Received: 9 August 2022 | Accepted: 15 August 2022

DOI: 10.1002/mgg3.2044

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

# JAK2 rs10974944 is associated with both V617F-positive and negative myeloproliferative neoplasms in a Vietnamese population: A potential genetic marker

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**Funding information**
Ministry of Science and Technology; Vietnam's National Foundation for Science and Technology Development; Ministry of Science and Technology; Vietnam's National Foundation for Science and Technology Development

## Abstract

The *JAK2* gene encodes for a non-receptor tyrosine kinase that plays a key role in the JAK/STAT signaling transfer pathway. Genetic polymorphisms of this gene have been indicated to be associated with myeloproliferative neoplasm-associated thrombosis in recent studies. This research aimed to evaluate the association between the variant *rs10974944* and different types of Myeloproliferative neoplasms disorders in the Vietnamese population. DNA samples were obtained from 172 essential thrombocythemia patients, 14 primary myelofibrosis patients, 76 polycythemia vera patients, and 192 healthy controls. The *JAK2 rs10974944* and V617F genotypes were identified by the polymerase chain reaction-restriction fragment length polymorphism genotyping and Sanger sequencing methods. Results showed that there was a strong association between *rs10974944* and Myeloproliferative neoplasms phenotype ($p < .0001$) and the most significant association was observed in the recessive model of the mutant allele (G). The G allele carriers had a 1.74, 2.86, and 3.03 higher risk of getting essential thrombocythemia, primary myelofibrosis, and polycythemia vera, respectively. Interestingly, this effect of *rs10974944* seemed to be independent of the *JAK2* V617F genotype. The distribution of *rs10974944* genotypes were significantly different between V617F-positive and negative groups ($p = .008$). Moreover, the GG genotype of *rs10974944* was observed to be associated with the risk of getting Myeloproliferative neoplasms both in *JAK2* V617F-positive group, and for the first time in *JAK2* V617F-negative patients. A systematic meta-analysis in different populations strengthened the evidence regarding the correlation between *rs10974944* and myeloproliferative neoplasm disorders. To sum up, our results suggested that *rs10974944* can be used as a predisposition screening marker for predicting Myeloproliferative neoplasms susceptibility.

**KEYWORDS**

haplotype 46/1, Janus kinase, myeloproliferative neoplasms, rs10974944, V617F mutation

## 1 | BACKGROUND

Myeloproliferative neoplasms (MPNs) are a rare group of hematologic cancer, caused by an abnormality of the mature peripheral blood cell production in the bone marrow. These diseases were reported to cause a higher mortality rate compared to healthy controls: In 5 years, the survival rate of MPNs patients was 55% compared to 90% in the matched control (Hultcrantz et al., 2015). MPNs are categorized into two groups: the Philadelphia chromosome-positive (Ph-positive), which is associated with the translocation t(9;22) (q34;q11) of the *BRC* (OMIM: 151410) gene in chromosome 22 and the *ABL1* (OMIM: 189980) gene in chromosome 9 to form the fusion gene called *BCR-ABL1*; and the negative Philadelphia group (Ph-negative), which includes three disorders: essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) (Arber et al., 2016).

ET is characterized by a high platelet production in peripheral blood by megakaryocytes ($450 \times 10^9$/L or higher). The prevalence of this disorder among US citizens was about 38 to 57 patients in 100,000 people (Tefferi, 2014). PV is the uncommon condition of bone marrow that overproduces erythrocytes, with hemoglobin levels greater than 16.5 g/dL in males and 16.0 g/dL in females. In the US, prevalence of PV was estimated to be approximately 44–57 per 100,000 of the population (Mehta et al., 2014). In PMF, the abnormal proliferation of hematopoietic stem cells in bone marrow causes fibrosis and scar tissue and thus, bone marrow cannot produce enough normal blood cells (Tefferi, 2014). Many studies have indicated that the host genetic factor might play a critical role in the risk of getting MPNs. Among those, the abnormal of the JAK/STAT signaling interaction pathway are considered as the most important criterion of MPNs pathogenesis with many driving mutations belonging to different genes such as *JAK2* (OMIM: 147796), *MPL* (OMIM: 159530), *CALR* (OMIM: 109091) and many other genes (Greenfield et al., 2021; Viny & Levine, 2014). Especially, the missense mutation *JAK2* V617F or NM_004972.4 (*JAK2*):c.1691G>T p.Arg564Leu (*rs77375493*) was identified as the most common mutation leading to MPNs as this mutation was detected in 95% in patients with PV, 50% to 70% in ET, and 40% to 50% in PMF (Vainchenker & Kralovics, 2017).

In this study, we investigated the association of the variant *JAK2 rs10974944* with 262 MPNs patients and 192 healthy controls in a Vietnamese population. We also compared the allele frequency of *rs10974944* in each *JAK2* V617F genotype to investigate the linkage disequilibrium between these two variants. Finally, we performed a meta-analysis to understand more clearly the correlation between *rs10974944* and the risk of MPNs in different populations. These initial data can be used for further studies on exploring the progression of MPNs and their application in the genetic diagnosis of the disease.

## 2 | MATERIALS AND METHODS

### 2.1 | Studied population

The studied population included 262 MPNs patients (172 of ET, 14 of PMF, and 76 of PV patients), and 192 healthy controls, recruited at the Vietnam Military Medical University during 2018–2019. All participants were well informed about the research and signed the informed consent. This research was approved by the Institutional Review Board of the Institute of Genome Research, Vietnam Academy of Science and Technology (No 4-2021/NCHG-HDDD).

### 2.2 | Variant genotyping

Total peripheral blood samples of all the participants were collected for gDNA extraction by the QIAamp® DNA Mini Blood Kits (QIAGEN) according to the manufacturer's protocol. The accession number of *JAK2* Genbank reference sequence is NM_004972.4. Genotypes of the two genetic markers *JAK2* V617F (*rs77375493*) and *rs10974944* were identified by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using specific primers (Table 1). After size verification by 1% agarose gel, the PCR products were digested with the *BsaXI* and *BclI* restriction enzymes for the variant *rs77375493* and *rs10974944*, respectively. The genotype of each individual was accordingly determined by electrophoresis on 3% agarose gel. And 10% of the obtained genotypes were sent to sequenced by the Sanger method

**TABLE 1** Primers and restriction enzymes (RE) used for PCR-RFLP

| Name of oligo | Sequence | PCR product size | RE |
|---|---|---|---|
| *rs77375493*-FP | TCCTCAGAACGTTGATGGCAG | 453 (bp) | *BsaXI* |
| *rs77375493*-RP | ATTGCTTTCCTTTTTCACAAGAT | | |
| *rs10974944*-FP | ACATGGGTTTTGCATCCTATGAA | 492 (bp) | *BclI* |
| *rs10974944*-RP | TCTGCTTGCTAGTGGGTGAAT | | |

at Apical Scientific Laboratory (Malaysia) to verify the result was identical. The genotypes of the two markers were screened at the same time.

### 2.3 | Linkage disequilibrium and statistical analysis

The linkage disequilibrium and statistical analysis were implemented using the R software version 4.0.2 and Rstudio. Linkage disequilibrium was assessed between *rs77375493* and *rs10974944* using the LDlinkR package of R language (Myers et al., 2020). The associations between genotypes or allele groups and MPNs phenotypes were checked using the Chi-squared test and Fisher's exact test, accordingly. The odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using Microsoft Excel following the formula by Szumilas et al (Szumilas, 2010). All of the statistical tests were applied as two-sided. An obtained *p*-value less than 0.05 was considered statistically significant.

### 2.4 | Meta-analysis

The literature search was conducted on the association between *rs10974944* and MPNs phenotype using Pubmed database (https://pubmed.ncbi.nlm.nih.gov/). All the Review papers, Case reports, replication studies on the same population, researches on un-relevant diseases were excluded from further analysis. The meta-analysis was carried out by METAL (Willer et al., 2010). Potential publication bias in meta-analyses was identified by the Egger's test.

## 3 | RESULTS

### 3.1 | Population characteristics

All 454 participants involved in this study were Vietnamese people belonging to the Kinh ethnicity group. The gender ratio (Male/Female) of the studied population was 0.76 (196 Males and 258 Females) and the age mean of all the population was 56.32±11.38. Detailed information on the gender and age structure of each group was listed in Table 2. There was no observed significant difference between the MPNs group and the healthy group in term of Age, Gender, or Ethnicity.

### 3.2 | The distribution of JAK2 rs77375493 and rs10974944

In this studied population, 161 individuals carried the *JAK2* V617F mutation (account for 35.5% of all population and 61.5% of MPNs patients). Among those, 99/172 (57.6%) of the ET patients, 9/14 (64.3%) of the PMF patients, 53/76 (69.7%) of the PV patients and none of the Control group were *JAK2* V617F positive.

The result of *rs10974944* genotyping showed that the genotype distribution (CC/GC/GG) in all the population was 177/173/104, in Control group was 90/82/20, 63/64/45 in ET patients, 4/4/6 in PMF patients and 20/23/33 in PV patients. The correlation between *JAK2 rs10974944* and *JAK2* V617F mutation status was shown in Table 3. The linkage disequilibrium analysis indicated that there was a slight linkage disequilibrium between these two variants, though it was not tight linkage ($D' < 0.8$) (Figure 1). If only the MPNs patients were taken into account (excluded the controls), there was a significant difference in the genotype distribution of *rs10974944* between the V617F-positive and negative group: the frequency of GG genotype was higher in the V617F-positive group (38.5% compared to 21.8%), the frequency of CC was lower (27.3% compared to 42.6%) while the heterozygous genotype GC was the same (34.2% and 35.6%) ($p = .008$).

**TABLE 2** Characteristics between MPNs patients and healthy controls

| Group | Number N | Age mean ± St.d | Gender male/female (% of male) | Ethnic |
|---|---|---|---|---|
| Control | 192 | 52.61 ± 9.52 | 88/104 (45.8%) | Kinh (100%) |
| ET | 172 | 53.65 ± 12.58 | 60/112 (34.9%) | Kinh (100%) |
| PMF | 14 | 61.64 ± 8.75 | 4/10 (28.6%) | Kinh (100%) |
| PV | 76 | 58.16 ± 12.11 | 44/32 (57.9%) | Kinh (100%) |
| *p*-value | | 0.39[1] | 0.327[2] | N/A |

[1]*p*-value obtained by Mann–Whitney U test.
[2]*p*-value obtained by Chi-squared test.

**TABLE 3** Genotype distribution between the two variants JAK2 V617F (rs77375493) and rs10974944 in each group

| | *JAK2* V617F negative | | | *JAK2* V617F positive | | |
|---|---|---|---|---|---|---|
| ***rs10974944* genotype** | **CC** | **GC** | **GG** | **CC** | **GC** | **CC** |
| Control | 90 | 82 | 20 | 0 | 0 | 0 |
| Essential thrombocythemia | 31 | 27 | 15 | 32 | 37 | 30 |
| Primary myelofibrosis | 2 | 2 | 1 | 2 | 2 | 5 |
| Polycythemia vera | 10 | 7 | 6 | 10 | 16 | 27 |
| **All population** | **133** | **118** | **42** | **44** | **55** | **62** |

The difference in the genotype distribution of rs10974944 between the V617F-positive and negative group was significant with p = 0.008 are indicated in bold.

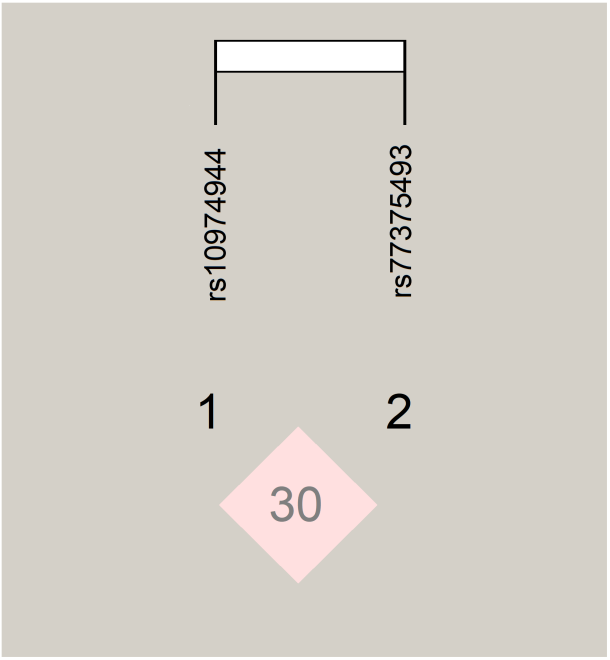


**FIGURE 1** Linkage study consisted of JAK2 rs77375493 and rs10974944. D′ value was shown in the LD block

### 3.3 | Association of *JAK2 rs10974944* with MPNs in the studied population

Statistical analysis showed that the genotype of *rs10974944* was associated with ET, especially in the additive model ($p$ = .000421) and in the recessive model (OR = 3.047, 95% CI = 1.716–5.413, $p$ = .00009). The G allele of this variant also increased the risk of getting ET in comparison to the C allele (OR = 1.74, 95% CI = 1.286–2.354, $p$ = .0003) (Table 4). Similarly, this polymorphism showed a significant link with PMF and PV risk. The most significant model was also the recessive model (OR = 6.45, 95% CI = 2.03–20.48, $p$ = .0004 in PMF; OR = 6.6, 95% CI = 3.452–12.62, $p \sim 10^{-9}$ in PV). The frequencies of allele G were significantly higher in the patient groups compared to control (OR = 2.86, 95% CI = 1.31–6.24, $p$ = .006 in PMF; OR = 3.03, 95% CI = 2.06–4.47, $p \sim 10^{-8}$ in PV) (Tables 5 and 6).

Result of statistical analysis also indicated that *rs10974944* associated with both *JAK2* V617F-negative MPNs and V617F-positive MPNs in this studied population. In the V617F-negative MPNs patients group, frequency of the GG genotype was twice as high compared to control (21.8% to 10.4%) (OR = 2.395, 95% CI = 1.24–4.64, $p$ = .0097). Among the V617F-positive MPNs patients, frequency of GG genotype was even four times higher than control (38.5% to 10.4%) (OR = 5.3859, 95% CI = 3.07–9.44, $p$ < .0001). In term of allele effect, while the G allele of *rs10974944* seemed to dramatically increase the risk of getting MPNs in the V617F-positive group (OR = 2.69, 95% CI = 1.98–3.66, $p$ < .0001), this effect was no longer statistically significant in the V617F-negative group (OR = 1.41, 95% CI = 0.99–2.01, $p$ = .0584).

**TABLE 4** Association of *rs10974944* with essential thrombocythemia

| | Control ($n$ = 192) | Case ($n$ = 172) | Odd ratio | 95%CI | $p$-value |
|---|---|---|---|---|---|
| Addtive model | | | | | |
| CC | 90 (46.9%) | 63 (36.6%) | 1.00 | | 0.000421 |
| GC | 82 (42.7%) | 64 (37.2%) | 1.115 | 0.705–1.764 | |
| GG | 20 (10.4%) | 45 (26.2%) | 3.214 | 1.734–5.959 | |
| Dominant model | | | | | |
| CC | 90 (46.9%) | 63 (36.6%) | 1.00 | | 0.048 |
| GC + GG | 102 (53.1%) | 109 (63.4%) | 1.527 | 1.003–2.324 | |
| Recessive model | | | | | |
| CC + GC | 172 (89.6%) | 127 (73.8%) | 1.00 | | 0.00009 |
| GG | 20 (10.4%) | 45 (26.2%) | 3.047 | 1.716–5.413 | |
| Overdominant model | | | | | |
| CC + GG | 110 (57.3%) | 108 (62.8%) | 1.00 | | 0.285 |
| GC | 82 (42.7%) | 64 (37.2%) | 0.795 | 0.522–1.21 | |
| Alleles | | | | | |
| C | 262 (68.2%) | 190 (55.2%) | 1.00 | | 0.000308 |
| G | 122 (31.8%) | 154 (44.8%) | 1.74 | 1.286–2.354 | |

**TABLE 5** Association of *rs10974944* with primary myelofibrosis

| | Control ($n$ = 192) | Case ($n$ = 14) | Odd ratio | 95%CI | $p$-value |
|---|---|---|---|---|---|
| Addtive model | | | | | |
| CC | 90 (46.9%) | 4 (28.6%) | 1.00 | | 0.00776 |
| GC | 82 (42.7%) | 4 (28.6%) | 1.098 | 0.266–4.533 | |
| GG | 20 (10.4%) | 6 (42.9%) | 6.75 | 1.741–26.16 | |
| Dominant model | | | | | |
| CC | 90 (46.9%) | 4 (28.6%) | 1.00 | | 0.267 |
| GC + GG | 102 (53.1%) | 10 (71.4%) | 2.206 | 0.669–7.278 | |
| Recessive model | | | | | |
| CC + GC | 172 (89.6%) | 8 (57.1%) | 1.00 | | 0.000418 |
| GG | 20 (10.4%) | 6 (42.9%) | 6.45 | 2.031–20.48 | |
| Overdominant model | | | | | |
| CC + GG | 110 (57.3%) | 10 (71.4%) | 1.00 | | 0.3 |
| GC | 82 (42.7%) | 4 (28.6%) | 1.864 | 0.565–6.152 | |
| Alleles | | | | | |
| C | 262 (68.2%) | 12 (42.9%) | 1.00 | | 0.006029 |
| G | 122 (31.8%) | 16 (57.1%) | 2.863 | 1.314–6.237 | |

### 3.4 | Meta-analysis on the association of *rs10974944* with MPNs

After all the unsuitable articles were excluded from the literature mining, a total of 7 studies were eligible for the final pooled analysis. The related information of 7 included studies and data from this study were represented in Table 7. The sample size of each study was from 146 to 962 participants, with the average size as 486 individuals. Three studies were conducted in the European population, three studies in the Asian population, 1 in the South American population and 1 study with an unknown population.

In general, the meta-analysis showed a statistically significant relation between the *JAK2 rs10974944* genotype and the risk of getting MPNs disorders (OR = 1.908, 95% CI = 1.529–2.381, $p = 10^{-8}$) under the random-effects model (Figure 2). Although 6/8 studies obtained significant results, the analysis detected a potential evidence of heterogeneity in the results for the above association ($I^2 = 77\%$, $\tau^2 = 0.075$, $p$-value for heterogeneity <.01).

In term of publication bias, a review of the funnel plot indicated no potential for publication bias as no signs of asymmetry or hole was observed (Figure 3). The Egger's test confirmed that there was no clear evidence of publication bias ($p$-value for Egger = .709).

**TABLE 6** Association of *rs10974944* with polycythemia vera

| | Control ($n = 192$) | Case ($n = 76$) | Odd ratio | 95%CI | $p$-value |
|---|---|---|---|---|---|
| Addtive model | | | | | |
| CC | 90 (46.9%) | 20 (26.3%) | 1.00 | | $6.35 \times 10^{-9}$ |
| GC | 82 (42.7%) | 23 (30.3%) | 1.262 | 0.646–2.466 | |
| GG | 20 (10.4%) | 33 (43.4%) | 7.425 | 3.553–15.52 | |
| Dominant model | | | | | |
| CC | 90 (46.9%) | 20 (26.3%) | 1.00 | | 0.002043 |
| GC + GG | 102 (53.1%) | 56 (73.7%) | 2.471 | 1.378–4.430 | |
| Recessive model | | | | | |
| CC + GC | 172 (89.6%) | 43 (56.6%) | 1.00 | | $9.7 \times 10^{-10}$ |
| GG | 20 (10.4%) | 33 (43.4%) | 6.6 | 3.452–12.62 | |
| Overdominant model | | | | | |
| CC + GG | 110 (57.3%) | 53 (69.7%) | 1.00 | | 0.06 |
| GC | 82 (42.7%) | 23 (30.3%) | 1.718 | 0.975–3.028 | |
| Alleles | | | | | |
| C | 262 (68.2%) | 63 (41.4%) | 1.00 | | $1.06 \times 10^{-8}$ |
| G | 122 (31.8%) | 89 (58.6%) | 3.034 | 2.059–4.471 | |

## 4 | DISCUSSION AND CONCLUSION

The *JAK2* gene encodes the Janus kinases 2, one of the four members of the JAK-family (JAK1, JAK2, JAK3, and TYK2) – the non-receptor tyrosine kinase that activates cytokine-mediated signals by the JAK–STAT pathway (Sopjani et al., 2021). *JAK2 rs10974944* is part of the *JAK2* 46/1 haplotype, which consists of four main SNPs (*rs10974944, rs1159782, rs3780367*, and *rs12343867*) and hundreds of other SNPs located in the three genes: Insulin-like 4 *(INSL4*), Insuline-like6 (*INSL6*), and *JAK2* (Olcaydu, Harutyunyan, et al., 2009; Olcaydu, Skoda, et al., 2009). These four SNPs were indicated in complete linkage disequilibrium with each other in many populations (Anelli et al., 2018; Tanaka et al., 2013), thus they were also referred to as "GGCC" haplotype as their mutant alleles.

In this study, results showed that the *rs10974944* was strongly associated with MPNs in the Vietnamese population. In detail, the G allele of *rs10974944* significantly increased the chance of getting ET, PMF, and PV disorder 1.74, 2.86, and 3.03 times, respectively. This result seemed to be consistent with other publications on the association between *JAK2 rs10974944* and MPNs phenotypes worldwide as our meta-analysis data showed a significantly different distribution of *rs10974944* genotypes between

**TABLE 7** The general characteristics of studies included in the meta-analysis

| | | | MPN patients | | | Control | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Author | Population | Year | GG | GC | CC | GG | GC | CC | H-W $p$-value | Ref |
| Pagliarini-e-Silva et al | Brazilian | 2013 | 18 | 20 | 18 | 12 | 25 | 53 | 0.0046 | Pagliarini-e-Silva et al. (2013) |
| Koh et al | Chinese | 2014 | 29 | 76 | 23 | 40 | 198 | 232 | 0.8061 | Koh et al. (2014) |
| Matsuguma et al | Japanese | 2019 | 55 | 82 | 64 | 33 | 127 | 206 | 0.0419 | Matsuguma et al. (2019) |
| Hsiao et al | unknown | 2011 | 10 | 26 | 25 | 8 | 46 | 52 | 0.6168 | Hsiao et al. (2011) |
| Zerjavic et al | Slovenian | 2013 | 12 | 50 | 73 | 41 | 164 | 254 | 0.0558 | Zerjavic et al. (2013) |
| Soler et al | Spanish | 2015 | 18 | 62 | 49 | 19 | 115 | 136 | 0.4227 | Soler et al. (2015) |
| Trifa et al | Romanian | 2016 | 88 | 281 | 160 | 35 | 171 | 227 | 0.7258 | Trifa et al. (2016) |
| ***This study*** | Vietnamese | 2021 | 84 | 91 | 87 | 20 | 82 | 90 | 0.8365 | |

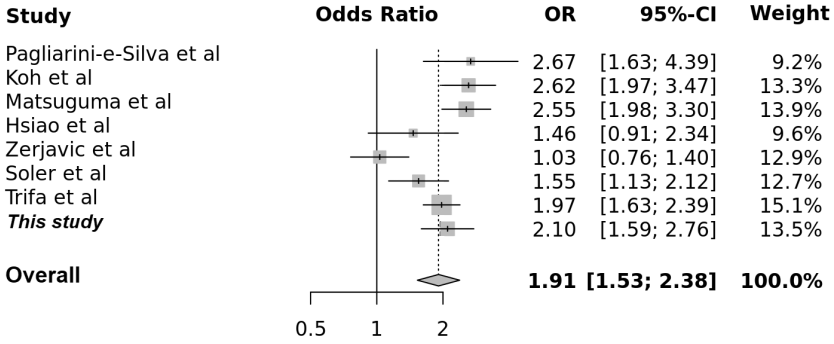


**FIGURE 2** Forest plot demonstrated the association between JAK2 rs10974944 and MPNs susceptibility

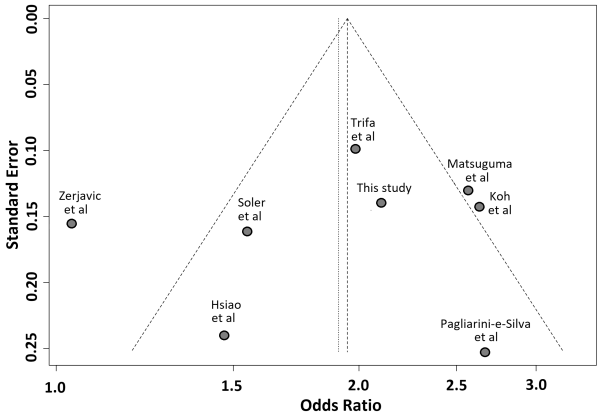


**FIGURE 3** Funnel plot of publication biases on the association between JAK2 rs10974944 and MPNs

MPNs patients and healthy controls (OR = 1.908, 95% CI = 1.529–2.381, $p = 10^{-8}$).

Several previous studies found that *rs10974944* was associated with the development of V617F-positive MPNs (Jones et al., 2009; Kilpivaara et al., 2009; Tanaka et al., 2013). This observation might be due to the linkage between the *JAK2* 46/1 and V617F as many studies had demonstrated that this haplotype was associated with V617F-positive myeloproliferative neoplasms in Brazilian (Macedo et al., 2015), Romanian (Trifa et al., 2010), Japanese (Tanaka et al., 2013) and other populations (Anelli et al., 2018; Stolyar et al., 2018). However, the results of our study indicated that in the Vietnamese population, the linkage disequilibrium between *rs10974944* and *rs77375493* (V617F) was not tight, yet *rs10974944* still had a strong association with MPNs, suggested that the effect of *rs10974944* on MPNs phenotype was independent of V617F profile. In addition, our research observed a significant association between the *rs10974944* GG genotype and the risk of getting V617F-negative MPNs. Up to our knowledge, this correlation is novel and has not been published in any other population.

In conclusion, in this study, we detected an association between *JAK2 rs10974944* and MPNs in a Vietnamese population. This association seemed to be independent with the *JAK2* V617F genetic profile of the MPNs patients, since the correlation between *rs10974944* and MPNs was observed in both V617F-positive and V617F-negative groups compared to controls. Our result was confirmed by a meta-analysis of 7 other studies on Brazilian, Chinese, Japanese, Slovenian, Spanish, Romanian populations. Further functional analysis should be implemented to investigate the possible pathogenic role of *rs10974944* as well as the haplotype *JAK2* 46/1 on the MPNs phenotypes.

## AUTHOR CONTRIBUTIONS

Nguyen Thy Ngoc (N.T.N) designed the study. N.T.N received the grant for the study. Nguyen Ba Vuong (N.B.V) and Nguyen Thi Xuan (N.T.X) carried out the sampling. Bui Bich Hau (B.B.H) and N.T.N carried out the laboratory work. N.T.N analyzed the data and wrote the manuscript, with input from all authors.

## ACKNOWLEDGMENT

We sincerely thank all the MPNs patients and healthy control volunteers for participating in this study. This study was granted by the Vietnam's National Foundation for Science and Technology Development (NAFOSTED) – Ministry of Science and Technology, Vietnam (Grant No. 108.01-2020.02).

## CONFLICT OF INTEREST

No potential conflict of interest was reported in this study.

## DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are openly available within the article. The raw data are available from the corresponding author, upon reasonable request. The raw data are not publicly available due to privacy or ethical restrictions.

## ETHICS STATEMENT

The authors stated that they have obtained the appropriate institutional review board approval and followed the principles outlined in the Declaration of Helsinski for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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**How to cite this article:** Ngoc, N. T., Hau, B. B., Vuong, N. B., & Xuan, N. T. (2022). JAK2 rs10974944 is associated with both V617F-positive and negative myeloproliferative neoplasms in a Vietnamese population: A potential genetic marker. *Molecular Genetics & Genomic Medicine*, *10*, e2044. https://doi.org/10.1002/mgg3.2044