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Localization of two genes encoding plasma membrane Ca^{2+} ATPases isoforms 2 (ATP2B2) and 3 (ATP2B3) to human chromosomes 3p26→p25 and Xq28, respectively

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Abstract. The plasma membrane Ca^{2+} ATPases (PMCA) represent a highly conserved, widely dispersed, multigene family in eukaryotes consisting of at least four functional genes. The genes for PMCA isoforms 1 and 4 (ATP2B1 and ATP2B4) have been previously localized to human chromosomes 12q21→q23 and 1q25→q32, respectively. Based upon results of fluorescence in situ hybridization (FISH), analysis of somatic cell hybrids, and genetic linkage analyses, we now report localization of ATP2B3 (PMCA isoform 3) to human chromosome Xq28, and confirm the recent localization of ATP2B2 (PMCA isoform 2) to chromosome 3p26→p25. In contrast to ATP2B1 and ATP2B4, recent studies have suggested tissue specific regulation of expression of both ATP2B2 and ATP2B3 particularly in the nervous system. The genes for several neurological and neuromuscular diseases have been assigned to the distal portion of Xq, and ATP2B3 is a candidate gene for these diseases.

Plasma membrane Ca^{2+} ATPases (Carafoli, 1991; Strehler, 1991; Carafoli, 1992) are members of the P class of ion-motive ATPases characterized by the formation of an acylphosphate intermediate as part of the reaction mechanism (Pedersen and Carafoli, 1987a, b). They are distinguished from other P-type ATPases by their higher molecular mass and by the presence of a C-terminal regulatory region containing a calmodulin binding domain as well as sites for phosphorylation by a cAMP-dependent protein kinase (Caroni and Carafoli, 1981) and protein kinase C (Wang et al., 1991). These large enzymes (i.e. Mr 130,000 to 150,000) play a critical role in cells of higher eukaryotes in maintaining a low concentration of free intracellular Ca^{2+} in the presence of high concentrations of this ion in the extracellular medium. Members of this family have very similar structures including regions of highly conserved nucleotide and amino acid sequences interspersed with large regions containing more limited homology (Strehler, 1991). The fact that this multigene family has been highly conserved during evolution suggests that there may be subtle differences in function between different members or, more likely, that the presence of multiple genes may allow tissue and cell specific regulation of function. Recent work (Stauffer et al., 1993) has led to the suggestion that human ATP2B1 and ATP2B4 are uniformly expressed in all tissues, whereas ATP2B2 and ATP2B3 are expressed in a tissue-specific way. Very interestingly, recent work on rat genes has shown that the products of ATP2B2 and ATP2B3 are particularly abundant in some brain regions (Stahl et al., 1992). Determination of the chromosomal location of these genes might assist in assessment of them as possible candidate genes in various genetic diseases.

We have previously localized ATP2B1 and ATP2B4 to human chromosomes 12q21→q23 and 1q25→q32, respectively (Olson et al., 1991). Recently, ATP2B2 has been mapped to chromosome 3 (Brandt et al., 1992; Latif et al., 1993a) very close to the gene for the von Hippel-Lindau syndrome (Latif et al., 1993b). We now report localization of ATP2B3 to human chromosome Xq28, and confirm localization of ATP2B2 to 3p26→p25.

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Table I. Segregation of ATP2B3 with the X-chromosome

Human chromosome	Gene/Chromosome				% Discordancy
	+/+	+/−	−/+	−/−	
1	19	28	11	25	47
2	15	32	10	26	51
3	20	27	6	30	40
4	32	15	15	21	36
5	18	29	5	31	41
6	28	19	16	20	42
7	20	27	18	18	54
8	21	26	11	25	45
9	19	28	11	25	47
10	11	36	4	32	48
11	23	24	7	29	37
12	18	29	8	28	45
13	18	29	15	21	53
14	32	15	20	16	42
15	27	20	17	19	45
16	25	22	11	25	40
17	30	17	22	14	47
18	24	23	16	20	47
19	16	31	11	25	51
20	25	22	12	24	41
21	35	12	18	18	36
22	20	27	6	30	40
X	47	0	0	36	0

ATP2B3 was detected as a single band by Southern blot hybridization of a panel of human/rodent somatic cell hybrid DNAs with a 2.3-kb *Eco*RI genomic fragment containing exons 3–6 and introns 2–5 of the human gene. No cross-hybridizing rodent sequences were detected at high stringency. Detection of ATP2B3 is correlated with the presence or absence of each human chromosome in the hybrid panel. Discordancy indicates the presence of the gene in the absence of the chromosome (+/-) or absence of the gene despite the presence of the chromosome (-/+), and the sum of these numbers divided by total hybrids examined (× 100) represents the percent discordancy. The human-hamster hybrids consisted of 29 primary hybrids and 13 subclones (29 positive of 42 total). The human-mouse hybrids represented 15 primary hybrids and 26 subclones (18 positive of 41 total). The gene could be sublocalized to Xq13→qter by examination of hybrids containing specific translocations (see text).

Materials and methods

Preparation of probes. A 2.3-kb *Eco*RI genomic DNA fragment containing exons 3–6 and introns 2–5 of ATP2B3 was excised from lambda phage (H115.2) and subcloned into pUC19. A 0.9-kb *Eco*RI cDNA fragment of ATP2B2 containing 210 bp of the 3′ coding sequence and the entire 3′ untranslated region (Heim et al., 1992a) was also subcloned into a pUC vector. Each insert was excised, purified by gel electrophoresis, labeled with ^{32}P-dCTP by random hexanucleotide primed synthesis (Feinberg and Vogelstein, 1983), and used as probes for Southern blots. A recombinant lambda phage (H115.22) containing a 17-kb genomic ATP2B3 DNA insert, including the 2.3-kb DNA fragment, was used as a probe for FISH. A lambda clone containing the 5′ end of ATP2B2 was similarly used as a probe for in situ hybridization. FISH probes were labeled with biotin-14-dATP by nicktranslation.

Cell Hybrids and Filter Hybridization. Isolation and characterization of a panel of human/rodent somatic cell hybrids has been described (McBride et al., 1982b). Hybrid cells were analyzed for the presence of all human chromosomes except Y by standard isoenzyme analyses, by Southern analysis with probes from previously localized genes, and by cytogenetic analysis. Southern blots of *Eco*RI digested hybrid cell DNA were hybridized with ^{32}P-labeled probes (Olson et al., 1991) under high stringency conditions allowing no more than 10% divergence of hybridizing sequences.

In situ hybridization. Experiments were performed as described (Kim et al., 1992) using peripheral blood lymphocytes from a normal male (46;XY) which were synchronized with BrdU. Hybridization was detected with FITC-avidin (5 μg/ml). Chromosome banding was obtained by treatment of slides with Hoechst 33258 (150 μg/ml) for 30 min, followed by exposure to long wave length (365 nm) UV light. FITC signals were observed and photographed with a blue filter (490 nm excitation and 510 nm emission), and banded chromosomes were observed with a violet filter (365 nm excitation and 460 nm emission). Photographs were projected and superimposed to permit alignment of the hybridization signal with the chromosome bands.

DNA Restriction Fragment Length Polymorphisms. DNAs from 10 unrelated normal individuals were examined for the presence of RFLPs using 12 different restriction enzymes (Olson et al., 1991).

Linkage Analysis. DNAs from 40 large, three-generation CEPH families (Dausset et al., 1990) were analyzed using the ATP2B3 2.4-kb *Eco*RI fragment as probe. RFLP typing was performed by standard Southern blot analysis of *Bam*HI-digested DNAs under high stringency. All parental DNAs were initially examined, and all family members from informative matings (i.e. heterozygous mothers) were then genotyped. Two-point linkage analyses were performed using LINKAGE v 5.10 (Lathrop et al., 1984). All relevant published X-chromosomal markers (Drayna and White, 1985; Feil et al., 1990) in the CEPH database v 5 were used in these analyses. The probe-enzyme combinations for these loci are: DXS52 is St14–1 with *Taq*I; DXS15 is DX13 with *Bgl*II; F8C is F8C probe with *Bcl*I; DXS296 is VK21A probe with *Taq*I; F9 probe used *Taq*I; DXS51 is 52A with *Taq*I; and HPRT is pDSK1 with *Bam*H1.

Results

ATP2B3 was localized to the human X-chromosome by Southern blot analysis of the hybrid DNA panel using the 2.3-kb genomic probe. The gene segregated concordantly with the X-chromosome and discordantly (≥ 36%) with all other chromosomes in the hybrid panel (Table I). This localization was strongly supported by detection of the gene in one human-mouse hybrid containing only the human X chromosome and a portion of 2p and in a human-hamster hybrid containing only human chromosome 22, 6pter→q13, and X. The gene could be regionally assigned to Xq13→qter by examining a series of human-hamster hybrids (McBride et al., 1982a) isolated after fusion of human fibroblasts (GM0073) containing a reciprocal X;14 (q13;q32) chromosome translocation. Three independent hybrids retaining only the Xpter→q13 translocation chromosome in the absence of the normal X or the reciprocal translocation chromosome did not retain ATP2B3 whereas ten independent hybrids retaining only the Xq13→qter translocation chromosome retained the gene. A series of cell lines containing only fragments of the human X chromosome in a mouse background following chromosome-mediated gene transfer (Olsen et al., 1981; McBride et al., 1982c) was also examined, and the gene was retained in only one line (A9S2) which contained the entire distal one-third to one-half of the X chromosome long arm thereby narrowing the localization to Xq22→qter. The locus was further narrowed to Xq26→q28 by examining a human-hamster hybrid which contained a spontaneous break with deletion of the distal long arm of human X. The precise breakpoint was characterized using the hybrid cell DNA as template for PCR amplification with species specific oligonucleotide primers for X-chromosomal sequences. These results indicated that DXS72 (Xq21), DXS456, DXS990, DXS1001 (q25), HPRT (q26.1→q26.2), and DXS994 (q26) are retained in this hybrid whereas DXS548 (q27), G6PD (q28), F8C (q28), and DF2 (qter) are absent. ATP2B3 as well as biglycan (Xq27→qter), the oncogene MCF2 (Xq26.3→q27.1), and the vasopressin receptor gene (Xq27→q28) are absent from this hy-

Table II. Two-point Lod scores for ATP2B3 vs other X-chromosomal loci

Locus[a]	θ max[b]	Z max[b]	Physical location[c]	Confidence interval[d]
DXS52	0.00	9.3	Xq28	0.00–0.069
DXS15	0.00	4.2	Xq28	0.00–0.151
F8C	0.00	3.3	Xq28	0.00–0.19
DXS296	0.14	0.9	Xq27.3→q28	
F9	0.40	0.1	Xq26→q27	
DXS51	0.34	0.15	Xq26	
HPRT	0.27	0.6	Xq26	

[a] Probe described in Methods.
[b] Most likely recombination fraction (θ max) and Lod score (Z max) between ATP2B3 and each locus.
[c] Loci are listed in probable order starting from the telomere of Xq; locations based upon mapping in YACs and in situ hybridization combined with linkage analysis (Mandel et al., 1992; NIH/CEPH Collaborative Mapping Group, 1992).
[d] Confidence intervals for recombination fractions over a 10-fold range of likelihood.

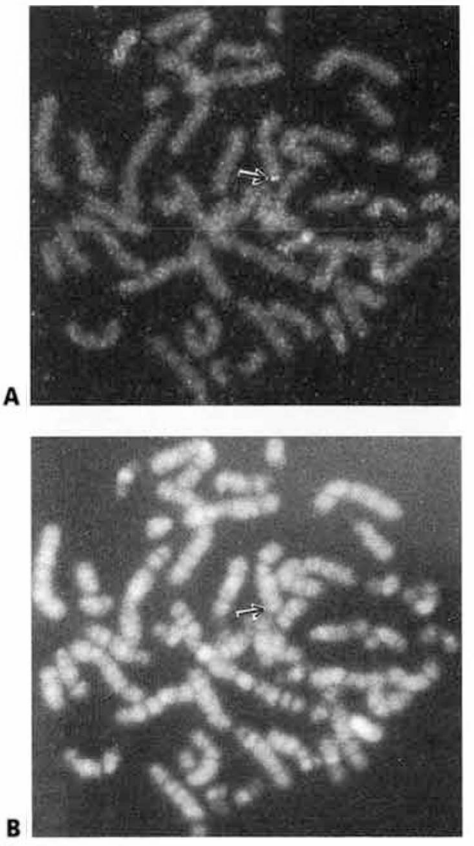

Fig. 1. In situ hybridization with ATP2B3. A 17-kb genomic insert of ATP2B3 was labeled with biotin and used for hybridization with human chromosomes. (**A**) Typical metaphase spread showing fluorescent hybridization signal on both chromatids on Xq28. (**B**) The same metaphase spread showing the fluorescent G-banding pattern.

brid. ATP2B3 was further localized to Xq28 by in situ hybridization (Fig. 1) in all twenty metaphases examined.

The 2.3-kb ATP2B3 fragment was also used as a probe to screen for RFLPs, and an infrequent polymorphism was detected in *Bam*HI digests; the frequency of allele A1 (10.1 kb): A2 (8.5 kb) = 0.04: 0.96 (120 haploid equivalents examined). No other RFLPS were detected with 11 other restriction enzymes. *Bam*HI digests of DNAs from all CEPH parents were genotyped with this probe, and four of the forty mothers were heterozygotes. All members of these four informative families were genotyped, and tested for linkage with other loci in the CEPH database (Table II). Despite the paucity of informative families, the results demonstrate close linkage with all three loci in the most telomeric band of X (i.e., q28) with no recombinants and highly significant lod scores of 3.3–9.3. The four families were informative with at least one of these three probe-enzyme combinations, and DXS52 was informative with ATP2B3 in three of the families. These three reference loci are included in a region spanning about 2 mbp (Kenwrick and Gitschier, 1989), and DXS52 and DXS15 are present in a 500-kbp interval (Feil et al., 1990). In contrast, recombinants were found between ATP2B3 and loci (DXS296, F9, DXS51, HPRT) in Xq27 and Xq26. Each of these four probe-enzyme combinations was informative with ATP2B3 in a single family, but three of the four families were informative with one or more of these four probes. Although only limited linkage data is available, the results clearly indicate that ATP2B3 can be localized to Xq28 both by genetic linkage analysis and by in situ hybridization.

ATP2B2 (PMCA isoform 2) was similarly localized to human chromosome 3 by Southern analysis of the same hybrid DNA panel with a 0.9-kb ATP2B2 cDNA probe. In the complete panel of 92 hybrids (33 positive and 59 negative), the gene segregated concordantly with chromosome 3 and discordantly (≥20%) with all other chromosomes. Examination of two hybrids containing spontaneous breaks involving chromosome 3 (Chin et al., 1991) permitted regional localization of ATP2B2. One hybrid retained only 3q and human ATP2B2 was absent. The other hybrid contained a large deletion in 3p extending from 3p25 to 3p21 including RAF1 (3p25), and it retained ATP2B2. This indicates that ATP2B2 must be located in band 3p26 or in region 3p21→cen. More importantly, the FISH results (Fig. 2) localized the gene to the proximal portion of 3p26. This confirms the previous assignment by Latif et al. (1993).

Discussion

All plasma membrane Ca^{2+} pump isoforms share essential features of the reaction mechanism and membrane architecture. They differ, however, in the portions involved in their regulation; the four human genes undergo alternative splicing that is likely to affect the regulatory properties of the protein products. Although information on possible functional conse-

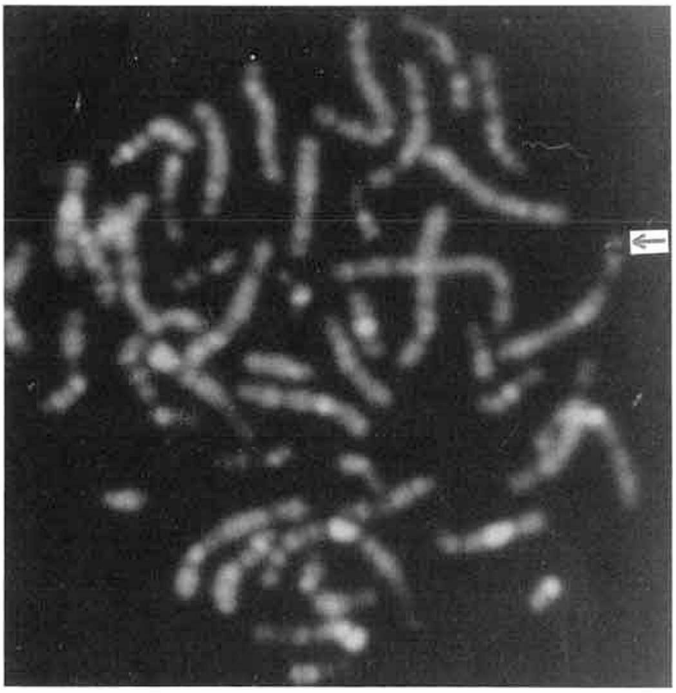

Fig. 2. In situ hybridization with ATP2B2. A 15-kb genomic insert of ATP2B2 was labeled with biotin and used for hybridization with human chromosomes. Typical metaphase showing hybridization signal (arrow) over both chromatids near the border of bands q25 and q26 on one copy of chromosome 3. Twenty six metaphase spreads were examined and the hybridization signal was present at this same location in all cases.

quences of the splicing process is still very limited, indications are that the various splicing options may indeed confer particular properties to the protein product (Kessler et al., 1992).

Information on functional properties is currently available only for the C-terminal portion of the protein produced by ATP2B1. Previous studies on the purified erythrocyte plasma membrane Ca^{2+} pump have shown that both ATP2B1 and ATP2B4 are expressed in these cells (Strehler et al., 1990). Thus, the regulatory and functional properties of the purified preparations of the erythrocyte pump evidently reflect the combined characteristics of isoforms 1 and 4. The latter isoform has recently also been expressed in COS cells and in baculovirus systems (Adamo et al., 1992; Heim et al., 1992b). Although the protein expressed by the latter system has been purified, no significant information on its regulatory properties is yet available at the protein level. However, information has recently become available on all four human genes at the mRNA level (Stauffer et al., 1993); ATP2B1 and ATP2B4 are expressed in a relatively uniform manner in all human tissues that have been studied, and thus they appear to be housekeeping genes. The levels of mRNA for ATP2B2 and ATP2B3, on the other hand, vary widely in different tissues; in particular, that of ATP2B2 appears to be enriched in the central nervous system (Stauffer et al., 1993), where it may reach as much as one fifth of the total plasma membrane calcium pump mRNA. Moreover, a recent study on rat genes (Stahl et al., 1992) has shown that within complex tissues like the central nervous system, the mRNA of ATP2B2, and even that of ATP2B3, may be absolutely predominant in some regions (Stahl et al., 1992). That is the case in Purkinje cerebellar cells for ATP2B2, and of the habenula and the third and fourth ventricle choroid plexus for ATP2B3. The reasons for this striking tissue/cell specificity of the products of the non-house-keeping genes are at the moment obscure, but it is difficult to avoid suggesting that they must be related to differences in their function. Studies on the protein expressed by these genes, either isolated from tissues or artificially expressed in suitable systems, are clearly necessary.

The possible relationship of the PMCA genes to genetic diseases also deserves consideration. As was perhaps to be expected, the proposed housekeeping genes ATP2B1 and ATP2B4 have not yet been found to colocalize with any of the disease-related genes known so far on chromosomes 1 and 12 (Olson et al., 1991); given the importance of their products for the regulation of cellular Ca^{2+} homeostasis and their presence in all cells, including those that express genes ATP2B2 and ATP2B3, alterations, at least severe alterations, in the product of genes ATP2B1 and ATP2B4, probably cannot be tolerated. The situation may be different for ATP2B2 and ATP2B3 whose products exhibit such a distinctive pattern of tissue expression even in tissues/cells where the two housekeeping genes are expressed. Hence the recent finding by Latif et al. (1993a) that the PMCA gene for isoform 2 on chromosome 3 was a possible candidate gene for the Von Hippel-Lindau syndrome was of great interest; however, more recent results indicate that another closely situated gene is actually the gene involved in this syndrome (Latif et al. 1993b). Nevertheless, it appears likely that ATP2B2 and ATP2B3 will be found to be implicated in some diseases probably involving the nervous system, based upon the pattern of expression and importance of these genes. The genes for several neurologic and neuromuscular diseases have been assigned (Mandel et al., 1992) to the vicinity of the gene for ATP2B3 including an X-linked hydrocephalus, HSAS (Xq28), MASA (Xq28) which is a complicated spastic paraplegia which may be allelic with HSAS, EMD or Emery-Dreifuss muscular dystrophy (Xq28), MTM1 which is X-linked myotubular myopathy (Xq28), EFE2 which is Barth syndrome, a cardioskeletal myopathy and neutropenia (Xq28), and CDR1, a cerebellar degeneration-related (34 kDa) protein (Xq27.1→q27.2). The Waisman syndrome is an X-linked recessive basal ganglia disorder with mental retardation, and the gene, WSN, has also been localized in this region to Xq27.3→qter (Gregg et al., 1991) with close linkage to DXS52, DXS15, and F8C. The ability to assess ATP2B3 as a candidate gene for these diseases requires the identification of more informative polymorphisms at this locus, and this will probably involve either microsatellites or single-strand DNA polymorphisms (SSCPs).

Despite the structural similarity between members of the PMCA family of genes, there is sufficient nucleotide sequence divergence that cross-hybridization between these genes is usually not observed. Nevertheless, a cross-hybridizing 21-kb band was detected in *Eco*RI digests with two different ATP2B4 cDNA probes. Whereas, the ATP2B4 gene was clearly located at 1q25→q32, the cross-hybridizing band was found on the X-

chromosome in the region Xq13→qter (Olson et al., 1991). It now appears most likely that the previously unidentified sequence represents cross-hybridization with ATP2B3. Proof of this identity would require Southern hybridization of *Eco*RI digests with additional ATP2B3 cDNA and genomic DNA probes or cross-hybridization of full-length ATP2B4 and ATP2B3 probes.

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