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SHORT COMMUNICATION

Localization of a Human T-Cell-Specific Gene, RANTES (D17S136E), to Chromosome 17q11.2–q12

T. A. DONLON,* A. M. KRENSKY,† M. R. WALLACE,‡ F. S. COLLINS,‡
M. LOVETT,§ AND C. CLAYBERGER†

*Departments of *Pathology and †Pediatrics, Stanford University Medical Center, Stanford, California 94305; ‡Howard Hughes Medical Institute and Department of Human Genetics, University of Michigan, Ann Arbor, Michigan 48109; and §Genelabs Incorporated, Redwood City, California 94063*

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We report here the localization of the gene for a human T-cell-specific molecule, designated RANTES, to human chromosome region 17q11.2–q12 by *in situ* hybridization and analysis of somatic cell hybrids using a cDNA probe to the gene. We have recently shown that this gene, which encodes a small, secreted, putative lymphokine, is a member of a larger gene family some of whose members reside on chromosome 4 but most of whose members have not to date been mapped. A secondary hybridization peak was noted on the region of human chromosome 5q31–q34, which may represent the location of other members of the gene family. Interestingly, this latter region overlaps with the location of an extended linked cluster of growth factor and receptor genes, some of which may be coregulated with members of the RANTES gene family.

T lymphocytes mediate many of their regulatory functions through a group of small, secreted molecules which are collectively referred to as lymphokines. Recently we have used a human cDNA library that was enriched by subtractive hybridization for sequences expressed by T but not B lymphocytes to isolate a gene, designated RANTES, which encodes a novel T-cell-specific molecule (Schall *et al.*, 1988). This gene is expressed by growth factor-dependent, antigen-specific T-cell clones that function as either helper or cytotoxic cells *in vitro*. However, RANTES is not expressed in unstimulated peripheral blood lymphocytes or in established T-cell tumor lines. RANTES expression is induced by antigen or mitogen stimulation of peripheral blood lymphocytes. The RANTES gene product is predicted to be 10 kDa and, after cleavage of the signal peptide, approximately 8 kDa. Of the 68 residues, 4 are cysteines and there are no sites for N-linked glycosylation. There is significant homology (30–70%) between the RANTES sequence and several other T-cell genes, suggesting that they constitute a family of small, secreted T-cell molecules.

Here we report the chromosomal locations of the RANTES gene and discuss its relation to other lymphokine genes.

The cDNA clone for RANTES (Schall *et al.*, 1988) was digested with *Eco*RI and *Apa*I and the 480-base insert, which corresponds to the 5′ end of the gene, was isolated by electrophoresis in low-melting-temperature agarose. The insert was labeled with ^{3}H to a specific activity of 8.4×10^{7} cpm/μg (Feinberg and Vogelstein, 1983).

In situ hybridization was performed on normal, 46,XX chromosome preparations essentially as previously described (Harper and Saunders, 1981). Briefly, the radiolabeled probe was hybridized overnight at 42°C at a final concentration of 10 pg/μl in 50% formamide and 2× SSC and exposed to autoradiography for 8 days. Chromosome identification was performed using simultaneous fluorescent R-banding/transmitted light as described (Donlon *et al.*, 1983).

Ten micrograms of DNA from each source was digested to completion with *Pst*I, electrophoresed, and transferred to Hybond N nylon. The filter was hybridized with 50 ng of oligo-labeled insert from the RANTES plasmid and washed to a final stringency of 0.1× SSC, 0.1% SDS at 65°C. The rat DNA is from hepatoma cell line PCTA-7A (Leach *et al.*, 1989) and the mouse and human DNAs are of lymphocytic origin. Hybrid MH-22 contains one normal human chromosome 17 as its only human DNA on a mouse background, while P12.3B contains 17pter–q12 and SP-3 possesses 17q11.2–qter, also on mouse backgrounds

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(VanTuinen *et al.*, 1987). L17nC is a mouse hybrid containing human 17q (Leach *et al.*, 1989). DCR-1 (Menon *et al.*, 1989) and NF13 (Ledbetter *et al.*, 1989) are mouse hybrids derived from neurofibromatosis (NF1) patients possessing constitutional translocations involving band 17q11.2, and both hybrids contain 17q11.2–qter.

Analysis of the distribution of silver grains after *in situ* hybridization with a cDNA probe for the RANTES gene to chromosome preparations demonstrated that the gene was located on chromosome 17 (Fig. 1). Of 100 cells examined, 39 showed hybridization over the 17q11–q21 region and 39/416 grains were localized over this region. In addition, a secondary peak of hybridization was found on chromosome 5q31–q34. Twenty percent of the cells examined showed this secondary peak, which may represent hybridization to other members of the RANTES gene family (see below).

A panel of somatic cell hybrids was used to localize the RANTES gene more specifically (Fig. 2). Hybridization of the RANTES probe to this panel revealed the following. The probe detects the same two human fragments (6.0 and 2.6 kb) in all of the hybrids, thereby specifically localizing this probe to the 17q11.2 to 17q12 region, between the NF1 and the P12.3B breakpoints. This probe also detects homologous fragments in both mouse and rat DNA, indicating a conserved sequence.

When the RANTES probe is hybridized at moderate stringency to human genomic DNA, it detects several fragments in addition to those shown in Fig. 2 (not shown). It is possible that hybridization to one or more of these related sequences accounts for the minor peak of hybridization found over 5q31–q34. However, attempts to confirm this chromosome 5 localization by Southern blotting and hybridization to hamster × human somatic cell hybrid DNAs resulted in very high cross-species hybridization to hamster genomic DNA that either comigrated with or obscured the minor human fragments.

We have localized the RANTES gene to human chromosome 17 by *in situ* hybridization. The major peak of hybridization was over the chromosomal region 17q11–q21. A minor peak of hybridization was found at chromosome 5q31–q34. A panel of somatic cell hybrids was used to further localize the gene to region 17q11.2–q12 of chromosome 17.

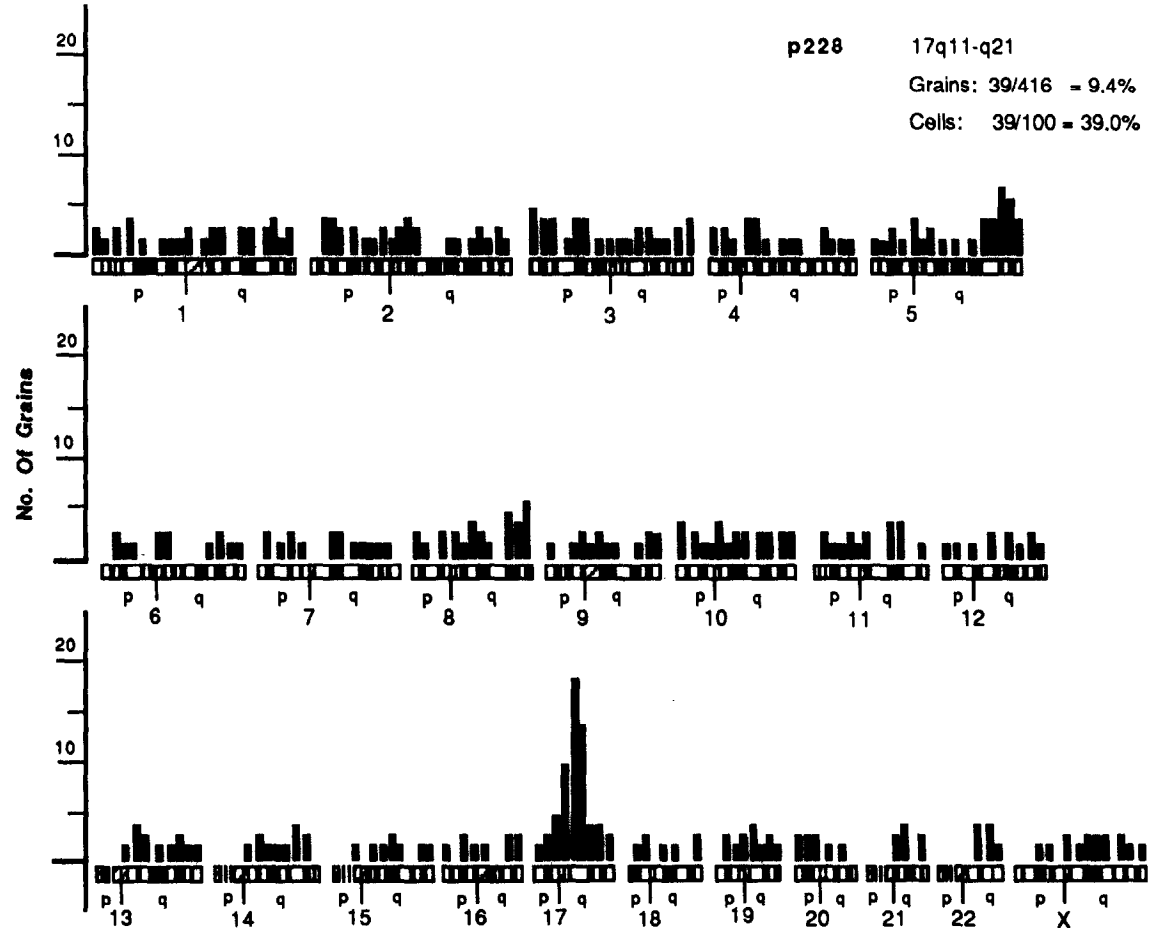

FIG. 1. Silver grain distribution after *in situ* hybridization with the RANTES cDNA probe.

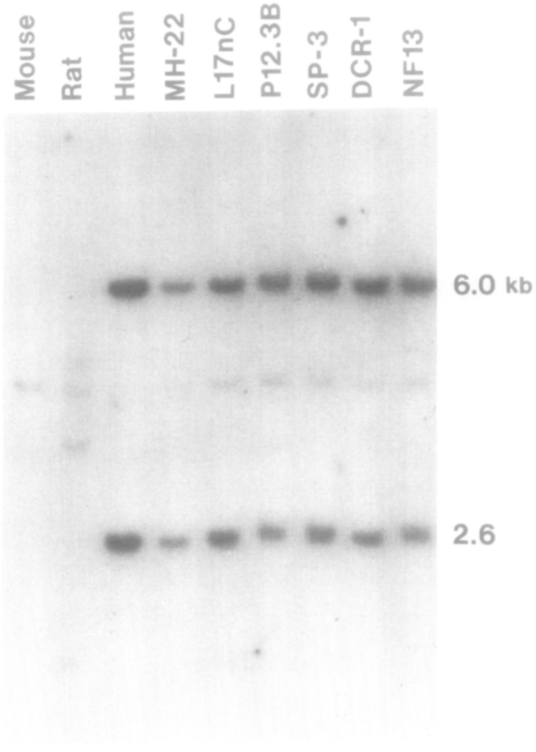

FIG. 2. Hybridization of somatic cell hybrid panel with RANTES probe.

A comparison of amino acid sequences, and especially the spacing of the four cysteine residues, revealed that RANTES is a member of a gene family that can be subdivided into an immediate or highly similar group and an extended, or less similar, group (Fig. 3). Included in the former are the genes designated TCA3.0 (Burd *et al.*, 1987) and TY5 (Brown *et al.*, 1988), both isolated from activated murine helper T cells; pLD78 (Obaru *et al.*, 1986), isolated from activated human tonsillar lymphocytes, and the nearly identical pAT 464 (Zipfel *et al.*, 1989), isolated from activated human peripheral blood; Act2 (Lipes *et al.*, 1988) and pAT 744 (Zipfel *et al.*, 1989), two identical clones independently isolated from activated human peripheral T cells; MIP-1 (macrophage inflammatory protein) (Wolpe *et al.*, 1988), isolated from murine macrophages; and JE (Rollins *et al.*, 1988), isolated from activated murine fibroblasts. When the first two cysteines are separated by one residue, a larger family is revealed, including three fibroblast-derived molecules designated c9E3/CEF-4 (Van Damme *et al.*, 1988; Sugano *et al.*, 1987), GRO (Anisowicz *et al.*, 1987), and KC (Rollins *et al.*, 1988); two platelet-specific genes designated PF4 (platelet factor-4) (Poncz *et al.*, 1987) and PBP (platelet basic protein) (Holt *et al.*, 1986); MIP-2 (Wolpe *et al.*, 1988); IP10 (Luster *et al.*, 1985), a gene expressed in lymphocytes, monocytes, fibroblasts, and endothelial cells after treatment with interferon-γ; and the monocyte factor designated MDNCF (monocyte-derived neutrophil chemotactic factor) (Walz *et al.*, 1987), 3-10C (Schmid and Weissman, 1987), or NAF (neutrophil activating factor) (Matsushima *et al.*, 1988), three identical but independently identified proteins that activate neutrophils.

To date, only a few members of the RANTES gene family have been mapped for chromosomal location. PF4 and IP10, which are members of the extended gene family, have been mapped to chromosome 4 (Luster *et al.*, 1987), as has a molecule related to GRO (Richmond *et al.*, 1988). Thus, it seems likely that at least a part of this family arose through gene duplication and subsequent divergence. In this report we show that the RANTES gene maps to chromosome 17q11.2–q12. To date, no other members of the immediate gene family have been mapped for chromosomal localization. Other genes that have been localized to 17q11–q12 include granulocyte colony-stimulating factor-3 (CSF3, 17q11.2–q12) (LeBeau *et al.*, 1987a), ERBA1 (THRA1) (17q11–q12) and ERBB2 (17q11–q12) (Spurr *et al.*, 1984), and neurofibromatosis (NF1, 17q11.2) (Barker *et al.*, 1987; Schmidt *et al.*, 1987).

The minor peak on chromosome 5q31–q34 identified by *in situ* hybridization may represent hybridization with other as-yet-unidentified members of the RANTES family. This region of chromosome 5 contains at least six other unrelated growth factor genes, including interleukin 3 (IL-3, 5q23–q31) (LeBeau *et al.*, 1987b), macrophage colony-stimulating factor-1 (CSF1, 5q33.1) (Pettenati *et al.*, 1987), macrophage/granulocyte colony-stimulating factor-2 (CSF2, 5q23–q31) (Huebner *et al.*, 1985), the acidic fibroblast growth factor (FGFA, 5q31.3–q33.2) (Jaye *et al.*, 1986), interleukin 4 (IL-4, 5q23–q32) (Sutherland *et al.*, 1988b), and interleukin 5 (IL-5, 5q23.3–q32) (Sutherland *et al.*, 1988a). At least some of these genes have been shown by pulse-field gel analysis to be very close. For example, the IL-3 and CSF2 genes are tandemly linked within a very short region (Yang *et al.*, 1988). In addition, a number of genes encoding receptors have been localized to this general region, including β_2-adrenergic receptor (ADRB2R, 5q31–q32) (Kobilka *et al.*, 1987), platelet-derived growth factor receptor (PDGFR, 5q31–q32) (Yarden *et al.*, 1986), CSF1 receptor (CSF1R, 5q33–q34) (Nienhuis *et al.*, 1985), and the monocyte differentiation antigen CD14 (5q22–q32) (Goyert *et al.*, 1988). Of these, the closely related platelet-derived growth factor receptor and CSF1 receptor are within 500 bp of each other (Roberts *et al.*, 1988). Several of these loci on 5q (CSF1 and CSF2) are syntenic on mouse chromosome 11 with loci that are on human chromosome 17q (CSF3, ERBA1, and ERBA2) and may have evolved from common precursor genes through regional chromosomal duplication. Interestingly, the c-kit gene, which is closely related to both

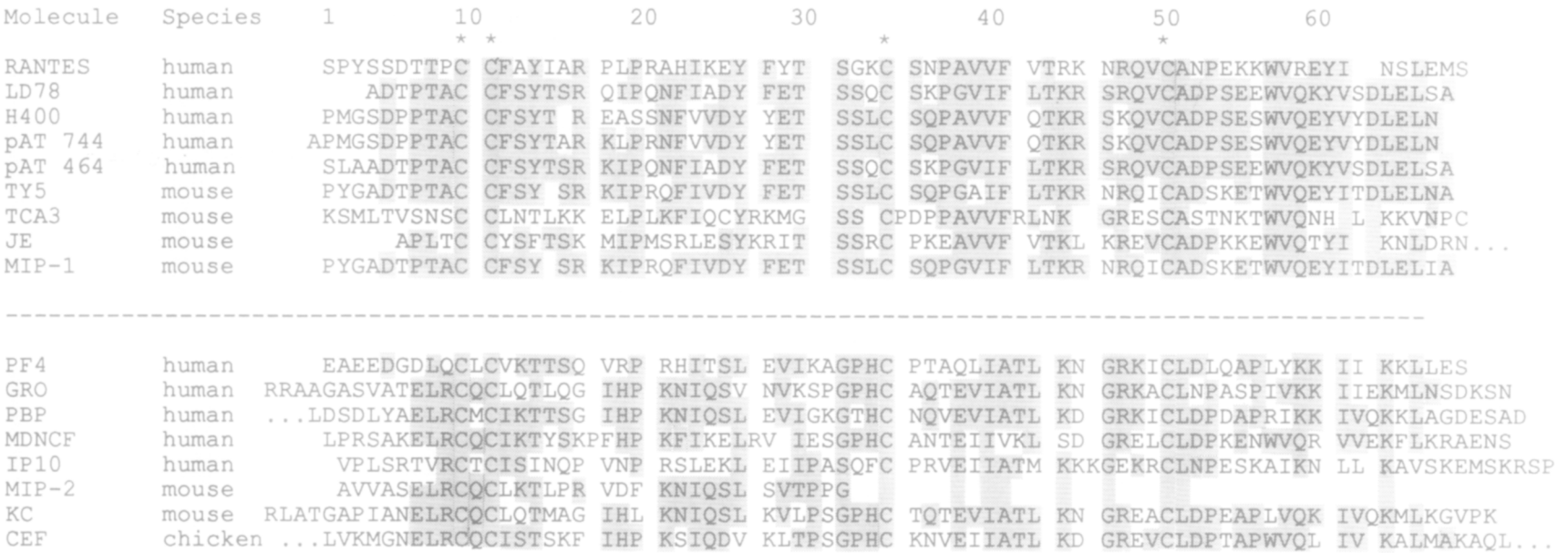

FIG. 3. Homologies between RANTES and other genes. The deduced amino acids of RANTES and other related genes are aligned to reveal maximal overall homology consistent with minimal insertion/deletion changes. The amino acids are shaded where four or more residues are identical. The * indicates the four conserved cysteine residues.

FIG. 3. Homologies between RANTES and other genes. The deduced amino acids of RANTES and other related genes are aligned to reveal maximal overall homology consistent with minimal insertion/deletion changes. The amino acids are shaded where four or more residues are identical. The * indicates the four conserved cysteine residues.

the platelet-derived growth factor and CSF1 receptors, resides on chromosome 4 (Yarden *et al.*, 1986), as do several members of the extended RANTES gene family.

Collectively, these results suggest that chromosomes 17q11–q12 and 5q31–q34 include the immediate RANTES gene family and may have arisen by divergence and limited chromosomal dispersion (Leipoldt, 1983). An earlier gene divergence may have given rise to the extended family members on human chromosome 4.

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