A Novel t(1;9)(p36;p24.1) *JAK2* Translocation and Review of the Literature

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Abstract

The *JAK2V617F* point mutation has been implicated in the pathogenesis of the vast majority of myeloproliferative neoplasms (MPNs), but translocations involving *JAK2* have increasingly been identified in patients with *JAK2V617F*-negative MPNs. Here, we present a case of a patient diagnosed with *JAK2V617F*-negative polycythemia vera (PV) that transformed to the MPN-blast phase. Cytogenetic and FISH analysis revealed a novel translocation of t(1;9)(p36;p24.1), causing a *PEX14-JAK2* gene fusion product. The t(1;9)(p36;p24.1) represents a new addition to the list of known translocations involving *JAK2* that have been identified in hematologic malignancies. Although the prognostic and treatment implications of *JAK2* translocations in MPNs have not been elucidated, positive outcomes have been described in case reports describing the use of JAK inhibitors in these patients. Further research into the role of *JAK2* translocations in the pathogenesis and outcomes of hematologic malignancies is warranted.

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Introduction

The JAK (Janus kinase) proteins are a family of cytoplasmic tyrosine kinases involved in the JAK-STAT signaling pathway and are essential in maintaining normal hematopoiesis. The *JAK2* gene, located on chromosome 9p24, encodes for a receptor predominantly responsive to type I cytokine ligands, including erythropoietin, thrombopoietin, and granulocyte-macrophage colony-stimulating factor. Ligand binding to *JAK2* leads to autophosphorylation and activation of STAT (signal transducers and activators of transcription) proteins, which mediate the expression of genes involved in hematopoiesis [1].

Constitutive activation of the JAK-STAT pathway through the acquired point activating mutation on exon 14 (*JAK2V617F*) has been implicated in the pathogenesis of myeloproliferative neoplasms (MPNs). This mutation is present in 98% of polycythemia vera (PV), 40–50% of essential thrombocythemia (ET), and 50–60% of primary myelofibrosis (PMF) [2, 3], and is present in 20% of patients with non-classical MPNs [4]. Additionally, a subset of patients with *JAK2V617F*-negative MPNs is found to have translocations involving *JAK2*, which result in gene fusion products that lead to *JAK2* amplification or consti-

Table 1. Summary of cytogenetic and FISH results

Date	Diagnosis	Tissue	Karyotype (number of cells)	I-FISH for chimerism (% of abnormal cells)
11/24/2009		PB	46,XX,t(1;9)(p36;p24.1)[15]/46,XX[15]	
12/24/2009	MPN accelerated phase 15% blasts	PB	46XX,t(1;9)(p36;p24.1)[8]/46,XX[12]	n.d.
04/14/2010	PV with 9% peripheral blasts	PB	46XX,t(1;9)(p36;p24.1)[18]/46,idem,t(7;17)(q22.1;q25.3),der(15)t(1;5)(q12;q26) [2] (trisomy 1q)	n.d.
09/23/2010	MF ¹	BM	n.d.	42% host (XX), 48% donor (XY)
10/01/2010	MF-AML ²	CSF	n.d.	1.4% host (XX), 98.6% donor (XY)
10/08/2010	MF-AML ²	PB	n.d.	56% host (XX), 44% donor (XY)
11/09/2010	AML	BM	46,XX,t(1;9)(p36.22;p24.1),t(7;17)(q21.2;q23),der(15)t(1;15)(q12;q26) [11]/46,XX,idem,der(21)t(8;21)(q13;q13)[7] /49,XX,idem,+7,+9,+10[1]/44,XX,idem,-3,-3,-6,+7,+8[1]	93% host (XX), 7% donor (XY)
11/09/2010		CSF	n.d.	95% donor (XY), 5% host (XX)

MPN, myeloproliferative neoplasm; PV, polycythemia vera; MF, myelofibrosis; AML, acute myeloid leukemia; PB, peripheral blood; BM, bone marrow; CSF, cerebrospinal fluid; n.d., not done.

¹ Status after gender-mismatched allogeneic stem cell transplant (allo-SCT).

² Day +58 status after allo-SCT.

tutive activation of the tyrosine kinase. These translocations are not limited to the MPNs, but have also been identified in de novo leukemias of both myeloid and lymphoid lineages (Table 2).

Here, we describe a case of *JAK2V617F*-negative PV with a novel *JAK2* translocation. We also provide a review of the known *JAK2* translocations associated with PV and other MPNs.

Case Report

A 52-year-old woman initially presented in 2008 with symptoms of headaches, dizziness, fatigue, shortness of breath, and paresthesias of the hands and feet with an HCT of 61% and normal WBC and PLT counts. Bone marrow biopsy showed a hypercellular marrow (95%) with increased megakaryocytes in clusters, without reticulin staining. The patient was found to meet the World Health

Organization's (WHO) diagnostic criteria for *JAK2V617F* mutation-negative PV and was initiated on treatment with aspirin and therapeutic phlebotomy, to maintain the HCT <42%.

A year later, the patient developed leukocytosis (WBC $30 \times 10^9/L$) and thrombocytosis (PLT 600,000/L). She was started on hydroxyurea, with subsequent improvement in leukocytosis and thrombocytosis, but developed treatment-emergent anemia. Repeat bone marrow biopsy showed a hypercellular marrow (100%) with trilineage hematopoiesis, marked granulocytic hyperplasia, increased immature forms, markedly increased eosinophils (31%), and 7% blasts. Peripheral blood flow cytometry showed a small CD33+ and CD34+ myeloblast population (1.4%).

Several months later, the patient developed constitutional symptoms. The WBC was found to be elevated to $72 \times 10^9/L$ and peripheral blasts were 21%, consistent with transformation to MPN-blast phase (MPN-BP), a form of secondary acute myeloid leukemia (AML). Decitabine was initiated and after receiving 4 cycles the patient underwent hematopoietic stem cell transplantation (HSCT) in August 2010 with cells from a 10/10 matched unrelated donor, with successful engraftment. The post-transplant bone marrow biopsy, however, showed persistent hypercellularity

(80–90%) and persistent myeloblast populations ranging from 1.1 to 8%, consistent with residual disease. Unfortunately, the patient's course was complicated by graft-versus-host disease of the gastrointestinal system and central nervous system. Ultimately, the patient succumbed to sepsis on day +106 post-transplant.

Materials and Methods

Cytogenetic and FISH Analysis

Conventional cytogenetic preparations and FISH (fluorescent in situ hybridization) analyses were performed as described previously [5, 6]. To detect the exact region involved in the novel translocation, 12 FISH probes were used: 9p24.1 (RP11-3H3), 9p24.1 (RP11-28A9; BACPAC Resources, Oakland, CA, USA), 1p36.22 (RP11-483P2), 1p36.22 (RP11-1107P2), RP11-1134M20, RP11-483P2, RP11-1107P2 (Empire Genomics, Buffalo, NY, USA), 9q34 (ABL1), 22q11.2 (BCR), 1p36 (p58), 1p36 (CEP108/T7), 1q25, WCP19, telomere 1p, telomere 19p (Abbott Molecular, Abbott Park, IL, USA). FISH chimerism was detected using XX/XY probes (Abbott Molecular). FISH probes, including bacterial artificial chromosomes (BACs), were fluorescently labeled by the manufacturer excluding RP11-3H3 and RP11-28A9, which were fluorescently labeled using the Nick translation kit (Abbott Molecular) following the manufacturer's procedure [5]. DNA isolated from bone marrow cells was subjected to whole-genome sequencing and analyzed by standard pipelines at the Sanger Institute, Hinxton, UK [7].

Confirmation of a *PEX14-JAK2* genomic DNA fusion was performed using a forward primer in *PEX14* exon 8 (5'CCACCAACTGGATCCTGGAGT) and reverse primer in *JAK2* exon 19 (5'AACCCAGGGCACCCTATCCT), on 25 ng of DNA using the Expand Long-Template LT-PCR system 2 (Roche, Burgess Hill, Sussex, UK) at an annealing temperature of 64 °C and an elongation time of 4 min. Sequencing across the breakpoint was performed using primer *PEX14* exon 9 (5'GTTCCTCCATCCCCATCAG), using an Applied Biosystems 3130 analyzer (Foster City, CA, USA).

The presence of *PEX14-JAK2* fusion mRNA was confirmed on random hexamer reverse-transcribed cDNA, using forward primer *PEX14* exon 8 and reverse primer in *JAK2* exon 21 (5' TTTTATGATTACGCCGACCAGCA) using the Expand High Fidelity PCR System, an annealing temperature of 64 °C, and an elongation time of 1 min. The product was sequenced in both directions using the same primers.

Results

A summary of the conventional cytogenetic analysis is shown in Table 1. Initial bone marrow cytogenetic analysis, a year after the diagnosis of PV, showed 50% of evaluated metaphase cells to have the t(1;9)(p36;p24.1) karyotype. Subsequent metaphase FISH analyses using BAC FISH probes (RP11-3H3 and RP11-28A9) revealed that the 3' portion of *JAK2* was translocated to 1p36, while the 5' portion remained on 9p24.1, indicating a *JAK2* structural rearrangement (Fig. 1). To investigate the exact

Fig. 1. The first row shows a partial karyotype of chromosomes 1 and 9. Metaphase FISH was performed using BAC FISH probes. RP11-3H3 (labeled in aqua) normally localized to the 5' portion of *JAK2* on 9p24.1 was translocated to 1p36, while the telomere of chromosome 1p (labeled in green) translocated to the derivative chromosome 9. The second row shows that the BAC FISH probe RP11-483P2 (labeled in aqua) normally localized on chromosome 1p36 was detected on 9p24.1, whereas BAC RP11-1107P2 (labeled in red) remained on 1p36. The chromosomal breakpoint on chromosome 1 was determined to be within band 1p36.22.

breakpoint on chromosome 1, we used a FISH BAC probe, and as shown in Figure 1, the BAC FISH probe RP11-483P2 normally localized on chromosome 1p36 was detected on 9p24.1 (aqua), whereas BAC RP11-1107P2 remained on 1p36. Therefore, the breakpoint on chromosome 1, involved in the *JAK2* translocation, was determined to be within band p36.22 on chromosome 1 [7].

Five months from the initial analysis, 100% of the cells had t(1;9) and 10% had developed a subclone consisting of balanced t(7;17)(q22.1;q25.3) and trisomy 1q in the form of unbalanced der(15)t(1;15)(q12;q26). Following HSCT, host cells were never eradicated (Table 1). A year after the initial cytogenetic analysis, the original abnormal host clone and a subclone were present in 100% of the cells with additional chromosomal abnormalities consistent with complex subclonal evolution.

To characterize the t(1;9) in detail, we performed whole-genome sequencing analysis of patient bone marrow DNA to identify the translocation breakpoints. Focusing on the analysis of *JAK2*, we identified two split reads that mapped to *PEX14* exon 9 and *JAK2* intron 18. *PEX14* maps to 1p36.22, and was thus a strong candidate to be fused to *JAK2*. To confirm a *PEX14-JAK2* fusion, we amplified patient and control DNA using primers located in *PEX14* exon 9 and *JAK2* exon 19. A product was obtained from the t(1;9) case only (not shown), which, upon sequencing, confirmed a break within *PEX14* exon 9 and *JAK2* intron 18 (Fig. 2). Amplification from cDNA also

Fig. 2. Sequence trace of the *PEX14*-*JAK2* amplicon from genomic DNA (above) plus the alignment of genomic sequences of *PEX14*, *PEX14*-*JAK2*, and *JAK2* in the relevant region (below). The two nucleotides from *JAK2* intron 18 that are retained in the mature mRNA are indicated in italics and the cryptic splice donor site in bold.

yielded a specific product from the t(1;9) case but not the controls (Fig. 3), sequencing of which showed a fusion between a truncated *PEX14* exon 9 and *JAK2* exon 19 (Fig. 2). Comparison of the cDNA and genomic sequences indicates that two nucleotides (TA) from *JAK2* intron 18 were retained in the mature mRNA that result in maintenance of the correct reading frame (Fig. 2). The TA dinucleotide is immediately followed by GT, which must have acted as a splice donor site.

Discussion

Subsequent to the 2005 discovery of *JAK2*V617F, knowledge of the genetic underpinnings of MPNs and the role mutations play in diagnosis, prognosis and therapy increased exponentially [8–11]. In stark contrast to the wealth of knowledge about the *JAK2*V617F-positive MPNs, there is a relative dearth of information on how to approach the small subset of patients with MPNs who lack this point mutation but contain *JAK2* translocations.

Translocations at 9p24.1 and resultant gene fusion products have been identified in a wide spectrum of hematologic malignancies of myeloid and lymphoid origin, including acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic eosinophilic lymphoma (CEL), and the *BCR-ABL1*-negative MPNs (Table 2). Additionally, several translocations involving 9p24.1 with subsequent gene fusion products involving *JAK2* have been seen in solid malignancies, such as breast cancer [12] and small cell lung cancer [13].

JAK2 translocations are likely more common in hematologic malignancies than previously recognized. Patnaik et al. [3] screened over 24,000 patient cytogenetic reports and found 5 patients harboring translocations at 9p24 with gene

Fig. 3. Specific amplification of cDNA from the t(1;9) case using primers to *PEX14* exon 9 and *JAK2* exon 19. The sequence of the mRNA junction with the *PEX14* sequence is in plain type, with *JAK2* in bold, and the two intron-derived nucleotides in italics.

fusion products involving *JAK2*. All 5 of the translocations described in this subset of patients had not previously been reported in the literature, but the *JAK2* fusion partners could not be identified. Four of the 5 patients carried diagnoses of *JAK2*V617F-positive MPNs (PMF and PV).

Though the above study found *JAK2* translocations only in patients with *JAK2*V617F-positive MPNs, structural rearrangements, including *JAK2* translocations, have been found frequently in chromosomal analysis of samples from patients with *JAK2*V617F-negative MPNs [14]. The discovery of several of these translocations has

Table 2. *JAK2* translocations and associated gene fusion products in hematologic malignancies

	Translocation	Gene fusion product	Diagnosis	Reference
Myeloid disorders	t(9;12)(p24;p13)	ETV6-JAK2	aCML	28–30
	t(9;22)(p24;q11.2)	BCR-JAK2	CML aCML MPN-U with eosinophilia CML-like MPN MDS	19, 31–34
	t(8;9)(p22;p24)	PCM1-JAK2	MPN aCML Erythroid leukemia with multiple bone tumors CEL PMF MDS	16, 35–37
	t(9;12)(p24;q13)	NF-E2-JAK2	MDS	14
	t(9;21)(p24.2;q21)	RUNX1-JAK2	MDS	14
	t(3;9)(q21;p24)	RPN1-JAK2	PMF	38
	t(1;9) (p36;p24.1)	PEX14-JAK2	PV, transformed to MPN-BP (<i>JAK2V617F</i> -negative)	Current case
Lymphoid disorders	t(8;9)(p22;p24)	PCM1-JAK2	Lymphoblastic T-cell lymphoma	39
	t(9;9)(p24;q22)	BICD2-JAK2	ALL Infant MLL-R ALL	40
	t(9;17)(p24;q21)	JAK2-SPAG9	ALL	41
	t(9;14)(p24;q12)	JAK2-STRN3	High-risk ALL	42
	t(1;9)(q21.3;p24.1)	TPM3-JAK2	T-ALL	22
	t(9;12)(p24;p13)	ETV6-JAK2	T-ALL	28
	t(X;9)(p22.1;p24.1)	OFD1-JAK2	B-ALL	43
	t(5;9)(q14.1;p24.1)	SSBP2-JAK2	Pre-B ALL	44
	t(9;9)(p13;p24)	PAX5-JAK2	Pre-B ALL	45
	t(8;9)(p22;p24)	PCM1-JAK2	Pre-B ALL	16
	t(4;9)(q21.22;p24)	SEC31A-JAK2	Classical Hodgkin's lymphoma	46
	t(8;9)(q13;p24)	Unknown partner with JAK2	Diffuse large B-cell lymphoma	3

aCML, atypical chronic myeloid leukemia; CML, chronic myeloid leukemia; MPN-U, myeloproliferative neoplasm unspecified; MPN, myeloproliferative neoplasm; MDS, myelodysplastic syndrome; CEL, chronic eosinophilic leukemia; PMF, primary myelofibrosis; PV, polycythemia vera; ALL, acute lymphoblastic leukemia; T-ALL, T-cell ALL; Pre-B ALL, precursor B-cell ALL; MLL-R ALL, MLL rearrangements ALL.

shed light on theories of the pathogenesis and unique patterns of the disease. A prime example of this is the identification of t(8;9)(p22;p24), resulting in a *PCM1-JAK2* fusion gene product in a variety of hematologic diseases, including many in the spectrum of MPNs, such as atypi-

cal CML (aCML), CEL, myelodysplastic syndrome/MPN-unclassified (MDS/MPN-U), and myelofibrosis. Identifying the common translocation in cases of these disparate disorders has led to the recognition that patients with t(8;9)(p22;p24) are more likely to be male,

have prominent erythroid dysplasia, and have high rates of peripheral blood and bone marrow eosinophilia [15]. *PCM1-JAK2* was identified in both myeloid and lymphoid neoplasms, leading to the conclusion that malignancies with acquired t(8;9)(p22;p24) result from disorders of the pluripotent hematopoietic stem cell [16]. Increased recognition of the role of *PCM1-JAK2* in hematologic malignancies has led to a relatively new categorization of “myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*” in the 2016 revision to the WHO classification of myeloid neoplasms and acute leukemia [17].

Similarly, both myeloid and lymphoid neoplasms with *ETV6-JAK2* fusions have been identified. Animal modeling using this translocation has led to a proposed pathogenic mechanism involving the rearranged genes, which appears to cause constitutive activation of several STATs [18]. A number of cases have also been noted in which *JAK2* fuses with the *BCR* gene on 9p24, resulting in aCML and unclassified MPNs [19, 20].

Here, we presented a case of a novel translocation t(1;9)(p36;p24.1) involving *JAK2* and peroxisomal biogenesis factor 14 (*PEX14*) found in a patient with *JAK2V617F*-negative PV, which transformed to an aggressive form of MPN-BP. *PEX14* is a membrane protein involved in protein docking on peroxisomes, with a role in peroxisome formation and degradation. It also has a unique function as a transcriptional corepressor and a polypeptide transport modulator. Upregulation of *PEX14* has been demonstrated in tissue from lung, rectal, ovarian, and esophageal carcinomas; however, its precise role in these malignancies remains unclear and information about its role in hematologic malignancies is absent [21]. Interestingly, like many other cases of *JAK2V617F*-negative, *JAK2* translocation-positive MPNs, this patient's disease was notable for prominent bone marrow eosinophilia of undetermined significance. *JAK2* was identified as a fusion gene partner with a gene on chromosome 1 in only 1 other case of a hematologic malignancy – a *TPM3-JAK2* fusion was found in a case of T-cell ALL [22].

Although commonalities between hematologic malignancies with *JAK2* rearrangements have been identified, the prognostic significance and therapeutic implications of the translocations are not fully elucidated. As the disease of our patient progressed to MPN-BP, cytogenetic analysis showed a gain of 1q. We recently reported this to be associated with progression of MPNs to myelofibrosis and AML [23]. In vitro studies utilizing cell lines

containing *JAK2* rearrangements suggest a promising role for JAK inhibitors in halting malignant cell proliferation [22, 24]. Early case reports of ruxolitinib treatment in patients with MPNs containing *JAK2* translocations also show positive outcomes in cytogenetic response and hematologic remission, although the durability of remission is variable and differences in outcomes are not well studied [25–27]. As data accumulates about newly identified *JAK2* translocations, further connections can be made between the specific translocations, disease course, and prognosis. Further information is needed to understand the translocations' oncogenicity and the potential for novel targeted therapies aimed at targeting the specific *JAK2* partners for this minority of MPN patients. In the future, MPNs may be stratified further into distinct entities that take into account specific *JAK2* translocations.

Statement of Ethics

The authors have no ethical disclosures to declare.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

H.L. and B.M. wrote the report. J.T. and D.G. performed cytogenetic and FISH studies. A.V.J. and N.C.P.C. performed molecular studies and analyses. J.M. was involved in clinical care and studies, and V.N. conceived and organized the work, and helped in preparing the report.

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