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Phylogenetically Interrelated *ETS* Genes, *ETV1, ERM* and *E1A-F* Locate on Different Chromosomes

ETV1, ERM and *E1A-F* are members of the multigene ETS domain containing a class of transcription factors, first identified in the genome of the avian retrovirus E26. Based upon extensive homology between these genes within their ETS domain (96% identity each other), these three genes comprise a distinct sub-family of *ETS* genes as a human *PEA3* sub-family. By analyzing somatic cell hybrid segregating human chromosomes, the genes encoding *ETV1, ERM* and *E1A-F* were localized to human chromosome 7, 3 and 17, respectively. Fluorescence in situ hybridization confirmed these assignments and allowed mapping of the genes to 7p22 (*ETV1*), 3q29 (*ERM*) and 17q12 (*E1A-F*). These results suggest the ancestral *PEA3* gene may have duplicated first, then dispersed to other chromosomal locations.

Key Words : *ETV1; ERM; E1A-F; Chromosome location*

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INTRODUCTION

The cellular *ETS* genes were isolated on the basis of their homology to *v-ETS* which is transduced by the E26 retrovirus and forms part of the 135 kDa *GAG-MYB-ETS* tripartite fusion protein that gives rise to a mixed erythroid and myeloid leukemia in chickens (1-3). Since the discovery of the cellular counterpart of *v-ETS, ETS* genes sharing a highly conserved DNA binding domain (ETS domain) have now been found over 30 members in species ranging from flies to humans (3). The *ETS* genes encode an increasingly growing family of transcription factors which are involved in normal development but some of these genes can become oncogenic by retroviral insertional mutagenesis or included in a chimeric protein as a result of a translocation event (4-6). Even if most of the *ETS* family members have the widely conserved ETS domain and bind to the core sequence 5'-AGGAAG-3' (7), the ETS domain of all *ETS* protein is, however, variable from member to member, allowing classification of *ETS* members in several sub-families with respect to their ETS domain sequence identity (8).

The *PEA3* which binds to the polyomavirus enhancer has been isolated in the mouse embryonic cells (9). Recently, the E1A enhancer binding protein, *E1A-F*, a human homologue of murine *PEA3* was isolated (10). Another homologue, human *ERM* which contains an ETS domain which shares 96% identity with *PEA3* was cloned (11). Furthermore, the isolation of *ETV1*, a human homologue of murine *ER81*, expands the members of *PEA3* sub-family (12, 13). Based upon the extensive homology between *ETV1, ERM* and *E1A-F* within their ETS domain, these three genes comprise a distinct sub-family of *ETS* genes in humans. Although little is known concerning the functional role of these proteins, Monte et al. (11) have demonstrated that human *ERM* is over-expressed in melanoma, and other solid and hematologic tumors. Moreover, the *ETV1* has been cloned in Ewing's sarcoma accompanying the chromosome translocation t (7;22) (p22;q12) (12). These results suggest that the *PEA3* sub-family might be related to oncogenesis.

The sequence conservation and the chromosome locations of the genes provide clues to gene duplication and divergence events that gave rise to this gene family. For example, *ETS1* and *FLI1* both are mapped to the same region of human chromosome 11q23 (5, 14), while *ETS2* and *ERG* both are mapped to 21q22 (14, 15). However, the homology between *ETS1* and *ETS2* and between *FLI1* and *ERG* is greater than the homology between those genes that map next to each other on the same chromosome (5). This suggests that the 'uncommitted' *ETS/ERG* ancestor was duplicated first to yield the distinct *ETS* and *ERG* progeny which remains closely linked on the same region of the genome. Then, the two 'uncommitted' *ETS* and *ERG* genes were duplicated and the pair might have been dispersed to another chromosome

(8). These findings could suggest that the ancestor of *PEA3* duplicated first, then dispersed to other chromosomes. We tested this hypothesis by assigning the human *PEA3* sub-family to each specific human chromosomes.

MATERIALS AND METHODS

Somatic cell hybrids

Hybrid cell lines with the prefix "GM" in Table 1 were obtained from the National Institute of General Medical Sciences Human Genetic Mutant Cell Repository (Coriell Institute for Medical Research, Camden, NJ); the characterization and human chromosome content of these hybrids are described in the repository catalog. Human x hamster somatic cell hybrid lines A1, A4, A5, A6, C1 and PB5-1 have been derived by polyethylene glycol fusion of cryopreserved leukemic marrow blasts with E36 hamster cells, according to the method used by Lemons et al. (16); A4, A5 and C1 hybrids contain a der (3) or der (5) from a balanced translocation, t (3; 5) (q25; q34), together with other human chromosomes, as indicated in Table 1.

Amplification of DNA from the human x hamster somatic cell hybrid lines

Analysis of genomic DNA from the 34 somatic cell hybrid lines (29 independent fusions) was performed by amplifying a 113-bp *ETV1* genomic target, 277-bp *ERM* target and 300-bp *E1A-F* target using PCR primers homologous to code and 3'-untranslated regions of each genes. In the cases of *ETV1*, we selected the forward PCR

Table 1. Assignment of the *ETV1, ERM* and *E1A-F* loci to human chromosomes 7, 3 and 17 in human X rodent somatic cell hybrids

Hybrid	*ETV1*	*ERM*	*E1A-F*	Human chromosomes																							Rearranged chromosomes*
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y	
1) GM06317	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	
2) GM07297	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	
3) GM07299	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	
4) GM07300	−	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	
5) GM07301	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	+	−	
6) GM08854	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	
7) GM09927	+	+	+	+	+	+	+	−	+	+	+	−	+	−	−	+	+	+	+	+	+	+	−	−	−	−	
8) GM09934	−	−	+	−	+	−	−	+	+	−	+	−	−	+	+	−	−	+	−	+	+	−	+	+	−	−	
9) GM10027	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	
10) GM10114	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
11) GM10115	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
12) GM10156	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
13) GM10253	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
14) GM10324	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	
15) GM10449	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	
16) GM10478	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	
17) GM10479	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	
18) GM10498	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	
19) GM10611	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
20) GM10629	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
21) GM10791	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
22) GM10826	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
23) GM10868	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	
24) GM10888	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	
25) GM10892	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	
26) GM10926	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	
27) GM11418	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	
28) GM11679	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
29) A1	+	+	−	−	−	+	−	+	+	+	−	−	−	−	+	+	−	+	−	−	−	−	−	+	+	+	−	
30) A4	+	+	−	−	−	+	−	−	+	+	−	−	−	−	+	−	−	−	+	−	+	−	+	+	+	+	−	der5
31) A5	+	+	−	−	−	+	−	−	+	+	−	−	−	−	+	−	−	−	+	−	+	−	+	+	+	+	−	der5
32) A6	−	−	−	+	−	−	−	−	−	−	+	−	−	−	−	+	−	+	−	−	−	+	−	+	−	+	−	der3
33) C1	−	+	−	−	−	+	−	−	−	−	−	+	−	+	+	−	−	−	−	−	−	−	−	−	−	+	−	
34) PB5-1	−	−	+	+†	+	−	−	+‡	−	−	−	−	+§	−	−	−	−	−	+	−	+	−	−	−	−	−	−	
% Discordant *ETV1*				24	18	12	21	24	15	0	24	24	18	30	21	18	18	21	9	24	12	24	15	9	15	26	21	
% Discordant *ERM*				26	26	0	24	26	18	18	26	24	21	26	18	21	21	21	12	24	15	26	18	21	18	18	24	
% Discordant *E1A-F*				12	6	26	15	12	21	24	12	18	12	12	26	18	9	15	15	0	12	12	15	24	24	32	15	

Note: Chromosomes were scored positive if they were present in ≥25% cells.
*der3 (3pter→3q25.1::5q34→5qter); der5 (5pter→5q34::3q25.1→3qter); +†, cen-p32; +‡, p33-qter; +§, cen-pter.

primer starting from nucleotide (nt) 1405 to 1428 (5'-CACCCCTACAACGAAGGCTACGTG-3') and reverse primer from nt 1500 to 1517 (5'-ATAAAACAAAGATTCAGC-3') (12). In the case of *ERM*, the forward primer consisted of nt 1693 to 1716 (5'-AGCAGCCTCCCCTATGCCGAAGGC-3') and the reverse primer consisted of nt 1942 to 1969 (5'-CCTCATCAGAATCAAGAGTTGAGGCACT-3') (11). Finally, we selected the *E1A-F* forward PCR primer starting from nt 1357 to 1380 (5'-CCATTTGGCCCCAAGGGTGGCTAC-3') and the reverse primer starting from nt 1629 to 1656 (5'-CTAGGAAGAAGCTGAGCTGAATTCCTCC-3') (10). The amplification conditions were 94℃ for 1 min, 60℃ for 2 min and 72℃ for 3 min repeated for 40 cycles. The products were separated on 1.5% agarose gels followed by ethidium bromide staining. The specific PCR product was confirmed by each corresponding size of the nucleotide. Localization of a human DNA sequence to a single chromosome was inferred by deduction.

Fluorescence in situ hybridization

Bromodeoxyuridine-synchronized, phytohemagglutin-stimulated peripheral blood lymphocytes from a normal donor were used as a source of metaphase chromosomes. Human genomic DNA clones representing *ETV1, ERM* and *E1A-F* in the P1 cloning vector, pAD10sacBII (Genomesystems, St Louis, MO), were nick-translated with digoxigenin-11-UTP and hybridized overnight at 37℃ to fixed metaphase chromosomes according to the method of Pinkel et al. (17), except for the inclusion of 500 μg/mL of highly reiterated human DNA self-annealed to C_0t 1 (Bethesda Research Laboratories, Gaithersburg, MD). Signals were detected by incubating the slides with fluorescein-conjugated sheep antidigoxigenin antibodies (Boehringer Mannheim, Indianapolis, IN) followed by counterstaining in propidium iodide solution containing antifade (1,4-diazabicyclo[2.2.2]octane; Sigma Chemical, St. Louis, MO). Fluorescence microscopy was performed with a Zeiss standard microscope equipped with fluorescein epifluorescence filters.

RESULTS

Human x rodent somatic cell hybrid analysis

DNA from a total of 34 hybrids (29 independent fusions) were analyzed. For *ETV1*, the 113-bp *ETV1*-specific amplified bands were observed in GM 09927, GM 10791, GM 11679, A1, A4 and A5. Therefore no hybrids discordant of chromosome 7 were identified. For *ERM*, 277-bp *ERM*-specific amplified bands were observed in GM 07297, GM 09927, GM 10253, A1, A4, A5 and C1. Therefore no hybrids discordant of chromosome 3 were identified. Furthermore, A4 and A5 [der 5 in t (3;5) (q25.1;q34)] came up positive but negative in A6 [der3 in t (3;5) (q25.1;q34)], indicating that the *ERM* gene maps are distal to the chromosome 3q25.1. For *E1A-F*, 300-bp *E1A-F*-specific amplified bands were observed in GM 09927, GM 09934, GM 10498, and PB5-1. Therefore no hybrids discordant of chromosome 17 were identified (Table 1).

Fluorescence in situ hybridization

To refine the localization on each chromosome of *ETV1, ERM* and *E1A-F*, we performed fluorescence in situ hybridization of metaphase chromosomes prepared from peripheral blood lymphocytes of a normal donor using genomic clones representing the three loci. Fluorescence hybridization signals were observed on 7p22 (*ETV1*), 3q29 (*ERM*) and 17q12 (*E1A-F*) (Fig. 1). These results corroborate our somatic cell hybrid mapping of these loci to chromosome 7, 3, and 17 and suggest that three phylogenetically related genes dispersed to each chromosomal location.

DISCUSSION

The *v-ETS* oncogene was originally discovered as part of a chimeric viral genome with *v-MYB* and *v-GAG* in the genome of the avian retrovirus E26 (1). Since the cellular counterpart of *v-ETS* was discovered, over 30 members of *ETS* superfamily have now been found in species ranging from flies to humans (3). Although, the core sequence of the DNA-binding domain, ETS domain, is well preserved, the variability with the ETS domains allows the classification of ETS members into different sub-families. For example, *ETS1* and *ETS2, ERG* and *FLI1* share between 96-98% homology within the ETS domain, respectively. By contrast, *PU1* is the most divergent homologue to human *ETS1* and shares only 36% identity with *ETS1*. Thus, ETS domain sequence divergence of *ETS* gene homologues allows classification of this family and some related evolutionary history (18). *ETS* genes can be classified based upon their similarity to *ETS1* as *ETS* (*ETS1* and *ETS2*), *ERG* (*ERG* and *FLI1*), *ELG* (*GABPb, DELG*), *PEA3, ELK, SAP1, ELF* (*ELF1, E74*) and *PU1* sub-family. The sub-families are more closely related amongst themselves than with the rest of the group (8).

PEA3, a polyomavirus enhancer binding transcription factor, has been isolated in the mouse (9). *PEA3* has a relatively unique ETS domain compared with other *ETS*

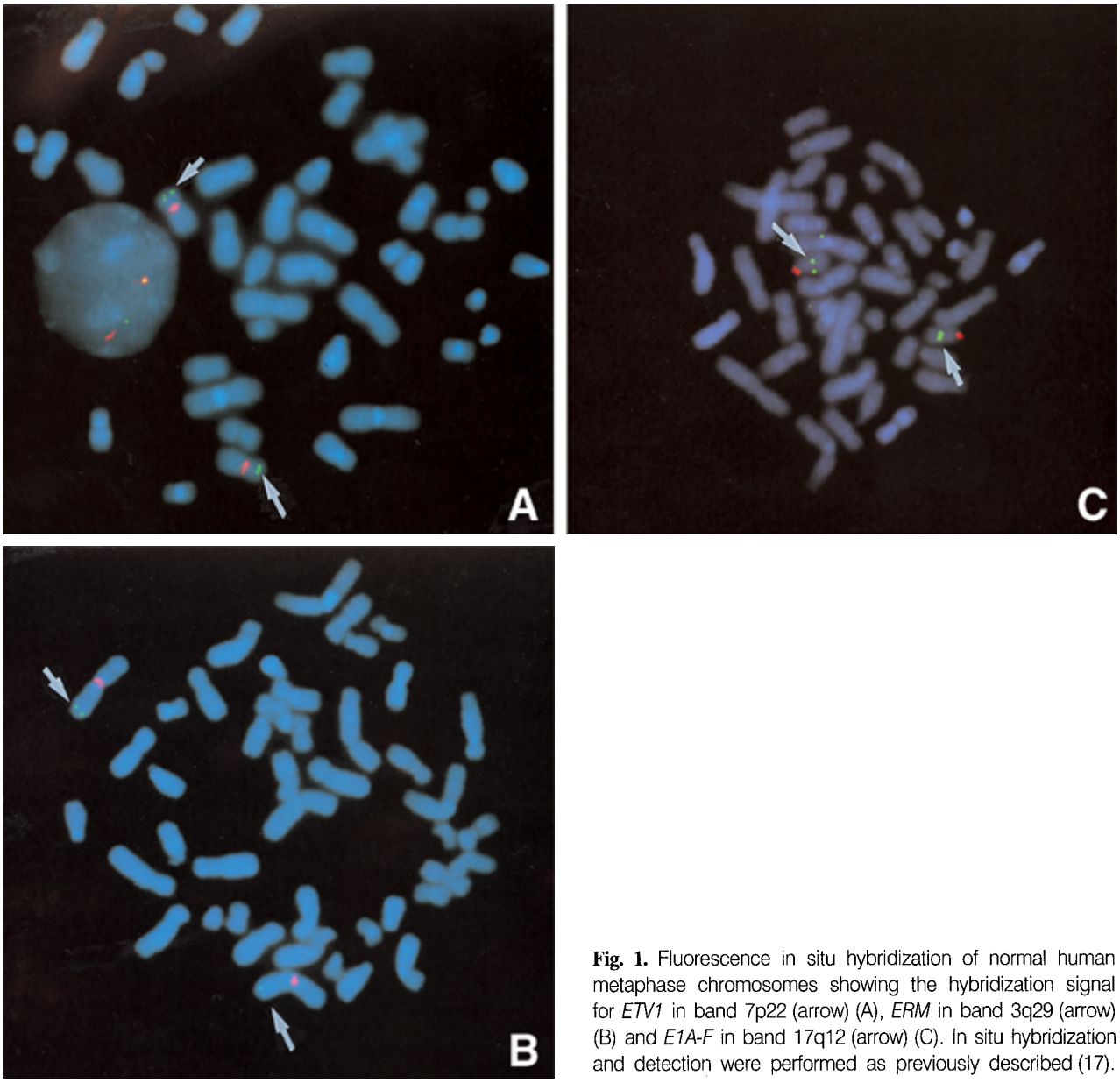

Fig. 1. Fluorescence in situ hybridization of normal human metaphase chromosomes showing the hybridization signal for *ETV1* in band 7p22 (arrow) (A), *ERM* in band 3q29 (arrow) (B) and *E1A-F* in band 17q12 (arrow) (C). In situ hybridization and detection were performed as previously described (17).

sub-family members and therefore constitutes an *ETS* sub-family. *ER81*, which is 96% identical within the ETS domain and about 50% identical with the full-length amino acid sequence of *PEA3*, has recently been classified as a member of the murine *PEA3* sub-family (19). The human homologues of this *ETS* sub-family were cloned. The E1A enhancer binding protein, *E1A-F*, a human homologue of murine *PEA3* shares 100% and 96% identity within the ETS domain with *PEA3* and *ER81*, respectively. It has also been classified as a member of this sub-family (10). Another member of this sub-family is human *ERM* which contains an ETS domain which shares 96% identity with *PEA3* and *ER81* (11). Furthermore, the isolation of *ETV1*, a human homologue of murine *ER81*, expands the members of human *PEA3* sub-family (12). Based upon the extensive homology between *ETV1, ERM* and *E1A-F* within their ETS domain (96% identity to each other), these three genes comprise a distinct sub-family of *ETS* genes in humans.

The human *ETS* family genes have been localized to several different chromosomes thus far. The *ETS1/FLI1* and *ETS2/ERG* are localized in 11q23 and 21q22, respectively (5, 14, 15). The *ELK1* and *ELK2* are in the chromosomal region Xp11.2 and 14q23, respectively (20). The other sub-family *SP1* is located in 11p11.2 (21). The fact that *ETS1/ETS2* and *FLI1/ERG* are homologues and that *ETS1/FLI1* and *ETS2/ERG* are closely linked on the same chromosome suggest that these sub-

families have arisen by gene duplication. From the analysis of the phylogenetic tree of *ETS* genes and the evolutional history, Lauder et al. (8) suggested that as a first step the *ETS/ERG* ancestor was duplicated to give rise to the *ETS* ancestor and the *ERG* ancestor. The two genes resulting from this duplication, occurring more than 500 million years ago, remains closely linked on the same region of the genome. Then the locus containing the two 'uncommitted' *ETS* and *ERG* genes was duplicated after the Arthropods/Vertebrates split, on the lineage which will give rise to the Vertebrates. The result of this last duplication was the two tandem genes we presently know: *ETS1* and *FLI1* on human chromosome 11 and *ETS2* and *ERG* on human chromosome 21. Thus, the sea urchin *ETS* and *ERG* are 'uncommitted' precursors, i.e. represent the 'not yet duplicated' ancestor. This hypothesis should be easy to test since it implies that there is only one *bona fide ETS* and *ERG* genes in *Drosophila* and sea urchin genomes. These findings could suggest that the ancestor of *PEA3* duplicated first, then dispersed to other chromosomes.

A role for the *ETS* gene family in oncogenesis has recently been underscored by the identification of the rearrangement of certain members in leukemias and Ewing's sarcoma. Several cases of leukemias containing human *ETS1* and *ETS2* involved translocation have been described (22). Similarly, *ERG* has been found to be rearranged in human myeloid leukemia with t(16;21) chromosome translocation (23). In addition, it has been demonstrated that the *FLI1, ERG* and *ETV1* are implicated in the Ewing's sarcoma and primitive neuroectodermal tumor by fusion to *EWS* (6, 12, 24).

Aberrations of the chromosome 7p22 have been observed in leukemias (ALL, AML and CML), lymphomas and carcinomas in breast and lung (25). Moreover, we recently cloned the *ETV1* in Ewing's sarcoma cell line with t(7;22)(p22;q22) representing a fusion with EWS (12). Thus, we could predict that the *ETV1* gene is to be considered among the genetic loci that could be affected by these chromosomal aberrations in human malignancies. Similarly, translocations and deletions involving the 3q29 have been reported in association with myelodysplastic syndrome, leukemias (AML, CML and rarely ALL), NHL and breast carcinoma (25). The 17q12 has been reported to be involved in chromosomal translocations and in sporadic deletions associated with acute leukemias and NHL (25). The molecular probes described in this report should prove useful for ascertaining the roles of the *ETV1, ERM* and *E1A-F* genes in these neoplastic cellular processes.

Based on the status of the comparative map of genes and anonymous loci that have been mapped in mice and humans, the assignment of *ER81* is predicted to the proximal half of mouse chromosome 6. This region now span at least 2 cM on the mouse genetic map between the *Npy* and *Ggc* loci (26). Similarly, the murine *ERM* might be assigned to the distal portion of mouse chromosome 9 (57 cM apart from the centromere, *Rbp* locus) or middle of mouse chromosome 16 (22.9 cM apart from centromere, *Gap43* locus) (27, 28). Finally, the assignment of *E1A-F* to human chromosome 17q12 could mean that the murine gene (*PEA3*) will be localized to the distal half of mouse chromosome 11. This region spans al least 13 cM on the mouse genetic map between the *Tcf 2* and the *Erbb2* loci (29).

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