Receptor Protein-Tyrosine Phosphatase γ is a Candidate Tumor Suppressor Gene at Human Chromosome Region 3p21

Author(s): S. LaForgia, B. Morse, J. Levy, G. Barnea, L. A. Cannizzaro, F. Li, P. C. Nowell, L. Boghosian-Sell, J. Glick, A. Weston, C. C. Harris, H. Drabkin, D. Patterson, C. M. Croce, J. Schlessinger and K. Huebner

Source: *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 88, No. 11 (Jun. 1, 1991), pp. 5036-5040
Published by: National Academy of Sciences
Stable URL: http://www.jstor.org/stable/2357189
Accessed: 04-12-2017 20:08 UTC

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 5036–5040, June 1991
Genetics

Receptor protein-tyrosine phosphatase γ is a candidate tumor suppressor gene at human chromosome region 3p21

(chromosome deletions/translocations/loss of heterozygosity/tyrosine phosphorylation/dephosphorylation/somatic cell hybrids)

S. LaForgia[a,b], B. Morse[c], J. Levy[d], G. Barnea[d], L. A. Cannizzaro[a], F. Li[e], P. C. Nowell[f], L. Boghosian-Sell[a], J. Glick[g], A. Weston[h], C. C. Harris[h], H. Drabkin[i], D. Patterson[j], C. M. Croce[a], J. Schlessinger[d], and K. Huebner[a,k]

[a]Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia, PA 19140; [c]Rhône–Poulenc Rorer Central Research, King of Prussia, PA 19406; [d]Department of Pharmacology, New York University Medical Center, New York, NY 10016; [e]Dana–Farber Cancer Institute, Boston, MA 02115; Departments of [f]Pathology and Laboratory Medicine and of [g]Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104; [h]Laboratory of Human Carcinogenesis, National Cancer Institute, Bethesda, MD 20892; [i]Department of Medicine, University of Colorado Health Sciences Center, Denver, CO 80212; and [j]Eleanor Roosevelt Institute, Denver, CO 80206

Contributed by P. C. Nowell, February 22, 1991

ABSTRACT ***PTPG*, the gene for protein-tyrosine phosphatase γ (PTPγ), maps to a region of human chromosome 3, 3p21, that is frequently deleted in renal cell carcinoma and lung carcinoma. One of the functions of protein-tyrosine phosphatases is to reverse the effect of protein-tyrosine kinases, many of which are oncogenes, suggesting that some protein-tyrosine phosphatase genes may act as tumor suppressor genes. A hallmark of tumor suppressor genes is that they are deleted in tumors in which their inactivation contributes to the malignant phenotype. In this study, one PTPγ allele was lost in 3 of 5 renal carcinoma cell lines and 5 of 10 lung carcinoma tumor samples tested. Importantly, one PTPγ allele was lost in three lung tumors that had not lost flanking loci. PTPγ mRNA was expressed in kidney cell lines and lung cell lines but not expressed in several hematopoietic cell lines tested. Thus, the PTPγ gene has characteristics that suggest it as a candidate tumor suppressor gene at 3p21.**

Changes in the level and pattern of phosphorylation of protein tyrosyl residues have been implicated in the control of cellular proliferation (for review, see refs. 1 and 2). The phosphorylation level found within cells is the result of a balance between the opposing activities of protein-tyrosine kinases and protein-tyrosine phosphatases (PTPs). Previous studies have focused on the role protein-tyrosine kinases play in controlling phosphorylation and cell growth (for review, see refs. 1 and 2). It has been demonstrated that a number of growth factor receptors are in fact protein-tyrosine kinases that transduce their mitogenic signal by molecular cascades that begin with tyrosine phosphorylation.

With the increase in reported cloning of PTP genes (3–5), the opposing side of phosphorylation regulation has received more attention. The role PTPs may serve in controlling cellular phosphorylation levels can be thought to exist as a continuum. At one extreme, PTPs may continually dephosphorylate tyrosyl residues and thus serve an indiscriminate housekeeping function. At the other extreme, PTPs may selectively dephosphorylate tyrosyl residues in response to changes in the cellular environment, analogous to, but opposing the role of growth factor receptors. This latter scenario is attractive in that it provides the cell with the regulatory apparatus necessary for rapid increases or decreases in tyrosine phosphorylation levels.

If PTP activity is found to be critical in the regulation of phosphorylation patterns and levels and, by extension, crucial in the control of cell growth, it is possible that alterations in PTP activity could be involved in neoplastic processes. If overexpression or constitutive activation characterizes the oncogenic derivatives of protein-tyrosine kinases (1, 2), underexpression or inactivity of protein product should characterize oncogenic derivatives of PTPs. That is, PTPs might act as tumor suppressors (6).

As the number of cloned members of the PTP family has increased, two distinct classes have emerged (3). One class, the cytoplasmic PTPs, are small soluble proteins; the other class, the receptor PTPs (RPTPs), are large transmembrane proteins. The transmembrane structure of the RPTPs suggests they may be involved in signal transduction, providing the cell with externally responsive growth suppressive pathways. Thus, RPTPs are ideal candidate growth suppressors. Recently, three human RPTP genes were cloned and preliminarily characterized (3). In this paper we report the localization of *PTPG*, the gene for one of these RPTPs, PTPγ, to chromosome 3 within a subregion of band p21.

Previous reports have demonstrated the occurrence of nonrandom chromosome 3p deletions in both renal cell carcinoma (RCC) (7–9) and lung carcinoma (LC) (10–13). Hemizygous deletions involving the PTPγ gene were observed in a subset of clinical samples and cell lines derived from RCC and LC tumors and preliminary studies demonstrate PTPγ expression in both cell types. Thus PTPγ may be a tumor suppressor whose functional loss is involved in the pathogenesis of kidney and lung tumors.

MATERIALS AND METHODS

Cells. Kidney-derived (293), RCC-derived (A498, A704, ACHN, Caki I, and Caki II), LC-derived (H128 and H69), and multiple-myeloma-derived (HS) cell lines were purchased from the American Type Culture Collection (ATCC) and maintained as suggested by the supplier. TL9542, a lymphoblastoid cell line carrying the t(3;8)(p14–21;q24) chromosome translocation characteristic of the familial predisposition to RCC (14), and Fr, a multiple-myeloma-derived cell line were maintained in 90% (vol/vol) RPMI 1640 medium/10% (vol/vol) fetal bovine serum/gentamicin (100 ng/ml).

Lung tumor tissue and unaffected peripheral lung tissue were collected and analyzed at the National Cancer Institute (13). SLF.1 lymphocytes were from a normal donor and AB cells were circulating lymphoma cells from a patient with

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: PTP, protein-tyrosine phosphatase; RPTP, receptor PTP; RCC, renal cell carcinoma; LC, lung carcinoma.

[b]To whom reprint requests should be addressed.
[k]To whom correspondence should be addressed.

Burkitt lymphoma having the karyotype: 46,XX,del(3)(p12p24),t(8;14)(q24;q32).

The panel of rodent–human somatic cell hybrids used in chromosomal localization of the PTPγ gene has been described (3, 15); chromosomes retained by individual hybrids in the panel are schematically summarized in Fig. 1. Six rodent–human hybrids were useful in regional localization and ordering of loci on the short arm of chromosome 3. Specific details of chromosome 3-linked probe retention in the regional hybrid panel will be presented in *Results*. Hybrid 5L.8 was clonally derived from fusion of a mouse fibroblast cell line with a human fibroblast cell line (2984) carrying the same chromosome translocation as TL9542. Hybrid 5L.8 retains the derivative chromosome 8 der(8)(8pter→8q24::3p14–p21→3pter) in the absence of the derivative chromosome 3 and normal chromosome 3. Conversely, hybrid 12.8 (16) carries the reciprocal derivative der(3)(3qter→3p14–p21::8q24→8qter) and has lost all other human chromosomes. Hybrids cl1, cl3, cl5, and cl9 are hybrid clones isolated after growth of hybrid GM7297 (Human Genetic Mutant Cell Repository, Coriell Institute, Camden, NJ) in medium containing 6-thioguanine. Hybrids cl1 and cl3 carry derivative chromosomes 3 to be described in the *Results*; hybrid cl9 carries an intact chromosome 3 and hybrid cl5 has lost chromosome 3.

Probes. The PTPγ probe is a 1699-base-pair (bp) partial cDNA clone (ref. 3; B.M., J.L., and J.S., unpublished results). Most other chromosome 3-linked probes used in regional chromosomal localization and ordering are listed in Table 1. Probes pH3H2, pHF12-32, and pCD were obtained from the ATCC; the RAF1 probe was kindly provided by Ulf Rapp (Frederick Cancer Research Center, Frederick, MD). Two probes, referred to in Table 1 as probe L and probe Z, detect loci on human chromosome 3 (J. Jongsta-Bilen, J. Jongstra, S.L., and K.H., unpublished data; P.-G. Pelicci, S.L., and K.H., unpublished data) and were used in characterization of hybrids retaining partial chromosome 3. Probes were radiolabeled by nick-translation with [^{3}H]deoxynucleotides (dNTPs) for *in situ* chromosomal hybridization or by nick-translation or random-priming with [α-^{32}P]dCTP for filter hybridization.

Table 1. Retention of chromosome 3-linked probes in hybrids containing partial chromosome 3

Locus	Approximate map site	Hybrid cell line 12.8	5L.8	cl1	cl3	cl9	cl5	Linkage group
RAF1	3p25	ND	+	−	−	+	−	A
D3F15S2	3p21	ND	+	−	−	+	−	A
D3S28	3p21	ND	+	−	−	+	−	A
D3S34	3p14–p21	ND	+	−	−	+	−	A
D3S2	3p21	−	+	−	−	+	−	A
Probe L	*	ND	−	−	+	+	−	B
D3S39	3p21	+	−	−	+	+	−	B
PTPγ	3p21	+	−	−	+	+	−	B
D3S3	3p14	+	−	−	+	+	−	B
D3S35	3p21	+	−	+	+	+	−	C
Probe Z	*	ND	−	+	+	+	−	C
TFRC	3q26.2–3qter	+	−	+	+	+	−	C

Southern blot hybridization of radiolabeled probes to filters containing hybrid DNA was used to test for presence of each locus. Plus signs (+) denote presence of the locus in the hybrid; minus signs (−) denote absence of the locus in the hybrid; ND denotes presence not tested. These six hybrid cell lines segregate chromosome 3-linked loci into three linkage groups (A–C). The hybrids alone cannot assign an order for the loci within a linkage group. Hybrid 12.8 carries the RCC-associated der3(3qter→3p14–21::8q24→8qter); hybrid 5L.8 carries the reciprocal RCC-associated der8(8pter→8q24::3p14–21→3pter); hybrids cl1 and cl3 carry a cytogenetically indistinguishable portion of chromosome 3 (3p21→3qter) translocated to a hamster chromosome; cl9 carries an intact chromosome 3, and cl5 is negative for chromosome 3. References for chromosome 3 location for most probes are cited in ref. 17. *, Unpublished.

Filter Hybridization. DNA from peripheral blood lymphocytes, clinical samples, and cell lines was obtained by a standard phenol/chloroform extraction procedure (15). Approximately 10 μg of DNA was digested to completion with appropriate restriction endonucleases and size-fractionated on 0.8% agarose gels. The gels were denatured, neutralized, and blotted to Duralon membranes (Stratagene) according to

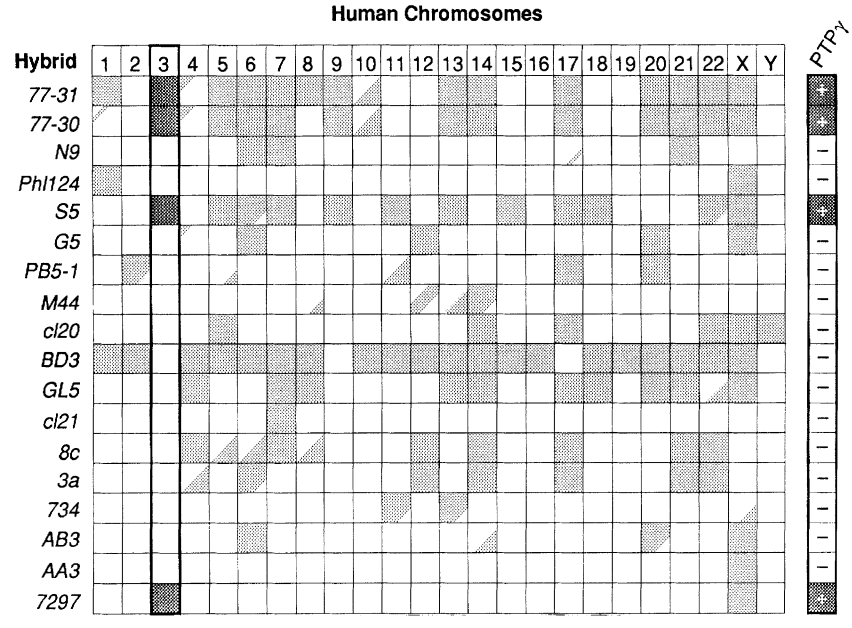

FIG. 1. Chromosomal localization of the human PTPγ gene by analysis of a panel of rodent–human somatic cell hybrids. A completely stippled box indicates that the hybrid contained the chromosome indicated in the upper row; lower-right stippling indicates presence of the long arm (or part of the long arm, indicated by a smaller fraction of stippling) of the chromosome; upper-left stippling indicates presence of the short arm (or partial short arm) of the chromosome; an open box indicates absence of the chromosome. The column for chromosome 3 is boldly outlined and stippled to highlight correlation of presence of this chromosome with the presence of the PTPγ gene. The pattern of retention of the human PTPγ gene in the hybrids is shown at right (PTPγ), where presence of the gene is indicated by a stippled box with a plus sign and absence of the gene is indicated by an open box enclosing a minus sign.

manufacturer's recommendations. Prehybridization and washing were performed as described (15). The hybridized filters were exposed to XAR-2 x-ray films (Kodak) with intensifying screens for 8–16 hr at −70°C.

Poly(A)$^+$ RNA was extracted from cell lines using the FastTrack kit (Invitrogen, San Diego). Approximately 2 μg of poly(A)$^+$ RNA per lane was resolved on 1% agarose/2.2 M formaldehyde gels. Size-fractionated RNA was transferred to Duralon membranes. Once transferred, the blots were treated essentially as described above for DNA filters except hybridized filters were exposed for 1–5 days.

Densitometry. Optical scanning of autoradiographs was performed with a Hoefer model GS300 scanning densitometer using the accompanying program (Hoefer GS-360 data system). Scans were repeated twice and essentially similar results were obtained both times.

Cytogenetic Analysis. Chromosomal *in situ* hybridization was performed as described (18). Cell lines were harvested as described (19), and metaphase chromosomes were G-banded using Wright stain prior to karyotype analysis. Giemsa-11 differential staining was performed as described (20).

RESULTS

Localization of the PTPγ Gene to Human Chromosome Region 3p14–p21. DNAs from 18 rodent–human somatic cell hybrids retaining overlapping subsets of the entire human genome were analyzed by filter hybridization for the presence of the human PTPγ gene. Briefly, *Eco*RI-digested DNAs from hybrid as well as mouse and human cell lines were transferred to filters and hybridized to a radiolabeled PTPγ probe. Two PTPγ-specific human fragments of ≈23 kbp and 4.5 kbp were distinguishable from rodent-specific fragments. The two human fragments, which cosegregated in hybrid DNAs, were present in all hybrids that retained human chromosome 3 as summarized in Fig. 1. *In situ* hybridization confirmed the mapping of the PTPγ gene to human chromosome 3 and refined the localization to region 3p14–p21 with the major peak at p21 (data not shown).

Regional Localization of the PTPγ Gene in Hybrids with Partial Chromosome 3. Regional localization of the PTPγ gene was determined by its presence in hybrids retaining defined portions of chromosome 3. To define the portion of human chromosome 3 contained within each hybrid, a collection of probes whose approximate positions on human chromosome 3 have been established (see Table 1) were mapped to the individual hybrids. The results of filter hybridizations, in which hybrid DNAs were tested for the presence of each locus, are summarized in Table 1. All loci that localize to the same region, as defined by the chromosome 3 breaks in this small panel of hybrids, can be considered part of a linkage group; thus the hybrid panel allows the assignment of the chromosome 3-linked probes into three linkage groups (A, B, and C), as shown in Table 1. Linkage group A contains all tested loci present in hybrid 5L.8 and consists of loci previously localized to the distal short arm and a subset of loci from the p14–21 region; linkage group B consists of loci present in hybrid cl3 but absent in hybrid cl1 and includes a distinct subset of loci from the p14–21 region; linkage group C consists of all loci present in hybrid cl1, containing the proximal portion of the short arm as well as the entire long arm of chromosome 3.

The PTPγ gene was localized on human chromosome 3 relative to the other 3p-linked probes using this mapping panel. Southern blot analysis shows the human PTPγ gene (represented by the 23-kbp and 4.5-kbp hybridizing bands) to be present in hybrids 12.8, cl3, and cl9 and absent in hybrids cl1, cl5, and 5L.8 (Fig. 2). This places PTPγ in linkage group B and localizes it to band p21, centromeric to the 3p breakpoint in the t(3;8) chromosomal translocation, as summarized in Table 1.

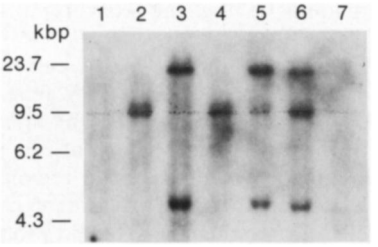

FIG. 2. Filter hybridization analysis of PTPγ gene segregation in hybrids retaining portions of human chromosome 3. Lanes: 1, DNA (≈10 μg) from mouse cell line; 2, hybrid cl5 retaining none of chromosome 3; 3, human cell line; 4, hybrid cl1 retaining 3p21–qter; 5, hybrid cl3 retaining 3p21–pter; 6, hybrid cl9 retaining all of chromosome 3; 7, hybrid 5L.8 retaining 3pter–p21 was cleaved with *Eco*RI and analyzed for the presence of the PTPγ gene.

Deletion of the PTPγ Gene in Tumor-Derived DNAs. PTPγ regional localization at 3p21 places it within a region nonrandomly deleted in a variety of solid tumors including RCC and LC. Such nonsporadic deletions are thought to signify the presence of a gene(s) whose functional inactivation is involved in the malignant process (for review, see ref. 21). As a first step to assessing a role for PTPγ in the pathogenesis of RCC and LC, densitometric analysis was performed to determine the frequency of PTPγ gene loss in these tumors.

Densitometry detects deletions based on reductions in hybridization signal intensity. Ideally, a 50% or 100% reduction in signal intensity is seen with hemizygous or homozygous deletions, respectively. Ideal ratios are rarely seen in clinical samples or tumor cell lines due to contaminating normal tissue or aneuploid karyotypes. For surgical samples, PTPγ signal intensities were compared between tumor and uninvolved peripheral tissue DNAs. For tumor cell lines, PTPγ signal intensity was compared to signal intensity for a linked uninvolved locus, the transferrin receptor gene (*TFRC*). *TFRC* was chosen because it maps to chromosome 3, thereby reducing effects of aneuploidy, and it is sufficiently distant (3q26.2–3qter) to be uninvolved in most cases exhibiting interstitial deletions.

DNA from 10 lung carcinoma surgical samples of various histopathologic types were compared to matched uninvolved peripheral tissue DNA. After normalization for differences in DNA loading, significant reduction in PTPγ signal intensity (38%–67%) could be demonstrated in 50% of tumors (Table 2). Because tumor samples often contain various amounts of both inflammatory infiltrate and uninvolved lung parenchyma, the signal reductions of between 38% and 67% in

Table 2. Densitometric analysis of PTPγ gene dosage in lung tumor tissue relative to matched normal tissue

Sample	Diagnosis	Tumor, % change	PTPγ gene
1	ADC	−05	Normal
2	SQC	−67	Deleted
3	ADC	−47	Deleted
4	SQC	−51	Deleted
5	ADC	−48	Deleted
6	LCC	−38	Deleted
7	ADC	−15	Normal
8	ADC	−10	Normal
9	NA	−16	Normal
10	LCC	−31	Normal

To normalize *PTPG* signal intensities, *TFRC* signal intensities were used to compensate for differences in DNA loading. ADC, adenocarcinoma; LCC, large cell carcinoma; SQC, squamous cell carcinoma; NA, not available.

samples 2–6 are considered to be consistent with the occurrence of a hemizygous deletion involving the PTPγ gene. A previous study of loss of heterozygosity (13) allows localization of the PTPγ gene to a minimally deleted region in LC. Three tumors (samples 4–6) in which the PTPγ gene appears to be deleted were heterozygous for D3F15S2, a locus consistently deleted in LC (11). Tumor 5 was also heterozygous for both D3S2 and *RAF1*, whereas tumor 6 retained both *RAF1* alleles and was noninformative at D3S2. Tumor 4 was noninformative at both D3S2 and *RAF1*. These results demonstrate PTPγ gene loss without concurrent loss of flanking loci and are thus consistent with the PTPγ gene being within the minimally deleted region in these tumors.

For densitometric evaluation of cell lines for which uninvolved tissue is no longer available, *TFRC* was used to establish an internal *TFRC/PTPG* signal ratio. As both probes are cDNAs and detect multiple bands, two bands of similar size were chosen for comparison. DNAs from peripheral blood lymphocytes of a healthy donor (SLF-1) and from lymphoma cells (AB) with a del3(3p12p24) were used as nondeleted and deleted controls, respectively. The *TFRC/PTPG* ratio was ≈1.0 for SLF, whereas AB showed a ratio of 1.6, which represents an ≈40% decrease in PTPγ dosage and is consistent with a hemizygous PTPγ deletion occurring within the tumor subpopulation, ≈80%, of this lymphoma. When five kidney tumor cell lines (Caki I, Caki II, ACHN, 498, and 704) and two lung tumor cell lines (H128 and H69) were evaluated for deletion, three of five kidney lines (Caki I, Caki II, and 704) and one of two lung tumor lines (H69) had *TFRC/PTPG* ratios greater than 1.6, consistent with a PTPγ deletion (Table 3). The remaining two kidney lines (498 and ACHN) had apparently normal ratios and the remaining lung tumor line (H128) had a borderline ratio of 1.37.

Cytogenetic analysis has been reported for both lung tumor lines (10) and indicates that both have large 3p deletions that should include the PTPγ gene. The H128 borderline ratio can be explained by noting in its karyotype that 94% of the cells also carry a 3q deletion. As *TFRC* resides on 3q, its simultaneous loss disguises any PTPγ loss. This and the fact that other mechanisms of loss such as entire chromosome loss with or without duplication of the other homolog can occur (22) suggest that our determination of PTPγ deletion frequencies are conservative estimates of actual loss.

Expression of the PTPγ Gene. Tumor suppressor genes thus far characterized may be expressed in a broad or narrow spectrum of tissue types (21) but they should at least be expressed in the normal counterpart of the tumor types they affect. Thus PTPγ expression was examined in various cell lines. Northern blot analysis on poly(A)$^+$ mRNA indicated that the PTPγ cDNA probe detects two major transcripts of ≈9.6 kilobases and 6.2 kilobases in all RCC and LC cell lines tested (Fig. 3). Similar analysis failed to demonstrate PTPγ expression in three hematopoietic cell lines (TL9542, HS, and Fr), suggesting some tissue specificity (data not shown).

Table 3. Densitometric analysis of PTPγ gene dosage in RCC and LC tumor cell lines

Sample DNA	Cell type	Peak 5/peak 4	PTPγ gene
SLF.1	PBL	0.98	Normal
AB	Lymphoma	1.62	Deleted
H128	LC	1.37	Normal
H69	LC	1.71	Deleted
498	RCC	1.23	Normal
704	RCC	2.36	Deleted
ACHN	RCC	1.22	Normal
Caki I	RCC	3.08	Deleted
Caki II	RCC	1.86	Deleted

To determine if the PTPγ gene was deleted in tumor cell lines, an internal comparison of signal intensity between *PTPG* and *TFRC* was made. Specifically, the intensity of the *PTPG* 4.5-kbp *Eco*RI band (peak 4) was compared to the intensity of the *TFRC* 3.5-kbp *Eco*RI band (peak 5). A comparison of this ratio (peak 5/peak 4) with the ratios from nondeleted (SLF.1) and deleted (AB) controls allows detection of deletions. PBL, peripheral blood leukocyte.

DISCUSSION

Various lines of evidence suggest that PTPγ may be a tumor suppressor gene. Firstly, it localizes to a chromosomal region nonrandomly deleted in a group of carcinomas. Recently, careful analysis of interstitial deletions and cloning of loci between probes flanking growth suppressor genes has been notably successful. The cloning of the retinoblastoma gene (23) as well as a Wilms tumor putative suppressor gene (24, 25) by this approach underscores its power and general applicability.

Application of this approach to the elucidation of growth suppressive events involved in RCC and LC has not yet led to isolation of candidate genes. The major obstacle is the large size of the deletions observed in RCC and LC. Cytogenetic reports suggest that the minimal deleted region is 3p14–23 in LC (10) and 3p14–pter in RCC (9). Two papers (22, 26) reported progress in defining a smaller minimally deleted region in LC. Rabbitts *et al.* (22) described a submicroscopic homozygous deletion involving the D3S3 locus in a LC cell line. The loss of both copies of this locus suggests that it may be close to a critical gene, whereas the fact that this deletion was cytogenetically invisible restricts its size to less than ≈5000 kbp. This represents a significant reduction in the previously defined minimally deleted region. Additional support for this conclusion came when the D3S3 locus was shown to be deleted in a LC tumor sample, whereas two other loci often involved in 3p deletions (D3F15S2 and D3S2) were shown to maintain two copies (26).

These data, thus, suggest that loss of the region surrounding D3S3 is critical in at least a subset of lung carcinomas. The localization of PTPγ to the same linkage group (B) as D3S3 and the fact that the region represented by this linkage group is also cytogenetically invisible (in hybrid cl3 relative to hybrid cl1) suggest PTPγ as a critical gene deleted in these tumors. Deletion analysis of LC samples supports this hypothesis by demonstrating PTPγ loss in tumors that maintain two copies of D3F1FS2 and D3S2. Linkage group B also represents the region directly centromeric to the t(3;8) breakpoint in hereditary renal cell carcinoma. If this translocation pinpoints a region critical in the pathogenesis of RCC, then PTPγ may be important in both LC and RCC. Whether or not the PTPγ genomic locus actually spans the t(3;8) breakpoint on chromosome 3 awaits the cloning of the full-length cDNA.

Not all LC and RCC samples examined in this study have demonstrated PTPγ deletions. This is not inconsistent with the above suggestion. The densitometric analysis used in this study provides conservative estimates of PTPγ loss. Loss of an entire chromosome 3 homolog, with or without reduplication, has been reported (22) and would not be detected by

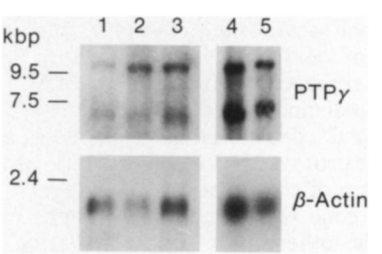

FIG. 3. Transcription of the PTPγ gene in kidney- and lung-derived cells. Poly(A)$^+$ RNA from Caki II (lane 1), 293 (lane 2), H69 (lane 3), 498 (lane 4), and ACHN (lane 5) cells was hybridized to the PTPγ probe (*Upper*) and the β-actin probe (*Lower*).

our analysis, nor would subtle changes that might result in functional inactivation of the gene. The involvement of multiple loci on 3p is also possible and has been suggested (22). Evidence for a similar scenario involving different loci on 11p is also developing for Wilms tumor (21).

PTPγ expression has been shown in RCC and LC cell lines and in an embryonal kidney cell line. The preliminary expression studies hint at the possibility of tissue-specific expression and provide the framework for future investigations.

We thank Teresa Druck for skillful technical assistance and acknowledge the cooperation of the University of Pennsylvania Cancer Center Leukemia/Lymphoma Study Group and thank Ms. Dawn Branca for preparation of the manuscript. This work was supported in part by National Institutes of Health Grants CA21124, CA42232, CA39860, and CA09644.

1. Hanks, S. K., Quinn, A. M. & Hunter, T. L. (1988) *Science* **241,** 42–52.
2. Ullrich, A. & Schlessinger, J. (1990) *Cell* **61,** 203–212.
3. Kaplan, R., Morse, B., Huebner, K., Croce, C., Howk, R., Ravera, M., Ricca, G., Jaye, M. & Schlessinger, J. (1990) *Proc. Natl. Acad. Sci. USA* **87,** 7000–7004.
4. Sap, J., D'Eustachio, P., Givol, D. & Schlessinger, J. (1990) *Proc. Natl. Acad. Sci. USA* **87,** 6112–6116.
5. Krueger, N. X., Streuli, M. & Saito, H. (1990) *EMBO J.* **9,** 3241–3252.
6. Hunter, T. (1989) *Cell* **58,** 1013–1016.
7. Kovacs, G., Erlandsson, R., Boldog, F., Inguarsson, S., Müller-Brechlin, R., Klein, G. & Sümegi, J. (1988) *Proc. Natl. Acad. Sci. USA* **85,** 1571–1575.
8. Zbar, B., Brauch, H., Talmadge, C. & Linehon, M. (1987) *Nature (London)* **327,** 721–724.
9. Walter, T. A., Berger, C. S. & Sandberg, A. A. (1989) *Cancer Genet. Cytogenet.* **43,** 15–34.
10. Whang-Peng, J., Kao-Shan, C. S., Lee, E. C., Bunn, P. A., Carney, D. N., Gazdar, A. F. & Minna, J. D. (1982) *Science* **215,** 181–182.
11. Kok, K., Osinga, J., Carritt, B., Davis, M. B., van der Hout, A. H., van der Veen, A. Y., Landswater, R. M., de Leij, L. F. M. H., Berendsen, H. H., Postmus, P. E., Poppema, S. & Buys, C. H. C. M. (1987) *Nature (London)* **330,** 578–581.
12. Brauch, H., Tory, K., Kotler, F., Gazdar, A. F., Pettengill, O. S., Johnson, B., Graziano, S., Winton, T., Buys, C. H. C. M., Sorenson, G. D., Poiesz, B. J., Minna, J. D. & Zbar, B. (1990) *Genes Chromosomes Cancer* **1,** 240–246.
13. Weston, A., Willey, J. C., Modali, R., Sugimura, H., McDowell, E. M., Resau, J., Light, B., Haugen, A., Mann, D. L., Trump, B. F. & Harris, C. C. (1989) *Proc. Natl. Acad. Sci. USA* **86,** 5099–5103.
14. Cohen, A. J., Li, F. P., Berg, S., Marchetto, D. J., Tsai, S., Jacobs, S. C. & Brown, R. S. (1979) *N. Engl. J. Med.* **301,** 592–595.
15. Durst, M., Croce, C. M., Gissman, L., Schwartz, E. & Huebner, K. (1987) *Proc. Natl. Acad. Sci. USA* **84,** 1070–1074.
16. Gerber, M. J., Miller, Y. E., Drabkin, H. A. & Scoggin, C. H. (1986) *Cytogenet. Cell Genet.* **42,** 72–74.
17. Naylor, S. L. & Bishop, D. T. (1989) *Cytogenet. Cell Genet.* **51,** 1105–1120.
18. Cannizzaro, L. A., Madaule, P., Hecht, F., Axel, R., Croce, C. M. & Huebner, K. (1990) *Genomics* **6,** 197–203.
19. Limon, J., Dal Cin, P. & Sandberg, A. A. (1986) *Cancer Genet. Cytogenet.* **28,** 305–313.
20. Friend, K. K., Chen, S. & Ruddle, F. H. (1976) *Somatic Cell Genet.* **2,** 183–188.
21. Marshall, C. J. (1991) *Cell* **64,** 313–326.
22. Rabbitts, P., Bergh, J., Douglas, J., Collins, F. & Walters, J. (1990) *Genes Chromosomes Cancer* **2,** 231–238.
23. Friend, S. H., Bernards, R., Rogelj, S., Weinberg, R. A., Rapaport, J. M., Albert, D. M. & Drja, T. P. (1986) *Nature (London)* **323,** 643–646.
24. Call, K. M., Glaser, T., Ito, C. Y., Buckler, A. J., Pelletier, J., Haber, D. A., Rose, E. A., Kral, A., Yeger, H., Lewis, W. H., Tores, C. & Housman, D. E. (1990) *Cell* **60,** 509–520.
25. Gessler, M., Poustka, A., Cavenee, W., Neve, R. L., Orkin, S. H. & Bruns, G. A. P. (1990) *Nature (London)* **343,** 774–778.
26. Daly, M. C., Douglas, J. B., Bleehen, N. M., Hastleton, P., Twentyman, P. R., Sundaresan, V., Carritt, B., Bergh, J. & Rabbitts, P. H. (1991) *Genomics* **9,** 113–119.