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Molecular characterization of a t(1;3)(p36;q21) in a patient with MDS. *MEL1* is widely expressed in normal tissues, including bone marrow, and it is not overexpressed in the t(1;3) cells

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Patients with myeloid malignancies and either the 3q21q26 syndrome or t(1;3)(p36;q21) have been reported to share similar clinicopathological features and a common molecular mechanism for leukemogenesis. Overexpression of *MDS1/EVI1* (3q26) or *MEL1/PRDM16* (1p36), both members of the PR-domain family, has been directly implicated in the malignant transformation of this subset of neoplasias. The breakpoints in both entities are outside the genes, and the 3q21 region, where *RPN1* is located, seems to act as an enhancer. *MEL1* has been reported to be expressed in leukemia cells with t(1;3) and in the normal uterus and fetal kidney, but neither in bone marrow (BM) nor in other tissues, suggesting that this gene is specific to t(1;3)-positive MDS/AML. We report the molecular characterization of a t(1;3)(p36;q21) in a patient with MDS (RAEB-2). In contrast to previous studies, we demonstrate that *MEL1*, the PR-containing form, and *MEL1S*, the PR-lacking form, are widely expressed in normal tissues, including BM. The clinicopathological features and the breakpoint on 1p36 are different from cases previously described, and *MEL1* is not overexpressed, suggesting a heterogeneity in myeloid neoplasias with t(1;3).
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The 3q21q26 syndrome is associated with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), and is characterized by trilineage dysplasia, in particular dysmegakaryocytopoiesis, and poor prognosis (Secker-Walker *et al*., 1995). A similar type of MDS/AML has been reported in the recurrent t(1;3)(p36;q21). Patients with both entities seem to share similar clinicopathological features and a common molecular mechanism. The leukemogenic mechanism in these aberrations has been suggested to be the ectopic expression of *EVI1* in patients with inv(3)(q21q26) and t(3;3)(q21;q26), and of *MEL1/PRDM16* in patients with t(1;3)(p36;q21) (Mochizuki *et al*., 2000), in both cases for juxtaposition with regulatory sequences of the housekeeping gene *RPN1*. The breakpoints (BPs) are outside the genes in most cases, and the 3q21 region, where *RPN1* is located, seems to act as an enhancer, activating the transcription of these genes. *MDS1-EVI1* (3q26) and *MEL1* (1p36) are members of the family of PR-domain genes along with *RIZ1/PRDM2* (1p36), *BLIMP-1/PRDM1* (6q21) and *PFM1/PRDM4* (12q23) (Schneider *et al*., 2002). The protein products of these genes are involved in human cancer in an unusual yin-yang fashion. It seems that two products are normally produced from a PR-domain family member, which differ by the presence or absence of the PR domain; the PR-plus product is disrupted or underexpressed, whereas the PR-minus product is present or overexpressed in cancer cells. This imbalance in the amount of the two products, a result of either genetic or epigenetic events, appears to be an important cause of malignancy (Huang, 1999).

MEL1 (1p36.3) encodes a zinc-finger protein that shares 63% sequence similarity to *MDS1-EVI1*, with a similar domain structure. Mochizuki *et al*. (2000) reported that *MEL1* is expressed in leukemia cells with t(1;3) but not in normal bone marrow (BM), suggesting that the ectopic expression of *MEL1* is specific to the t(1;3)-positive MDS/AML. Recently, the same group has identified two different *MEL1* products of 170 and 150 kDa by immunoblotting analysis, designated as full-length MEL1 and short-form MEL1S, respectively (Nishikata *et al*., 2003). Like *MDS1-EVI1* and *EVI1*, two mRNAs with and without the PR domain would be transcribed from this locus. MEL1 is the PR-containing form, with the PR domain coded from codon ATC91 (exon 2) to codon CCC223 (exon 5) (Mochizuki *et al*., 2000), and MEL1S is the PR-lacking form initiated from an internal codon ATG599 (exon 9) (Nishikata *et al*., 2003). The fusion of MEL1 or MEL1S to GAL4 DNA-binding domain made them GAL4-binding

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site-dependent transcriptional repressors. Moreover, overexpression of *MEL1S* blocked granulocytic differentiation induced by G-CSF in IL-3-dependent murine myeloid L-G3 cells, while *MEL1* could not block the differentiation. From these results, they conclude that overexpression of *MEL1*S could be one of the causative factors in the pathogenesis of t(1;3)-positive myeloid leukemia cells (Nishikata *et al*., 2003). Here, we report the molecular characterization of a translocation t(1;3)(p36;q21) in a patient with MDS (RAEB-2). The clinicopathological features and the BP on 1p36 are different from AML cases previously described, and *MEL1* is not overexpressed in our patient, suggesting a heterogeneity in cases with t(1;3). We also report the pattern of expression of *MEL1* and *MEL1S*, which we show is different from that previously described.

G banding and FISH analysis showed a single clone 46,XX,t(1;3)(p36;q21) in the karyotype of a patient with MDS (Figure 1). This 75-year-old woman was admitted because of leukocytosis, anemia and thrombocytopenia in June 1998. On physical examination, remarked bilateral edema, multiple bruises and petechiae and pallor, without hepatosplenomegaly or gingival swelling, was observed. BM examination showed hyperplastic marrow with an increased level of myeloblasts with monocytoid differentiation (18.6%). Refractory anemia with excess of blasts (RAEB-2) was diagnosed in the presence of 16% blasts. Treatment with cytosine-arabinoside, idarubicin and etoposide was started, but

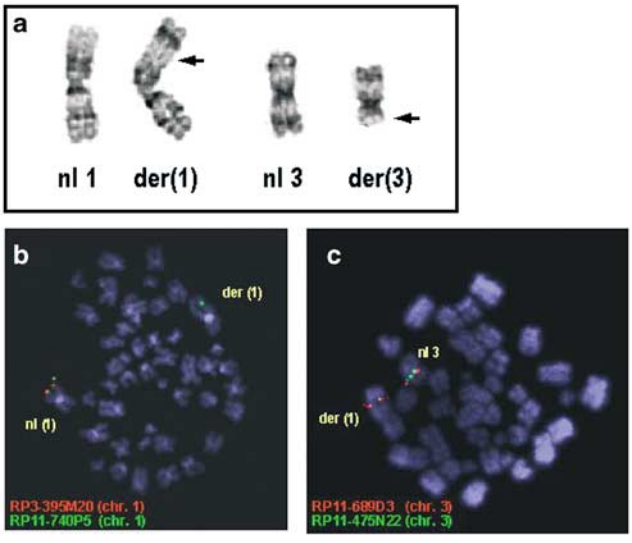

Figure 1 G banding and FISH analysis of a patient with t(1;3)(p36;q21). (**a**) Partial G-band karyotype. Arrows indicate BPs of rearranged chromosomes. (**b**) RP11-740P5 probe (green) from chromosome 1 labels normal chromosome 1 and der(1). RP3-395M20 probe (red) from chromosome 1 labels only normal 1, indicating that this region is deleted in the der(1). (**c**) RP11-689D3 probe (red) and RP11-475N22 (green) from chromosome 3 label normal chromosome 3 and der(1). The small green signal on der(1) suggests that part of this chromosome 3 probe is deleted. DNA from BAC and PAC clones was extracted using Qiaprep® Spin Miniprep kit (Qiagen, Hilden, Germany), and labeled with Spectrum Green® and Spectrum Orange® (Vysis, Downers Grove, IL, USA) by nick translation. FISH analysis was performed on BM metaphases as previously described (Odero *et al*., 2001)

the patient died 6 months later of respiratory distress. Fifteen BAC and PACs located on 1p36.3 and nine on 3q21 were used in metaphase FISH experiments. The BP on chromosome 1 was located between RP11-181G12 and RP11-740P5 (Figure 2a). RP3-395M20, located between the two BACs that defined the BP, was deleted. Therefore, we could define the BP on 1p36.3 located 300 kb telomeric to *MEL1*, and a cryptic deletion of less than 400 kb was detected (Figure 1b). The molecular characterization of similar translocations was first described by Mochizuki *et al*. in four patients with AML-M4 (Mochizuki *et al*., 2000); the BP on 1p36 was located in a 90-kb cluster telomeric to *MEL1*. Recently, Xinh *et al*. (2003) defined the localization of the BPs on 1p36 in two of these cases, and in a new patient with t(1;3). In the two patients reported by Mochizuki *et al*. (2000), the BP was in RP5-907A6 (BR-2), 78.4-kb telomeric to *MEL1*; in the new patient, who presented an unusual clinical profile, the BP was located in RP1-163G9 (BR-1), in the first intron of *MEL1*. Both BPs are centromeric to the BP we define in our patient with RAEB, that it is located 250 kb telomeric to *ARPM2* and 300 kb telomeric to *MEL1* (Figure 2a). This suggests a heterogeneity in cases with t(1;3), which could reflect the clinical features. The diagnosis of our patient was RAEB, the subtype most frequent (42.8%) among cases with MDS and t(1;3), whereas Xinh *et al*. defined the BP in three patients with AML-M4, the most frequent FAB subtype (53.8%) among cases with AML and t(1;3) (Xinh *et al*., 2003). The clinicopathological profile is also different in our patient, suggesting that not all cases sharing t(1;3) are similar to the 3q21q26 syndrome, and that a different molecular mechanism could be present in this patient. The BP in chromosome 3 was between RP11-525K18 and RP11-475N22 (Figure 2b). Both probes showed a small signal on the der(3) and der(1), respectively, suggesting that part of these chromosome 3 probes is deleted. Probes located between 525K18 and 475N22 showed no signal neither on der(3) nor on der(1), confirming that a region of about 500 kb is deleted (Figure 1c). Although the 3q21 BPs in cases with t(1;3) have been reported to cluster specifically in a region of 50 kb (BCR-C), centromeric to the 30 kb BCR of 3q21q26 syndrome cases (BCR-T), both downstream of the *RPN1* gene (Shimizu *et al*., 2000), a recent review revealed that in six cases with inv(3), four with t(3;3) and three with t(1;3), the BP was in BCR-C and in nine cases with inv(3), seven with t(3;3) and three with t(1;3) in BCR-T (Wieser, 2002). Therefore, both BCR may be affected by these alterations. The BP in our patient with t(1;3) and RAEB was less than 100 kb centromeric to *GR6* and *RPN1*, in the BCR-C region. 3′RACE experiments with primers in *GR6* showed no new sequences (data not shown). This is the first time that both, 1p36 and 3q21 BPs, have been defined in a t(1;3)(p13;q21).

On the basis of the positional relationship between *MDS1-EVI1* and *MEL1*, Mochizuki *et al*. (2000) suggested that both genes are transcriptionally activated by the translocation of the 3q21 region with *RPN1*.

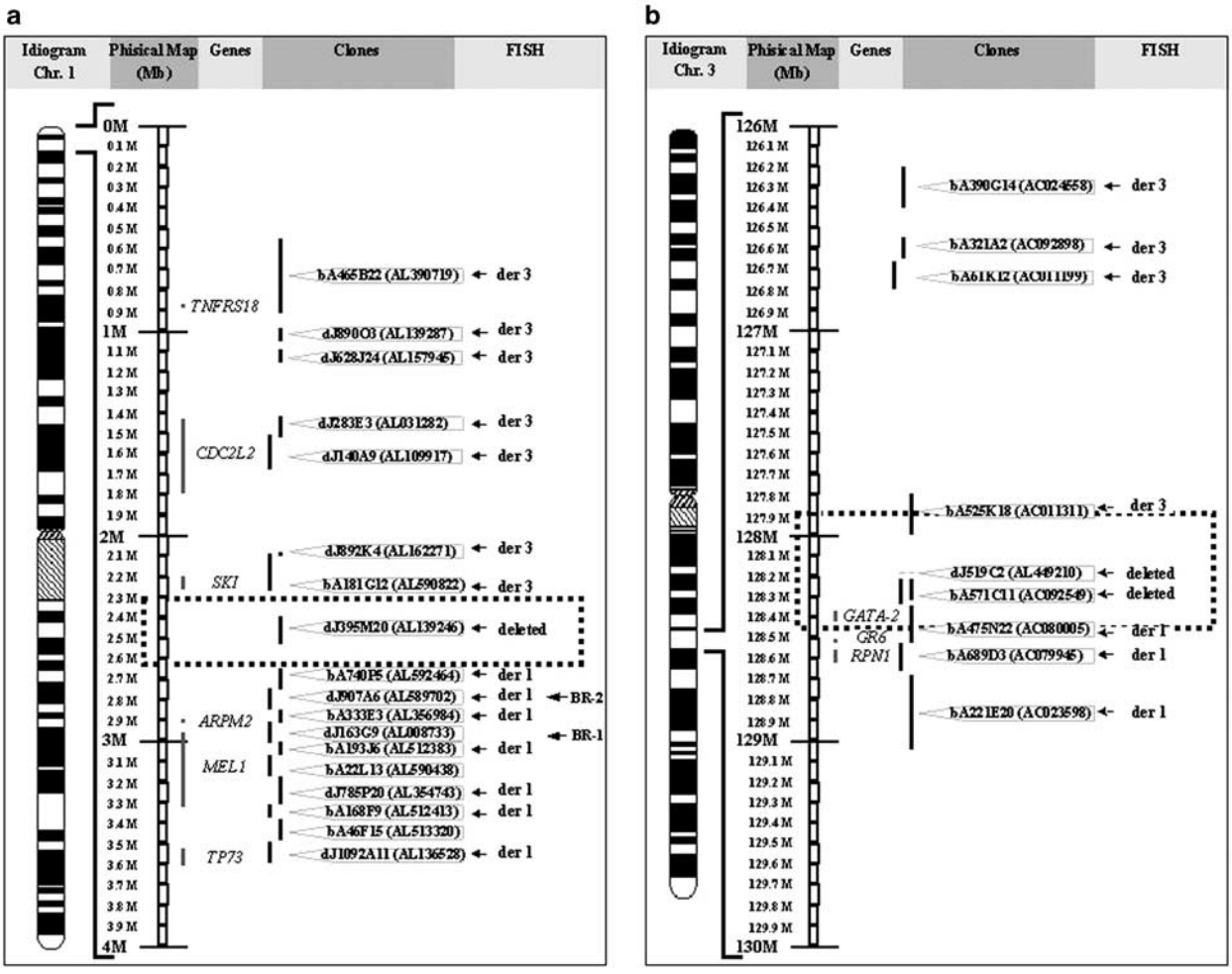

Figure 2 Integrate map of the 1pter-1p36.3 and 3q21 regions showing the ideograms of chromosomes 1 and 3 with the FISH results of a patient with t(1;3)(p36;q21). The physical map and relative size and position of genes involved in human cancer and of the clones used in this study (GenBank Accession number in brackets) are shown in the diagram. The clones were obtained from libraries from the Roswell Park Cancer Institute (Buffalo, NY, USA). (**a**) The BP on 1p36.3 in the patient with t(1;3) was located between RP11-181G12 and RP11-740P5. We found a cryptic deletion of less than 400 kb. BR-1 and BR-2: BPs of three patients with t(1;3) and AML-M4, described by Xinh *et al*. (2003). (**b**) The BP in chromosome 3 was between RP11-525K18 and RP11-475N22

Mochizuki *et al*. (2000) reported that *MEL1* is expressed in the uterus, fetal kidney, and specifically in leukemia cells with t(1;3), but not in other cell lines or in normal BM, spleen, or fetal liver, suggesting that the ectopic expression of *MEL1* is specific to the t(1;3)-positive MDS/AML (Mochizuki *et al*., 2000). The *MEL1* gene codes for two products that differ in the presence or absence of the PR domain. In order to distinguish the expression pattern of these two forms, we designed two sets of primers. We used primers MEL1N-F and MEL1N-R, located outside the PR-domain sequence, in a region conserved in all the splicing variants, to amplify the region common to *MEL1* and *MEL1S* (cMEL). It is not possible to discriminate between these two products, since *MEL1S* is contained in the *MEL1* sequence. Primers MEL1PR-F and MEL1PR-R were designed in exon 3 and exon 5, respectively, that code for the PR domain, to amplify only *MEL1* (Figure 3a). Primer sequences are shown in Table 1. We analysed the expression pattern of *MEL1* and cMEL (*MEL1* plus *MEL1S*) by RT–PCR separately on $CD34^+$ cells, BM and peripheral blood (PB) of a healthy donor, normal uterus, and in BM of the patient. All reactions showed bands of 260 and 200 bp, as expected for *MEL1* and cMEL amplifications, respectively, with the primers used (Figure 3a, b). Sequence analysis of the RT–PCR products confirmed these results. We also amplified *MEL1* and cMEL in a set of first-strand cDNAs from eight human tissues: heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas. The expression was detected in all the tissues of the panel, being stronger in the heart, lung, kidney and pancreas (Figure 3b). Therefore, *MEL1* and *MEL1S* were expressed in at least 11 normal tissues, including BM and PB, and in the BM of the patient. The set of primers used for Mochizuki *et al*. (2000) did not discriminate between *MEL1* and *MEL1S*; hence, their analysis really showed the expression of the region shared by both transcripts. The differences in these results could be explained because the RT–PCR conditions Mochizuki

Table 1 Oligonucleotide primer sequences

Primer	*Oligonucleotide sequence (5′–3′)*	*Gene*	*Nucleotides**
MEL1N-F	CCCCAGATCAGCCAATCTCACCA	*MEL1*	2943–2965
MEL1N-R	GGTGCCGGTCCAGGTTGGTC	*MEL1*	3142–3123
MEL1PR-F	CTGACGGACGTGGAAGTGTCG	*MEL1*	457–477
MEL1PR-R	CAGGGGGTAGACGCCTTCCTT	*MEL1*	717–697
BCR-F	GAGAAGAGGGCGAACAAG	*BCR*	2889–2906
BCR-R	CTCTGCTTAATTCCAGTGGC	*BCR*	3265–3246

*Nucleotide coordinates refer to GenBank Accession numbers NM-022114 (*MEL1*) and NM-004327 (*BCR*)

et al. used are more restrictive (30 versus 35 cycles), although in their experiments both Northern and RT–PCR showed the same results. However, our experiments showed a strong expression of *MEL1* and cMEL in the heart, lung, kidney and pancreas, which should have been easily detected by Mochizuki *et al*. (Figure 3b). Interestingly, a recent report showed the same profile expression in the analysis of *MDS1*/*EVI1* (PR positive) versus cEVI1, a region common to *MDS1*/*EVI1* and *EVI1* (PR negative type), using a similar experimental design (Vinatzer *et al*., 2003). The expression of both genes was stronger in the same tissues, with the only exception of placenta, where *MDS1-EVI1* and cEVI1 are highly expressed, whereas *MEL1* and cMEL are poorly expressed. Fractionated $CD34^+$ progenitor cell populations indeed showed high *MEL1* and *MEL1S* expression. Previous studies also confirmed *MDS1-EVI1* and *EVI1* expression in early $CD34^+$ progenitor cells, and suggest that transformation in these progenitors may be the result of a disturbance in the tightly controlled balance between *EVI1* and its fusion transcript (Barjesteh van Waalwijk van Doorn-Khosrovani *et al*., 2003). We designed a semiquantitative RT–PCR experiment to compare the expression of cMEL in the BM of the patient and that of a healthy donor, using

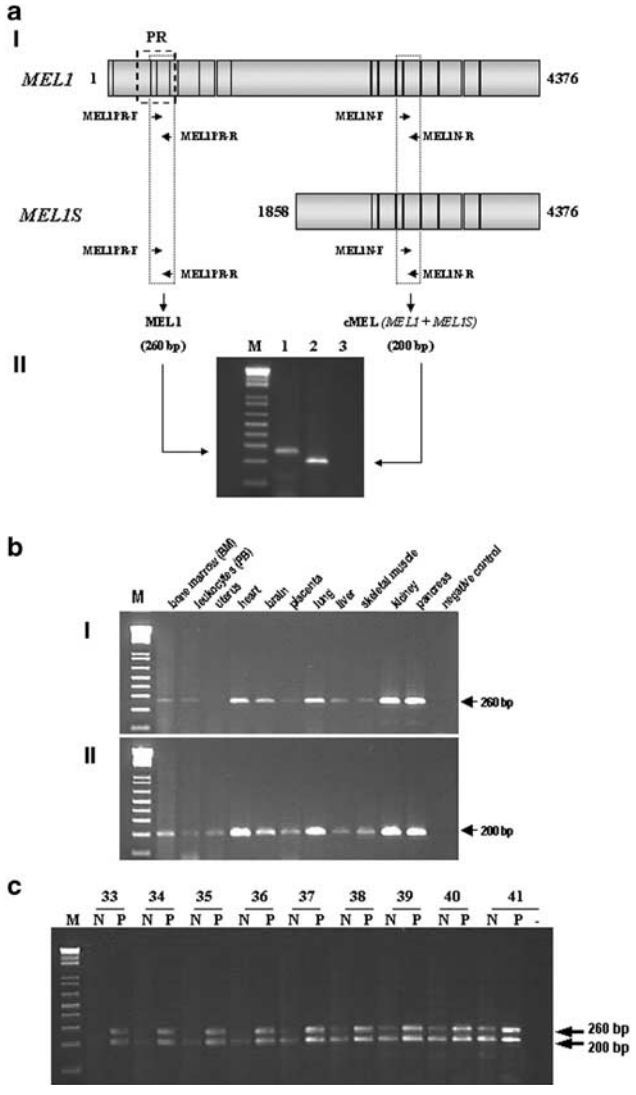

Figure 3 Pattern expression of the *MEL1* gene. (**a**) I. Diagram showing the structure of the *MEL1* and *MEL1S* transcripts and the relative location of the primers. Primers MEL1PR-F and MEL1PR-R, in exon 3 and exon 5, respectively, amplify only the PR-containing form *MEL1*; primers MEL1N-F and MEL1N-R, located in exon 12 and exon 13, respectively, amplify the region common to *MEL1* and *MEL1S* (cMEL). II. Analysis of the expression of *MEL1* (lane 1) and cMEL (*MEL1* plus *MEL1S*) (lane 2) in cDNA from normal $CD34^+$ cells. M: 1 kb plus molecular weight marker. Lane 3: Negative control. (**b**) Expression of *MEL1* (I) and expression of cMEL (II) was performed on cDNA from BM and PB of a healthy donor, normal uterus, and on a set of normalized, first-strand cDNA from eight different human tissues (Multiple Tissue cDNA Panels I; Clontech, Basingstoke, UK). (**c**) Multiplex-PCR to amplify *MEL1* and cMEL in the same reaction was performed to avoid differences in the amplification level derived from external causes such as variability of the PCR technique, using a mix of MEL1PR-F, MEL1PR-R, MEL1N-F and MEL1N-R primers. Multiplex-PCR was performed in BM of a healthy donor (N) and BM of the patient with t(1;3) (P). Aliquots of both reactions were taken from cycles 33–41, at the moment of the denaturation step, in order to ensure that amplifications were in the linear phase of amplification. Total RNA was extracted using the RNeasy Mini Kit (Qiagen, Hilden, Germany) from frozen cell pellets of BM and PB from a healthy donor, uterus and leukemic cells. The $CD34^+$ cells isolation was performed from mononuclear cells of normal BM, using the Direct CD34 Progenitor cell isolation kit (Miltenyi Biotec, Germany). Total RNA (1 μg) was used for cDNA synthesis using SuperScript™ II RNase H-RT (Invitrogen Life Technologies, Paisley, UK) with random hexamers. RT–PCR reactions were performed under standard conditions using AmpliTaq Gold® DNA Polymerase (Applied Biosystems, Foster City, CA, USA), annealing temperature 65°C and 35 cycles. PCR products were subcloned using the TOPO TA Cloning® Kit for Sequencing (Invitrogen Life Technologies, Paisley, UK). Candidate plasmid clones were sequenced with the ABI-PRISM™ d-Rhodamine Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) in an ABI PRISM™ 377 DNA Sequencer (Applied Biosystems, Foster City, CA, USA)

primers MEL1N-F and MEL1N-R. Amplification of *BCR* was used as an internal control. The expression pattern of cMEL in a normal BM in comparison with BM of the patient was 1/1.28, indicating that this gene is not overexpressed in our patient with t(1;3). In order to better discriminate between *MEL1* and *MEL1S*, we designed a multiplex RT–PCR experiment. In normal BM, expression of cMEL (*MEL1* plus *MEL1S*) was stronger than the expression of only *MEL1*, which accounted for around half of the total expression. In the patient sample, both amplifications had the same intensity, suggesting that *MEL1S* could be underexpressed (Figure 3c). The overexpression of zinc-finger proteins lacking the PR domain is considered one of the main factors in the pathogenesis of some leukemias, being present or overexpressed in many tumors (Huang, 1999, 2002). The yin-yang mechanism, well studied in the *RIZ* gene, was expected to be repeated in other PR family members. Gene silencing of *RIZ1*, but not *RIZ*2, is common in many types of tumors, and is associated with promoter DNA methylation; therefore, the PR domain has been associated with the tumor-suppressor properties of *RIZ1* (Du *et al*., 2001; Huang, 2002). Surprisingly, the form without PR (*MEL1S*) seems to be poorly expressed in our patient. However, a review of the literature shows that not all members of the PR-domain family work in the same way. Two recent studies detected in 17/21 (81%) patients with t(3;3) or inv(3) that high *EVI1* expression was associated with high *MDS1-EVI1* expression, the form with the PR domain (Barjesteh van Waalwijk van Doorn-Khosrovani *et al*., 2003; Vinatzer *et al*., 2003). Moreover, lack of expression of the PR-lacking form *EVI1* has been reported in several cases with syndrome 3q21q26 (Fichelson *et al*., 1992; Morishita *et al*., 1992; Soderholm *et al*., 1997; Langabeer *et al*., 2001), suggesting that the molecular mechanism of leukemogenesis is not the same in all patients. Barjesteh van Waalwijk van Doorn-Khosrovani *et al*. (2003) described a case with a translocation involving 3q26, which presented a similar pattern of expression detected in our case. They analysed the expression of *EVI1*, *MDS1* and *MDS1-EVI1* by real-time quantitative RT–PCR (RTQ-RT–PCR) in 319 *de novo* AML patients, 11 with 3q26 rearrangements. In a patient with RAEB and t(3;12)(q26;p13), the relative expression of *EVI1* when compared with *MDS1-EVI1* was 1/11585. This translocation t(3;12) is different from the classical t(3;3) or inv(3), although *EVI1* (3q26) is also involved. In the leukemic cells of the case presented here, with MDS and a t(1;3), *MEL1* is expressed and *MEL1S*, the PR-domain negative form, seems to be underexpressed. These data would confirm the results of previous reports about *MDS1-EVI1*, and could indicate that different molecular mechanisms are possible for the members of the family of PR-domain genes. On the other hand, data reported by Pekarsky *et al*. (1997) and Rynditch *et al*. (1997) suggest that the 3q21 region is gene rich, and additional genes instead of *RPN1* could be involved in these rearrangements. *GATA-2*, located in RP11-475N22, had been reported as a candidate gene involved in the 3q21 BP (Wieser, 2002). However, the location of the BP in our patient suggests that this gene is deleted. We have analysed the expression of *GATA-2* in the patient BM, and the level of expression was similar when comparing with normal BM and PB (data not shown).

In conclusion, the data presented here showed that *MEL1* and *MEL1S* are widely expressed in tissues, including PB and BM. We report the molecular characterization of a novel t(1;3)(p36;q21) in a patient with MDS (RAEB-2). The clinicopathological features and the BP on 1p36 are different from cases previously described, and *MEL1* was not overexpressed; instead, imbalance of a complete *MEL1* message with a PR domain and a short *MEL1* message lacking a PR domain (*MEL1S*) might be involved in the leukemogenesis of this patient. These observations suggest a heterogeneity in myeloid neoplasias with t(1;3), as has been reported for cases with 3q21q26 syndrome.

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