

# Genetic mapping of the human and mouse phospholipase C genes

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**Abstract.** To determine chromosome positions for 10 mouse phospholipase C (PLC) genes, we typed the progeny of two sets of genetic crosses for inheritance of restriction enzyme polymorphisms of each PLC. Four mouse chromosomes, Chr 1, 11, 12, and 19, contained single PLC genes. Four PLC loci, *Plcb1*, *Plcb2*, *Plcb4*, and *Plcg1*, mapped to three sites on distal mouse Chr 2. Two PLC genes, *Plcd1* and *Plcg2*, mapped to distinct sites on Chr 8. We mapped the human homologs of eight of these genes to six chromosomes by analysis of human × rodent somatic cell hybrids. The map locations of seven of these genes were consistent with previously defined regions of conserved synteny; *Plcd1* defines a new region of homology between human Chr 3 and mouse Chr 8.

## Introduction

The activation of phosphoinositide-specific phospholipase C (PLC) is one of several early cellular responses to many stimuli such as neurotransmitters, growth factors, and hormones. The activated PLC catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) to generate the two second messengers inositol 1,4,4-triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG) in response to the binding of various ligands to their cell surface receptors (Rana and Hopkin 1990). The IP<sub>3</sub> released into the cytoplasm mobilizes Ca<sup>2+</sup> from internal stores, whereas DAG activates protein kinase C (Rana and Hopkin 1990). This bifurcating messenger system controls many cellular processes, including neuronal signaling, cell growth, transformation, secretion, smooth muscle contraction, and sensory perception. PIP<sub>2</sub> also serves as a regulator of a number of actin-binding proteins and as a site needed for the membrane attachment of many signaling proteins with a pleckstrin homology domain (Lee and Rhee 1995).

The need to stringently regulate the cellular concentration of PIP<sub>2</sub> and its conversion to DAG and IP<sub>3</sub> is reflected in part by the fact that there are at least 10 distinct mammalian PLC isoforms and multiple mechanisms linking these subtypes to various receptors (Lee and Rhee 1995; Rhee and Choi 1992). All 10 PLCs are single polypeptide enzymes derived from distinct genes and can be divided into three types: PLC-β, PLC-γ, and PLC-δ, which include four, two, and four subtypes respectively. Although the overall amino acid sequence similarity between the three types of PLC is low, a significant similarity is apparent in two regions, one of ~170 amino acids and the other of ~260 amino acids, which are designated the X and Y regions respectively (Rhee et al. 1989). These homologous regions might thus constitute sites that are important for catalytic properties, such as the specific recognition of phosphoinositides or Ca<sup>2+</sup> (an activator of mammalian PLC) or the

hydrolysis of the phosphodiester bond (Rhee et al. 1989). Whereas PLC-β and PLC-δ contain short sequences of 50–70 amino acids separating the X and Y regions, PLC-γ instead has a long sequence of ~400 amino acids, which contain the so-called *src* homology (SH2 and SH3) domains, domains first identified as noncatalytic regions common to a variety of *src*-family tyrosine kinase. The carboxyl-terminal sequence following the Y region is ~450 amino acids long in PLC-β, although this region is almost nonexistent in PLC-δ. Thus PLC-δ is much smaller than PLC-β and PLC-γ. Single polypeptide PLCs with molecular masses of 62–68 kDa have been purified (Rhee et al. 1989). Although these smaller enzymes were named PLC-α, recent studies suggest that the putative PLC-α cDNA actually encodes a thiol:protein-disulfide oxidoreductase that carries no PLC activity (Martin et al. 1991).

As part of the effort to further define the role of PLC enzymes in normal signal transduction as well as to determine if mutations in any of these genes can be correlated with diseases, we have defined the chromosomal map locations in mouse and human of ten different PLCs.

## Materials and methods

**Probes.** When the amino acid sequences of ten different PLC subtypes were aligned, the sequences between the X and Y domains are more subtype specific than other regions in each PLC subtype (Rhee and Choi 1992). Therefore, to generate subtype-specific probes, we isolated fragments between X and Y domains from each PLC plasmid DNA by PCR. PCR reactions were performed by standard protocols and reagents from Perkin Elmer Cetus (Foster City, Calif.). Primer sequences and plasmid DNA clones for each PLC probe are given in Table 1. PCR conditions were 94°C for 3 min and 30 cycles of 94°C 1 min, 55°C 2 min, 72°C 3 min.

**Mouse genetic mapping.** Two sets of multilocus genetic crosses were analyzed for inheritance of the mouse genes encoding ten PLCs: (NFS/N or C58/J × *M. m. musculus*) × *M. m. musculus* (Kozak et al. 1990) and (NFS/N × *M. spretus*) × *M. spretus* or C58/J (Adamson et al. 1991). DNAs from the progeny of these crosses have been typed for over 850 markers that map to all 19 autosomes and the X Chromosome (Chr). Blot transfer methods and hybridization probes or isozyme typing methods have been previously described for the following markers: the Chr 1 markers *Gls* (glutaminase), *Mtap2* (microtubule-associated protein-2), and *Ugt1a1* (glucuronyltransferase family 1, member 1; Kozak et al. 1994); the Chr 2 markers *Hdc* (histidine decarboxylase), *Mtap1* (microtubule-associated protein-1), *Prn* (prion protein), *Pcna* (proliferating cell nuclear antigen), *Snap25* (synaptosomal-associated protein 25), *Src* (*src* oncogene), and *Cd40* (cluster designation 40; Chang et al. 1994; Pilon et al. 1993; Kozak et al. 1995a); the Chr 8 markers *Plat* (DNA polymerase beta), *Atrc2* (amino acid transporter, cationic 2), *Zfp42* (zinc finger protein-42), *Icshp* (interferon consensus sequence binding protein), and *Aprt* (adenine phosphoribosyl transferase; Hosler et al. 1993; Lyu and Kozak 1994; Kanno et al. 1993); the Chr 11 markers *Evi2* (ecotropic viral integration site-2), *Fkbp-rs* (FK-506-binding, protein-related protein), *Wnt3* (wingless-related MMTV integration site-3 *Int4*), *ErbB2* (avian erythroblastosis oncogene B, epidermal growth factor receptor), and *Pkca* (protein kinase α) (Kozak et al. 1995b).

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**Table 1.** cDNA, Primer sequences, and fragment sizes of each PLC.

PLC	Clone	Primers	Fragment Size (bp)	Reference
PLC-β1	pBI30-PLC-b1	GACCGCTGAGGAAGAGCCTGTCAT TGGCCATGGCCTCGTGCCAGCAG	510	Suh et al. 1988
PLC-β2	pMT2-PLC-b2	CACCCATGGCTTCAACCATGACCAC GCCTTGAGCTCTGTGAAGGACGAG	620	Park et al. 1992
PLC-β3	pTM1-PLC-b3	CGAGACAGCCTTCAAAGACCTCACC ACCTCACTGCTGGCTGTGCCCTCA	570	Jhon et al. 1993
PLC-β4	pBluescript-PLC-b4	CTCACCGGCCGGCAGTTTGGCGGA GCAACCGCTTCTTGTGACTGAAG	610	Lee et al. 1993
PLC-δ1	pBI20-PLC-d1	GGACATGGACCAGCCACTGAGTCA CGGAGAGCTCCGGCACCAGCTTTA	600	Suh et al. 1988
PLC-δ2	pMT2-PLC-d2	GGCCGCGCTCCAACCTGGACCTG GTCCTGGTAGAGAGGGTGGCAGGT	590	Meldrum et al. 1990
PLC-δ3	pMT2-PLC-d3	GTGATCCAAGCTGTGCGTGACCAC AGAGCCACCAGTTGACAGCCCGAG	690	This paper
PLC-δ4	pTM1-PLC-d4	GAGCCCGTTGTTATCATGGGCGT CACGGCATAGCTGTCTGGCATTGT	650	This paper
PLC-γ1	pBI31-PLC-g1	CAGCAGAGGAACATGGCCAGCAC TGCAGCGCAGGGGCACTTGTCTGAT	690	Suh et al. 1988
PLC-γ2	pMT2-PLC-g2	TTCAGGCCATCCGGGATCATGCCT GTAGTACTTCATGACCCACCCTC	650	Emori et al. 1989

Additional markers typed for this study and not previously described include the Chr 2 marker *Avp* (arginine vasopressin-neurophysin II), which was typed in both crosses as a *Bam*HI polymorphism using rat clone obtained from H. Gainer and H. Chin (NINDS, Bethesda, Md.) (Hara et al. 1990). The Chr 12 marker *Ahr* (aromatic hydrocarbon responsiveness) was typed by use of the probe *pSportAhr* obtained from American Tissue Culture Collection (ATCC, Rockville, Md.) (Burbach et al. 1992) following *Apa*I digestion in the *M. spretus* crosses and *Bst*EII digestion in the *M. m. musculus* crosses. The Chr 12 marker *Dld* (dihydroliipoamide dehydrogenase) was typed after digestion with *Bam*HI in the *M. spretus* crosses and *Xba*I in the *M. m. musculus* crosses by use as probe clone IB813 from the ATCC (Khan et al. 1992). The Chr 12 marker *Twist* (*Drosophila* twist homolog) was identified as a *Bam*HI polymorphism in the *M. spretus* crosses and a *Hpa*I polymorphism in the *M. m. musculus* mice with pEMBL18 + as probe (Wolf et al. 1991). Chr 12 markers *Odc* (ornithine decarboxylase) and *Odc-rs18* (ornithine decarboxylase-related sequence 18) were typed as *Sac*I fragments with clone pCR6 obtained from F.G. Berger (Univ. of South Carolina, Columbia, S.C.; Rheaume et al. 1989). Three additional Chr 19 markers were also typed. *Cd5* (cluster designation 5) was typed in all mice following *Hind*III digestion using an *Ly1* probe obtained from B. Mock (Mock et al. 1993). *Fth* (ferritin heavy chain) was typed as a *Pst*I polymorphism in both crosses with the pMHFY20 clone from ATCC (Yachou et al. 1991) used as probe, and *Pcna-ps2* (proliferating cell nuclear antigen pseudogene 2) was typed as a *Bam*HI polymorphism in the *M. spretus* crosses and a *Bgl*II polymorphism in the *M. m. musculus* crosses by use of the *Pcna* probe described previously (Pilon et al. 1993).

Typing data were stored and analyzed with the program LOCUS developed by C.E. Buckler (NIAID, Bethesda, Md.). Percentage recombination and standard errors between specific loci were calculated from the number of recombinants according to Green (1981). Loci were ordered by minimizing the number of recombinants.

**Human genetic mapping.** Human PLC genes were assigned to specific chromosomes by Southern blot analysis of a human × rodent somatic cell hybrid panel obtained from BIOS (New Haven, Conn.; Carlock et al. 1986). The panel consists of 19 human × hamster hybrids and 1 human × mouse hybrid.

## Results and Discussion

**Mouse genetic mapping.** To determine positions for the ten PLC genes on the linkage map, we typed the progeny of two sets of genetic crosses for inheritance of restriction enzyme polymorphisms of each PLC. The restriction enzymes used to identify typable polymorphisms and the fragment sizes observed in parental mice are given in Table 2. Inheritance of the variant fragments were compared with that of over 850 markers previously typed in

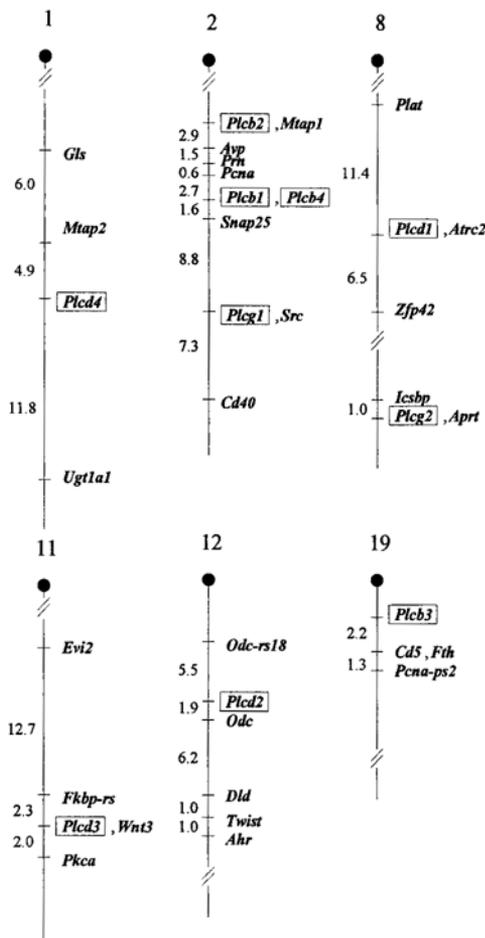
**Table 2.** Fragment size of PLC genes in parental mice of two sets of multilocus crosses.

Probe	Enzyme	Fragment Size (kb)		
		NFS/N, C58/J	<i>M. m. musculus</i>	<i>M. spretus</i>
<i>Plcb1</i>	<i>Bst</i> EII	22.0	12.5	
	<i>Apa</i> I	19.1	21.0	12.5
<i>Plcb2</i>	<i>Pst</i> I	3.4		3.0
	<i>Bgl</i> II	6.0	5.5	
<i>Plcb4</i>	<i>Apa</i> I	23.1, 6.8, 1.5	23.1, 19.4, 6.8	
		9.0, 7.0, 6.5, 6.2,		9.0, 6.5, 6.0, 5.2,
	<i>Pvu</i> II	5.2, 2.5		3.9, 2.7
<i>Plcd1</i>	<i>Hind</i> III	19.5		10.5
<i>Plcd2</i>	<i>Sca</i> I	11.0		7.5
<i>Plcd3</i>	<i>Eco</i> R1	17.5, 3.7, 2.2	18.5, 3.7, 2.2	
	<i>Pst</i> I	3.7, 2.6		4.5
<i>Plcd4</i>	<i>Hind</i> III	14.5, 5.7		12.5, 5.7
<i>Plcg1</i>	<i>Bam</i> HI	7.7		2.3
<i>Plcg2</i>	<i>Pst</i> I	8.0		3.4

the two sets of crosses. The ten mouse PLC genes were mapped to specific positions on six different chromosomes (Fig. 1).

*Plcd4*, *Plcd3*, *Plcd2*, and *Plcb3* were mapped to mouse Chr 1, 11, 12, and 19 respectively. Two PLC genes, *Plcd1* and *Plcg2*, mapped to Chr 8 but were separated by about 40 cM. Four *Plc* loci, *Plcb1*, *Plcb2*, *Plcb4*, and *Plcg1*, mapped to three sites on distal mouse Chr 2. As shown in Figure 1, two of these Chr 2 genes, *Plcb1* and *Plcb4*, were closely linked on this chromosome near *Snap25*. For these genes, no recombinants were observed in 83 mice of the *M. m. musculus* crosses and 101 mice of the *M. spretus* crosses, indicating that, at the 95% confidence level, these genes are within 1.6 cM. This suggests that these two genes, which show about 40% overall sequence identity in their coding regions, may have been derived from a common ancestral locus. *Plcb2* mapped approximately 6 cM proximal to these two genes in the *M. spretus* cross (recombination = 6/106), and *Plcg1* mapped to a more distal location, closely linked with *Src* (no recombinants in 80 mice). Previous studies had defined mouse map locations for *Plcg1* (Nelson et al. 1992; Argeson et al. 1995) and *Plcg2* (Hernandez et al. 1994; Argeson et al. 1995), which are consistent with the results reported here.

**Chromosome assignment of human PLC genes.** The same ten PLC probes used for the mouse mapping were used to screen 20 human × rodent somatic hybrid cell DNAs, and eight of these genes were assigned to human chromosomes. *PLCD2* was not mapped because five restriction enzymes tested produced identical-sized



**Fig. 1.** Genetic map locations of the ten mouse PLC genes. CentiMorgan distances between loci are given to the left of each map. Raw data used to derive these map locations are available through MGD, Accession Numbers MGD-CREX-521–529.

fragments in human and rodent DNAs. Human PLCB3 was not mapped because the human fragment identified by the mouse probe was too faint to read reliably in the hybrid DNAs. The remaining eight PLCs were typed in 18–20 human  $\times$  rodent hybrids. In all cases, a perfect correlation was observed for each PLC with only one chromosome; at least two discordant hybrids were identified for all other chromosomes.

According to this analysis, PLCB1, PLCB4, and PLCG1 mapped to human Chr 20, as expected from their positions on distal mouse Chr 2. PLCB2 mapped to Chr 15, consistent with the presence of a small region of conserved homology to this human chromosome in the middle of mouse Chr 2 (Siracusa and Abbott 1994).

Human PLCD3 and PLCD4 mapped to Chr 17 and 2, which contain regions of conserved synteny with mouse Chr 11 and Chr 2, respectively (Lossie et al. 1994; Siracusa and Abbott 1994). Human PLCG1 and PLCG2 could be assigned to Chrs 20 and 16, as expected from their positions on mouse Chr 2 and Chr 8 respectively (Siracusa and Abbott 1994; Ceci 1994). Although the location of PLCD1 was predicted to be human Chr 8 from its previously described homology to this region of mouse Chr 8 (Ceci 1994), our data place PLCD1 on human Chr 3. Human Chr 8 was excluded, since three hybrids (803, 811, and 909) contained Chr 8 but not PLCD1, and two hybrids (423, 1079) contained PLCD1, but not Chr 8. These results therefore suggest a new region of conserved synteny.

The map locations of the genes encoding eight human and mouse PLC genes are thus generally consistent with previously

defined regions of conserved synteny between these species with the single exception of PLC- $\delta$ 1. The map locations defined here are also consistent with previously determined map locations for several of these genes. The mouse map location of PLC- $\beta$ 3 on proximal Chr 19 predicts a human location of 11q12-13, consistent with the 11q13 assignment recently determined by Mazuruk and associates (1995). Our results are also consistent with previous studies which had defined human map locations for PLCB4, PLCG1, and PLCG2 (Alvarez et al. 1995; Bristol et al. 1988; Rothschild et al. 1992; Argeson et al. 1995). Although we were unable to map PLCD2 and PLCB3 in human, our mouse map locations for these genes suggest that the human counterparts of these genes are likely to map to 2p and 11q13 respectively.

**Disease gene correlations.** Malfunction in one of the PLC signaling pathways might be expected to result in disease, since other genetic disorders are associated with defects in genes that encode receptors, protein tyrosine kinases, or G-proteins. Tissue-specific expression of the various PLCs suggests important roles in erythroid differentiation and in signal transduction in response to light (Martelli et al. 1994; Alvarez et al. 1995). Along these lines, Alvarez and colleagues (1995) observed that defects in *Drosophila* norpA, a homolog of mammalian PLCB4, block phototransduction and lead to retinal degeneration. Mazuruk et al. (1995) suggested PLCB3 as a candidate for four human genetic disorders that map to 11q13, all of which are associated with retinopathy. Abnormal PLC expression has also been noted in other disorders, specifically hypertension in the rat (PLCD1) (Kato et al. 1992), and human colon, breast, and stomach cancers (PLCG1; Arteaga et al. 1991; Noh et al. 1994; Park et al. 1994). Although examination of the chromosomal regions around each of the ten genes mapped in the present study identified no disorders for which PLC genes are obvious candidates, information on the genetic map locations of these genes in human and mouse should assist in future efforts to determine their contribution to disease.

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