C2H2-171: A NOVEL HUMAN cDNA REPRESENTING A DEVELOPMENTALLY REGULATED POZ DOMAIN/ZINC FINGER PROTEIN PREFERENTIALLY EXPRESSED IN BRAIN

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Abstract—We describe a novel human zinc finger cDNA, C2H2-171. This cDNA represents an mRNA which encodes a protein of 484 amino acids and a calculated molecular weight of 54 kD. Four zinc finger-like domains are found in the C-terminal end of the protein. At the N-terminus, C2H2-171 contains a POZ/tramtrack-like domain similar to that found in the tumor associated zinc finger proteins LAZ-2:BCL-6 and PLZ-F, as well as in non-zinc finger proteins. C2H2-171 RNA is preferentially expressed in the brain, and increases during the course of murine development, with maximal expression in the adult. C2H2-171 RNA is differentially expressed in brain regions, with the highest level of expression in the cerebellum. C2H2-171 RNA was expressed at high levels in primary cerebellar granule cell neurons compared to astrocytes. The gene encoding C2H2-171 is highly conserved in vertebrates, and maps to the terminus of human chromosome 2 (1q44-ter). This chromosomal location is associated with a number of cytogenetic aberrations including those involving brain developmental anomalies and tumorigenesis. These data suggest that C2H2-171 may play an important role in vertebrate brain development and function. © 1997 ISDN. Published by Elsevier Science Ltd

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Genes encoding C2H2-type zinc finger containing proteins comprise one of the largest families in the human genome. First described in Xenopus TFIIIA, C2H2 type zinc finger proteins have been shown to act on the molecular level as transcriptional activators, or repressors, and to be involved in chromatin assembly. In addition, zinc-finger proteins have been demonstrated to function in developmental processes and tumorigenesis.

In addition to DNA binding domains, some zinc finger genes contain other conserved motifs, including FAX, KRAB, tramtrack, and homeodomains. The POZ/tramtrack domain is an amino-terminal conserved domain found in a number of cellular and viral proteins. In Drosophila, this domain has been shown to be involved in development, metamorphosis, and pattern formation. On the molecular level, the POZ domain may act as a mediator of protein–protein interaction, and in some cases, may function as an inhibitor of DNA binding. The POZ domain encoding regions of two POZ/zinc finger containing genes has also been associated with chromosomal translocations in non-Hodgkins lymphoma and acute promyelocytic leukemia.

In this study, we describe a novel human cDNA, C2H2-171, which represents an mRNA that encodes a protein containing both zinc finger and POZ-like domains. The gene encoding C2H2-171 is conserved in vertebrates, and maps to the terminus of human chromosome 2 (1q44-ter), a genetic region associated with developmental anomalies and human tumors. C2H2-171 RNA is preferentially expressed in the brain, and within the brain is expressed differentially, with highest

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levels of expression in the cerebellum. The RNA is expressed at higher levels in primary cultures of neurons than astrocytes. In addition, C2H2-171 RNA expression increases during development.

**EXPERIMENTAL PROCEDURES**

**Isolation of cDNA clones**

A human hippocampal cDNA library from a normal 2-year-old female in lambda-ZAP II vector (Stratagene #396205) was screened with a degenerate oligonucleotide specific for a conserved amino acid element (TGEKP) found in C2H2-type zinc finger proteins, as previously described. Two overlapping clones, C2H2-171 and C2H2-47 were obtained for full length cDNA sequencing.

**Automatic DNA sequencing**

Plasmid was prepared for sequencing using Qiawell 8-Plus (Qiagen, Inc.) as described by the manufacturer. Double stranded cDNA clones in pBluescript SK- vector (Stratagene, Inc.) were sequenced in both directions by creating nested deletions followed by sequence analysis. Sequencing reactions were performed on an Applied Biosystems robotic workstation and analyzed on an Applied Biosystems 373A automated DNA sequencer using fluorescent labeled vector primers.

**Database comparisons**

DNA and protein searches were performed using the BLAST network server at the National Center for Biotechnology Information (NCBI) against the DNA and protein non-redundant databases. Local sequences alignments were performed with the GCG based program FASTA.

**Northern analysis**

Total RNA from mouse (C57BL/6NCR) tissue or embryos were prepared using RNAzol™ (TelTest Inc., Friendswood, TX) according to manufacturer’s protocol. Poly A+ RNA was isolated using a mini-oligo (dT) spin column kit (5 prime-3 prime Inc., Boulder, CO). RNA was size fractionated on a 1% agarose, 0.66 M formaldehyde gel, transferred to a Gene Screen™ membrane (NEN, Boston, MA) and then hybridized with the C2H2-171 32P-labeled cDNA probe (EcoRI–EcoRI full length insert). The Northern blot containing mRNA from various human brain regions was obtained from Clontech (Palo Alto, CA). RNA from primary cerebral astrocytes and cerebellar granule cell neurons were produced as previously described. Human glyceraldehyde-3-phosphate dehydrogenase (1.2 Kb DNA fragment from Clontech, Palo Alto, CA) or chicken beta-actin were used to check the quantity and integrity of the mRNA. Hybridization was carried out at 42°C in a solution of 50 mM 1,4-piperazine bis-ethanesulfonic acid (PIPES), pH 7.0, 50% formamide, 100 mM NaCl, 1 mM EDTA, 0.5% SDS and 100 μg/ml denatured salmon sperm DNA for 20 h. Membranes were washed in 2×SSC, 0.1% SDS twice (1×SSC; 0.15 M NaCl, 0.015 M sodium citrate, pH 7.0) at 42°C and then washed once with 0.2×SSC, 0.1% SDS at 60°C for 30 min. The membranes were exposed to X-ray film at −80°C with an intensifying screen.

**Southern analysis**

Genomic DNA from various species was digested with EcoRI and separated by gel electrophoresis through a 1% agarose gel and transferred to nylon as described. C2H2-171 cDNA insert was labeled with 32P by random priming (Prime-It, Stratagene). Southern blots were hybridized for 2 h at 69°C in Quickhyb (Stratagene) and washed for 30 min at room temperature with 2×SSC and 0.1% SDS, followed by washing at 55°C with 1×SSC and 0.1% SDS. The filter was then dried and exposed to X-ray film at −80°C.

**Chromosomal localization**

PCR primers were designed to amplify a 147 bp product from the 3’ UTR of C2H2-171 cDNA (5’-GTTGTGGTACGGTCTAAAAAGCAG-3’, 5’-CACCCTCTATCTTGACCTTGCTC-3’). The NIGMS human-rodent somatic cell hybrid mapping panel 1 (Coriell Institute for Medical Research, Camden, NJ) was used in this mapping protocol. This panel is based on a mouse genetic background, with one human chromosome per hybrid cell line. However, one line containing human chromosome
is a human–hamster somatic cell hybrid. The yeast artificial chromosome (YAC) pools screened were from the CEPH “B” human mega-YAC library (Research Genetics, Huntsville, AL). PCR amplification was performed in 15 μl reactions containing 50 ng of genomic DNA from the somatic cell hybrid panel or 1.5 μl of each YAC pool DNA, 24 ng of a fluorescence-labeled forward oligonucleotide primer, 60 ng of a reverse, oligonucleotide primer, 0.45 U Taq polymerase, 50 mM KCl, 10 mM Tris (pH 8.3), 1.5 mM MgCl₂, 0.01% gelatin, and 50 μM of each dNTP. Each reaction was overlaid with 35 μl of mineral oil. The PCR was performed in a Techne MW-1 microplate thermocycler under the following conditions: denaturation at 94°C for 1 min, annealing at 55°C for 1 min, and extension at 72°C for 1 min. The cycle was repeated 30 times. Reactions were held at 4°C until analysis. The PCR reaction mix (3 μl) was loaded on a 6% PAGE sequencing gel. The samples were electrophoresed by exposure on the Fluorimager SI (Molecular Dynamics, Sunnyvale, CA), and a YAC address was obtained. Microsatellite markers on a near the YAC address and the position of the YAC relative to known markers was determined using the program “yacsr” (M. H. Polymeropoulos, unpublished). A cytogenetic location was determined by searching the cytogenetic location of nearby markers (MIT/Whitehead and GDB on-line databases).

RESULTS

Isolation of a novel cDNA representing an RNA which encodes a protein containing novel POZ and zinc finger-line domains

A human hippocampal cDNA library from a normal 2-year-old female was screened with a degenerate oligonucleotide specific for C2H2-type zinc finger genes. By partial expressed sequence tag (EST) sequence analysis, it was determined that 20 independent clones represented fragments of the same novel zinc finger coding cDNA. Two independent overlapping cDNA clones, C2H2-47 and C2H2-171, were sequenced in both directions. The sequence reveals a cDNA of 206 nucleotides, as presented in Fig. 1. The open reading frame codes for a protein of 484 amino acids with a predicted molecular weight of 55 kDa and an isoelectric point of 6.57. An ATG coding for a candidate initiator methionine is found at the 5’ end of the cDNA at nucleotide +41. This position is in consensus for a eukaryotic translational start codon, with a purine (A) at −3 and a G at −6, relative to the ATG. An in-frame termination codon exists immediately upstream of this methionine at position +8, further indicating that this is the initiator methionine. This initiator methionine corresponds to the beginning of an 112 amino acid region with sequence similarity to a group of POZ/tramtrack domain containing proteins. These related proteins contain members of the zinc finger family as well as non-zinc finger poxvirus proteins. C2H2-type zinc finger proteins which contain POZ domains, exhibit the POZ domain at the extreme amino-terminus. These data further support the ATG at nucleotide +41 as the initiator methionine of C2H2-171. The POZ-like domain of C2H2-171 is followed by a 223 amino acid region of no significant homology to other proteins. The C-terminal region of C2H2-171 contains four zinc finger-like domains. These domains closely resemble the TFIIIA prototype C2H2 type zinc finger domain, conforming to the zinc finger consensus C-X2-C-X3-F-X5-L-X2H-X3-H. The second, third, and fourth zinc fingers are linked by the conserved H/C linker and spaced by seven amino acids, while the spacing between the first and second fingers is anomalous at 19 amino acids. C2H2-171 is represented schematically in Fig. 1b. The amino acid sequence of the POZ-like domain of C2H2-171 is compared to that of other POZ domain proteins in Fig. 2. This POZ-like domain of C2H2-171 is 112 amino acids in length. The POZ-like domain of C2H2-171 is most similar to (50% identity) the POZ domain containing protein LP1.

RNA expression of C2H2-171

We carried out Northern blot analysis in order to determine the tissue expression pattern of C2H2-171 and to establish the size of the endogenous mRNA transcript. Poly A⁺ mRNA samples from mouse tissues were electrophoresed, blotted, and probed with a cDNA containing the entire coding region of C2H2-171. The approximately 4.1 kb RNA is seen in adult brain tissue, but not in thymus, heart, lung, liver, spleen, or kidney (Fig. 3a). Thus, C2H2-171 RNA is preferentially
Fig. 1. (a) Nucleotide and predicted amino acid sequences from the C2H2-171 cDNA. The nucleotide and amino acid sequences are numbered on the left and right respectively. The POZ/tramtrack domain is in bold. The zinc finger motifs are underlined. Potential poly A signals are doubled underlined. The nucleotide sequence of C2H2-171 cDNA from 23–1905 bp appears in the GenBank sequence database (accession number U27785). The sequence from 0–23 bp is derived from expressed sequence tags (ESTs) T20159, W57199, and W57088 present in the dbEST EST sequence database. These ESTs overlap with C2H2-171 and extend the sequence in the 5' direction by 23 bp which demonstrates an in-frame termination codon at +8 (marked by *). (b) Schematic of the protein product of C2H2-171.
expressed in the brain relative to non-brain tissues. A Northern blot containing mRNA isolated from various regions of human brain (Clontech, Palo Alto, CA) was probed to determine the relative levels of C2H2-171 RNA in each brain region. The cerebellum contained the highest level of C2H2-171 RNA expression. C2H2-171 RNA was also expressed in the occipital pole, frontal lobe, temporal lobe, putamen, amygdala, and hippocampus. Other regions including the medulla, spinal cord, caudate nucleus, corpus callosum, substantia nigra, subthalamic nucleus, and thalamus expressed very little or no C2H2-171 RNA (Fig. 2b). We also investigated the cellular expression of C2H2-171 RNA in primary cultures of post-natal mouse neurons and astrocytes. Cerebellar granule cell neurons exhibited greater expression of C2H2-171 RNA than astrocytes (Fig. 2c). In order to further determine the expression pattern of C2H2-171 in the brain, Northern blot analysis was performed on developing mouse embryos. Mouse embryos from day 01 to birth were separated into body and head fractions and used for mRNA isolation. Adult liver (AL), placenta (AP), and brain (AB) were also tested. An increasing level of C2H2-171 RNA expression is seen (Fig. 2d) in the head from day 15 until birth, with the highest level of expression found in the adult brain. Little or no expression is found in the embryonic body, or the adult liver or placenta.

Evolutionary conservation

A Southern blot containing genomic DNA digested with EcoRI from a broad range of animal species including yeast, was used to test evolutionary conservation of C2H2-171. Equivalent hybridization signal strength is demonstrated in all vertebrate species tested, with no detectable bands in Drosophila and yeast, suggesting conservation of C2H2-171 in vertebrates (Fig. 3).

Chromosomal location

C2H2-171 is contained on the YACs 902_D_5, 903_D_4, and 896_A_1. These YACs contain markers including IB3015 and D1S2693 that map to 1q44-1qter.

DISCUSSION

Proteins containing C2H2-type zinc finger motifs have been shown to play a fundamental role in gene expression, developmental processes, and in tumorigenesis. Here, we describe the cloning and characterization of C2H2-171, a novel human cDNA. C2H2-171 is predicted to contain four C-terminal zinc finger motifs and to be a member of a growing number of proteins which contain a 120 amino acid N-terminal domain called POZ, or in Drosophila, tramtrack. Previously a degenerate POZ-domain consensus sequence was identified. The sequence consisted of 32 of the most highly conserved amino acid residues in the approximately 120 amino acid POZ domain. Interestingly, C2H2-171 matches this degenerate consensus sequence at every position. In Drosophila, POZ/tramtrack domains have been associated with processes including pattern formation, oogenesis, and eye and limb development. Several POZ-domain containing zinc finger proteins have been proposed to function as transcriptional repressors. This may result from the ability of POZ domain proteins to mediate protein–protein interactions and to block DNA-binding activity of
Fig. 3. Northern blot analysis of C2H2-171 (A) Expression of C2H2-171 RNA in tissues. Poly (A)^+ mRNA (5 μg) from various adult mouse tissues was probed with a fragment containing the complete coding sequence of the C2H2-171 cDNA. (B) Expression of C2H2-171 RNA in brain regions. Poly (A)^+ mRNA (2 μg) from the indicated brain regions were probed with C2H2-171 cDNA. (C) Expression of C2H2-171 RNA in primary cultures. Total RNA (15 μg) isolated from cerebellar granule cell neurons and cerebral astrocytes purified from 8-day and 2-day-old mice, respectively, was probed with C2H2-171 cDNA. (D) Developmental expression of C2H2-171 mRNA. Poly (A)^+ mRNA from different embryonic mouse developmental stages (4 μg) was probed with the complete coding sequence for the C2H2-171 cDNA. Body and head samples are shown. The gestational age is given in days. Adult liver (AL), adult placenta (AP), and adult brain (AB) (6 μg) are also shown.
Novel POZ domain/zinc finger protein

Translocations involving genes encoding POZ-domain proteins including LAZ-3/BCL6 result in tumorigenesis.25,28,45

C2H2-171 RNA is selectively expressed in adult brain compared to other tissues examined. However, C2H2-171 may exist in non-brain tissues at concentrations below the level of detection of the Northern blot analyses described here. C2H2-171 appears to play a regionally specific function within the brain, since it is differentially expressed in brain regions, with maximal expression observed in the cerebellum. C2H2-171 RNA is preferentially expressed in primary neuron cultures relative to astrocytes. However, it is possible that it may be expressed in astrocytes at different stages of development and in other glia, including microglia and oligodendrocytes. This might explain the low levels of RNA detected in the corpus callosum, a structure composed primarily of glia and myelinated axons. Northern analysis also revealed that C2H2-171 RNA is absent in early development in both head and body tissues. RNA levels are detectable in the head at approximately day 15 in murine embryonic development, increase through birth, and are maximal in adult brain. This expression pattern may indicate that C2H2-171 functions in late stage brain development and in the adult nervous system. Interestingly, neurons of the deep cerebellar nuclei as well as cerebellar Purkinje cell neurons are generated near embryonic day 15 in the rodent.1 Likewise, a variety of morphological changes are occurring in the cerebellum during this stage of development including the differentiation of cerebellar granule cell neurons.

The evolutionary conservation of C2H2-171 was analyzed by cross species Southern blot hybridization. C2H2-171 shows equivalent hybridization signal strength among vertebrates. This pattern is consistent with the first of two Southern blot patterns seen in similar evolutionary studies of C2H2-type zinc finger genes. These patterns are: (a) equivalent hybridization signal strength in vertebrates or, (b) strong conservation in primates only.31 The observation that C2H2-171 gene is not present in Drosophila and yeast is consistent with C2H2-171 being important in vertebrate brain development.

C2H2-171 maps to the distal portion of chromosome 1 (1q44-ter) by PCR analysis of MEGAYAC clones. Another C2H2 type zinc finger gene, HZF-16, also maps to this region.36 Chromosomal duplication and deletion in this region is associated with numerous congenital anomalies including brain developmental anomalies.16 These include mental retardation, microcephaly, and autistic-like behavior.21,24,30,39 Chromosomal abnormalities in this region have also been associated with a number of human tumors including Wilms tumor,42 astrocytomas42 and AML,22 and with congenital ocular defects.12 Further analysis of this gene on the distal arm of chromosome 1q may provide clues to a possible role in brain development or tumorigenesis.
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