

NIN, a Gene Encoding a CEP110-Like Centrosomal Protein, Is Fused to *PDGFRB* in a Patient with a t(5;14)(q33;q24) and an Imatinib-Responsive Myeloproliferative Disorder¹

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Abstract

We describe a new *PDGFRB* fusion associated with a t(5;14)(q33;q24) in a patient with a longstanding chronic myeloproliferative disorder with eosinophilia. After confirmation of *PDGFRB* involvement and definition of the chromosome 14 breakpoint by fluorescence *in situ* hybridization, candidate partner genes were selected on the basis of the presence of predicted oligomerization domains believed to be an essential feature of tyrosine kinase fusion proteins. We demonstrate that the t(5;14) fuses *PDGFRB* to *NIN*, a gene encoding a centrosomal protein with CEP110-like function. After treatment with imatinib, the patient achieved hematological and cytogenetical remission, but *NIN-PDGFRB* mRNA remained detectable by reverse transcription-PCR.

Introduction

BCR-ABL-negative chronic myeloid leukemia is a term used to encompass a heterogeneous group of relatively uncommon diseases that includes atypical chronic myeloid leukemia (CML), chronic eosinophilic leukemia (CEL), and overlaps with at least a subset of patients with chronic myelomonocytic leukemia. Within the WHO classification, these patients either fall into the myelodysplastic/myeloproliferative disease or chronic myeloproliferative disorders groups, depending on whether or not they show dysplastic features (1). In general, unlike CML with the *BCR-ABL* fusion, the molecular events that give rise to these diseases is poorly understood, but reciprocal chromosomal translocations that disrupt genes encoding receptor tyrosine kinases, notably *PDGFRB* at 5q31-33 and *FGFR1* at 8p11, have been found in some patients. As a consequence of these translocations, constitutively active fusion proteins that are functionally and structurally analogous to *BCR-ABL* are produced (2). Clinically, *FGFR1* rearrangements are associated with the 8p11 myeloproliferative syndrome/stem cell leukemia-lymphoma syndrome (2) and the clinical phenotype associated with *PDGFRB* rearrangements has also been suggested as a discrete disease entity (3). These patients present with a CML/chronic myelomonocytic leukemia-like disease, usually with prominent eosinophilia an often with monocytosis and/or splenomegaly. Only a few progress to acute myeloid leukemia and the latency is highly variable. The extremely male bias in affected patients remains a striking and unexplained feature and finally it has been shown that *PDGFRB*-positive patients respond well to treatment with imatinib

mesylate (4–7) although this drug is inactive against *FGFR1* fusions (8). Consequently, identification of patients with *PDGFRB* rearrangements is very important for their clinical management. Rearrangement of *PDGFRB* was first described in patients with the t(5;12)(q31;p12), leading to the formation of the *ETV6-PDGFRB* fusion (9). Subsequently, *PDGFRB* has been found fused to *CEV14/TRIP11* by the t(5;14)(q31;p12) (Ref. 10); *HIP1* by the t(5;7)(q33;q11.2) (Ref. 11); *H4/D10S170* by the t(5;10)(q33;q11-q21) (Refs. 12, 13); *Rabaptin/RABEP1* by the t(5;17)(q33;p13) (Ref. 14), and *Myomegalin/PDE4DIP* by the t(1;5)(q23;q33) (Ref. 7). Here, we describe a new *PDGFRB* rearrangement in a patient with a t(5;14)(q33;q24) and an imatinib-responsive CML-like myeloproliferative disorder. We show that this reciprocal translocation fuses *PDGFRB* to *NIN*, a gene encoding a centrosomal protein with CEP110-like function.

Materials and Methods

Patient Clinical Data. A 35-year-old male was admitted to hospital in September 1989 with severe pain and swelling in the right ankle. No fever and no systemic symptoms were observed. He related a similar event 20 years before that responded to nonsteroidal anti-inflammatory drugs and analgesia. Normal color of skin and mucosae, functional incapacity of the right leg, and no adenopathies were observed, but spleen enlargement was found by ultrasonography and computed tomography scan. Blood count showed 155 g/liter hemoglobin and a WBC count of 52×10^9 /liter with 37% segmented neutrophils, 28% band neutrophils, 5% metamyelocytes, 6% myelocytes, 13% eosinophils, 1% basophils, 7% lymphocytes, and 3% monocytes. The platelet count was 280×10^9 /liter and neutrophil alkaline phosphatase activity was 2. Bone marrow aspirate showed an increase in myelopoiesis and a prominent eosinophilia, and the karyotypic analysis showed a t(5;14)(q35;q24) in 100% of the metaphases analyzed. On the basis of these data, a diagnosis of atypical CML in chronic phase was made. Treatment with α IFN (3 MU/day) was prescribed, and major hematological response was achieved. In 1995 a new painful episode of arthritis appeared that was interpreted as psoriatic arthritis because of the appearance of suggestive skin lesions. Karyotypic analysis showed persistence of t(5;14)(q35;q24) mitoses. Eosinophilia persisted, but no splenomegaly was observed. In March 1996, hematological remission was achieved again after treatment with α IFN (5 MU/day), psoriatic lesions were not observed, and α IFN administration was subsequently ceased. In 1997, moderate skin lesions were observed again with the WBC count progressively increasing, with eosinophilia, basophilia, and mild splenomegaly. The patient refused α IFN and was subsequently treated with hydroxyurea (1 g/day), resulting in good hematological but not cytogenetical control. Reverse transcription (RT)-PCR for *BCR-ABL* was negative (15). In May 2002, due to the detection of *PDGFRB* involvement in the chromosomal rearrangement (16), treatment with imatinib mesylate was instigated. The initial dose of 400 mg/day was not well tolerated, and the patient decided to stop. In February 2003, imatinib (at 200 mg/day) was given again, resulting in hematological and cytogenetical remission but not complete molecular remission by RT-PCR (see below). On the basis of these data, the dose of imatinib was raised to 400 mg/day in November 2003.

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FISH Analysis. Whole chromosome painting was performed using the STAR*FISH human whole chromosome specific probes (Cambio, Cambridge, United Kingdom), with probes for chromosome 5 and 14 labeled with Cy3 and FITC, respectively. FISH analysis on bone marrow metaphases to narrow the breakpoint on 14q24 were performed with bacterial artificial chromosomes from the BACPAC Resource Center⁴ at Children's Hospital Oakland Research Institute (Oakland, CA) or from the Sanger Institute Mapping Core Group⁵ at The Wellcome Trust Sanger Institute (Hinxton, United Kingdom). *NIN* gene on chromosome 14 was studied with bacterial artificial chromosomes RPCI-11 286O18 (centromeric to *NIN*) and RPCI 248J18 (which covers almost the whole gene). *NIN* clone positions were based on data provided by the University of California–Santa Cruz version hg16 (July 2003) available at the University of California–Santa Cruz Genome Browser.⁶

Southern Analysis of PDGFRB. Ten μ g of patient DNA and a control DNA without 5q31-q33 rearrangement were digested with *HindIII*, *BamHI*, *EcoRI*, and *BglIII*, blotted using standard conditions and hybridized with an 813-bp α^{32} P-dCTP-labeled *PDGFRB* intron 10 probe obtained by amplification by PCR with primers PD3-C and PD3-D (Table 1) from normal human genomic DNA.

PCR-Based Methods. 5'-Rapid amplification of cDNA Ends was performed with the GeneRacer kit (Invitrogen-Life Technologies, Inc., Paisley, United Kingdom) according to the manufacturer's instructions, using reverse primers located in the *PDGFRB* exons 10, 11, 12, and 14 and total RNA extracted using the RNeasy Mini kit (Qiagen, Hilden, Germany). *Vectorette* libraries were generated with Universal *Vectorette* System (Sigma-Genosys, The Woodlands, TX) and checked by PCR with the same primers. PCR and RT-PCR were performed according to standard procedures and primers are listed on Table 1. RT-PCR reactions to check the putative *NIN-PDGFRB* translocation were carried out with Immolase DNA polymerase heat activated (Biolone; London, United Kingdom) using NIN-1 to NIN-6 as forward primers and PDGFRB-1 and PDGFRB-2 as reverse primers in separate and multiple combinations. To amplify the genomic breakpoint, long PCR with JumpStart REDAccuTaq LA DNA polymerase (Sigma-Aldrich Co, St. Louis, MO) from genomic DNA was performed according to manufacturer's instructions.

DNA Cloning and Sequencing. Fresh PCR products were cloned using the TOPO TA Cloning kit for Sequencing (Invitrogen-Life Technologies, Inc.). Colonies with recombinant plasmids containing PCR products were screened by boiling-PCR insert amplification. Positive recombinant plasmids were cultured again and plasmid DNA was extracted with QIAprep Spin Miniprep kit (Qiagen), checked again by *EcoRI* digestion and sequenced with ABI PRISM D-Rhodamine Terminator Cycle Sequencing kit (Applied Biosystems, Foster City, CA) in an ABI PRISM 377 DNA Sequencer (Applied Biosystems, Foster City, CA).

Computational Analysis. Search for candidate genes in the 14q21.1-q32 chromosomal region was done using *Ensembl* as data retrieval tool from data held in the *Ensembl* database Human release 11.31.1 from March 2003 (built around the National Center for Biotechnology Information 31 assembly). Protein sequences were then analyzed using the pepcoil program from the EMBOSS Package.⁷ Pepcoil predicts coiled-coil regions by calculating the probability of a coiled-coil structure for windows of 28 residues through a protein sequence using the method of Lupas *et al.* (17).

Results

Rearrangement of PDGFRB. We have previously used two-color FISH analysis to show that the t(5;14) targets *PDGFRB* (16). Using Southern blot hybridization, we identified rearranged bands with two restriction enzymes (Fig. 1), thus confirming rearrangement of *PDGFRB* and furthermore that the breakpoint must lie in the vicinity of intron 10, as found for all other fusions involving this gene. However, multiple attempts to identify the putative *PDGFRB* 5'-partner gene using 5'-rapid amplification of cDNA ends PCR and screening of *vectorette*-based libraries were unsuccessful.

Table 1 Oligonucleotide primer sequences used in PCR assays

Primer	Sequence (5' → 3')	Gene	Position ^a
NIN-1	TACCAAGAACAGCATTACCAGGCG	<i>NIN</i>	1247–1271
NIN-2	GCGGCAGTGCAGGGTACTACAAGAC	<i>NIN</i>	1763–1787
NIN-3	CGCCTGGACAGAAGAGAAGGTGAGAG	<i>NIN</i>	2384–2409
NIN-4	GGAGGAAGAGCTGAAGGCAATGAT	<i>NIN</i>	4601–4624
NIN-5	GTCCCGATCTCTGACTTCCAGCA	<i>NIN</i>	5215–5239
NIN-6	TGCTTTGGCAAGAGAATGAGAGGCT	<i>NIN</i>	5692–5716
NIN-7	TCCTTACCATTGCGTCTGCCTTAGT	<i>NIN</i>	6243–6267
NIN-8	GTCATGGAGGAACGAATGATAGAAG	<i>NIN</i>	6345–6370
PD3-C	AGGTGGACAGGACTCCCTA	<i>PDGFRB</i>	
PD3-D	TGGAGGCAGAGATGAGAGCA	<i>PDGFRB</i>	
PDGFRB-1	CACAGACTCAATCACCTTCCATCG	<i>PDGFRB</i>	2049–2071
PDGFRB-2	GATATAGATGGTCCCTTTGGTG	<i>PDGFRB</i>	2369–2393
PDGFRB-2b	ACGTACTGGGAGGAGGAGCAGGAGT	<i>PDGFRB</i>	1797–1821

^a Nucleotide positions are referred to GenBank accession numbers NM_020921 (*NIN*) and NM_002609 (*PDGFRB*).

Identification of Candidate Partner Genes on Chromosome 14.

To narrow down the position of the chromosome 14 breakpoint we performed FISH analysis on patient metaphases. We found that the breakpoint was located between bacterial artificial chromosomes RPCI-11 596C23 at 14q21.3 and RPCI-11 368A1 at 14q22.1, an interval of ~1 Mb that contains 13 *RefSeq* genes. Additional attempts to refine the chromosome 14 breakpoint by FISH were unsuccessful. *PDGFRB* translocation partner genes encode proteins with oligomerization domains (most of them coiled-coil domains), an essential feature required for the observed constitutive tyrosine kinase activity of the fusion proteins (2). We therefore tested each gene in the interval for their potential to encode proteins with coiled-coil domains, an analysis that resulted in three candidates for involvement in the t(5;14): *SDCCAG1*; *SAVI* (SAIVador homologue 1 *Drosophila*); and *NIN*. *SDCCAG1*, the gene for a Serologically Defined Colon Cancer Antigen 1 codes for a putative nuclear protein with three coiled-coil domains. *SAVI* encodes a protein which contains two WW domains and a coiled-coil region. Ninein, the product of the *NIN* gene, is a centrosomal protein that is predicted to consist of coiled-coils throughout most of its sequence. Its structure resembles that of another centrosomal protein, CEP110, a known fusion partner of *FGFR1* in 8p11 myeloproliferative syndrome (18). For this reason, we considered *NIN* as the most likely fusion partner in the t(5;14).

Identification of NIN-PDGFRB. To determine whether *NIN* was fused to *PDGFRB*, we performed multiple PCR analyses on patient and control cDNAs with forward primers located in several *NIN* exons and reverse primers located in *PDGFRB* exons 12 and 14. Positive results were obtained with forward primers located toward the 3'-end of *NIN*, sequencing of which showed an in-frame fusion between *NIN* exon 28 and *PDGFRB* exon 12 (Fig. 2A1). The breakpoint was confirmed by RT-PCR with different primer combinations (data not shown) and also by amplifying the genomic breakpoint (Fig. 2A2). The breakpoint position is consistent with the rearranged bands observed by Southern analysis (Fig. 1). RT-PCR with primers PDGFRB-2b and NIN-7 showed very weak amplification of the predicted reciprocal *PDGFRB-NIN* fusion, the identity of which was confirmed by sequencing (Fig. 2A.3).

The fusion gene is predicted to encode a *NIN-PDGFRB* protein of 300 kDa (2595 amino acids) retaining most of *NIN* protein (2047 of the wild-type 2116 amino acids) and most of the intracellular domain of *PDGFRB* (548 amino acids), including the entire tyrosine kinase domain (Fig. 2B). One unique aspect of the fusion is that the mRNA junction involves *PDGFRB* exon 12, whereas all other reported *PDGFRB* fusion involve exon 11. Consequently, *NIN-PDGFRB* lacks the *PDGFRB* transmembrane domain. From ninein, the fusion would retain the potential GTP-binding site, a large coiled-coil domain, four leucine-zipper domains, and a glycogen synthase kinase-3 β binding

⁴ Internet address: <http://www.chori.org/bacpac/>.

⁵ Internet address: <http://www.sanger.ac.uk/Teams/CloneRes>.

⁶ Internet address: <http://genome.ucsc.edu>.

⁷ Internet address: <http://www.hgmp.mrc.ac.uk/Software/EMBOSS/>.

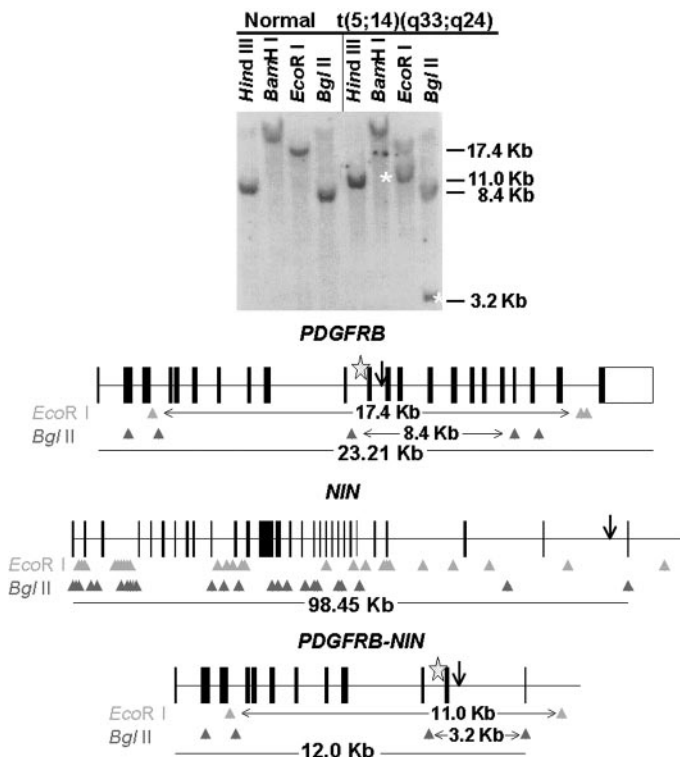


Fig. 1. Southern blot analysis. Southern blot of digested genomic DNA from bone marrow of the patient, together with digested control genomic DNA, probed with an 813-bp fragment from *PDGFRB* intron 10 (*). ■ indicates exons. Clearly rearranged fragments are seen in *EcoRI* and *BglII* digests and are indicated with white asterisks on the blot. A cartoon is shown below that explains the fragments detected and the restriction sites indicate as ▼ (the *EcoRI* 9.5 kb rearranged *PDGFRB-NIN* fragment versus the 17.4 Kb normal *PDGFRB* fragment, and the *BglII* 3.2 kb rearranged *PDGFRB-NIN* fragment versus the 7.5 Kb normal *PDGFRB* fragment).

site (19). The large size of the *NIN* portion retained in the fusion explains the failure of 5'-rapid amplification of cDNA ends because the methodology we used was based on the selection of mature and complete capped mRNAs.

Response to Imatinib Treatment. Once the partner gene was identified, it was possible to monitor the molecular response to imatinib mesylate using an RT-PCR assay with primers *NIN*-8 and *PDGFRB*-2. Molecular detection of the fusion transcript was possible in every available sample before imatinib treatment and also in May 2002, when treatment with imatinib mesylate was started and karyotype analysis showed 91% of metaphases with the translocation. As described above, imatinib treatment was stopped but restarted in February 2003. From April 2003, the patient was found to be in cytogenetical remission (30 metaphases analyzed) but in November 2003 remained RT-PCR positive. On the basis of these data, the imatinib dose was raised to 400 mg/day in November 2003. The course of the patient is illustrated on Fig. 3.

Discussion

We have identified *NIN*, encoding the centrosomal-associated protein ninein, as the seventh gene that is fused to *PDGFRB* in hematological disorders. *NIN* shares features in common with other tyrosine kinase fusion partners, namely widespread expression and the presence of putative oligomerization domains. Although we have no direct experimental proof, it is likely that the *NIN* promoter drives expression of the chimeric gene in hemopoietic progenitor cells, and the oligomerization domain(s) result in ligand-independent activation of the *PDGFRB* kinase moiety by mimicking the normal process of ligand-induced receptor dimerization.

NIN is the second centrosomal protein-encoding gene that is fused to a tyrosine kinase in myeloproliferative diseases, the first being *CEP110*, the partner of *FGFR1* in 8p11 myeloproliferative syndrome with the t(8;9)(p12;q33) (Ref. 18). In a typical somatic cell, the centrosome is composed of a pair of centrioles surrounded by a mass

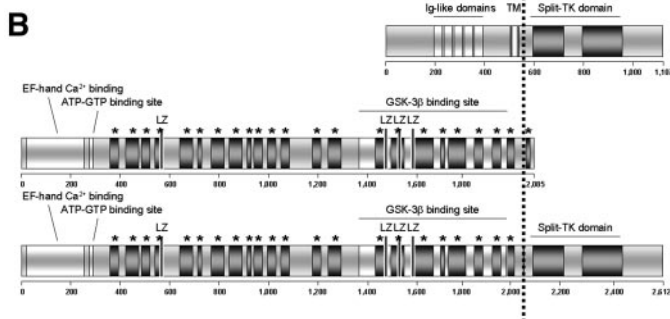
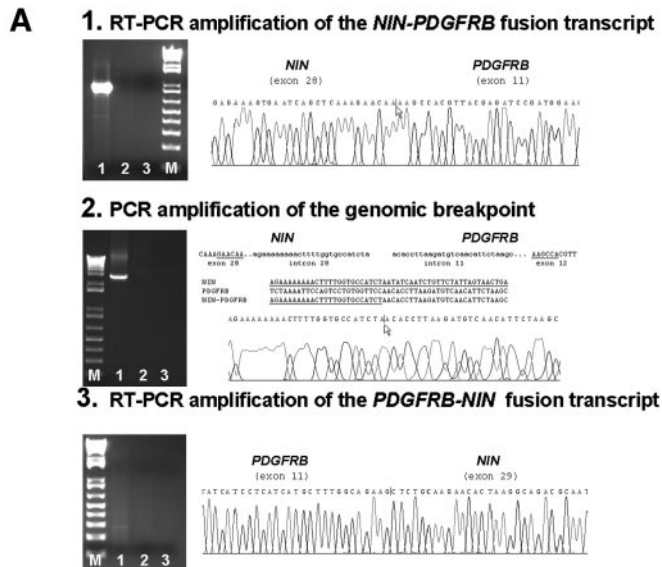


Fig. 2. *A*, molecular analyses (b) left: one-step reverse transcription (RT)-PCR amplification of the *NIN-PDGFRB* chimeric transcript (1004 bp) with primers *NIN*-6 and *PDGFRB*-2. Right: sequence analysis of the amplification product showing the fusion between *NIN* exon 28 and *PDGFRB* exon 12. (b) left: PCR amplification with primers *NIN*-8 and *PDGFRB*-1 of the *NIN-PDGFRB* genomic fusion (2.5 Kb). Right: sequence analysis of the amplification product showing the fusion between *NIN* intron 28 and *PDGFRB* intron 11. (c) left: one-step RT-PCR amplification with primers *PDGFRB*-2b and *NIN*-7 of the *PDGFRB-NIN* reciprocal chimeric transcript (272 bp). Right: sequence analysis of the amplification product showing the fusion between *PDGFRB* exon 10 and *NIN* exon 29. In all cases: Lane *M*, 1 kb plus DNA ladder molecular weight marker (Invitrogen-Life Technologies, Inc.); Lane 1, cDNA or gDNA from the patient; Lane 2, cDNA or gDNA from a normal donor; Lane 3, water. *B*, schematic representation of *PDGFRB*, *NIN*, and the putative chimeric *NIN-PDGFRB* structures. TM, transmembrane domain; TK, tyrosine-kinase domain; LZ leucine zipper domain. Coiled-coil domains on *NIN* and *NIN-PDGFRB* are indicated with asterisks.

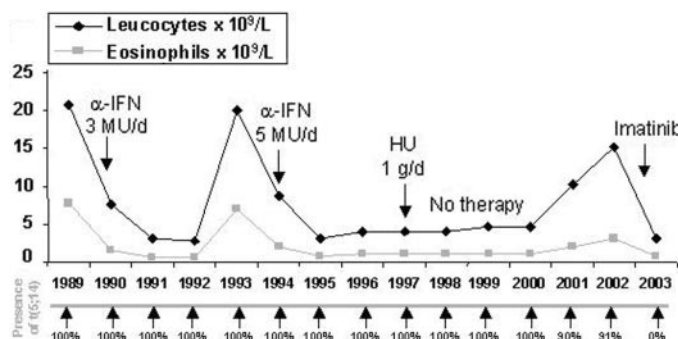


Fig. 3. Hematological and cytogenetical course of the t(5;14) patient.

of amorphous pericentriolar material that contain complexes of α -tubulin, centrin, pericentrin, and ninein. Ninein has been demonstrated to play an important role in microtubule minus end capping, centriole positioning, anchoring, and in centrosome maturation (19). Ninein levels decline at metaphase and anaphase and reaccumulate at the telophase-G₁ transition of the next cell cycle; consequently, it has been suggested that ninein might play a role in ensuring equal chromosome segregation before telophase/cytokinesis (19). However, because no additional karyotypic changes appeared over >13 years, it is unlikely that the t(5;14)-positive cells in this patient had centrosome abnormalities and genetic instability as a consequence of ninein involvement.

Six of the seven *PDGFRB* fusions described to date have been found in patients with chronic eosinophilic leukemia, atypical CML, or chronic myelomonocytic leukemia, with eosinophilia using being present (3). *CEV14-PDGFRB*, associated with the t(5;14)(q31;p12), is the exception, having only been found as a secondary event in a patient with relapsed acute myeloid leukemia. As in the case described here, some patients also displayed skin lesions, and it is conceivable that these arise as a consequence of aberrant *PDGFRB* signaling because this receptor is normally involved in wound healing and repair of skin lesions. Alternatively, these skin lesions may be a consequence of eosinophilic infiltrations (3).

Identification of patients with *PDGFRB* rearrangements is important because they respond well to treatment with imatinib mesylate (4–7). In these studies, patients were most commonly treated with 400 mg/day of imatinib as a standard dose, although in some cases, it was necessary to increase it (4–7). Our patient achieved hematological and cytogenetical remission with imatinib mesylate at 200 mg/day, but on finding expression of *NIN-PDGFRB* by single-step PCR after 6 months of treatment, the dose of imatinib was raised to 400 mg/day.

In summary, we have described a myeloproliferative disease patient with a novel *PDGFRB* fusion gene, identified in part by bioinformatic techniques. Characterization of the translocation enabled the patient to be treated by signal transduction therapy and for that treatment to be tailored by monitoring the molecular response. The partner gene, *NIN*, is functionally related to *CEP110*, supporting the concept of a network of tyrosine kinases and partners giving rise to CML-like diseases (2).

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