0%) of these mutations [32]. This clear contrast further highlights how differences in cohort selection, sample size, or assay sensitivity can yield widely varying results [18, 32]. A Vietnamese study of 76 PV patients found exon 12 variants in 4 of 23 *V617F*-negative cases (~17%), but in silico prediction suggested that the two detected exon-12 variants were likely benign, prompting the authors to suggest alternative genetic causes in that subgroup [19].

Indian and Malaysian reports generally show that *JAK2 V617F* accounts for most PV cases, and that exon

Table 2. *In Silico* Predictive Metrics for *JAK2* Intronic Variants

Variant	Acceptor Loss (Δ)	Donor Loss (Δ)	Acceptor Gain (Δ)	Donor Gain (Δ)	Pangolin Loss	Pangolin Gain	CADD PHRED	PhyloP
NC_000009.12:g.5070231_5070235 delTCTTA	0.00	0.00	0.00	0.00	0.05	0.00	N/A	N/A
NC_000009.12:g.5070319C>T	0.00	0.00	0.00	0.00	0.00	0.00	0.333	–0.021

Note: All genomic coordinates refer to the GRCh38 (NC_000009.12) reference sequence. A threshold of Δ score ≥ 0.2 was used for SpliceAI as an indicator of high-sensitivity potential splicing alterations

12 coding variants are uncommon in unselected cohorts [33–35]. Small, phenotype-enriched series (patients with isolated erythrocytosis) report higher exon-12 yields, whereas large registry or single-center studies report low-to-moderate frequencies. Differences in patient selection, assay sensitivity (PCR, fragment analysis, Sanger, NGS), and referral patterns likely drive these variations. In Pakistan, a recent well-characterized study (n=159) found *JAK2* exon 12 to be absent across their cohort when tested using fragment analysis and PCR, while an earlier small Pakistani series identified rare exon 12 events among a limited number of *V617F*-negative cases [20, 36]. Although the recent dataset suggests a potentially low frequency in certain cohorts, the true population-level rarity cannot be confidently inferred without uniform diagnostic criteria and the systematic application of more sensitive sequencing methods to well-defined *V617F*-negative cases [20].

To further assess the population-level representation of the aforementioned 5-bp intronic deletion (NC_000009.12:g.5070231_5070235delTCTTA; GRCh38) [28] we queried gnomAD v4.1.0 across the region chr9:5070210–5070250. Although this queried interval contains several other documented variants, including comparable short indels and SNVs (such as c.1641+179_1641+184del and c.1641+183A>G) [37], our exact 5 bp deletion was completely absent [28]. This unrepresented status in global population databases suggests that the NC_000009.12:g.5070231_5070235delTCTTA (GRCh38) variant may be a population-specific allele (a possible founder effect) or may simply reflect the systematic underreporting of noncoding indels in large-scale databases. This reinforces the need for transcript-level validation and more extensive regional sequencing efforts. However, without matched normal tissue or orthogonal assays, we cannot fully exclude sequencing artifacts or alignment anomalies. Regarding the second finding, the singleton variant (NC_000009.12:g.5070319C>T; GRCh38) matched a rare gnomAD entry, including nine homozygotes, making a strongly pathogenic role less likely [30]. Although computational predictions (SpliceAI, Pangolin, CADD, and PhyloP) suggested a minimal impact on canonical splice motifs [29], we acknowledge that these in silico tools are primarily optimized for canonical splice boundaries, rendering their negative predictions for deep intronic variants less informative. As others have noted, deep intronic variants can affect auxiliary splicing elements or activate cryptic sites in ways that in silico models may miss [38]. Given the high frequency of the 5 bp deletion in our cohort, functional assays, such as minigene constructs or RNA-based analyses of patient samples, are critical to resolve this issue and to definitively confirm its status as a benign polymorphism within the Indonesian population.

In Indonesia, innovative diagnostic tests, such as *JAK2 V617F* and exon 12 screening, are not fully covered by the national health insurance (BPJS) [39, 40]. This condition forces patients with MPN to pay the entire out-of-pocket or through private insurance. This financial barrier drives diagnostic delays and low testing uptake, particularly among lower-income groups, which may contribute to an underestimation of true mutation rates and the postponement of targeted therapy initiation. Incorporating these assays into the BPJS coverage would promote equitable access, enhance diagnostic accuracy, and enable more timely and optimized management of MPNs nationwide. Integrating allele-specific PCR with targeted Sanger sequencing is straightforward and cost-effective, particularly in resource-constrained settings. These methods enable focused examinations of specific regions of interest using equipment commonly available in Indonesian laboratories. However, we may overlook mutations outside the targeted fragments. As sequencing costs continue to decrease, incorporating next-generation sequencing panels may expand our understanding of MPN genetics within this population. The discovery of a frequent intronic deletion of unknown clinical significance in a local population that is not found in global databases highlights this problem. Because many groups, particularly Southeast Asians, are not well represented in large-scale genetic data collections, population-specific variants can easily be missed or misinterpreted. Adding Southeast Asian genetic information to large databases will help us better understand genetic differences and make personalized medicine fair for everyone.

The limitation of this study is that we sequenced only a subset of cases (57/198). Although partially randomized, the inclusion of an enriched subset based on atypical PCR bands introduces a potential selection bias. Furthermore, given the low expected detection rate of exon 12 mutations (approximately 2-5%), this limited sample size lacks sufficient statistical power to confidently detect such rare variants. Additionally, we only covered exon 12 plus ~250 bp of the downstream intron; therefore, variants outside the amplicon could have been missed. Although allele-specific PCR is highly sensitive for known hotspots, the Sanger sequencing used for broader screening has a higher limit of detection than targeted NGS, and relying on a cohort from a single region restricts our ability to estimate the true national allele frequencies of the observed intronic variants. Functional conclusions relied on in silico predictions without RNA or cellular assays. Additionally, the absence of a matched healthy Indonesian control cohort makes it difficult to determine whether the 5-bp deletion is a disease-associated variant, a population-specific trait, or a benign polymorphism. Future studies involving a healthy local population are necessary to clarify this. Therefore, larger, multi-center studies using more sensitive methods and RNA-level validation are needed.

In this Indonesian cohort of *V617F*-negative MPN patients, we found no canonical *JAK2* exon 12 coding mutations. Instead, two intronic variants emerged: one common deletion that was absent from major databases and a rare SNV. Computational analyses suggest that neither variant alters the core splice sites; however, RNA-level studies remain indispensable for detecting finer effects. Although our workflow combining allele-specific PCR and targeted sequencing provides a feasible initial strategy for laboratories working under similar constraints, further validation using positive control cohorts is required to confirm its diagnostic

reliability.

Author Contribution Statement

All authors have read and approved the final manuscript for submission. Farmaditya EP Mundhofir and Nani Maharani conceived and designed this study. Raisa Tahira and Amelia Syabani performed the experiments and collected the data. Ferdy K. Cayami interpreted the variant findings and critically revised the manuscript. Farmaditya EP Mundhofir, Nani Maharani, and Endang Mahati conducted laboratory work and coordinated clinical sample collection. Farmaditya EP Mundhofir analyzed the data and drafted the manuscript. Nydia RB Sihombing, Endang Mahati, and Tri I Winarni provided intellectual input and edited the manuscript.

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Ethical Declaration

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Diponegoro, and was conducted in accordance with the 2008 Declaration of Helsinki.

Scientific Approval

This research was an independent scientific project approved by the Faculty of Medicine, Universitas Diponegoro.

Availability of Data

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflicts of interest.

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