

A novel gene, *MEL1*, mapped to 1p36.3 is highly homologous to the *MDS1/EVII* gene and is transcriptionally activated in t(1;3)(p36;q21)-positive leukemia cells

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The reciprocal translocation t(1;3)(p36;q21) occurs in a subset of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), which is frequently characterized by trilineage dysplasia, in particular dysmegakaryocytopoiesis, and poor prognosis. Previously, the breakpoint cluster region (BCR) at 3q21 was identified within a 60-kilobase (kb) region centromeric to the BCR of 3q21q26 syndrome and that at 1p36.3 within a 90-kb region. In this study, genes were searched near the breakpoints at 1p36.3, and a novel gene was isolated that encoded a

zinc finger protein with a PR domain, which is highly homologous to the *MDS1/EVII* gene. The novel gene, designated as *MEL1* (*MDS1/EVII*-like gene 1), with 1257 amino acid residues is 64% similar in nucleotide and 63% similar in amino acid sequences to *MDS1/EVII* with the same domain structure. The *MEL1* gene is expressed in leukemia cells with t(1;3) but not in other cell lines or bone marrow, spleen, and fetal liver, suggesting that *MEL1* is specifically in the t(1;3)(p36;q21)-positive MDS/AML. On the basis of the positional relationship between the *EVII*

and *MEL1* genes in each translocation, it was suggested that both genes are transcriptionally activated by the translocation of the 3q21 region with the Ribophorin I gene. Because of the transcriptional activation of the *EVII* family genes in both t(1;3)(p36;q21)-positive MDS/AML and 3q21q26 syndrome, it is suggested that they share a common molecular mechanism for the leukemogenic transformation of the cells. (Blood. 2000;96:3209-3214)

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Introduction

On the long arm of chromosome 3, various types of translocational breakpoints are clustered in the q21 and q26 regions, such as inv(3)(q21q26), t(3;3)(q21;q26), t(1;3)(p36;q21), t(3;5)(q21;q31), t(3;8)(q21;q24), t(3;21)(q26;q22), and t(3;12)(q26;p13).¹ We previously characterized chromosomal breakpoints of 3q21q26 syndrome. 3q21q26 syndrome is a group of diseases with a recurrent translocation, inversion, or insertion between the regions of 3q21 and 3q26 and is associated with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).^{2,3} 3q21q26 syndrome has specific clinical features, including normal or elevated platelet counts at the initial diagnosis, hyperplasia with dysplasia of megakaryocytes, poor response to chemotherapy, and poor prognosis. We have shown that chromosomal breakpoints at 3q26 are clustered at the 5' region of the *EVII* gene in t(3;3)(q21;q26) and at the 3' region in inv(3)(q21q26).^{4,6} However, the breakpoints at 3q21 in both t(3;3)(q21;q26) and inv(3)(q21q26) are clustered within a 50-kilobase (kb) region near the Ribophorin I (*RPNI*) gene, which is a member of membrane proteins of rough endoplasmic reticulum. On the basis of these results, it is suggested that the region of 3q21 with the *RPNI* gene translocated to the q26 region near the *EVII* gene may activate *EVII* expression as an enhancer element.

Along with 3q21q26 syndrome, a similar type of MDS/AML has been reported to have recurrent t(1;3)(p36;q21) transloca-

tions.⁷⁻⁹ Recently, we have identified the breakpoint cluster region (BCR) in 4 cases of t(1;3)(p36;q21)-positive MDS/AML.¹⁰ Clinicopathological features of the t(1;3)(p36;q21)-positive MDS/AML are similar to those of 3q21q26 syndrome, including normal or elevated platelet counts, hyperplasia with dysplasia of megakaryocytes, poor response to chemotherapy, and poor prognosis. BCRs were detected within a 60-kb region at 3q21 adjacent to the BCR of 3q21q26 syndrome and within a 90-kb region at 1p36. The BCR in 1p36 was mapped to 1p36.3 by fluorescence in situ hybridization (FISH) and by radiation hybrid mapping analyses.

To identify genes that are involved in leukemogenesis of t(1;3)(1p36;3q21)-positive MDS/AML, we have extensively searched for genes near the BCRs at 3q21 and 1p36. A novel gene encoding a zinc finger protein was isolated near the BCR at 1p36 and is transcriptionally activated in leukemia cells with t(1;3)(p36;q21). Interestingly, the gene, designated as *MEL* (*MDS1/EVII*-like gene 1), was highly homologous to *MDS1/EVII*, which is an alternatively spliced transcript of the *EVII* gene. Because of the transcriptional activation of the *EVII* family genes in both t(1;3)(1p36;3q21)-positive MDS/AML and 3q21q26 syndrome, it was suggested that they have a common molecular mechanism for the leukemogenic transformation of the cells.

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BCR at 1p36.3 is within an approximate 90-kb region in 4 cases with t(1;3)(p36;q21). To search for genes near the BCR, a 300-kb contig of BAC and P1 clones covering the breakpoint at 1p36 region was constructed.

Exon trapping, cDNA hybrid selection, and Northern hybridization using small genomic fragments as probes were used for identifying exons near the BCRs at 1p36 and 3q21 regions. Two cDNA clones, including the *RPN1* at the 3q21 region, and 3 cDNA clones, including an F11 cDNA fragment at the 1p36 region, were isolated by the exon trapping method (data not shown) (Figure 1). On the one hand, the mRNA expression pattern of these cDNA clones did not match the t(1;3)(p36;q21)-positive cases. On the other hand, a 7.5-kb *EcoRI* fragment from the BAC209F clone at 1p36 was specifically hybridized to RNA from the t(1;3)(p36;q21)-

positive leukemia cells and detected a band of approximately 8 kb in size by Northern hybridization (data not shown). Therefore, we constructed a cDNA library from the patient's RNA and screened using the 7.5-kb *EcoRI* fragment as a probe. A 5450-base pair (bp) cDNA-contig was made with 45 bp of 5' and 1634 bp of 3' noncoding regions by these cDNA clones. Deduced amino acid sequences from the cDNA was compared with whole registered amino acid sequences in SWISSPORT using a BLAST search program in NCBI and the GenomeNet World Wide Web server. Interestingly, the first 222 amino acid residues of the amino acid sequences were highly homologous to the PR domain in the *MDS1* gene, and the rest of the sequence was homologous to the *EVI1* gene (Figure 2A-B). Therefore, the novel gene was designated as *MEL1*.



Figure 2. Comparison of the predicted amino acid sequences with *MDS1/EVI1* and *MEL1*. (A) Alignment of the predicted amino acid sequences of the human *MEL1* (upper) and *MDS1/EVI1* (lower) proteins. "*" indicates identical amino acids, "." and "." indicate similar amino acids, and "-" represents a gap that has been introduced to optimize the homology. The sequences were compared by the Clustalw program of The EMBL-European Bioinformatics Institute (EBI). Underlines indicate the position of metal binding cysteines and histidines in zinc finger motif. (B) Comparison of the domain structure between *MDS1/EVI1* and *MEL1*. Each abbreviation is indicated by the following letters: PRD, PR domain; DBD-1, DNA binding domain-1; PRR, proline-rich domain; RD, repressor domain; DB-2, DNA binding domain-2; AD, acidic domain. (C) Sequence comparison of the conserved PR domain among RIZ, BLIMP1, *MDS1/EVI1*, and *MEL1*.

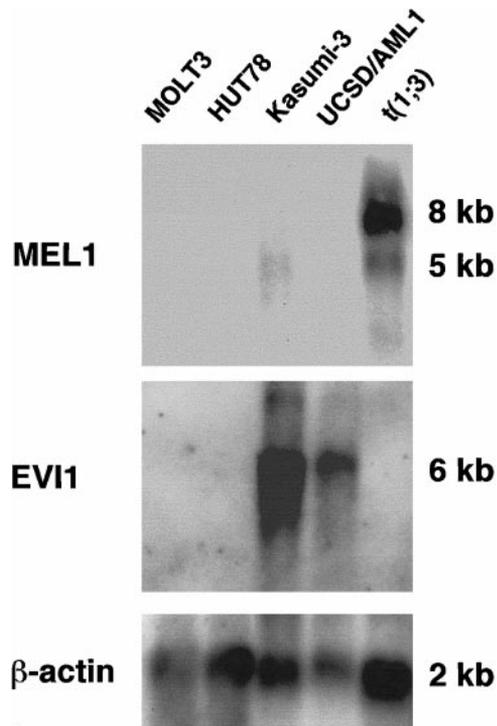


Figure 3. Expression of the *MEL1* gene in mRNA from leukemia cells with t(1;3)(p36;q21) by Northern hybridization. The *MEL1* transcript (8 kb) was expressed in leukemia cells with t(1;3)(p36;q21) (lane 5). However, the *MEL1* gene did not express in other leukemia cell lines, HUT78 (lane 1), MOLT3 (lane 2), Kasumi-3 (lane 3), and UCSD/AML1 (lane 4). The same membrane was hybridized to *EVI1* or β -actin probes, sequentially. *EVI1* transcripts (6 kb) were expressed in both Kasumi-3 with t(3;7)(q26;q22) (lane 3) and UCSD/AML1 with t(3;3)(q21;q26) (lane 4).

The *MEL1* gene is a member of the *MDS1/EVI1* gene family

As a translational start point of the *MEL1* gene, the position of the first methionine was defined as the same position of the first methionine of the *MDS1* gene and the coding region of the cDNA contig was 3771 bp long with deduced 1257 amino acid residues. According to the sequence comparison for the BESTFIT program in UWGCG between *MEL1* and *MDS1/EVI1*, similarities were 64.3% in nucleotide and 64.2% in amino acid sequences, and identities were 63.2% in nucleotide and 56.0% in amino acid sequences, respectively (Figure 2A). The domain structure of the *MEL1* gene product was the same as that of the *EVI1* protein (Figure 2B). First, *MEL1* protein has 2 DNA binding domains, which are 7 zinc finger repeats of the C₂-H₂ type at the N-terminal region and 3 zinc finger repeats at the C-terminal region. The amino acid sequence of the second DNA binding domain in the *MEL1* protein showed 96% identity with that of *EVI1* protein. Second, a 132-amino acid stretch at the N-terminal end of the *MEL1* protein was 52% identical to the N-terminal PR domain of the *MDS1* protein, which is reported as a transcriptional regulator with conservation among RIZ, BLIMP1, egl-43, and *MDS1* (Figure 2C).^{21,22} In a sequence comparison of the PR domain among RIZ, BLIMP1, *MDS1*, and *MEL1*, the PR domain of the *MEL1* protein retained the consensus sequence of A, B, and C boxes, but an extra 17 amino acid stretch is inserted in the middle of the PR domain in the *MEL1* protein. Third, the repressor domain was conserved in the middle of the *MEL1* protein, which was found as a consensus binding sequence for the C-terminal binding protein (CtBP2) in BKLf, AREB6, FOG, and Krüppel zinc finger proteins.²³

Also, proline-rich and acidic amino acid cluster regions are conserved in both proteins. Thus, *MEL1* is a novel member of the *MDS1/EVI1* family genes.

Expression of the *MEL1* and *EVI1* genes in various leukemia cell lines and AML with t(1;3)

MEL1 expression was analyzed in several cell lines, including leukemia cells with t(1;3)(p36;q21), by Northern blot hybridization. A major 8.0-kb *MEL1* transcript was detected only in leukemia cells with t(1;3) (Figure 3, lanes 5 and 6). The *MEL1* gene was not expressed in either myeloid leukemia cell lines (UCSD/AML-1, Kasumi-3) or lymphoid leukemia cell lines (HUT78, MOLT-3). However, a 6.0-kb transcript for the *EVI1* gene was detected in RNA from UCSD/AML-1 with t(3;3)(q21;q26) and Kasumi-3 with t(3;7)(q26;q22). Along with these leukemia cells, we have analyzed *MEL1* expression in several other leukemia cell lines, including 5 myeloid (UCSD/AML1, HEL, KP-L-RY, F36, and Kasumi-3) and 3 lymphoid (Jurkat, SKW3, and MOLT16) leukemia cells, but a *MEL1* transcript was not detected in these cell lines by Northern blot analysis (data not shown). Therefore, it is likely that the *MEL1* gene is not expressed in myeloid and lymphoid leukemia cells but ectopically expressed in the leukemia cells with t(1;3).

Expression of the *MEL1* gene in the various cell lines and organs

MEL1 expression was determined in various leukemia cells, including t(1;3)-positive leukemia, and in various organs by RT-PCR using specific primers for *MEL1* (see "Materials and methods"). As shown in Figure 4A, a 935 bp of the PCR product was amplified only from RNA of the leukemia cells with t(1;3)(p36;q21), but it was not amplified from RNA of other leukemia cells (KG-1, MOLT4, Kasumi-4, and CMK). This result suggested that *MEL1* is transcriptionally activated in t(1;3)(p36;q21)-positive MDS/AML cells but not in t(1;3)(p36;q21)-negative cells. To further investigate whether the *MEL1* gene is expressed in hematopoietic organs, we performed RT-PCR to RNA from various human organs. The *MEL1* cDNA was amplified from the RNA of uterus and fetal kidney but not from other organs, including bone marrow, spleen, and fetal liver (Figure 4B). Therefore, the expression profile in the organs of the *MEL1* gene may be distinctly different from that of the *EVI1* gene. On the basis of the results, it was indicated that the *MEL1* gene is not expressed in hematopoietic cells but is specifically expressed in t(1;3)-positive leukemia cells.

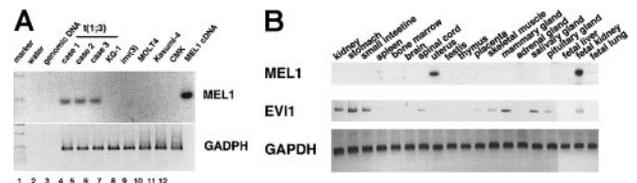


Figure 4. Detection of the *MEL1* expression in patient RNA, cell lines, and organs by RT-PCR. (A) Expression of the *MEL1* gene in RNA from patient leukemia cells or cell lines by RT-PCR. Each transcribed cDNA from leukemia cells with t(1;3)(p36;q21) or cell lines as source of RT-PCR was amplified by the *MEL1* specific primers (see "Methods and materials"). Lanes are indicated as follows: 1, 1-kb ladder marker (Promega Biotech); 2, negative control (water); 3, control genomic DNA; 4 to 6, leukemia cells with t(1;3)(p36;q21), cases 1 to 3¹⁰; 7, KG-1; 8, leukemia cells with inv(3); 9, MOLT4; 10, Kasumi-4; 11, CMK; and 12, *MEL1* cDNA fragment (N1163) as a positive control. (B) Expression of the *MEL1* gene in various organ RNAs by RT-PCR. The *MEL1* and *EVI1* expressions were analyzed in various organs by RT-PCR using each specific primer set.

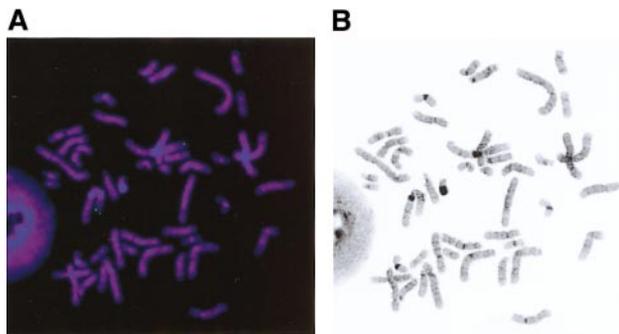


Figure 5. The *MEL1* gene is localized to 1p36.3 by fluorescence in situ hybridization (FISH) analysis. FISH was carried out with the *MEL1* cDNA clone (N1163) as a probe by the method described previously. Hybridization of an FITC-labeled probe to human metaphase spread shows specific green signals (A) on chromosome 1 at band p36.3 (B). Original magnification $\times 1000$.

Chromosomal mapping of the *MEL1* gene by FISH analysis

To define the precise location of the *MEL1* gene in the restriction map of the 1p36 region with BCR of t(1;3), an E7K fragment with exon(s) of the *MEL1* gene was hybridized to the isolated BAC and P1 clones. The E7K fragment was mapped within a 50-kb *Sfi*I fragment, which was approximately 90 kb centromeric to the BCR (Figure 1). The C-terminal region of the *MEL1* gene is hybridized to BAC273 but not to BAC209, suggesting that the *MEL1* gene is directed to the centromere of chromosome 1 (Figure 1). FISH analysis revealed that the *MEL1* gene was mapped to 1p36.3 (Figure 5), which was the same position as the BCR mapped in the previous study.

Discussion

Recurrent translocation between chromosome bands 1p36 and 3q21 has been reported as one of the chromosomal abnormalities associated with MDS. In this study, we identified a novel gene near the BCR at 1p36.3 of t(1;3)-positive MDS/AML. Because the novel gene is a member of the *MDS1/EVI1* gene family, we designated it as the *MEL1* gene. The *MEL1* gene is expressed in t(1;3)-positive MDS/AML leukemia cells but not in other leukemia cell lines and normal hematopoietic cells, suggesting that the *MEL1* gene is transcriptionally activated in association with t(1;3)(p36;q21) and contributes to the pathogenesis of MDS and AML with t(1;3)(p36;q21).

In this study, we have isolated 2 genes from the BCRs of t(1;3)(p36;q21), which are the *RPN1* gene at 3q21 and the *MEL1* gene at 1p36. In AML, many transcription factors have been isolated as fusion proteins by the translocation, except the *EVI1* protein in 3q21q26 syndrome. In MDS-derived AML with t(3;3) or inv(3), the 3q21 region with the *RPN1* gene near the BCR, was translocated to the 5' region of the *EVI1* gene by the t(3;3)(q21;q26) and to the 3' region of the *EVI1* gene by the inv(3)(q21q26) with high expression of the *EVI1* gene. It was reported that a fusion transcript between the *RPN1* and *EVI1* genes was detected in a leukemia case with t(3;3)(q21;q26) by RT-PCR.²⁴ However, we did not detect any fusion transcripts or proteins between the 2 genes in the cases with t(3;3)(q21;q26) by Northern hybridization⁵ and by Western blotting analyses (data not shown). In MDS-derived AML with t(1;3)(p36;q21), the same 3q21 region with the *RPN1* gene was also translocated to the 5' region of the *MEL1* gene at 1p36 with high expression

of the *MEL1* gene. We examined the expression of both *RPN1* and *MEL1* genes in leukemia cells with t(1;3) by Northern hybridization and RT-PCR. A 2.4-kb *RPN1* transcript was expressed in all of the leukemia cells,¹⁰ and 8-kb and 5-kb *MEL1* transcripts were expressed in the cases with t(1;3). No fusion cDNA was detected in the leukemia cells with t(1;3). Therefore, it is likely that transcriptional activation of the *EVI1* gene and the *MEL1* gene may have occurred by a common molecular mechanism in both types of chromosomal translocations (Figure 6). In a previous report,²⁵ it was shown that the 5' flanking regions of the rat *RPN1* gene contained 2 GC-rich elements and an octamer motif, which were required for basic and responsive promoter activities, respectively. Therefore, it can be speculated that the 3q21 region with the *RPN1* gene activated transcription of the *MEL1* gene as an enhancer mechanism.

By comparison to the *EVI1* protein, the *MEL1* protein has an extra PR domain at the N-terminal end. The PR (PRDI-BF1, RIZ1) domain is in the coding region of *MDS1* with noncoding exon 2 in the *EVI1* gene and is conserved among RIZ, PRDI-BF1, and egl-43^{21,22} and is homologous to the SET (Suvar3-9, Enhancer-of-zeste, Trithorax) domain that is involved in chromatin-mediated gene activation and silencing.²⁶ We have isolated *MEL1* cDNAs with the PR domain (*MDS1/EVI1* type) but not without the PR domain (*EVI1* type). By comparison of amino acid sequences between *EVI1* and *MEL1*, the first and second methionine residues in the *EVI1* protein were replaced to valine residues in the *MEL1* protein. Thus, it is possible that translation of a truncated *MEL1* protein starts from 2 internal methionine residues in the PR domain (Figure 2A). Interestingly, it is reported that *EVI1* protein is a transcriptional repressor protein, but *MDS1/EVI1* protein is a transcriptional activator protein,²⁷ suggesting that the PR domain changed its transcriptional regulation. Moreover, it is reported that *EVI-1* represses transforming growth factor β 1 (TGF- β 1)-mediated growth suppression in 32Dcl3 cells, but *MDS1/EVI1* enhances TGF- β 1 signaling and strengthens its growth-inhibitory effect.²⁸ On the basis of these studies, it is suggested that the *MEL1* protein with the PR domain may have distinctly different functions of transcription regulation and TGF- β 1 responsiveness from those of the *EVI1* protein. In our preliminary data, 2 different-sized *MEL1* proteins were detected by in vitro transcription and translation analysis. Therefore, we are currently trying to identify and characterize 2 forms of *MEL1* proteins expressed in the leukemia cells with t(1;3).

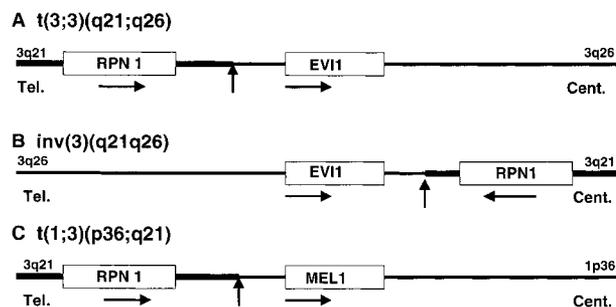


Figure 6. Schematic illustration of gene activation model in each chromosomal abnormality of 3q21q26 syndrome and t(1;3)-positive AML. The position and orientation of *RPN1*, *EVI1*, and *MEL1* are indicated by a horizontal arrow. Tel indicates telomere; Cent, centromere. The vertical arrows indicate the position of breakpoint cluster regions.

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