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Research Article

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Rearrangements of the Retinoic Acid Receptor Alpha and Promyelocytic Leukemia Zinc Finger Genes Resulting from t(11;17)(q23;q21) in a Patient with Acute Promyelocytic Leukemia

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Abstract

Cytogenetic study of a patient with acute promyelocytic leukemia (APL) showed an unusual karyotype 46,xy,t(11;17)(q23;q21) without apparent rearrangement of chromosome 15. Molecular studies showed rearrangements of the retinoic acid receptor alpha (RAR α) gene but no rearrangement of the promyelocytic leukemia gene consistent with the cytogenetic data. Similar to t(15;17) APL, all-*trans* retinoic acid treatment in this patient produced an early leukocytosis which was followed by a myeloid maturation, but the patient died too early to achieve remission. Further molecular analysis of this patient showed a rearrangement between the RAR α gene and a newly discovered zinc finger gene named PLZF (promyelocytic leukemia zinc finger). The fusion PLZF-RAR α gene found in this case, was not found in DNA obtained from the bone marrow of normals, APL with t(15;17) and in one patient with AML-M2 with a t(11;17). Fluorescence in situ hybridization using a PLZF specific probe localized the PLZF gene to chromosomal band 11q23.1. Partial exon/intron structure of the PLZF gene flanking the break point on chromosome 11 was also established and the breakpoint within the RAR α gene was mapped ~ 2 kb downstream of the exon encoding the 5' untranslated region and the unique A2 domain of the RAR α 2 isoform. (*J. Clin. Invest.* 1993. 91:2260–2267.) Key words: novel gene rearrangements • retinoic acid receptor • leukemia

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1. *Abbreviations used in this paper:* APL, acute promyelocytic leukemia; ATRA, all-*trans* retinoic acid; PLZF, promyelocytic leukemia zinc finger; PML, promyelocytic leukemia; RAR α , retinoic acid receptor alpha; RT-PCR, reverse transcription PCR.

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Introduction

Acute promyelocytic leukemia (APL)¹ is characterized by the chromosomal translocation t(15;17)(q22;q21) that is present in almost all patients (1, 2). Recently, molecular studies showed that the t(15;17) results in a chimeric gene (PML-RAR α) with fusion between promyelocytic leukemia (PML) and retinoic acid receptor alpha (RAR α) genes normally localized on bands 15q22 and 17q21, respectively (3, 4). RAR α is a member of the nuclear receptor superfamily gene, whereas PML may be a transcription factor belonging to a new family of DNA binding proteins (5–7). The chimeric PML-RAR α gene is thought to play an important (but as yet undefined) role in differentiation and/or proliferation of APL cells.

Variant translocations have been reported in APL. They are in most instances three way translocations involving chromosomes 17, 15, and a third chromosome (8). Here we present clinical and cytogenetic data on a Chinese patient with APL and a variant translocation t(11;17)(q23;q21) between a newly discovered gene (9), designated as PLZF (promyelocytic leukemia zinc finger), and the RAR α locus. The PLZF gene is normally situated on a band 11q23.1 and is fused to RAR α as a result of the above reciprocal translocation to form two new chimeric genes PLZF-RAR α and RAR α -PLZF. Additionally, we show that both PLZF(A)-RAR α and PLZF(B)-RAR α mRNAs were expressed in the bone marrow cells isolated from this patient.

Methods

Cytological and cytogenetic studies. The diagnosis of APL (M3) was established according to the criteria of the FAB classification (10). Cytogenetic analysis was performed on 24 h in vitro cultures of bone marrow cells. GTG-banding and RHG-banding techniques were applied. Chromosomes were classified according to the international nomenclature (11).

DNA and RNA analysis. The high molecular weight DNA was extracted according to standard procedures (12). For controls, a number of DNA samples from APL with the common t(15;17) and one AML-M2 with t(11;17)(q23;q21) were analyzed. DNAs were digested with EcoRI, BglII, and HindIII to completion, size fractionated on 0.7% agarose, and Southern blotted.

Molecular cloning. Using the PLZF specific cDNA probe (9), a previously described human genomic DNA library (13) was screened. A positive phage clone 20+ was obtained (Fig. 3A, IV). The restriction map was established using a series of double digestions. A 2.3-kb BamHI-BglII fragment (probe MB) hybridizing to the PLZF probe

and free from repetitive sequences was isolated for in situ hybridization and Southern analysis. Subsequently, a 2.1-kb BglIII-EcoRI fragment situated just 3' to the MB probe was generated to perform the chromosome walking.

In situ hybridization. Fluorescence in situ hybridization to high resolution R-banded metaphase chromosomes was performed with the biotinylated probe MB, according to (14). Chromosomes were examined with a Leitz fluorescence microscope as previously described (14).

Reverse transcription PCR (RT-PCR) analysis. RNAs were extracted with the guanidium thiocyanate CsCl gradient method. The general conditions of RT-PCR were according to the previously described procedure (15). PLZF specific primers were designed according to the PLZF cDNA sequence (9) whereas primers homologous to PML and RAR α were according to the previously published sequences (6) (see Fig. 6A) for the positions of each oligos). In both PML-RAR α and PLZF-RAR α analyses, the same set of RAR α derived oligonucleotides were used as retrotranscription primer (oligo g: 5' GTTCGTAGTGTATTTGCCAGCTGGCAGAG 3') and the 3' PCR primer (oligo f: 5' GGCTGTAGATGCGGGTAG 3'). The 5' primer used in PML-RAR α RT-PCR was derived from PML exon 3 (5' ATGGCTTCGACGAGTTCAAG 3') allowing the detection of both long (L) and short (S) PML-RAR α isoforms (15). For analyzing the PLZF-RAR α isoforms, different PLZF specific 5' primers were used: oligo a (situated upstream of the alternatively spliced exon): 5' GACAATGACACGGAGGCCAC 3'; oligo c (situated within the alternatively spliced exon): 5' AACCACAAGGCTGAC-GCTGT 3'. Different oligonucleotide probes were also used including: oligo e (for RAR α): 5'

GCTGGGCACTATCTCTTCA 3'; oligo c (for the alternatively spliced PLZF exon): 5' ATTGAGCATGCCGTCTCCG 3'; oligo b (upstream to the alternatively spliced PLZF exon): 5' AGGACCGCAAGGCTCGGTAC 3' and an oligo probe specific for PML exon 3: 5' AGCTCTTGCATACCCAGG 3'.

Sequence analysis. DNA sequence was established according to the dideoxynucleotide method using the Sequenase Version II Kit (U.S. Biochemical Corp., Cleveland, OH).

Results

Clinical data. The patient was a 67-yr-old man complaining about weakness and anorexia for 1 mo, as well as coughing and gingival bleeding for a few days. Physical examination noted pallor, signs of bronchitis, purpura of the tongue without other obvious bleeding signs, cervical lymphadenopathy, and absence of hepatosplenomegaly. The renal and hepatic function tests were normal. Disseminated intravascular coagulation was not diagnosed, but occult blood in the stool was detected. The peripheral white blood cell count was 4.1×10^9 /liter. Bone marrow was hypercellular with 69% APL-like promyelocytes, but without Auer rods. The myeloperoxidase reaction was strongly positive.

The patient was classified as APL and was given all-*trans* retinoic acid (ATRA) at a dose of 60 mg/d. On day 8, the white blood cell count increased to 61×10^9 /liter with 72% promy-

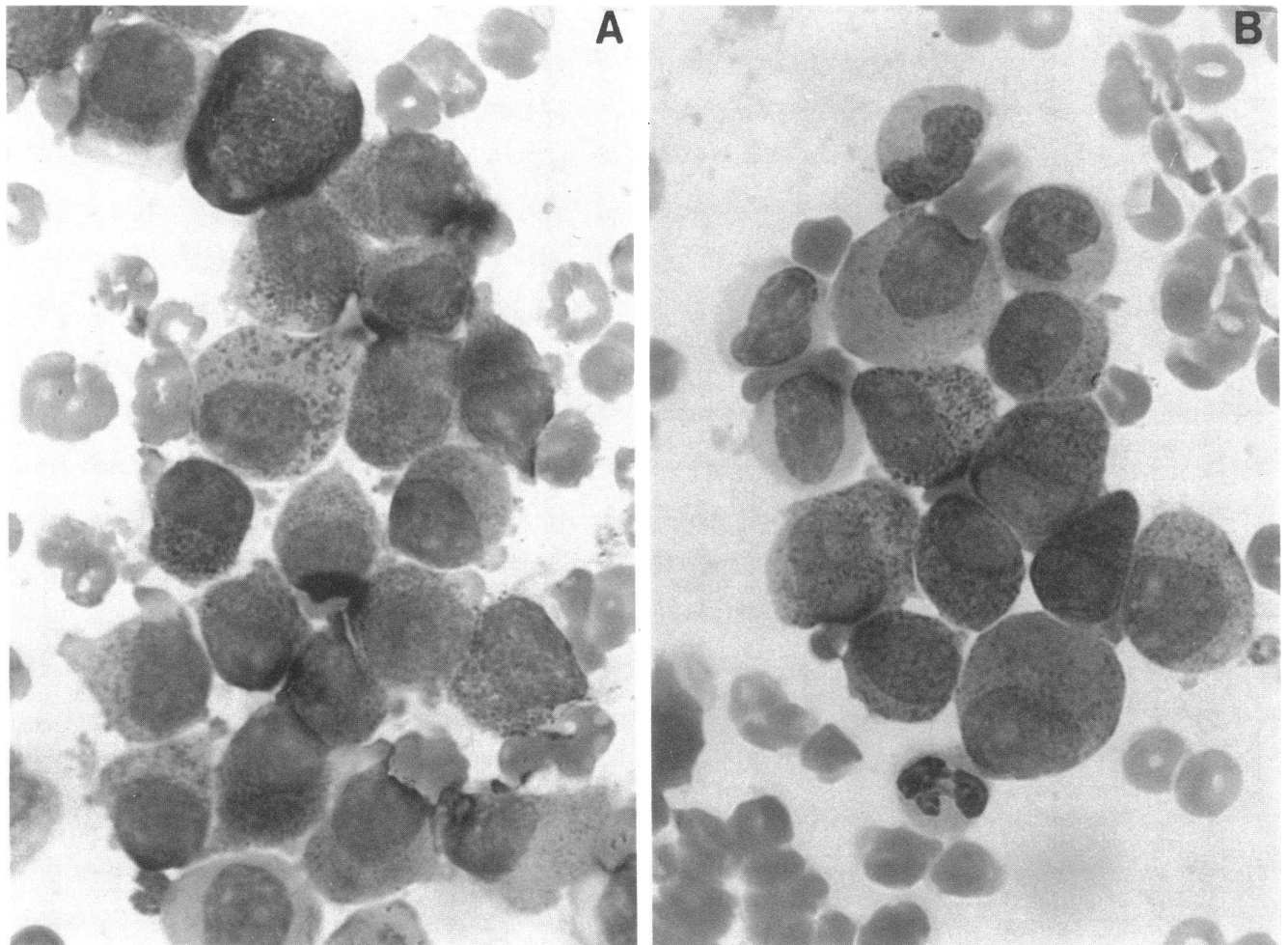


Figure 1. Bone marrow sample of the patient with APL t(11;17). (A) Hypergranular leukemic promyelocytes before treatment. (B) After 16 d of all-*trans* retinoic acid treatment, the blast cells were still present while some mature myeloid cells could be observed.

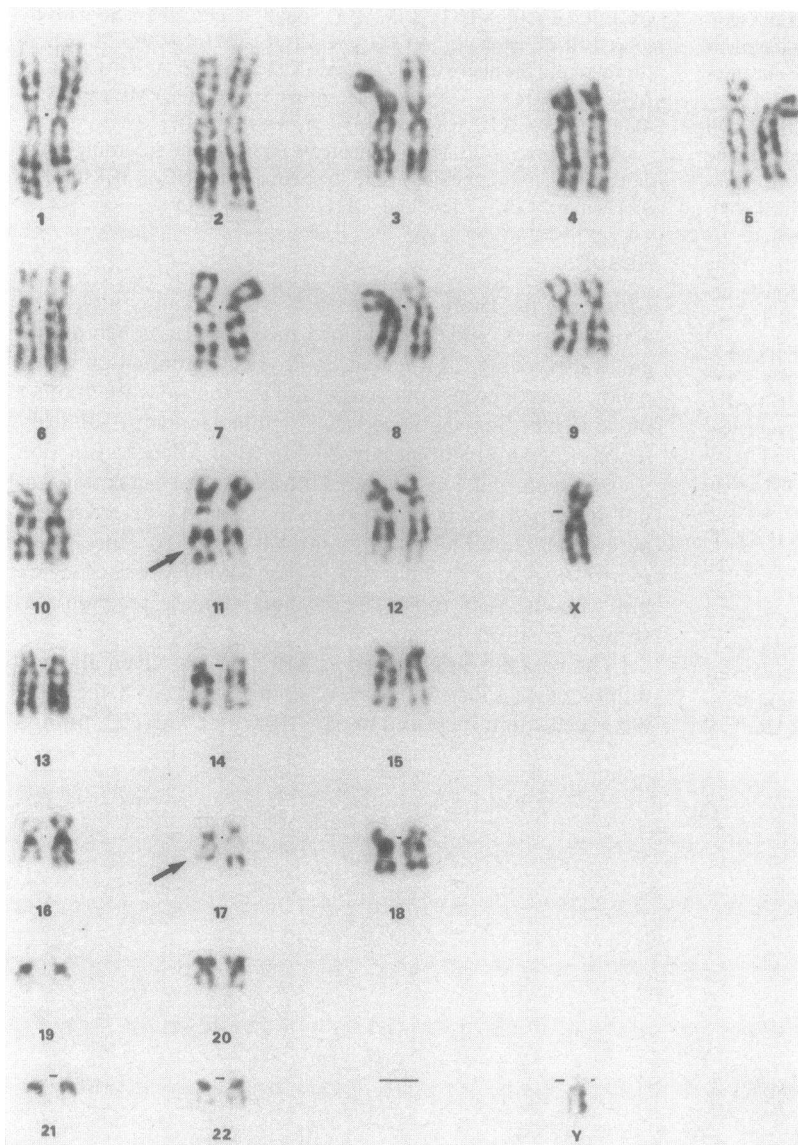


Figure 2. Karyotype analysis of the bone marrow of the patient with APL $t(11;17)$ (GTG bands): $46,XY,t(11;17)(q23;21)$.

elocytes and the bone marrow contained 77% promyelocytes. The white blood count increased to 131×10^9 /liter on day 11 (promyelocytes 75%) and hepatosplenomegaly was noted for the first time. On day 16, the white blood cells decreased to 71×10^9 /liter with 63% promyelocytes present in bone marrow smears, although an increase in more mature myeloid cells began to appear (Fig. 1). The ATRA treatment was continued until day 19. However, the patient developed pneumonia and respiratory failure, and he died on day 20.

Cytogenetics. Out of 20 metaphases examined, two were normal, $46,XY$, and 16 were abnormal: $46,XY,t(11;17)(q23;21)$ (Fig. 2). The two remaining metaphases showed the $t(11;17)$ and chromosome random losses.

Molecular evidence demonstrating the fusions between the $RAR\alpha$ and $PLZF$ genes. Southern analysis of DNA obtained from the patient with $t(11;17)$ APL revealed no rearrangement of the PML gene (data not shown) and using a $PLZF$ genomic DNA probe (MB) (see Fig. 3 A, IV) revealed rearranged bands following $EcoRI$ and $HindIII$ digestion (Fig. 3 B). No rearrangements or $PLZF$ were detected in bone marrow DNAs in three normals, 10 APL patients with $t(15;17)$, and one AML-M2 with a $t(11;17)$ (data not shown).

The $RAR\alpha$ gene was also rearranged in this case and the rearranged bands in $EcoRI$ and $HindIII$ revealed by both probes had the same size. According to our previously established $RAR\alpha$ restriction map (Fig. 3 A, I) (13), this rearrangement is located in the intron between exon 3 encoding the 5' untranslatable region and the unique A2 domain of the $RAR\alpha$ isoform and exon 4 encoding the B region of $RAR\alpha$.

The $PLZF$ gene is localized on chromosomal band 11q23.1 by *in situ* hybridization. *In situ* hybridization of the 2.3-kb MB probe to normal metaphases showed hybridization signal as twin spots on the chromatids of one chromosome 11, subband 11q23.1 in 18 metaphases. Only one metaphase had double spots on both chromosome 11. Two metaphases showed aberrant double spots on bands 1p34 and 15q21 respectively, in addition to the localization on 11q23. It was concluded that the 2.3-kb MB probe representative of the $PLZF$ gene was localized on 11q23.1 (Fig. 4).

Molecular characterization of partial genomic $PLZF$ gene region harboring the breakpoint on chromosome 11. The genomic studies allowed us to clone a partial $PLZF$ region of 70 kb containing the 3' part exonic sequence in the open reading frame (Fig. 3 A, IV). We identified the exon just upstream of

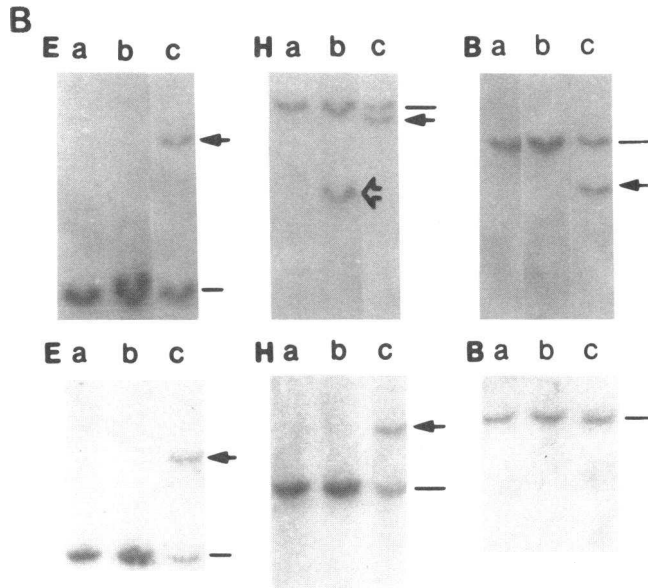
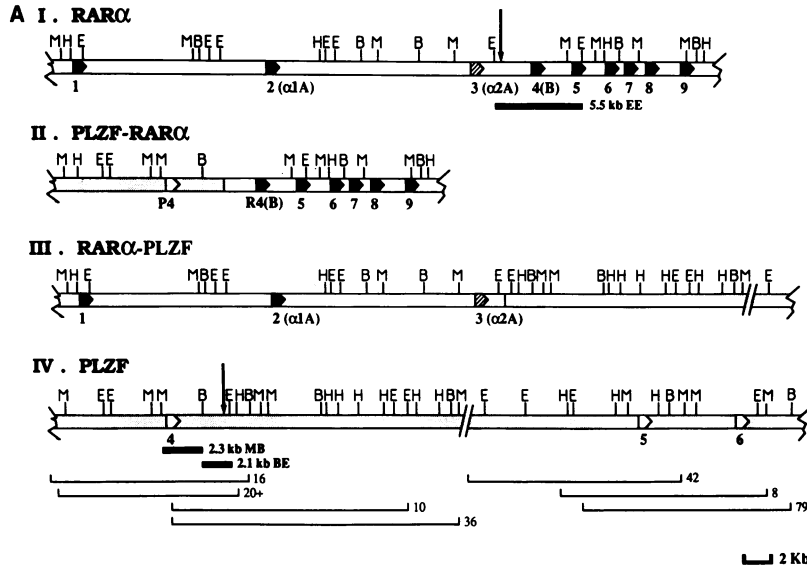


Figure 3. Chromosomal breakpoints in the RAR α and PLZF genes. (A) I. Genomic organization of the RAR α gene. Arrowed black boxes represent exons. Exons 2, 3, and 4 encode the α 1 isoform A region, α 2 isoform A region, and the RAR α B region respectively. The chromosome 17 breakpoint was located within intron 3 (arrow). The position of the 5.5 kb EcoRI-EcoRI (EE) genomic probe is shown below the map. Abbreviations for restriction sites: B, BglIII; E, EcoRI; H, HindIII; M, BamHI. II. PLZF-RAR α restriction map III. RAR α -PLZF restriction map. II and III are deduced from I and IV. IV. Partial restriction map of the PLZF gene established from the analysis of seven phage clones (bottom). The three open arrowhead boxes correspond to the exons upstream (4) and downstream (5 and 6) of the breakpoint (arrow). (B) Southern analysis of the RAR α (I) and PLZF (II) genes in APL patients with t(15;17) (b) and t(11;17) (c), and in a control (a) with the EE and MB probes, respectively. E, EcoRI; H, HindIII; B, BglIII. The rearranged bands are identified by arrows.

the breakpoint and two exons downstream (Fig. 5 for sequence). The chromosome 11 breakpoint was within an intron which separate exons encoding the second and the third PLZF zinc fingers, respectively. There is an uncloned region in this intron as shown in Fig. 3 A, predicting PLZF to be a very large gene.

Both PLZF (A)-RAR α and PLZF (B)-RAR α chimeric transcripts are expressed in patient with t(11;17) positive APL. Recently, we have described the existence of two PLZF isoforms (A) and (B), differing by a proline-rich 369-bp exon that probably resulted from an alternative splicing mechanism (9). As the proline-rich domain has been implicated in transcription regulation, it was important to see if both PLZF isoforms could be transcribed in the PLZF-RAR α fusion gene mRNA. Therefore, we performed RT-PCR using primers homologous to this exon and to the RAR α B region. A specific band was obtained in the t(11;17) sample but not in two t(15;17) samples (Fig. 6 B). Furthermore, when the 5' primers were replaced by those just upstream of this exon, two amplified bands

were observed (Fig. 6 B). These results were confirmed by sequence analysis and demonstrated that two PLZF-RAR α isoforms existed in the t(11;17) patient, which differed from each other by the presence or absence of one PLZF exon. As shown in previous work, two isoforms of RAR α -PLZF transcripts were also present in this case by the use of RAR α 1 or RAR α 2 promoters. This is consistent with the genomic structure of the reciprocal fusion gene RAR α -PLZF (Fig. 3 A, III) (9).

Discussion

Cytogenetic study of a patient with APL showed an unusual karyotype 46,XY,t(11;17)(q23;21) without apparent rearrangement of chromosome 15. Molecular studies showed rearrangement of the RAR α gene but no rearrangement of PML consistent with the cytogenetic data. The leukemic cells resembled the abnormal promyelocytes seen in the usual APL, with



Figure 4. Fluorescence in situ hybridization of the MB probe to control R-banded metaphase cell. A hybridization signal is visible on the two chromatids of a chromosome 11, on band 11q23. Counterstaining by propidium iodide.

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GGATCCAGGGATGTGTTTCCATCGGTGCCCTCCTGTCCCTCCGCCTGTCACCTGCCAG 60
AGGGATGGCTGCCAAGCCCCAGGTAGGGGATGGCCCTGCCTCTTGTCAGCCAGAGCAG 120
      ← Zf1
      K L H S G M K T Y G
CAGCAACCTCTCTTTTCCTTTCCCTTACAGGAAGCTGCACAGTGGGATGAAGACGTACGG 180
┌── Zf2 ──┘
C E L C G K R E L D S L R L R M H L L A 240
GTGCGAGCTCTGCCGGAAGCGGTTCCCTGGATAGTTGCGGCTGAGAATGCACTTACTGGC
H S
TCATTCAGGTAGGCAAGTTCGCCTTAGTGGCCCGTTCAGATACAGGCAACCATCTCCTGC 300
TTGCCTTTACCCCTCCTCAGAGCCTGTGTGGCCTGCATGTGGGACTGCCCGCTGGGGC 360
CCTGGTCCATCTTGTTCCTGGACCCTCCCTCCAGGCTTATGACACAGAAGATCCATCCT 420
GATGGCGGGGCCACTTGGATGAACCCACCTTCAAGCTCTCGTGGGTTTCCAGGCATCAG 480
TGCCAACCAGTGCCTGTGTGATCTACCTTCCAAAGTAGACTGCAG 525

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Figure 5. Nucleic acid sequence of the 525-bp PstI genomic DNA fragment containing the PLZF exon 4. The splicing acceptor (AG) and donor (GT) signals are underlined. The amino acid sequence encoded by this exon is shown in one-letter codes above the DNA sequence. One histidine at the end of the first PLZF zinc finger and two cysteins and two histidines constituting the second C2H2 zinc finger are circled. This exon is situated upstream of the PLZF breakpoint and is fused to the RAR α B region in PLZF-RAR α chimeric transcripts.

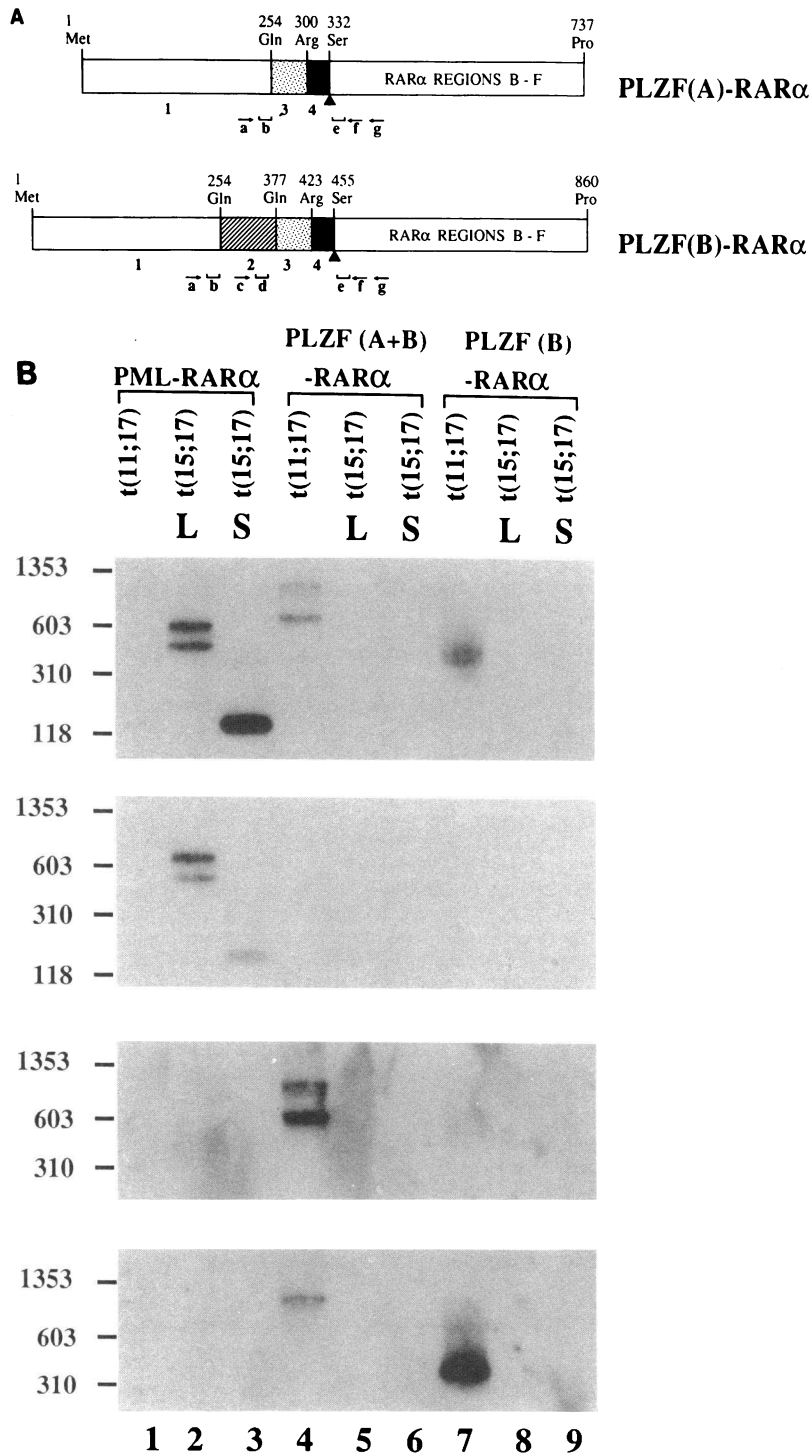


Figure 6. (A) Schematic representation of the protein-coding region of the two PLZF-RAR α isoforms that differ by the presence (PLZF(B)-RAR α) or absence (PLZF(A)-RAR α) of PLZF B isoform exon (here temporarily referred to as exon 2). The exon which was fused to RAR α B-region is defined by genomic DNA analysis (exon 4, see Fig. 5). The sequence between exons 2 and 4 could be one PLZF exon (exon 3). The exon composition in the region 1 remains to be established. The first and last amino acids, as well as those at the ends of exons 1 to 4, are represented by three-letter codes and are numbered according to Chen et al. (9). The black triangles indicate the junction between PLZF and RAR α coding sequences. The positions of oligonucleotides used in PCR analysis of PLZF-RAR α isoforms are indicated either by arrows (primers) or by bars (probes). The nucleic acid sequences of these oligonucleotides are shown in Materials and Methods. (B) RT-PCR experiments showing the specific presence of PLZF(A)-RAR α and PLZF(B)-RAR α isoforms in leukemic cells with the t(11;17). RNA derived from the t(11;17) cells (lanes 1, 4, and 7), the t(15;17) cells expressing the long (L, lanes 2, 5, and 8) or short (S, lanes 3, 6, and 9) PML-RAR α fusion transcripts were analyzed. The retrotranscription was carried out in all cases using oligonucleotide g corresponding to the B region of RAR α . For detecting the PML-RAR α fusion transcripts (lanes 1-3), 5' primer homologous to the PML exon 4 and 3' primer situated in RAR α B region (oligonucleotide f) were used. For analyzing PLZF-RAR α isoforms, two different 5' primers were used, which allow to amplify either both isoforms (oligonucleotide a, lanes 4-6) or only the PLZF(B)-RAR α isoform (oligonucleotide c, lanes 7-9) when the same 3' primer (oligonucleotide f) were used. PCR products on the same blot were hybridized sequentially to different probes specific for RAR α B region (oligonucleotide e, I); PML exon 3 (II); PLZF region 1 (oligonucleotide b, III); and PLZF B form exon (oligonucleotide d, IV). Molecular standards are shown in basepairs on the left. Note that the PML-RAR α PCR products were present only in the t(15;17) samples, while those of the PLZF-RAR α were detected only in t(11;17) cells. In addition, in different sets of PCR, two bands corresponding to the PLZF(A)-RAR α and PLZF(B)-RAR α (lane 4, I and III) or one band specific for the PLZF(B)-RAR α (lane 7, I and IV) were obtained when appropriate primer pairs were used.

the exception that Auer rods were not present. Similar to t(15;17) APL, ATRA treatment exacerbated a leukocytosis that was followed by morphologic evidence of myeloid maturation, but the patient died before treatment could be fully evaluated. These data are consistent with the diagnosis of APL, with a variant translocation.

Variant translocations have been reported in APL. These may involve three or more chromosomes including 15 and 17. In other cases, only two chromosomes were apparently involved and the translocations were between 17 and another

chromosome in most instances. In these cases, the two 15 chromosomes were morphologically normal (16). This is reminiscent of the variant Ph translocations in chronic myelogenous leukemia, in which a BCR-ABL rearrangement was consistently found even when chromosomes appeared normal under the microscope (17). There is, however, no data presently available describing molecular rearrangements associated with variant translocations of APL. The RAR α gene was not rearranged in one patient without apparent involvement of chromosome 17 (5). Rearrangement of the RAR α and PML genes was pres-

ent in another patient with an unusual abnormal karyotype without apparent chromosome 15 rearrangement (Baranger et al., manuscript submitted for publication).

A variant t(11;17) positive APL was previously reported (18) but not studied for molecular rearrangements. In the present case, the t(11;17) was associated with rearrangement of the RAR α gene while the PML gene was structurally intact. The chromosome 11 gene (PLZF) involved in rearrangement with RAR α in this unique case of APL has recently been cloned (9). This gene has some homology with the zinc finger gene MZF-1 (19) and is also retinoic acid responsive and preferentially expressed in myeloid cells (19). Because of t(11;17), the PLZF gene is disrupted in its zinc finger containing region, with fusion of two zinc fingers to the RAR α B region in the PLZF-RAR α fusion gene, while seven zinc fingers joined the RAR α region in the reciprocal RAR α -PLZF chimeric gene. It is noteworthy that the RAR α gene was disrupted in its third intron as commonly found in the standard t(15;17). The association of both PML-RAR α and PLZF-RAR α fusions with the APL phenotype argues for a key role for RAR α in the hybrid genes. In support of this is the observation that two cases of myelodysplastic syndrome transformed to APL with trisomy 11 without RAR α rearrangements, failed to respond to ATRA (20). However, since the role of PML and PLZF in leukemic cell proliferation and differentiation remains largely unknown, it is also possible that PML and PLZF have an equivalent function when rearranged with the RAR α gene.

Chromosomal band 11q23 is rearranged in several varieties of hematopoietic malignancies (17). Breakpoints of chromosome 11 in acute leukemias with t(4;11), t(6;11), t(9;11) and t(11;19) have been localized within 300 kb downstream of the CD3D gene (21–24). The breakpoint was found more distal in a leukemia with t(11;19) than in leukemias with one of the other three translocations (25), suggesting that there is a heterogeneity in the localization of the breakpoints within the band 11q23, as already shown for the t(11;14)(q23p;q32) translocation of lymphoid malignancies (26, 27). The localization of the PLZF gene on 11q23.1, which is centrometric to the other breakpoint localizations of most of the recurrent translocations of hematopoietic malignancies, also argues in favor of the breakpoint heterogeneity of malignancies with 11q23 rearrangements. Interestingly, the molecular study of another translocation t(11;17) detected in a patient with acute myeloblastic leukemia M2, and thus clinically and cytologically different from APL, did not show rearrangements of the RAR α nor PLZF genes. In our most recent studies, we have identified a second case of t(11;17) APL (in collaboration with Wilson Miller) which expressed the PLZF-RAR α fusion gene. This is concordant with the specificity of the gene rearrangements in APL. The PLZF gene is a putative transcription factor that appears to be associated with myeloid differentiation (9) and may be deranged in other myeloid malignancies. The identification of PLZF justifies that molecular studies of other APL variant translocations should be systematically performed to determine if genes other than PML (or RAR α) may be involved in these APLs.

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