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*JAK2*V617F VAF and Presence of Copy Neutral-LOH at Chromosome 9p Predicts Transformation to Myelofibrosis in Patients With Polycythemia Vera Enrolled in REVEAL

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Introduction

- Polycythemia vera (PV) is characterized by clonal erythrocytosis and activating *JAK2* mutations; >90% of patients harbor a *JAK2*V617F driver mutation[1]
- Copy neutral loss of heterozygosity (CN-LOH) at chromosome 9p is common in PV and leads to increased *JAK2*V617F variant allele frequency (VAF)
- Studies suggest treatment-induced reduction of VAF is associated with improved outcomes, including decreased thrombotic events and transformation[2,3]
- It is unclear if quantitative VAF and CN-LOH at chromosome 9p are predictive of clinical outcomes

Objective

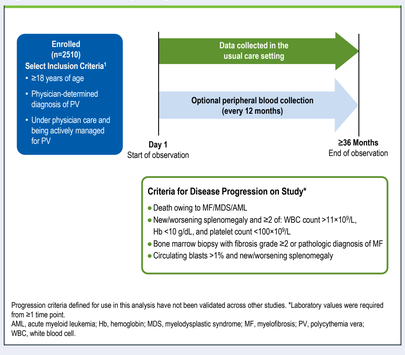
- To use clinical and genomic data from the Prospective Observational Study of Patients With Polycythemia Vera in US Clinical Practices Trial (REVEAL; NCT02252159) to evaluate *JAK2*V617F VAF as a predictor of transformation to myelofibrosis (MF), and to evaluate the association of CN-LOH with *JAK2*V617F VAF and transformation

Methods

Study Design

- REVEAL is a prospective, observational, open-label study of patients with PV across 227 US community and academic study sites (NCT02252159; **Figure 1**)[4]
- Of 2510 patients enrolled in REVEAL,1524 had an available biospecimen and confirmed *JAK2* mutation by droplet digital polymerase chain reaction (ddPCR)
- 114/1524 patients had transformation during the study based on modified World Health Organization criteria **(Figure 1)**

Figure 1. REVEAL Study Design

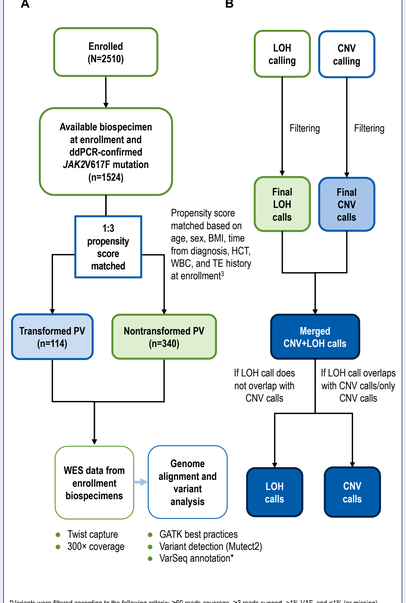


Progression criteria defined for use in this analysis have not been validated across other studies. *Laboratory values were required from ≥1 time point.
AML, acute myeloid leukemia; Hb, hemoglobin; MDS, myelodysplastic syndrome; MF, myelofibrosis; PV, polycythemia vera; WBC, white blood cell.

Genomic Analysis

- Whole exome sequencing (WES) was performed on pretransformation enrollment biospecimens from 114 patients with and 340 patients without transformation (control cohort), propensity score matched (1:3) by age, sex, PV duration, body mass index, and thrombosis history **(Figure 2A)**
- WES was performed using the Illumina (paired-end) platform at an average depth of 300× and processed using Genome Analysis Toolkit (GATK) best practices
- Copy number variation (CNV) was called using GATK's somatic CNV workflow
- LOH events were detected by fitting the allelic imbalance of common single-nucleotide polymorphisms (SNPs) to the circular binary segmentation algorithm[5]
- For CNV and LOH calling, we applied comprehensive filtering criteria such as size and number of SNPs supporting the event
- CN-LOH was defined as segments without significant overlap with any CNV call **(Figure 2B)**

Figure 2. Genomic Analysis (A) and CNV and LOH Calling (B)



*Variants were filtered according to the following criteria: ≥60 reads coverage, ≥3 reads support, >1% VAF, and <1% (or missing) minor allele frequency in the Genome Aggregation Database.
BMI, body mass index; CNV, copy number variation; ddPCR, droplet digital polymerase chain reaction; GATK, Genome Analysis Toolkit; HCT, hematocrit; JAK, Janus kinase; LOH, loss of heterozygosity; PV, polycythemia vera; TE, thrombotic event; VAF, variant allele frequency; WBC, white blood cell; WES, whole exome sequencing.

Results

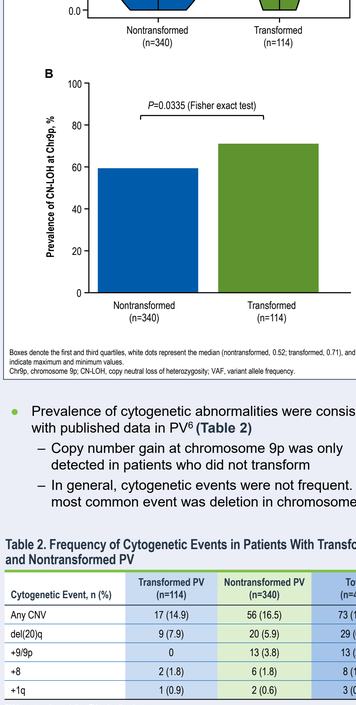
Table 1. Enrollment Demographics and Clinical Characteristics in Patients With Transformed and Nontransformed PV

Characteristic	Transformed PV (n=114)	Nontransformed PV (n=340)
Age at enrollment, median (range), years	69.0 (32, 92)	68.0 (31, 95)
≥65 years, n (%)	71 (62.3)	223 (65.6)
Male, n (%)	65 (57.0)	181 (53.2)
Time from PV diagnosis to enrollment, median (range), years	7.2 (0, 34.1)	5.8 (0, 38.5)
PV risk at enrollment, n (%)		
High risk	97 (85.1)	288 (84.7)
History of TE at enrollment, n (%)	36 (31.6)	95 (27.9)
PV treatment at enrollment, n (%)		
Watchful waiting only	7 (6.1)	18 (5.3)
Phlebotomy	21 (18.4)	78 (22.9)
Hydroxyurea	41 (36.0)	114 (33.5)
Hydroxyurea and phlebotomy in combination	**21 (18.4)**	**96 (28.2)**
Other*	**24 (21.1)**	**34 (10.0)**
Hematocrit >0.45 L/L at enrollment, n (%)	39 (34.2)	120 (35.3)
WBC count >11×10⁹/L at enrollment, n (%)	50 (43.9)	145 (42.6)
Platelet count >400×10⁹/L at enrollment, n (%)	32 (28.1)	128 (37.6)

Values that are significantly different between transformed vs nontransformed cohorts ($P<0.05$) are shown in **bold** font.
*"Other" includes treatments such as ruxolitinib, recombinant interferon-alfa, pegylated recombinant interferon-alfa, busulfan, and anagrelide.
PV, polycythemia vera; TE, thrombotic event; WBC, white blood cell.

- Patient demographics and clinical characteristics at enrollment are shown in **Table 1**
- Median peripheral whole-blood *JAK2*V617F VAF at enrollment was a significant predictor of transformation (**Figure 3A,** P=0.014)
- Prevalence of CN-LOH at chromosome 9p was also significantly higher in patients who transformed (**Figure 3B,** P=0.0335)

Figure 3. *JAK2*V617F VAF (A) and LOH Status (B) in Patients With vs Without Disease Transformation



Boxes denote the first and third quartiles, white dots represent the median (nontransformed, 0.52; transformed, 0.71), and the whiskers indicate maximum and minimum values.
Chr9p, chromosome 9p; CN-LOH, copy neutral loss of heterozygosity; VAF, variant allele frequency.

- Prevalence of cytogenetic abnormalities were consistent with published data in PV[6] **(Table 2)**
  - Copy number gain at chromosome 9p was only detected in patients who did not transform
  - In general, cytogenetic events were not frequent. The most common event was deletion in chromosome 20q

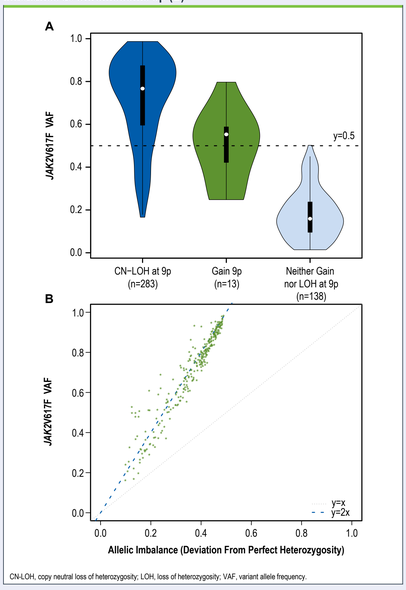
Table 2. Frequency of Cytogenetic Events in Patients With Transformed and Nontransformed PV

Cytogenetic Event, n (%)	Transformed PV (n=114)	Nontransformed PV (n=340)	Total (n=454)
Any CNV	17 (14.9)	56 (16.5)	73 (15.6)
del(20)q	9 (7.9)	20 (5.9)	29 (6.4)
+9/9p	0	13 (3.8)	13 (2.9)
+8	2 (1.8)	6 (1.8)	8 (1.8)
+1q	1 (0.9)	2 (0.6)	3 (0.7)

CNV, copy number variation; PV, polycythemia vera.

- 283 patients (62%) had CN-LOH, 13 (3%) had a copy number gain, and 138 (30%) had no chromosomal abnormality at chromosome 9p **(Figure 4A)**
  - Most patients with *JAK2*V617F VAF >0.5 had CN-LOH; however, *JAK2*V617F VAF <0.5 did not rule out absence of CN-LOH
  - Level of allelic imbalance significantly correlated with *JAK2*V617F VAF (n=283; Spearman's rho ~0.96; $P<2.2\times10^{-16}$) **(Figure 4B)**

Figure 4. *JAK2*V617F VAF by Cytogenetic Status at Chromosome 9p (A) and Association Between *JAK2*V167F VAF and the Level of Allelic Imbalance at Chromosome 9p (B)



CN-LOH, copy neutral loss of heterozygosity; LOH, loss of heterozygosity; VAF, variant allele frequency.

- The presence of LOH at chromosome 9p is associated with **transformation** (P=0.0335, Fisher exact test; **Table 3**; **Figure 3B**), and the presence of copy number gain at chromosome 9p is associated with **lack of transformation** (P=0.0451, Fisher exact test; **Table 4**)
- Hematologic characteristics, SNV/small indels, and CNV/LOH may predict disease transformation in patients with PV

Table 3. Association Between LOH at Chromosome 9p and Disease Transformation Status

	Transformed PV (n=114)	Nontransformed PV (n=340)	
LOH at chromosome 9p	81	202	**28.6% (n=81/283)**
No LOH at chromosome 9p	33	138	19.3% (n=33/171)

Significant values are shown in **bold** font.

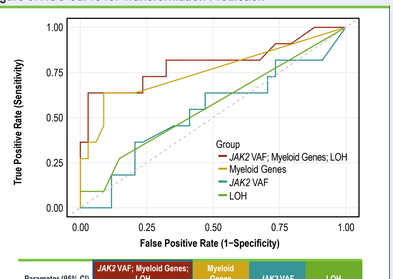
Table 4. Association Between Copy Number Gain at Chromosome 9p and Disease Transformation Status

	Transformed PV (n=114)	Nontransformed PV (n=340)	
Gain at chromosome 9p	0	13	**0% (n=0/13)**
No gain at chromosome 9p	114	327	25.9% (n=114/441)

Significant values are shown in **bold** font.

- Random forest classifiers based on individual molecular features and their combinations were trained to predict patients at high risk of disease transformation **(Figure 5)**
- Integration of *JAK2* VAF with CN-LOH and nondriver somatic mutations in a subset of 26 myeloid-related genes resulted in superior prediction of patients at high risk of disease transformation

Figure 5. ROC Curve for Transformation Prediction



Parameter (95% CI)	*JAK2* VAF; Myeloid Genes; LOH	Myeloid Genes	*JAK2* VAF	LOH
AUC	0.80 (0.63, 0.97)	0.75 (0.57, 0.93)	0.53 (0.33, 0.73)	0.56 (0.36, 0.76)
Sensitivity	0.636 (0.35, 0.85)	0.636 (0.35, 0.85)	0.364 (0.15, 0.65)	0.273 (0.10, 0.57)
Specificity	0.971 (0.85, 0.99)	0.912 (0.77, 0.97)	0.794 (0.63, 0.9)	0.853 (0.70, 0.94)
PPV	0.875 (0.53, 0.98)	0.700 (0.40, 0.89)	0.304 (0.16, 0.51)	0.375 (0.14, 0.69)
NPV	0.892 (0.75, 0.96)	0.886 (0.74, 0.95)	0.818 (0.61, 0.93)	0.784 (0.63, 0.89)

AUC, area under the curve; CI, confidence interval; LOH, loss of heterozygosity; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; VAF, variant allele frequency.

Conclusions

- **Patients who transformed had higher *JAK2*V617F VAF compared with patients who did not transform; however, this feature alone is not sufficient to predict transformation**
- **CN-LOH at chromosome 9p significantly impacts *JAK2*V617F VAF; both are predictive of transformation from PV to MF**
- **Copy gain at chromosome 9p is associated with lack of transformation**
- **The presence of CN-LOH at 9p can be integrated with VAF to better estimate the zygosity of *JAK2*V617F and improve understanding of mutant vs wild-type cell fractions**
- **Integration of mutations in myeloid genes, LOH, and *JAK2* VAF together improves prediction of patients at high risk of disease transformation**
- **Additional genetic data and clinical data will be integrated into this model to improve prediction of transformation as well as validation in an independent cohort of the model**

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References

1. Tefferi A, Barbui T. *Am J Hematol.* 2020;95:1599-1613. **2.** Harrison CN, et al. *J Clin Oncol.* 2023;41:3534-3544. **3.** Guglielmelli P, et al. *Am J Hematol.* 2024;99:1550-1559. **4.** Grunwald MR, et al. *Clin Lymphoma Myeloma Leuk.* 2018;18:788-795.e2. **5.** Seshan VE, Olshen A. 2024. DNAcopy: R package v.1.64.0. **6.** Tang G, et al. *Haematologica.* 2017;102:1511-1518.

Disclosures

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