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Assignment of Human Genes for Phosphorylase Kinase Subunits α (*PHKA*) to Xq12-q13 and β (*PHKB*) to 16q12-q13

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Summary

Phosphorylase kinase (PHK), the enzyme that activates glycogen phosphorylases in muscle, liver, and other tissues, is composed of four different subunits. Recently isolated rabbit muscle cDNAs for the larger two subunits, α and β, have been used to map the location of their cognate sequences on human chromosomes. Southern blot analysis of rodent × human somatic cell hybrid panels, as well as in situ chromosomal hybridization, have provided evidence of single sites for both genes. The α subunit gene (*PHKA*) is located on the proximal long arm of the X chromosome in region Xq12-q13 near the locus for phosphoglycerate kinase (*PGK1*). X-linked mutations leading to PHK deficiency, known to exist in humans and mice, are likely to involve this locus. This hypothesis is consistent with the proximity of the *Phk* and *Pgk-1* loci on the mouse X chromosome. In contrast, the β subunit gene (*PHKB*) was found to be autosomal and was mapped to chromosome 16, region q12-q13 on the proximal long arm. Several different autosomally inherited forms of PHK deficiency for which the *PHKB* could be a candidate gene have been described in humans and rats.

Introduction

Glycogen phosphorylases catalyse the degradation of glycogen to form glucose-1-phosphate in muscle, liver, and brain. The tissue-specific enzymes are encoded by genes on different chromosomes. The gene for muscle phosphorylase has been assigned to human chromosome 11q12-q13 (Lebo et al. 1984; Glaser et al. 1987), and the liver phosphorylase locus is on chromosome 14 (Newgard et al. 1987). The brain enzyme was cloned and found to hybridize to sequences on human chromosomes 10 and 20 (Newgard et al. 1988). The enzymes exist in an inactive phosphorylase *b* form and are activated by phosphorylase kinase (PHK) to the active phosphorylase *a* form. The structural changes that result from the phosphorylation have recently been elucidated (Sprang et al. 1988). Thus, PHK (ATP: phosphorylase-*b* phosphotransferase: E.C.2.7.1.38) can be considered a regulatory protein kinase.

PHK is a large multimeric enzyme with four different subunits. The small γ subunit carries the catalytic activity. The δ subunit is a member of the calmodulin family. It binds calcium and controls the response of PHK to calcium ions. Cloning of calmodulin cDNA has revealed the existence of more than one active calmodulin gene in humans and in several other species (Sen Gupta et al. 1987). The α and β subunits are the largest, confer regulation of the enzyme by phosphorylation, and exist as multiple tissue-specific isoforms, at least in skeletal and cardiac muscle. DNA sequences encoding the α and β subunits have recently been cloned from a rabbit muscle cDNA library (Kilimann et al. 1988; Zander et al. 1988). The deduced polypeptides are 1,237 (α) and 1,092 (β) amino acids long and contain extensive regions of sequence homology. Phosphorylation sites and putative calmodulin binding sites have been identified (Kilimann et al. 1988).

Inherited deficiencies of PHK lead to glycogen storage disease (GSD). Partial deficiency of the liver en-

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zyme produces a glycogenosis, GSD type VIII (Huijing 1970) or type IX (Schimke et al. 1973), that is variable in severity and inherited as an X-linked recessive trait. The muscle enzyme seems to be normal in most of these patients (Schimke et al. 1973). X linkage has further been demonstrated by the finding of two distinct types of fibroblast cell clones, cultured from individual female heterozygotes, with deficient or normal PHK activity (Migeon and Huijing 1974).

PHK deficiency in both liver and muscle was found in affected brother and sisters with hepatomegaly and accumulation of glycogen in both liver and muscle (Bashan et al. 1981). The presumed autosomal recessive inheritance in this family suggests an autosomal location of at least one PHK subunit gene. Furthermore, PHK deficiency in cardiac muscle only was described in a boy (Mizuta et al. 1984; Eishi et al. 1985) and a girl (Servidei et al. 1988) who both died at a few months of age from cardiac failure and were found to have cardiomegaly with increased amounts of glycogen in the heart muscle.

Animal models reveal genetic heterogeneity as well. Liver PHK deficiency in rats is inherited as an autosomal recessive trait (Malthus et al. 1980). In V strain mice, PHK activity is reduced and an abnormal protein has been identified. The inheritance of the defect is X linked dominant (Varsanyi et al. 1980). In the I strain of mice, a mutation causing PHK deficiency in skeletal muscle and reduced PHK amounts in heart, brain, and kidney is X linked recessive (Lyon et al. 1967). It is not clear whether this *Phk* locus represents a structural or a regulatory gene (Cohen et al. 1976). It has been mapped 12 cM proximal to the structural gene for phosphoglycerate kinase (*Pgk-1*), with the gene for testicular feminization (*Tfm*), caused by a defect in the androgen receptor, located between the two (Davisson et al. 1988). On the basis of comparative mapping considerations and on the basis of the X-linked recessive inheritance of the human hepatic kinase deficiency (GSD type VIII), one would predict that at least one of the PHK subunit genes will be found on the X chromosome in humans as well.

It will be very interesting to unravel the molecular basis of these different clinical disorders. In an enzyme with four different subunits and multiple tissue-specific isoforms that can be activated by several heterogeneous stimuli, complex and heterogeneous phenotypes are expected to be associated with deficiency. As a first step toward this goal, we have determined the number and location of sites on human chromosomes that contain sequences homologous to the cloned rabbit skeletal muscle α and β probes. Two independent approaches, somatic cell hybrid analysis and in situ chromosomal hybridization, revealed consistent results.

Material and Methods

The primary assignment panel consists of 12 Chinese hamster × human somatic cell hybrids derived from five independent fusion experiments. The origin and characterization of these hybrid lines have recently been summarized (Yang-Feng et al. 1986). For regional mapping on the X chromosome, six hybrid lines containing defined parts of the human X chromosome were used. These cell lines allowed us to distinguish five contiguous regions on the X short arm and the long arm as a whole (de Martinville et al. 1985; U. Francke, unpublished data).

For mapping of the α subunit gene, a 1.2-kb *Pvu*II fragment (αPP2) from the 3′ end of the rabbit cDNA was used for hybridization to Southern blots, and a plasmid (pαPhk-D1) containing the complete 4.5-kb cDNA was used for in situ hybridization (Zander et al. 1988). For mapping of the β subunit gene, a 2.25-kb fragment (βP1) was used for in situ hybridization and a 1.1-kb fragment (βPv2-Psl) was used for Southern blotting (Kilimann et al. 1988).

DNA extraction and Southern blotting were carried out according to methods described elsewhere (Barton et al. 1987). Since the rabbit cDNA probes for the β subunit were hybridizing poorly to DNA from other species, hybridizations had to be carried out at room temperature for 2 d (50% formamide, 42°C) to obtain a specific signal for human DNA. In situ hybridization of tritium-labeled probes to metaphase spreads from short-term lymphocyte cultures derived from different normal human donors followed established procedures (Harper and Saunders 1981; Yang-Feng et al. 1985).

Results

The α Subunit (PHKA) Is Mapped to Xq12-Xq13.1

The α subunit cDNA fragment αPP2 from the 3′ end of the cDNA hybridized with three *Hind*III fragments (approximately 4–6 kb in size) in human DNA. The intensity of these fragments was proportionally increased in DNA from a 48,XXXX cell line. In a somatic cell hybrid mapping panel, all three fragments were concordant with the human X chromosome. Table 1 shows exclusion of all autosomes by at least three discordant hybrids. In addition, two independently de-

Table 1

Correlation of Human PHKA Sequences with Human Chromosomes in Rodent × Human Somatic Cell Hybrids

	Human Chromosomes																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X
Concordant:																							
+ / +	3	1	4	3	1	5	2	2	2	2	2	3	3	5	4	3	1	5	5	2	4	6	3
− / −	3	3	2	3	1	2	2	0	2	3	2	3	0	2	1	3	2	1	2	1	2	1	2
Discordant:																							
+ / −	6	8	5	3	8	4	6	6	7	7	5	6	6	3	5	5	8	4	4	7	4	2	0
− / +	0	0	1	0	1	1	0	3	1	0	1	0	3	0	2	0	1	2	1	2	1	2	0
Total discordant hybrids	6	8	6	3	9	5	6	9	8	7	6	6	9	3	7	5	9	6	5	9	5	4	0
Total informative hybrids	12	12	12	9	11	12	10	11	12	12	10	12	12	10	12	11	12	12	12	12	11	11	5

Note.—The numbers of hybrids that are concordant (+ / + or − / −) and discordant (+ / − or − / +) with the human PHKA sequence are given for each chromosome. Hybrids in which a particular chromosome was present only in part or in fewer than 10% of cells were excluded; for example, the X chromosome was only partially present in seven hybrid lines.

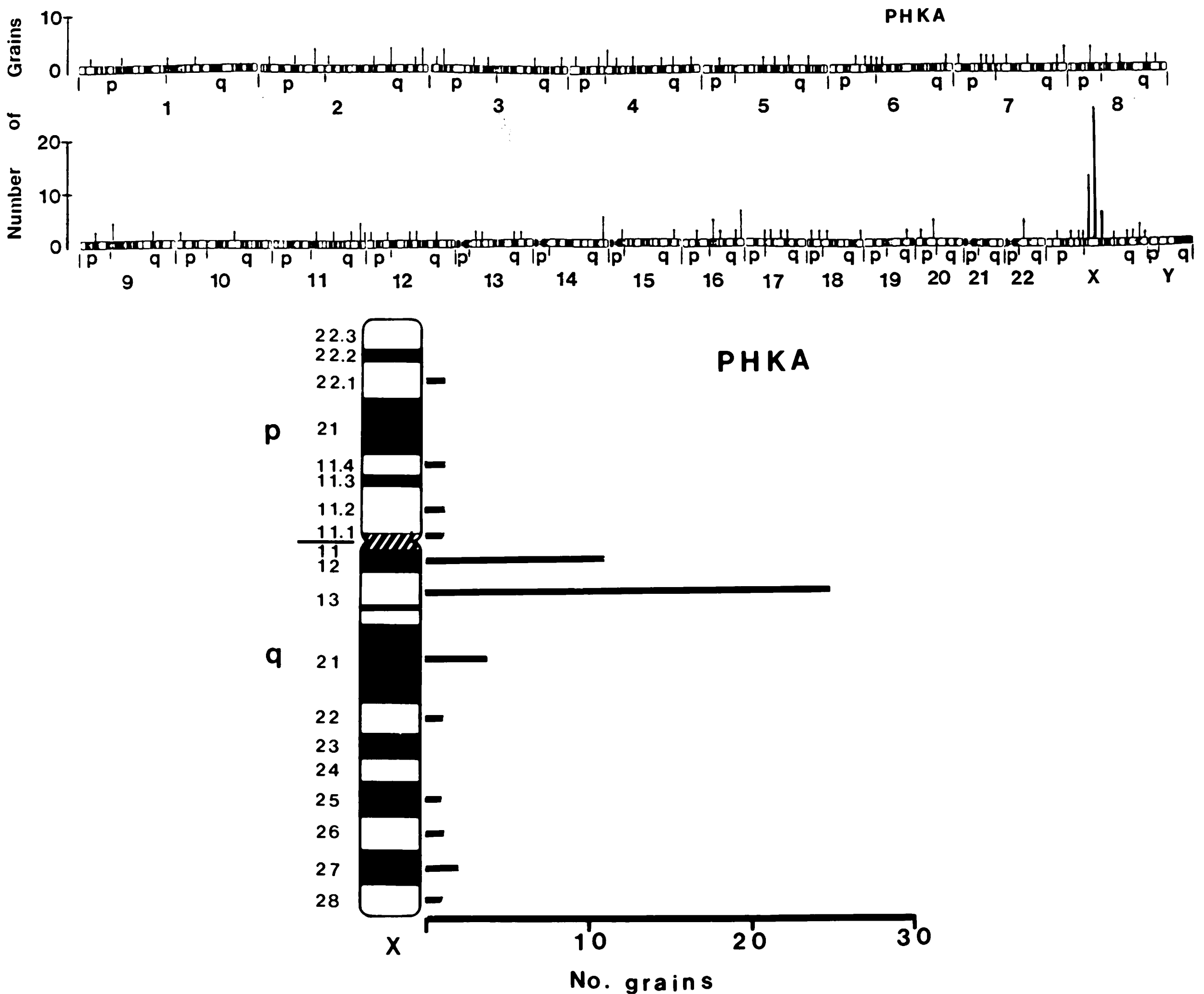

Figure 1 *A*, Assignment of *PHKA*. Localization of 154 autoradiographic silver grains associated with chromosomes in 61 metaphase spreads. The ideograms represent the G-banding pattern present on the chromosomes after hybridization with α subunit cDNA probe and autoradiography. Only a single site of nonrandom accumulation is present on the proximal long arm of the X chromosome. *B*, Grain distribution pattern on the X chromosome, revealing localization of the PHKA sequence in the proximal part of band q13 (equivalent to subband Xq13.1). Since on this low-resolution ideogram band q13 is normally not subdivided, the darkly staining dividing band Xq13.2 has been drawn in.

rived hybrid cell lines with the X chromosome as the only human chromosome were positive for the human-specific fragments. The results obtained with hybrids that contain only part of the X chromosome assigned the gene to the long arm of the X (not shown).

For more precise localization, a plasmid containing the entire cDNA was labeled by nick-translation to a specific activity of 2.8×10^7 cpm/μg and was hybridized in situ to chromosome preparations from blood lymphocytes of two normal human donors. Cells were selected that had between one and five autoradiographic silver grains associated with chromosomes. Of 61 spreads analyzed, 55 were female and six were male. The total number of grains on chromosomes was 154 (average 2.6 grains/cell). A single specific site of hybridization was identified at Xq12-q13 with 36 grains (23%) at this site and with 32 cells (52%) labeled at this site. The remaining grains were distributed randomly. There was no evidence for the existence of a second related locus and, in particular, no peak over chromosome 16 (fig. 1*A*). On the basis of the grain distribution pattern on the X chromosome (fig. 1*B*), we assign the *PHKA* locus to region Xq12-q13.1

The β Subunit (PHKB) Is Mapped to 16q12-q13

When the 1.1-kb *Pvu*II-*Pst*I fragment from the 5′ region of the β subunit cDNA was used to probe Southern filters with *Hin*dIII-digested human DNA, five fragments (approximately 9, 5.5, 5, 2.7, and 1.5 kb) were seen. The four that were distinguishable from the two (2.7- and 2.3-kb) Chinese hamster fragments were concordant with each other and with human chromosome 16. All the other chromosomes were excluded as carrying related sequences by three or more discordant hybrids (table 2). A hybrid cell line with a deleted chromosome 16 missing region q22→qter was still positive for the human-specific fragments. This result excludes region 16q22-q24—to which we have previously mapped the gene for tyrosine aminotransferase (*TAT*) (Barton et al. 1986)—as containing PHKB sequences.

The PHKB gene on chromosome 16 was mapped more precisely by in situ hybridization. A 2.25-kb *Pst*I fragment comprising the 5′ half of the rabbit cDNA was labeled by nick-translation to a specific activity of 2.1×10^7 cpm/μg. The metaphase spreads were selected on the basis of having between one and six labeled chromosomal sites. In 58 metaphase spreads from short-term lymphocyte cultures of a normal human female, 190 labeled sites were identified (an average of 3.3 sites/cell). A single specific site of hybridization was found at 16q11→q13, with 29 (15%) of all signals in this region and 27 (47%) of all cells labeled at this site. The remainder of the silver grains were randomly distributed and were considered background (fig. 2*A*). The distribution of grains on chromosome 16 suggests band q12 as the most likely site for the human PHKB gene (fig. 2*B*).

Discussion

Our data provide evidence for the existence of single sites for PHK subunit genes *PHKA* and *PHKB* in humans. The findings are consistent with the hypothesis that single genes give rise to differentially spliced multiple transcripts which encode the tissue-specific isoforms of the enzyme. The alternative possibility of tandemly

Table 2

Correlation of Human PHKB Sequences with Human Chromosomes in Rodent × Human Somatic Cell Hybrids

	Human Chromosomes																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X
Concordant:																							
+/+	3	1	4	2	0	3	0	2	1	0	1	3	2	3	4	4	0	4	3	1	4	3	0
−/−	6	7	4	4	4	4	3	3	5	5	4	6	3	3	3	7	5	4	4	4	4	1	2
Discordant:																							
+/−	2	4	1	2	5	2	5	3	4	5	3	2	3	1	1	0	5	1	2	4	1	2	0
−/+	1	0	3	1	2	3	2	4	2	2	2	1	4	3	4	0	2	3	3	3	2	5	3
Total discordant hybrids	3	4	4	3	7	5	7	7	6	7	5	3	7	4	5	0	7	4	5	7	3	7	3
Total informative hybrids	12	12	12	9	11	12	10	12	12	12	10	12	12	10	12	11	12	12	12	12	11	11	5

Note.—The numbers of hybrids that are concordant (+/+ or −/−) and discordant (+/− or −/+) with the human PHKB sequence are given for each chromosome. Hybrids in which a particular chromosome was present only in part or in fewer than 10% of cells were excluded.

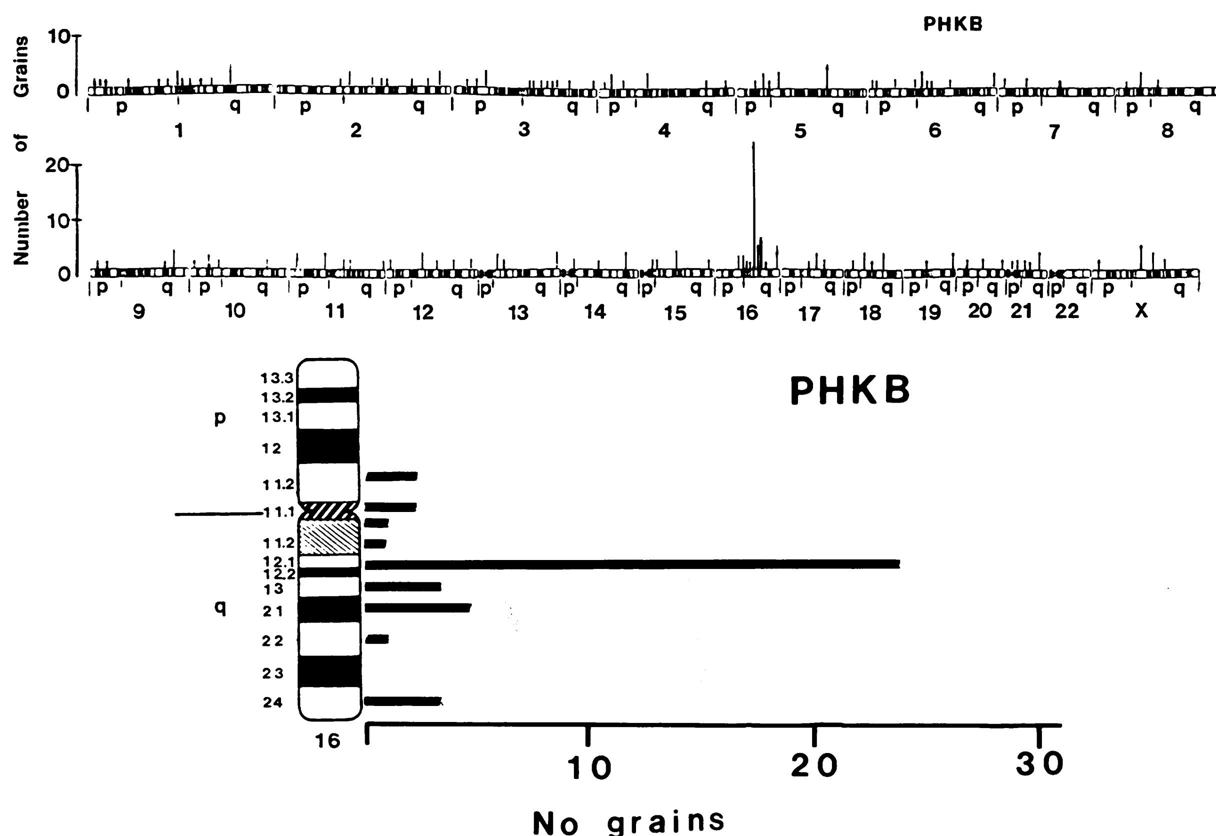

Figure 2 *A*, Assignment of *PHKB*. After in situ hybridization of tritium-labeled PHK β subunit cDNA probe to human metaphase spreads, 190 labeled sites were identified on chromosomes in 58 cells. They are distributed randomly, except for a single peak on the proximal long arm of chromosome 16. *B*, Distribution of silver grains on chromosome 16, assigning the *PHKB* gene to band q12.

duplicated genes that are functioning and in close physical proximity to each other cannot be ruled out by our data.

The *PHKA* gene on Xq12-Xq13.1 seems likely to be homologous to the *Phk* locus in the mouse. The conserved region includes the loci *Pgk-1* and *Tfm* (Lubahn et al. 1988) and flanks the Searle's T(X;16)16H translocation breakpoint that has been mapped to region D (Eicher et al. 1972; Lyon 1988). Not included in the conserved region is the *mdx/dmd* locus that is homologous to the dystrophin gene responsible for Duchenne/Becker types of muscular dystrophy (*DMD/BMD*) in humans (Ryder-Cook et al. 1988). On the mouse X chromosome, *mdx* is only one map unit proximal to *Phk* (Davisson et al. 1988), but in humans *DMD/BMD* is on the short arm, in band Xp21 (Francke et al. 1985). The *DMD* region is separated from the *PHKA, PGK1, DHTR* (*TFM*) region by another group of conserved genes—synapsin I (*SYN1/Syn-1*), tissue inhibitor of metalloproteinase (*TIMP/Timp*), ornithine transcarbamylase (*OTC/spf*) and chronic granulomatous disease, or cytochrome b_{245} β-subunit (*CGD/Cybb*)—that are on the proximal short arm of the human X and near the centromere on the mouse X chromosome (Lindgren et al. 1984; Yang-Feng et al. 1986; Jackson et al. 1987; Spurr et al. 1987; Brockdorff et al. 1988). An updated summary of the comparative mapping of the human and mouse X chromosome is provided in figure 3.

On human chromosome 16, *PHKB* is not the first protein kinase gene. The gene for protein kinase C, β type, has also been located there, most likely on the proximal short arm. Our original assignment, reported as 16p12-q11.1 (Coussens et al. 1986), reflected the total nonrandom distribution of silver grains. However, bands q11.1 and p11.1 represent the centromeric heterochromatin region, and the peak of grains was clearly over band 16p11.2 (Francke et al. 1986). Therefore, the

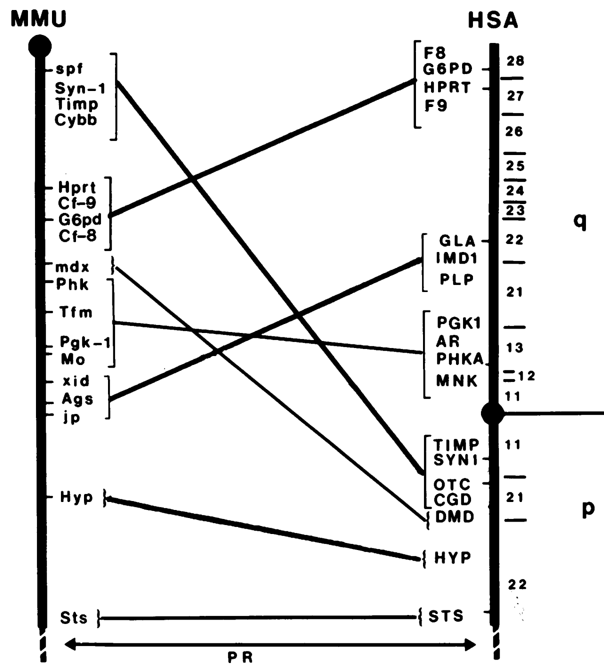

Figure 3 Homologous genes on murine (MMU) and human (HSA) X chromosomes that have been regionally mapped on the linkage map (MMU) or the physical map (HSA). Potentially conserved regions are bracketed and connected by lines. The order of loci within brackets is not always known (update of fig. 5 of Yang-Feng et al. 1986). For abbreviations and references, see text, Human Gene Mapping 9 (1987) and 9.5 (1988), and Mouse gene list (1988). PR = pairing region.

most likely location of *PKCB* is in 16p11.2, which is almost a mirror-image position with regard to *PHKB* on 16q12-q13.1 adjacent to the heterochromatin region on the long arm. Comparative high-resolution banding analysis of great-ape chromosomes suggests that a small pericentric inversion of chromosome 16 has occurred during primate evolution (Yunis and Prakash 1982). Therefore, the possibility that these two kinase genes may have arisen by duplication of a common ancestral sequence has been considered. Sequence comparisons, however, have not revealed any homology between the two proteins (Kilimann et al. 1988).

The *PHKA* and *PHKB* loci are asyntenic with the genes encoding (1) the different types of glycogen phosphorylases, on chromosomes 10, 11, 14, and 20, (2) the tissue-specific forms of phosphofructokinase, on chromosomes 1, 10, 12, and 21 (for references, see Human Gene Mapping 9 1987; Human Gene Mapping 9.5 1988), (3) two of the three sites that hybridize with calmodulin cDNA probes, on chromosomes 7 and 14 (Scambler et al. 1987), and (4) the sites that hybridize with the PHKγ subunit cDNA on chromosomes 7 and 11 (Chamberlain et al. 1987).

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