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Genetics

Identification of a human transcription unit affected by the variant chromosomal translocations 2;8 and 8;22 of Burkitt lymphoma

(*MYC*/plasmacytomas/protooncogenes/*PVT*)

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ABSTRACT **Chromosomal translocations in Burkitt lymphoma and mouse plasmacytomas typically lie within or near the protooncogene *MYC*. In some instances, however, these tumors contain variant translocations with breakpoints located more distant from and downstream of *MYC*, in a domain commonly known as *pvt-1*. Until now, there has been no evidence that *pvt-1* marks the location of a functional gene. Here we report the identification of a large transcriptional unit in human DNA that includes *pvt-1*. We have designated this unit as *PVT*. *PVT* begins 57 kilobase pairs downstream of *MYC* and occupies a minimum of 200 kilobase pairs of DNA. Some of the translocations that occur downstream of *MYC* in Burkitt lymphoma transect *PVT*; others lie between the two genes. None of the translocations we have studied appear to enhance transcription from an intact allele of *PVT* (indeed, they may inactivate that transcription), but some are associated with the production of abundant and anomalous 0.8- to 1.0-kilobase RNAs that contain the 5′ exon of *PVT* and sequences transcribed from the constant region of an immunoglobulin gene (the reciprocal participant in the translocation). Identification of *PVT* should facilitate the exploration of how translocations downstream of *MYC* and insertions of retroviral DNA in the vicinity of *pvt-1* might contribute to tumorigenesis.**

A variety of chromosomal translocations and insertions of retroviral DNA are thought to elicit tumorigenesis by disturbing the regulation of transcription from protooncogenes (1, 2). The archetypes of these events involve the protooncogene *MYC* (3), which is affected by translocations in Burkitt lymphomas and mouse plasmacytomas and by retroviral insertions in a variety of avian, feline, and murine lymphomas. The most common translocations in Burkitt lymphomas, t(8;14), and mouse plasmacytomas, t(12;15), have breakpoints that lie within or near *MYC* (4). In some instances, however, these tumors contain variant translocations with breakpoints located more distant from and downstream of *MYC* (5–9).

A cluster of the variant breakpoints in mouse plasmacytomas occurs in a domain known as *pvt-1* (10, 11); the same domain is a recurrent site for insertion of retroviral DNA in lymphomas of mice (12) and rats (13, 14), in which setting the domain has also been known as *mis-1* and *Mlvi-1*; and the counterpart in human DNA is the site of at least occasional translocations (15, 16). One interpretation of these findings is that *pvt-1* marks the location of a gene whose altered function can contribute to tumorigenesis; but until now, the postulated gene has gone undetected. Here we report the identification of a human transcription unit (designated *PVT*) that encompasses the human counterpart of the murine *pvt-1*, and we provide an initial description of how translocations in Burkitt lymphomas can affect that unit. For convenience, we refer to the transcription unit as a gene, although we have yet to prove that the unit serves any purpose.

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MATERIALS AND METHODS

Molecular Clones. Molecular clones of DNA are summarized in Fig. 1. The Y2 cDNA clone was isolated from a library prepared with RNA from the COLO320-DM cell line, as described (17). The clone cosY14 was isolated by screening a cosmid library of human DNA with a probe prepared from the 0.16-kilobase-pair (kbp) *Eco*RI–*Bgl* II fragment at the 5′ end of Y2 cDNA (E.S., unpublished work). The clone λ64.26 was obtained by a "chromosome walk" that began with *MYC* and proceeded downstream of the gene (18). The clone λ8q3 was isolated by screening a λ-phage library of human DNA with a probe for the chromosome 8 breakpoint in the translocation of the JBL2 cell line (19, 27). The breakpoint of t(2;8) in the JBL2 Burkitt lymphoma cell line lies within the domain represented by λ8q3, as diagrammed in Fig. 1. The location of the cloned DNA downstream of *MYC* was determined by restriction mapping with pulsed-field electrophoresis (27). The boundaries of the first exon of *PVT* in cosY14 were defined by nucleotide sequencing, the boundaries of the downstream exon in λ8q3 by mapping with restriction enzymes and RNase assays with riboprobes.

Analysis of RNA. Polyadenylylated RNAs were prepared from various human cell lines and then analyzed in either of two ways. Analysis with riboprobes and RNase was performed by hybridization with a radioactive RNA probe, treatment with RNase A and T1, and analysis of the products by gel electrophoresis. Alternatively, RNAs were first fractionated by electrophoresis through agarose in the presence of formaldehyde (5 μg per lane), then transferred to GeneScreen*Plus* membranes, and detected by molecular hybridization according to the manufacturer's protocol (DuPont).

RESULTS

The Molecular Cloning of *PVT*. We initially encountered *PVT* as an unidentified gene that is coamplified with *MYC* in at least four lines of human tumor cells (17, 20). Those findings raised the possibility that *MYC* and the coamplified gene might be linked in the human genome. In pursuit of this possibility, we discovered that the unidentified gene includes the domain *pvt-1* (see below). Therefore, we designated the gene *PVT* and, for convenience, have used this term hereafter.

We began by isolating a cDNA clone that represents a portion of *PVT* (designated Y2 in Fig. 1*A*), then used an *Eco*RI–*Bgl* II fragment from the 5′ end of the cDNA to isolate the corresponding region of the human genome, in the form of a cosmid clone, designated cosY14 (Fig. 1*B*). The restriction map of cosY14 proved to be identical to that of a

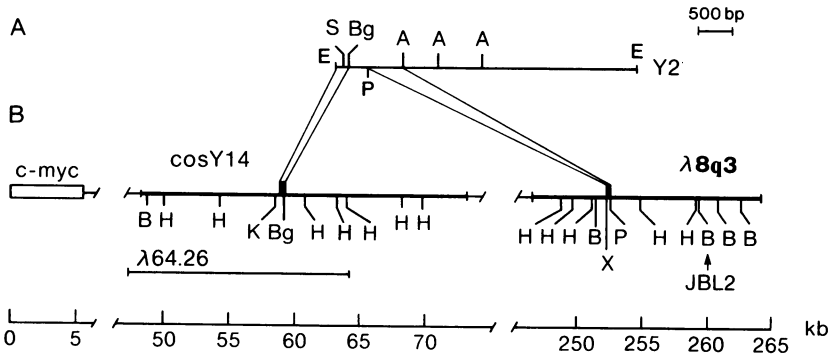

FIG. 1. The location and topography of *PVT*. The figure illustrates the topography of a cDNA clone (Y2) that represents a portion of *PVT* (*A*) and two regions of human chromosome 8 that bear portions of *PVT* (*B*). The domains of Y2 representing identified exons of *PVT* are connected by lines to the locations of the exons within the clones of genomic DNA (solid boxes). Restriction sites in the three clones are designated as follows: A, *Acc* I; B, *Bam*HI; Bg, *Bgl* II; E, *Eco*RI; H, *Hin*dIII; K, *Kpn* I; P, *Pst* I; and X, *Xba* I. The *Eco*RI sites were created by molecular cloning, the other sites occur naturally in the DNA. The scale along the bottom of the diagram gives the distance in kbp downstream of the 5′ end of *MYC*.

previously identified domain of DNA located 47–65 kbp downstream of *MYC* (represented by clone λ64.26 in Fig. 1*B*; see ref. 18). Exploring the apparent identity, we demonstrated that the *Eco*RI–*Bgl* II fragment from the 5′ end of the PVT cDNA hybridized exclusively with a 0.7-kbp *Kpn* I–*Bgl* II fragment in the clone λ64.26 (Fig. 1*B*). These findings place the first exon of *PVT* 57 kbp downstream of *MYC*.

To localize precisely the region of homology between PVT cDNA and *PVT* genomic sequences, the fragment from cosY14 that hybridized to the probe for the 5′ end of the cDNA was partially sequenced (Fig. 2). The sequences of the cDNA and the corresponding genomic region were identical through the first 177 nucleotides of the cDNA. The polarity of RNA coding sequences within the genomic locus indicated that transcription of *PVT* proceeds in the same direction as that of *MYC*. No apparent "TATA box" sequences were encountered in genomic DNA upstream to the 5′ end of the cDNA. The genomic region immediately preceding the beginning of cDNA homology as well as sequences within the 5′ domain of the first exon have a very high G+C content (80%).

Direction of Transcription from *PVT*. To confirm that the direction of transcription from *PVT* is the same as that of *MYC*, we prepared radioactive probes of RNA representing the two DNA strands of the first exon of *PVT* and hybridized these with RNA from several cell lines. The probe with polarity identical to that of MYC mRNA failed to react (data not shown). By contrast, hybridization of the complementary probe produced a heterogeneous family of RNase-resistant fragments with lengths from 140 to 210 nucleotides (Fig. 3). Primer extension from the 78-nucleotide *Sma* I–*Bgl* II fragment of Y2 cDNA, end-labeled at the *Bgl* II site, gave identical results (17). We conclude that transcription from *PVT* initiates at multiple sites (producing heterogeneity at the 5′ ends of the RNA) and then proceeds in the same direction as transcription from *MYC*.

***PVT* Encompasses the *pvt-1* Domain.** In search of additional exons of *PVT*, we took cognizance of the fact that the first intron of *PVT* is >80 kbp (E.S., unpublished data). Therefore, we analyzed restriction fragments from the molecular clone λ8q3 that contains DNA from *ca.* 220–265 kbp downstream of *MYC*, encompasses the counterpart of mouse *pvt-1* on human chromosome 8, and contains the site of the translocation breakpoint in the Burkitt lymphoma line JBL2 (Fig. 1*B*). A probe prepared with the 0.6-kbp *Pst* I–*Acc* I fragment of Y2 cDNA hybridized specifically with a 0.250-kbp *Xba* I–*Pst* I fragment within clone λ8q3 (Fig. 1). Moreover, an RNA probe representing the *Xba* I–*Pst* I fragment hybridized with cellular RNA to give a RNase-resistant fragment 135 nucleotides long (data not shown). We conclude that the human counterpart of *pvt-1* contains at least one exon of *PVT*. That exon can be located with some accuracy by pulsed-field electrophoresis, which has been used to map the *pvt-1* domain and the translocation breakpoint of the Burkitt lymphoma cell line JBL2 to a region *ca.* 260 kbp downstream of *MYC* (Fig. 1*B* and ref. 27). We found that the *PVT* exon resides 7 kbp upstream of the JBL2 breakpoint. We conclude that exons represented within the 5′ 1.0 kbp of Y2 cDNA are dispersed over 200 kbp of the human genome (from 57 kbp to 253 kbp downstream of *MYC*) and that additional exons of *PVT* lie even farther downstream. As a consequence, several of the translocations studied here (JBL2 and others; see

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CCCCCCTCCCCCGAGGCCCGAGCGCGAGCCGCCGTGACGTCACGGCAACCCGCCAGCCCC   60
                                ┌ exon I
                                │
GCGCTCTCCGGGCAGAGCGCGTGTGGCGGCCGAGCACATGGGCCGCGGGCCGGGCGGGCT  120
                                                        SmaI
CGGGGCGGCCGGGACGAGGAGGGGCGACGACGAGCTGCGAGCAAAGATGTGCCCCGGGAC  180

CCCCGGCACCTTCCAGTGGATTTCCTTGCGGAAAGGATGTTGGCGGTCCCTGTGACCTGT  240
                          exon ┬ intron
                   BglII       │
GGAGACACGGCCAGATCTGCCCTCCAGTAAGTTCCAATTTTGTCCCCTGCGTTTCTGGAA  300

ACTCTCGAGACTTGGCCCTGAGTAGGGATGCGCTGTGAGTAGTCGGACGGAGGAAAGGGG  360
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FIG. 2. Sequence of the genomic region containing the first exon of *PVT*. The polarity of the sequence shown is the same as that of the *MYC* transcription unit (toward the telomere). The limits of identity between Y2 cDNA and the genomic region were used to define the boundaries of exon I. In reality, however, transcription from *PVT* initiates at multiple sites and the left-hand boundary of the exon is consequently heterogeneous (see below, Fig. 3).

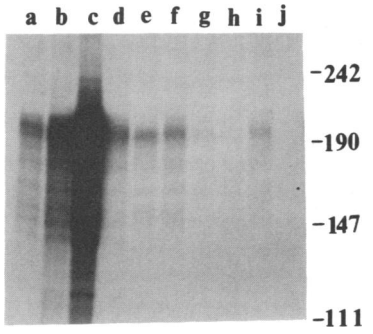

FIG. 3. The direction of transcription from *PVT*. Polyadenylylated RNA was isolated and analyzed with riboprobes. The probes were prepared by placing the 0.7-kbp *Kpn* I–*Bgl* II fragment of clone cosY14 into the vector pGEM7z and transcription with either SP6 or T7 RNA polymerase. Separate probes represented the strands of DNA with polarity identical or complementary to that of *MYC* mRNA. The former probe failed to react with cellular RNA, the latter gave the results illustrated here. Analysis of RNAs from the following cell lines is shown: Lanes: a, SK-M-NC, neuroepithelioma; b, H82, small cell lung carcinoma; c and d, COLO320-DM and COLO320-HSR, respectively, carcinoma of the colon; e–h, BL64, BL21, PA682, and Daudi, respectively, Burkitt lymphoma; and i, HL60, promyelocytic leukemia. The samples analyzed for lanes a–c contained 2 μg of polyadenylylated RNA, and those for lanes d–i contained 5 μg of RNA. Lane j represents a blank, obtained by carrying 20 μg of yeast tRNA through the analysis. The numbers along the side of the figure represent the lengths (in nucleotides) and positions of markers.

below) transect *PVT* and presumably interrupt its transcription.

Effect of Translocation on *PVT*. Having demonstrated that the location of *PVT* exposes it to damage by translocations downstream of *MYC*, we examined the effect of translocations on transcription from *PVT* (Fig. 4 and Table 1). A probe representing the 5′ domain of *PVT* cDNA detected a heterogeneous array of polyadenylylated RNAs in a variety of human cell lines, including all the Burkitt lymphoma lines examined. The most prominent of these RNAs had a length of 4.8 kilobases (kb), the others had lengths ranging from 1 to 11 kb. The RNAs were relatively scarce and, consequently, were difficult to detect and enumerate. We cannot presently say which of these RNAs are functional mRNAs as opposed to nuclear precursors; but, because of their prevalence in cells both with and without translocations affecting chromosome 8, we presume that they all represent normal products

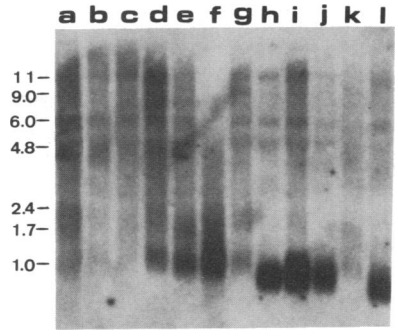

FIG. 4. Cellular RNAs representing *PVT*. Polyadenylylated RNAs were analyzed by electrophoresis in agarose and molecular hybridization. Hybridization was performed with a radioactive probe representing the 0.45-kbp *Eco*RI–*Pst* I fragment of the Y2 cDNA (see Fig. 1*A*). Autoradiograms were exposed for 4 days. RNAs came from the following cell lines. Lanes: a, MG63, osteogenic sarcoma; b–l, Raji, Daudi, ROS16, PA682, LY66, JBL2, BL64, BL21, LY91, JI, and MWIKA, respectively, all Burkitt lymphoma.

Table 1. Transcription from *PVT* in tumor cell lines

Cell line	Translocation	Location of breakpoint, kbp	Anomalous transcripts from PVT
JI	2;8	+25	−
BL21	2;8	+140	+
BL64	2;8	+140	+
LY91	2;8	+140	+
JBL2	2;8	+260	−
LY66	2;8	ND	+
ROS16	2;8	ND	−
PA682	8;22	>+47	+
MWIKA	8;22	ND	+
Raji	8;14	−1.4	−
Daudi	8;14	>−25	−

Cytogenetic analysis has characterized the translocations in the Burkitt lymphoma cell lines JI (6,7), BL21 (21), BL64 (22), LY91 (22), JBL2 (22), LY66 (22), ROS16 (23), PA682 (24), MWIKA (25), Raji (22) and Daudi (22). The locations of breakpoints are given as distances in kbp either upstream (−) or downstream (+) of the 5′ end of *MYC*. Data were obtained from the literature for the lines JI (9), PA682 (9), Raji (26) and Daudi (3), and for BL21, BL64, LY91, and JBL2 (27). ND, not determined. Some of the cell lines contained anomalous 0.8 to −1.0-kb *PVT* RNAs (+); others did not (−). The normal collection of polyadenylylated RNAs representing *PVT* was present in all instances.

of transcription from *PVT*. Work reported elsewhere sustains this view (17).

Chimeric RNAs Arising from *PVT* and Immunoglobulin Genes. A single anomaly was noticed among the RNAs that hybridized with the probe for exon 1: the presence of relatively abundant 0.8- to 1.0-kb RNAs in six of the Burkitt cell lines, but in none of the other lines examined here and elsewhere (17). We explored the origins of these RNAs by using probes derived from regions of the PVT cDNA on the 3′ side of the *Pst* I site (Fig. 1*A*). These probes reacted with all except the 1.0- and 1.7-kb normal transcripts of PVT but with none of the 0.8- to 1.0-kb RNAs (data not shown). It, therefore, appears that the immediate 5′ domain of *PVT* is represented in the anomalous RNAs (no more than 0.45 bkp, the distance from the 5′ end of Y2 cDNA to the *Pst* I site) and that they contain additional nucleotide sequence. We have found (unpublished work) that cDNA clones representing the anomalous RNAs hybridize with the constant regions of genes for immunoglobulin light chains—κ chains for t(2;8) and λ chains for t(8;22). We conclude that the anomalous RNAs are chimeras that arise because translocation juxtaposes the 5′ domain of *PVT* to a light chain immunoglobulin gene. The details of that juxtaposition are not yet available.

Although the chimeric RNAs occurred in all three cell lines with translocations located 140 kbp downstream of *MYC* and thus within *PVT*, they were absent from the JBL2 line, which also has a breakpoint within *PVT* located further downstream than the translocations that give rise to the chimeric RNAs (see Fig. 1*B* and Table 1). Even when translocations transect *PVT*, the multiple normal transcripts from the gene persist at low levels and presumably arise from a remaining unrearranged allele (see Table 1; note that the presence of the 0.8- to 1.0-kb RNAs obscures detection of the normal 1.0-kb RNA).

DISCUSSION

Three sorts of genetic damage in tumor cells may affect the chromosomal domain occupied by *PVT* and its murine counterpart: translocations (5–11), insertions of retroviral DNA (12, 14), and an interstitial deletion of human chromosome 8 (16). It has been generally assumed that if any of these lesions contribute to tumorigenesis, they do so by affecting

the function of a cellular gene. Until now, the only candidate to suffer the effect has been *MYC*, whose location is quite distant from many of the genetic lesions in question (translocations and insertions in *pvt-1*, for example). The work reported here brings a second player on the stage by identifying a human gene (*PVT*) that is the site of the translocations in a number of Burkitt lymphomas. We assume but have yet to prove that the murine counterpart of *PVT* will be affected by the variant translocations of mouse plasmacytomas, t(6;15), and by the retroviral insertions in the *pvt-1* domain of mouse and rat lymphomas.

The functional consequences of translocations in or near *PVT* remain a puzzle. In no instance have we found activation of transcription from the intact gene. On the contrary, some of the translocations described here transect and presumably inactivate *PVT*. The cell lines in which the inactivations occurred continue to produce transcripts from the other allele of *PVT* and, thus, may suffer no absolute defect in the function of the gene. Alternatively, mutations may have inactivated the protein product of the remaining allele of *PVT*, making the tumor cells homozygous for recessive defects of the gene. It also remains possible that the occurrence of translocations within *PVT* is fortuitous and that the translocations activate a still unidentified gene located on either side of or within *PVT*—or even the distant *MYC* gene, as has been proposed (4). We have no evidence that bears on these possibilities.

The translocations involving *PVT* are reciprocal, moving either part or all of *PVT* into the midst of immunoglobulin genes on chromosome 2 or 22 (5–9). But in preliminary studies, we have found no evidence that expression of the translocated portion of *PVT* is enhanced; and if the translocations were to elicit appreciable changes in expression of immunoglobulin genes, we doubt that those changes would contribute substantially to tumorigenesis. We, therefore, suspect that the reciprocal breakpoint has no functional significance.

We have detected one abnormality of *PVT* expression in association with translocations: the relatively abundant production of 0.8- to 1.0-kb RNAs that apparently arise from a chimeric transcriptional unit that includes the 5′ domain of *PVT* and constant regions of immunoglobulin light chain genes. The chimera is formed by translocation that juxtaposes the 5′ domain of *PVT* on chromosome 8 to an immunoglobulin constant region on either chromosome 2 (κ light chain) or chromosome 22 (λ light chain). To explain the abundance of these RNAs, we suggest that translocation has brought the promoter for *PVT* under the influence of an enhancer for an immunoglobulin gene. We have yet to determine the full nucleotide sequence for any of the chimeric RNAs and, thus, do not know whether they encode proteins that might contribute to tumorigenesis.

The significance of *PVT* in tumorigenesis deserves further exploration. Both chromosomal translocations and retroviral insertions may cluster in or near the gene in a variety of lymphoid tumors. Clustering of this sort is likely to result from selection for a biological effect. We hope to gain insight into this conundrum by comparing the effects of retroviral insertions on the expression of *PVT* with those of translocation. Identification and isolation of the murine equivalent of *PVT* will make this comparison possible.

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