The t(8;9)(p22;p24) Is a Recurrent Abnormality in Chronic and Acute Leukemia that Fuses PCM1 to JAK2

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Abstract

We have identified a t(8;9)(p21-23;p24-23) in seven male patients (mean age 50, range 32-74) with diverse hematologic malignancies and clinical outcomes: atypical chronic myeloid leukemia/chronic eosinophilic leukemia (5), secondary acute myeloid leukemia (6), and pre-B-cell acute lymphoblastic leukemia (1). Initial fluorescence in situ hybridization studies of one patient indicated that the nonreceptor tyrosine kinase Janus-activated kinase 2 (JAK2) at 9p24 was disrupted. Rapid amplification of cDNA ends-PCR identified the 8p22 partner gene as human autoantigen pericentriolar material (PCM1), a gene encoding a large centrosomal protein with multiple coiled-coil domains. Reverse transcription-PCR and fluorescence in situ hybridization confirmed the fusion in this case and also identified PCM1–JAK2 in the six other t(8;9) patients. The breakpoints were variable in both genes, but in all cases the chimeric mRNA is predicted to encode a protein that retains several of the predicted coiled-coil domains from PCM1 and the entire tyrosine kinase domain of JAK2. Reciprocal JAK2–PCM1 mRNA was not detected in any patient. We conclude that human autoantigen pericentriolar material (PCM1)–JAK2 is a novel, recurrent fusion gene in hematologic malignancies. Patients with PCM1–JAK2 disease are attractive candidates for targeted signal transduction therapy. (Cancer Res 2005; 65(7): 2662-7)

Introduction

The diagnosis of chronic myeloid leukemia (CML) is based on specific clinical and hematologic features in combination with the presence of the Philadelphia-chromosome (Ph) and/or the BCR-ABL fusion. The constitutive tyrosine kinase activity of the BCR-ABL oncoprotein is selectively inhibited by imatinib mesylate, which has recently been shown to induce high rates of complete hematologic and complete cytogenetic responses in the great majority of CML patients (1).

Patients with clinical characteristics of CML who lack the Ph chromosome and/or the BCR-ABL fusion gene are usually referred to as having atypical CML. In many cases, the hematologic features overlap with other recognized subtypes of chronic myeloproliferative disease or myelodysplastic/myeloproliferative disorders, particularly chronic eosinophilic leukemia and chronic myelomonocytic leukemia. The molecular pathogenesis of these BCR-ABL–negative diseases is largely unknown, but analysis of the small proportion of affected individuals who present with acquired reciprocal chromosomal translocations has revealed diverse tyrosine kinase fusion genes, most commonly involving the receptors FGFR1, PDGFRα, or PDGFRB (2–11). These fusions are believed to deregulate hematopoiesis in a manner analogous to BCR-ABL and, consequently, it is anticipated that affected patients may be amenable to treatment by targeted signal transduction therapy. Indeed, PDGFRα and PDGFRB are sensitive to imatinib and patients with fusions involving the genes encoding these receptors usually exhibit dramatic responses to imatinib treatment (11, 12).

We report here five patients with CML-like disorders and two patients with acute leukemia in association with an acquired t(8;9)(p21-23;p24-23). We show that the translocation fuses the human autoantigen pericentriolar material (PCM1) gene to the Janus-activated kinase 2 (JAK2) gene in all seven cases, further substantiating the hypothesis that deregulated tyrosine kinases play a major role in the pathogenesis of atypical CML and related myeloproliferative disorders.

Materials and Methods

Case Reports

Case 1. A 54-year-old male presented with splenomegaly and marked pancytopenia. The bone marrow showed extensive myelofibrosis with numerous islands of blast cells. Cytogenetic analysis revealed a t(8;9)(p23;p24). A diagnosis of blastic transformation of myelofibrosis was made. The patient achieved complete hematologic remission after several courses of intensive chemotherapy. One year after diagnosis, INF-α was commenced and continued for 6 years without achievement of a cytogenic response. The patient remains off treatment in complete remission.

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hematologic remission but with a slightly enlarged spleen 15 years after diagnosis.

Case 2. A 47-year-old male was diagnosed with chronic eosinophilic leukemia due to splenomegaly, marked eosinophilia, and myeloid precursors in the peripheral blood. Bone marrow histology revealed hyperplasia, myelofibrosis plus marked eosinophilia, and cytogenetic analysis showed a translocation t(8;9)(p22;p23). A progressive debilitating cerebellar syndrome developed shortly after diagnosis owing to oligovipontocerebellar degeneration. The patient achieved a major cytogenetic response on treatment with IFN. Unfortunately, the cerebellar symptoms worsened and he ultimately developed pneumonia. He died of respiratory failure 7.5 years after diagnosis of chronic eosinophilic leukemia.

Case 3. A 74-year-old male presented with mild eosinophilia. The trephine biopsy showed hyperplasia caused by eosinophil precursors and areas of myelofibrosis. A t(8;9)(p22;p24) was identified by cytogenetic analysis. The patient was followed for 4 years without any treatment. Six years after diagnosis, secondary acute myeloid leukaemia was diagnosed. Cytogenetic analysis showed duplication of both t(8;9) derivative chromosomes and trisomy 4. The patient died 1 month after diagnosis of acute myeloid leukaemia.

Case 4. A 50-year-old male was referred with anemia and mild leukocytosis. A common pre-B acute lymphoblastic leukemia was diagnosed by immunophenotyping. Cytogenetic analysis revealed a t(8;9)(p21;p24). On day 32 after start of induction chemotherapy, the patient developed a bilateral pneumonia and died shortly afterward from multorgan failure.

Case 5. A 42-year-old male presented with mild leukocytosis and eosinophilia. Bone marrow features resembled CML, but cytogenetic analysis revealed a t(8;9)(p21;p24). An allogeneic stem cell transplantation from a matched unrelated donor was done 1 year after diagnosis. The patient is currently well in complete remission with only mild graft-versus-host disease of the skin.

Case 6. A 72-year-old male presented with massive leukocytosis, anemia, and thrombocytopenia. The differential was consistent with CML, but cytogenetics revealed a t(8;9)(p22;p23) plus an ins(1;1)(p34;p36p34). The patient rapidly developed renal failure and died 96 hours after admission.

Case 7. A 32-year-old male was diagnosed with atypical CML in association with a t(8;9)(p21;p24). The disease transformed to acute lymphoblastic leukemia 7 months after diagnosis and the patient received an allogeneic stem cell transplantation from a matched unrelated donor 2 months later. The patient is alive and well 53 months after transplantation with only mild graft-versus-host disease of the skin.

Fluorescence In situ Hybridization

Bacterial artificial chromosome clones for the 5’ and 3’ regions of JAK2 (RP11-3H3 and RP11-28A9) and bacterial artificial chromosome clones for the 5’ and 3’ regions of PCM1 (RP11-9F3 and RP11-3K23) were identified from http://wwwensembl.org and obtained from the Sanger Institute (Cambridge, United Kingdom). Dual color fluorescence in situ hybridization (FISH) was done according to standard procedures.

5’-Rapid Amplification of cDNA Ends-PCR

5’-Rapid amplification of cDNA ends-PCR was done according to the manufacturer’s instructions (Roche Diagnostics, Mannheim, Germany). Briefly, 1 μg RNA extracted from peripheral blood leukocytes using the RNeasy system (Qiagen, Hilden, Germany) was reverse transcribed using primer JAK14: 5’-CGTCTCCACACACATCTCC-3’. Nested PCR was done with primer JAK13: 5’-CATGCTGGACGCTAGTCTCTC-3’ in the first step and primer JAK12: 5’-GAGGTTGGACGACTACAAACC-5’ in the second step in conjunction with rapid amplification of cDNA anchor primers supplied by the manufacturer. Products were cloned using the TOPO cloning kit (Invitrogen, Leek, The Netherlands) and sequenced.

Reverse Transcription-PCR

RNA was extracted and reverse transcribed with random hexamers using standard techniques. Primers used to detect PCM1-JAK2 cDNA were PCM25/1+: 5’-CATGTTGAAGTGGACATCTC-3’, PCM25/2+: 5’-CTCCTCCATGAGCCACGCTC-3’, PCM28/1+: 5’-GAGGTTGATAGACTGAGGTC-3’, PCM28/2+: 5’-TGCTGTGGACGTAGTCTCAGG-3’, PCM35/1+: 5’-AGTCTGGCCATAGAGTGC-3’ or PCM35/2+: 5’-GGACCTCTAGTGGCAGTATGC-3’ in combination with JAK2/1: 5’-CTCGTGAGCTCATCTATAGG, JAK2/2: 5’-GGTTGGTTGATACGACATCTC, JAK9/1: 5’-GGTTGGTGGGCAACCATATTAG-3’ or JAK9/2: 5’-GAGGCGACAGTTTCATCCTGTA-3’. Primers used to search for reciprocal JAK2-PCM1 fusion transcripts are not shown but are available on request. All amplification reactions were done for 32 cycles with an annealing temperature of 60°C.

Results

Identification of a novel recurrent cytogenetic abnormality.

We identified seven t(8;9) patients for whom the breakpoints assigned by cytogenetics varied from 8p21-23 and 9p23-24, although in some cases the precise band of breakage was reported as uncertain. To our knowledge, this translocation has not been described before as a recurrent abnormality, although one other patient with atypical CML has been described (13) and we have previously reported case 2 as being negative for rearrangement of FGFR1 at 8p11-12 (14). Five patients presented with a CML-like disease (atypical CML, chronic eosinophilic leukemia, or related disorder), one with acute myeloid leukemia secondary to myelofibrosis, and one with pre-B acute lymphoblastic leukemia. The characteristics of the seven patients are summarized in Table 1.

The t(8;9) disrupts JAK2. Analysis of other acquired translocations in CML-like diseases has revealed the presence of diverse fusion tyrosine kinases. We, therefore, focused our analysis on this class of gene, considering as possible candidates PTK2B at 8p21, BLK at 8p23, and JAK2 at 9p24. FISH analysis with bacterial artificial chromosome clones closely flanking JAK2 showed a fused signal, as expected for normal chromosome 9, plus a split signal in the majority of cells for three of five cases who had fixed cells available for analysis (cases 3, 4, and 6). This strongly suggested that the t(8;9) disrupted JAK2 at least in these individuals. The remaining two patients (cases 1 and 5) both showed a fusion signal on the normal chromosome 9, a 3’ JAK2 signal on the der(9) but no reciprocal 5’ JAK2 signal on the der(8), suggesting a translocation within or close to JAK2 accompanied by deletion of upstream sequence. Representative results from two patients are shown in Fig. 1.

Identification of the partner gene. All fusion tyrosine kinases reported to date share a common structure, with a 5’ partner gene fused to a 3’ kinase. To identify the partner gene, we, therefore, did 5’-Rapid amplification of cDNA ends-PCR on patient RNA using JAK2 primers selected according to the breakpoints identified elsewhere in cases harboring the ETV6-JAK2 fusion. The initial analysis was done on case 5, and the resulting rapid amplification of cDNA products were found to consist of sequences derived from a known 8p22 gene, human autoantigen pericentriolar material 1 (PCMI; National Center for Biotechnology Information reference sequence NM_006197), fused to JAK2.

Detection of PCM1-JAK2 by reverse transcription-PCR.

Chimeric PCM1-JAK2 fusion transcripts were confirmed by reverse transcription-PCR (RT-PCR) in case 5 and, in addition, the same fusion was also amplified from five of five other patients (cases 2, 3, 4, 6, and 7) for whom cDNA was available for analysis (Fig. 2). Four different types of in-frame fusion

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transcripts were identified (Fig. 3). Three were regular exon to exon, in-frame fusions between PCM1 exon 26 and JAK2 exon 7 (case 3), PCM1 exon 36 and JAK2 exon 7 (case 2), or PCM1 exon 36 and JAK2 exon 9 (cases 5 and 6). An unusual in-frame fusion between PCM1 exon 36 fused to a short 12 bp sequence derived from PCM1 intron 36 and a truncated JAK2 exon 9 was found in case 4. Transcripts with a similar structure have been reported for BCR-PDGFRα and FIP1L1-PDGFRα (8, 11) and arise from one of the translocation breakpoints falling within an exon rather than an intron. No material was available from the time of diagnosis for case 7; however, residual PCM1-JAK2 fusion transcripts could be amplified by nested RT-PCR after the patient had undergone allogeneic hemopoietic stem cell transplantation. Two transcripts were detected with fusions between PCM1 exon 28 or PCM1 exon 29, respectively, and JAK2 exon 1. Neither of these fusions are in frame and we suggest that the genuine in-frame fusion transcript could not be detected because treatment had reduced it to below the detection limit of RT-PCR. Minor bands were also amplified from cases 2 to 6 that resulted from various out-of-frame PCM1-JAK2 fusions and reciprocal JAK2-PCM1 transcripts were not detected in any patient using several different primer combinations.

**Consistent PCM1-JAK2 fusion as a consequence of the t(8;9).**
To further confirm the fusion of PCM1 to JAK2, we did additional FISH tests. Analysis of patients with differentially labeled probes flanking PCM1 indicated that this gene was disrupted in all five cases for whom FISH had already identified a split within JAK2. For three patients (cases 3, 5, and 6), both 5’ and 3’ PCM1 signals were seen on the der(9) and der(8), respectively. For cases 1 and 4, the 3’ PCM1 signal was deleted from the der(8). Using probes 5’ to PCM1 and 3’ to JAK2 indicated the expected fusion signal on the der(9) in all cases. Representative results are shown in Fig. 1.

Overall, FISH and/or RT-PCR identified PCM1-JAK2 in all seven t(8;9) patients (RT-PCR and FISH, n = 4; RT-PCR only, n = 2; FISH only, n = 1). The finding of gross deletions at the reciprocal breakpoint in three of five patients partly explains the absence of detectable JAK2-PCM1 transcripts.

**The PCM1-JAK2 fusion protein.** The PCM1-JAK2 fusion gene is predicted to encode a protein of 257 to 310 kDa, depending on the positions of the breakpoints that contain the coding sequence for up to 96% of PCM1 and up to 61% of JAK2. PCM1 is predicted to contain multiple high probability coiled-coil domains (Coils v2.1; http://www.ch.embnet.org/software/COILS_form.html; ref. 15), all of which are retained in the fusion. The predicted structure of PCM1-JAK2 is shown on Fig. 4.

**Discussion**
We report here the identification of a novel fusion between PCM1 and JAK2 as a consequence of a recurrent t(8;9) in seven patients who presented with clinical and hematologic features resembling chronic phase CML, chronic eosinophilic leukemia, acute leukemia similar to blast crisis of CML, or BCR-ABL–positive acute lymphoblastic leukemia. Although cytogenetic analysis assigned the breakpoints as varying between 8p21-23 and 9p23-24, the precise translocation based on gene assignment is t(8;9)(p22;p24). It is remarkable that this abnormality has not been identified previously as a recurrent event. This may be due partly to the apparent variable positions of the breakpoints and also to the diversity of clinical features associated with this translocation.

The involvement of PCM1-JAK2 in both myeloid and lymphoid malignancy shows that there is no clear lineage specificity to this fusion gene and is consistent with the idea that PCM1-JAK2

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**Table 1. Patients’ characteristics and summary of results**

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<th>Case no.</th>
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<td>t(8;9)(p22;p24)</td>
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<tr>
<td>FISH</td>
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<td>PCM1 exon 36-JAK2 exon 7</td>
<td>PCM1 exon 26-JAK2 exon 7</td>
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<tr>
<td>RT-PCR</td>
<td>NA</td>
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<td></td>
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<tr>
<td>Clinical course</td>
<td>Secondary acute leukemia, extensive myelofibrosis</td>
<td>IFN initiated 16 mo after diagnosis with achievement of complete remission</td>
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<td></td>
<td>Death due to neurodegenerative disease 7.5 y after diagnosis</td>
<td>Secondary acute myeloid leukemia 60 mo after diagnosis</td>
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<tr>
<td></td>
<td></td>
<td>Maintenance with IFN for 6 y</td>
<td>Death 61 mo after diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alive 15 y after diagnosis</td>
<td></td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>NA</td>
<td>++</td>
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(Continued on the following page)
disease, like CML, is a stem cell disorder. Of note, the marrow displayed variable degrees of myelofibrosis when reported with one patient diagnosed as transformation of myelofibrosis due to the extensive presence of fibers in the trephine biopsy. Eosinophilia was prominent in some, but not all, patients. Similar to typical CML, the clinical course was highly variable with survival ranging from a few days to >15 years. A significant response, but not complete cytogenetic remission, was seen in one patient with IFN; however, allogeneic stem cell transplantation may be the only curative treatment currently available.

PCM1-JAK2 is the third fusion gene that involves JAK2, the other two being ETV6/TEL-JAK2, which arises as a consequence of a t(9;12) or variant translocations in patients with a chronic myeloproliferative disease or acute lymphoblastic leukemia (16, 17), and BCR-JAK2 in a single individual with atypical CML (18). Remarkably, all seven PCM1-JAK2 cases reported here were male. The three cases with ETV6-JAK2 in the literature were also males, although the BCR-JAK2 case was female. Nevertheless, the male bias is significant (P = 0.00049, n = 11), assuming a male-to-female ratio of 1:1 in the healthy population and random sampling of patients. A similar significant male bias is seen for patients with PDGFA and PDGFRB fusion genes (9, 11, 19–22) and, currently, the reasons for this remain obscure. No sex bias is seen for patients with FGFR1 fusions (7), although a small but significant male excess is seen in BCR-ABL–positive CML (23). Significant male excesses have also been described in subsets of other hematologic malignancies (e.g., young patients with non-Hodgkin's lymphoma or Hodgkin's disease and middle aged patients with chronic lymphocytic leukemia or lymphocytic lymphoma; ref. 24).

PCM1 was originally identified as an autoantigen in a patient with systemic sclerosis and was first characterized as a ubiquitously expressed 228 kDa protein that exhibits a distinct cell cycle–dependent association with the centrosome complex (25). The protein is predicted to contain multiple coiled-coil motifs and is believed to be involved in recruitment of specific proteins to the centrosome (26). Interestingly, the gene encoding one of these recruited proteins, NIN, has recently been shown to fuse to PDGFRB in an imatinib-responsive chronic myeloproliferative disease (27) and two further centrosomal genes, FOP and CEP1, are fused to FGFR1 in the 8p11 myeloproliferative syndrome with the t(6;8) and t(8;9), respectively (5, 6). PCM1 also fuses to RET in papillary thyroid carcinoma (28). It remains to be established whether centrosomal proteins are recurrent partners for tyrosine kinases in malignancy simply because they are widely expressed and contain self-association motifs, or whether the fusions also result in a pathologic alteration of centrosome function.

The four members of the nonreceptor Janus tyrosine kinase family, JAK1, JAK2, JAK3, and TYK2, normally regulate tyrosine phosphorylation of a number of essential signaling pathways via coupling a variety of cytokine, IFN, and other growth factor receptors to downstream intracellular signaling molecules, particularly signal transducers and activators of transcription proteins. Constitutive activation of different JAKs and signal transducers and activators of transcriptions are believed to mediate neoplastic transformation and promote abnormal cell proliferation in various malignancies (29), and JAK2 may be specifically involved in abnormal cell growth induced by BCR-ABL in CML (30). As has been found for other tyrosine kinase fusion proteins, it is very likely that one or more of the coiled-coil motifs from PCM1 result in dimerization or oligomerization of the PCM1-JAK2 chimera, with consequent constitutive activation of the JAK2 kinase domain. By analogy with BCR-ABL, it is likely that PCM1-JAK2 is the sole abnormality in the chronic phase of

Table 1. Patients’ characteristics and summary of results (Cont’d)

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<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
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<tr>
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<td>t(8;9)(p21;p24)</td>
<td>t(8;9)(p22;p23)</td>
<td>t(8;9)(p21;p24)</td>
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<tr>
<td>+</td>
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<td>NA</td>
</tr>
<tr>
<td>PCM1 exon 36-ins-ΔJAK2 exon 9</td>
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<td>PCM1 exon 36-JAK2 exon 9</td>
<td>PCM1 exon 28-JAK2 exon 1 (no ORF)*</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>IFN for 10 mo</td>
<td>Death within 96 h after admission</td>
<td>PCMI exon 29-JAK2 exon 1 (no ORF)*</td>
</tr>
<tr>
<td>Death 5 wk after start of chemotherapy due to pneumonia and multiorgan failure</td>
<td>Allogeneic hematopoietic stem cell transplantation from matched unrelated donor 10 mo after diagnosis</td>
<td>Alive 13 mo after transplant</td>
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</tr>
<tr>
<td>−</td>
<td>+</td>
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<tr>
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Abbreviations: NA, not available; AL, acute leukemia; CEL, chronic eosinophilic leukemia; ALL, acute lymphoblastic leukemia; aCML, atypical CML; −, normal; +, elevated; ++, strongly elevated; ++++, extensively elevated.

*Transcripts were amplified by nested PCR after allogeneic stem cell transplantation.
the disease, but additional mutations may be required for transformation to acute leukemia. Although the activity of JAK2 is not inhibited by imatinib, it is abrogated by the tyrphostin AG-490, opening up the possibility of targeted signal transduction therapy for patients with JAK2 fusion genes (31).

In summary, we have identified a novel PCM1-JAK2 fusion in seven patients with diverse hematologic malignancies. This finding further supports a prominent role for deregulated tyrosine kinases in the pathogenesis of BCR-ABL–negative chronic myeloproliferative diseases and provides the basis for more accurate diagnosis, a mechanism to monitor response to treatment and, potentially, targeted therapy.

**Figure 1.** FISH analysis for cases 1 and 3. Both cases show a fusion signal with 5' PCM1 and 3' JAK2 probes corresponding to PCM1-JAK2 as indicated by the arrows on the bottom of the two panels. Case 3 shows separation of one set of JAK2 and PCM1 probes, confirming disruption of these genes (top and center, right), with the overlapping/fused signals corresponding to the normal chromosomes 9 and 8, respectively. Case 1 shows loss of both derivative (5' JAK2 and 3' PCM1) signals, indicating a deletion on the derived chromosome 8 (top and center, left).

**Figure 2.** RT-PCR to confirm the presence of PCM1-JAK2 fusion transcripts in six patients (lanes 1-6). Cases 5, 6, 4, and 2 were amplified with primers derived from PCM1 exon 35 and JAK2 exon 9 (lanes 1-4). Case 3 was amplified with primers derived from PCM1 exon 25 and JAK2 exon 9 (lane 5). Case 7 was amplified by nested PCR with primers derived from PCM1 exon 28 and JAK2 exon 2 (lane 6). Additional lanes represent negative controls with cDNA from patients with CML and healthy individuals.

**Figure 3.** The four different in-frame PCM1-JAK2 fusion junctions identified in this study. PCM1 sequences are in plain type, JAK2 sequences in bold, the 12 bp intron-derived insert seen in case 4 is shown in lower case with the corresponding amino acids underlined.
References


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Figure 4. Diagramatic representation of normal JAK2, normal PCMI, and the PCMI-JAK2 fusion protein.
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