LETTER

Identification and Analysis of Expression of Human *VACM-1*, a Cullin Gene Family Member Located on Chromosome 11q22-23

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We have localized the human homolog of the rabbit vasopressin-activated calcium-mobilizing receptor *VACM-1* to a region close to the gene for ataxia telangiectasia *ATM* on chromosome 11q22-23. We have determined the complete amino acid sequence of the human Hs-*VACM-1* protein, which is 780 amino acids long. The human and rabbit sequences are highly conserved, differing at only seven amino acids. Northern analysis of the human gene showed expression in a wide range of human tissues. The Hs-*VACM-1* gene has homology with the *Caenorhabditis elegans* gene *Ce-cul-5*, a member of a family of cullin genes that are involved in cell cycle regulation and that might, when mutated, contribute to tumor progression.

[The sequence data described in this paper have been submitted to GenBank under accession no. X81882.]

The gene for rabbit arginine vasopressin (AVP)-activated calcium-mobilizing receptor *VACM-1* was isolated recently from a renal medullary cDNA library by expression cloning in *Xenopus laevis* oocytes (Burnatowska-Hledin et al. 1995). Expression of this novel gene in COS-1 cells produced an increase in high-affinity AVP binding and enhanced AVP-induced Ca²⁺ mobilization leading to elevated intracellular calcium concentrations. Analysis of the distribution of *VACM-1* in rabbit kidney by immunofluorescent staining with anti-peptide antibodies showed that the protein was present in collecting tubule epithelia in both the renal medulla and the cortex. Additionally the pattern of immunofluorescent staining found in COS-1 cells transfected with a *VACM-1* expression construct showed that *VACM-1* protein was present on the cell surface, consistent with the identification of a putative transmembrane region in the amino acid sequence of the protein, and as expected of a peptide hormone receptor. The lack of any structural similarity to any previously identified receptor suggested that *VACM-1* might be one of a new family of peptide receptors. More recently, however, *VACM-1* was

found to have homology with a newly identified family of *Caenorhabditis elegans* genes, designated cullins, which are involved in the control of the cell cycle (Kipreos et al. 1996) and, because they contain putative nuclear targeting sequences and lack signal peptides or membrane-spanning domains, were purported to act intracellularly. Mutation of the *C. elegans* gene *Ce-cul-1* causes hyperplasia in all tissues, and the mutant phenotype indicates that Cul-1 is required for cell cycle exit to the G₀ state or for transition to an apoptotic pathway. By analogy with the Cul-1 phenotype it was suggested that mutation of mammalian cullin homologs might be implicated in clonal expansion and tumorigenesis (Kipreos et al. 1996).

In this paper we present the complete amino acid sequence of the human homolog for the rabbit *VACM-1* gene and analyze the expression of this gene in a variety of different tissues.

RESULTS

While searching for expressed genes in the AT gene region on chromosome 11q22-23 we isolated an exon 6.82 that had no homology to any recognized gene but that matched an expressed sequence (Z21447) isolated from a testis cDNA library. This exon was used to identify several clones in arrayed human thymus and frontal cortex brain cDNA libraries, and the sequence of a long open reading

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frame was completed using additional clones from a human embryonic brain cDNA library and a hybridization selected clone derived from a lymphoblastoid cell line. The open reading frame was found to potentially encode a protein of 780 amino acids, the complete sequence of which is shown in Figure 1. The identity of this new human gene was revealed when the sequence of the rabbit (*Oryctolagus cuniculus*) VACM-1 receptor gene *Oc-VACM-1* was released. This rabbit protein was found to have exactly the same number of amino acids as the protein encoded by the human gene that was identified by the 6.82 exon. Additionally the amino acid sequences of the two proteins were found to be 99% identical (Fig. 1), indicative of an important gene

that had been highly conserved through mammalian evolution. A PCR assay for the 6.82 exon was also found to amplify the same sized product from human, monkey, dog, rabbit, and mouse but failed to amplify any bands from chicken or yeast (*Saccharomyces cerevisiae*) DNA (data not shown). This provided further evidence of the conservation of the VACM-1 gene in mammalian evolution. The failure to amplify a product from chicken might be attributable to the evolutionary distance between mammals and birds or could be a reflection of the putative role of this gene in osmoregulation and differences in this process between mammals and birds.

The amino acid sequence of the human Hs-VACM-1 protein in Figure 1 is also shown in com-

Hs-VACM-1	MATSNLLKNGKSLQFEDKWFMRPIVLKLLRQESVTKQQWFDLFSVHAVCLWD-----D--KG-----PAK-----IHQALKEDILE
Oc-VACM-1	MATSNLLKNGKSLQFEDKWFMRPIVLKLLRQESVTKQQWFDLFSVHAVCLWD-----D--KG-----PAK-----IHQALKEDILE
Ce-CUL-5	-----MQFDEEWSKADPIVHALHQQSVTPAAWQDLFVYHVYKITSWV-----D--DG-----PLK-----IRDLITRCIND
Ce-CUL-1	--MTNSEPRRMTCDSEVVWKKLQDGLDVAYRRENMAPKDYMTLYTSVYDYCTSIITLSTSRRDGEDGRAESSTPARTAGADFPVGHMYQRVEE
Hs-VACM-1	FIKQAQARVLSHQDDTA---LLKAYIVEWRKFFFTQCDILPKPFCQLEITLMGKQGSNNKSNVEDSIVRKLMMLDTWNESIFSNIKNRLQDSAM
Oc-VACM-1	FIKQAQARVLSHQDDTA---LLKAYIVEWRKFFFTQCDILPKPFCQLEITLMGKQGSNNKSNVEDSIVRKLMMLDTWNESIFSNIKNRLQDSAM
Ce-CUL-5	YVHEANKRIRSLQTDGS---LLIGYIKENRFRYQANILPLPFFKIDESSRRRS---VPETPEESIRTVMLEKWNIEIFMNISEQLLVEAL
Ce-CUL-1	YVKAYVIAVCEKGAELSGEDLLKYTTTEWENFRISSKVMDGIFAYLNRHWIRRELD--EGHENIYMYVTALAVVWKNRNLFDLKDQVIDAML
Hs-VACM-1	KLVHAERLGEAFDSQLVIGVRESYVNLCSNP-----EDKLQIYRDNFEKAYLDSTERFYRTQAPSYLQNG--VQNYMKYADAKLKEE
Oc-VACM-1	KLVHAERLGEAFDSQLVIGVRESYVNLCSNP-----EDKLQIYRDNFEKAYLDSTERFYRTQAPSYLQNG--VQNYMKYADAKLKEE
Ce-CUL-5	RLVKEERDGNIIAQNVIGIRSFVALNDRAG-----EDPLLVYRQSFERQFIEQTTEYKKICGNLLNELG-VLEYMVYADKKLEE
Ce-CUL-1	ELIRSERTGSMINSRYISGVVECLVELGVDDSETDAKKDAETKKLAVYKEFPEVVFLEATRQFYTQEAANFLSNGGNVTDYMIKIVETRLNQE
Hs-VACM-1	EKRALRYLETRECNSVEALMECCVNALVTSFKETILAECCQGMIRKNETEKLHLMFSLMDKVPNGIEPMLKDLEEHIISAGLADMVAAAEETI
Oc-VACM-1	EKRALRYLETRECNSVEALMECCVNALVTSFKETILAECCQGMIRKNETEKLHLMFSLMDKVPNGIEPMLKDLEEHIISAGLADMVAAAEETI
Ce-CUL-5	QQRAKRYLEMN--SPTSGKHMEKAVIALVESFEDTILAECSKLASKDVERLQRLYRLIRRTSGIDTTLKCIDTHIRTEGLNDMRNNAENL
Ce-CUL-1	DDRCQLYLNSS---TKTPLATCCESVLISNQDLFQRHFGGLLVDRDDLSRMFKLCDRVPNGLDELKRSLENHIAKEGHQALERVAMEA
Hs-VACM-1	TTDSEKYVEQLLTLFNRFSLVKEAFQDDPRFLTARDKAYKAVVNDATIFKLELPLKQKGVGLKTQPESKCPPELLANYCDMLLRKTPLSKKL
Oc-VACM-1	TTDSEKYVEQLLTLFNRFSLVKEAFQDDPRFLTARDKAYKAVVNDATIFKLELPLKQKGVGLKTQPESKCPPELLANYCDMLLRKTPLSKKL
Ce-CUL-5	STDPERYVQQLLLMDFKFSLSLVREGFCDDARLLTARDKAFRAVNDSSIFKTEMNNKK--GRTLVSVEKCAELLANYCDMLLRKTPLSKKL
Ce-CUL-1	ATDAKLYVKTLLVEHRYQSLVNRSFKNEPFGMQSLDKAATSFNNNAVTKRAPPQAQ-----LTKSAELLARYCQDLRKS--SKMP
Hs-VACM-1	*TSEEIEAKLKEVLLVLKYVQNKDVFMRYHKAHLTRRLILDISADSEIEENMVWEWLREVGMPADYVKNKLARMFQDIKVSDELNQAFKEMHK-
Oc-VACM-1	TSEEIEAKLKEVLLVLKYVQNKDVFMRYHKAHLTRRLILDISADSEIEENMVWEWLREVGMPADYVKNKLARMFQDIKVSDELNQAFKEMHK-
Ce-CUL-5	TSEEIDKLNQVLLVLKYVENKDVFMRFHRAHLRRLLLEMSADQEKKEEMMVTKLR-ECGMPSDAVNKLRLQDIENLNDMNSFFKALFTG
Ce-CUL-1	DEAELEELQTKIMVVFYIDDKDVFYSKYFTKMFSKRLISELSASDEAEANFITKLSKMCGY--EYTLARLSKMVNDTQVSKDLTADFKEKKA-
Hs-VACM-1	NNKLALPADSVNIKILNAGAWSRS-SEKVFVSLPTELEDLIPVEEYFKYKNSGRKLHWHHLSNGIITFKNEVG-QYDLEVTTFQLAVLFA
Oc-VACM-1	NNKLALPADSVNIKILNAGAWSRS-SEKVFVSLPTELEDLIPVEEYFKYKNSGRKLHWHHLSNGIITFKNEVG-QYDLEVTTFQLAVLFA
Ce-CUL-5	TNNKSIADSNIMKVLNGGAWGGGSEIRFSLPRELEDVPEMEAFYKKQHNGRKLWMMHWSGTMVFGTANGGRFDLECTTFQMAVLFC
Ce-CUL-1	-DMLGQKSVEFNVVLSSGSWPTF--PTTPITLPQQLSKTIEIFGQFYNEKFNRRLLTWVYSQSRGEITSTAFPK-KYVFATTATQACTMML
Hs-VACM-1	WNQRPREKISFENLKLATELPDAELRRLTWSLVAFPKLRQVLLDYPQVN--SPKDFTEGTLFSVNQEFSLIKNAKVQKRGKINLIGRLQLT
Oc-VACM-1	WNQRPREKISFENLKLATELPDAELRRLTWSLVAFPKLRQVLLDYPQVN--SPKDFTEGTLFSVNQEFSLIKNAKVQKRGKINLIGRLQLT
Ce-CUL-5	FNDRAHDKISLETTLRLATELPDAELNRLTSLVAYPKMRYQILLCDVPSTTVDARTDFTSTKFLINHDFNVVKNKGSQQRGKVNLIIGRLQLS
Ce-CUL-1	FNEQ--DSYTVTEQIAAATKMDKESAPAIVGSILKN---LVLKADTELQ--KEDEVPMATVSLNKAY---MNKKVRVDLSKFTMKQDAVR
Hs-VACM-1	TERMREEENEGIVQLRILRTQEAIIQIMKMRKKISNAQLQTELVEILKNMFLPQKKMIKEQIEWLIEHKIRIDESDINTIFIMMA
Oc-VACM-1	TERMREEENEGIVQLRILRTQEAIIQIMKMRKKISNAQLQTELVEILKNMFLPQKKMIKEQIEWLIEHKIRIDESDINTIFIMMA
Ce-CUL-5	LEANAEKEHESIVALRELVRQEGIVKILKTRKTYTLAQLTMELVEILKPLFIPNRKIIKEQIDWLIENKYMERRADDINTIFVVIS
Ce-CUL-1	DTENVQKNVE---EDRSVISACIVRIMKTRKRQHQQLMTEVITQLSGRFKPKVEMIKRCIGSLIEKEMLELSTEGQKDLVEMLA

Figure 1 The complete amino acid sequence of the protein encoded by the human *Hs-VACM-1* gene and comparison to the rabbit VACM-1 and *C. elegans* CUL proteins. The putative transmembrane domain is overlined, and the hypothetical nuclear localization motif is underlined. Conserved residues that identify the tyrosine rich-motif at the carboxyl terminus of each protein are boxed. The amino acids in the human Hs-VACM-1 protein that differ to those in the rabbit Oc-VACM-1 protein are indicated by solid boxes above the amino acids. Putative cAMP-dependent protein kinase A phosphorylation sites are indicated by a series of asterisks above the site. Plus signs (+) above asparagine residues indicate potentially glycosylated amino acids.

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parison to those of the *C. elegans* Ce-CUL-1 and Ce-CUL-5 proteins. The *Ce-cul-1* gene was identified recently as a negative regulator of the cell cycle in *C. elegans* and is thought to act intracellularly, and perhaps intranuclearly on the basis of a potential bipartite nuclear targeting sequence. *Ce-cul-5* is one of four additional related *C. elegans* genes that together with *Ce-cul-1* form the cullin family of genes. Phylogenetically *Ce-cul-1* and *Ce-cul-5* were apparently separated at the earliest duplication of the ancestral gene and the branching of the cullin family, whereas the rabbit *Oc-VACM-1* gene is most closely related to *Ce-cul-5*. As might be expected on the basis of the nearly identical sequence of the rabbit and human VACM-1 genes, the human gene is more closely related to *Ce-cul-5* than it is to *Ce-cul-1*. The putative transmembrane domain encompassing amino acids 259–279 in the rabbit sequence (Burnatowska-Hledin et al. 1995) is perfectly conserved in the human protein (Fig. 1), as are the hypothetical protein kinase A phosphorylation sites at Thr⁴²⁶ and Ser⁷³⁰ and the possible glycosylation sites at Asn¹⁴⁴, Asn²⁸⁸, and Asn⁵⁶⁵ (Burnatowska-Hledin et al. 1995). Of the 21 amino acids that comprise the putative transmembrane domain, 13 are conserved in Ce-CUL-5, compared to only 4 in Ce-CUL-1. The bipartite nuclear localization consensus motif (2 basic amino acids followed by 10 of any kind, then 3 basic residues in the next 5) postulated to be present in Ce-CUL-1 is not conserved in either VACM-1 protein or Ce-CUL-5. Interestingly this region contains 4 of the 7 amino acid differences between the VACM-1 proteins, and 3 of these 4 residues are conserved between human VACM-1 and Ce-CUL-5 (overall four of the seven amino acid differences are conserved between Hs-VACM-1 and Ce-CUL-5). All three proteins contain the conserved sequence of basic residues R-X-X-R-X₆₋₇-K-X-R-K in this region, which could perhaps represent a variant nuclear localization signal specific to this branch of the cullin family. The carboxyl terminus of the human protein contains the tyrosine-rich motif Y-X₂-R-X₆₋₇-Y/F-X-Y-X-A/S, which was noted as a striking feature of the ends of the *C. elegans* cullin proteins and *Oc-VACM-1* (Kipreos et al. 1996).

We have submitted to the DNA database 3601 bp of *Hs-VACM-1* cDNA sequence (accession no. X81882) that contains 720 bp of additional sequence at the 3' end relative to the published rabbit sequence, which ends in a poly(A) sequence. We have an additional 367 bp of imperfect sequence from the 5'-untranslated sequence that even in its incomplete state shows 75% identity with the 5'-untranslated sequence of the rabbit gene. Attempts

to obtain additional 5' sequence by rapid amplification of cDNA ends (RACE) indicated that the sequence compiled from cDNA clones that were isolated from cDNA libraries was essentially complete. The 3968 bp of sequence that we have at present would therefore seem to represent the complete *Hs-VACM-1* sequence. Analysis of the expression of the *Hs-VACM-1* gene in a variety of tissues, however, identified a major transcript of ~7.5 kb (Fig. 2). Minor species of ~4 kb were detected in skeletal muscle and heart, and there was a suggestion of additional species intermediate in size between the 7.7- and 4-kb transcripts in skeletal muscle. The highest level of expression was found in skeletal muscle, with lower levels being apparent in all other tissues. Expression in kidney, the tissue from which the rabbit VACM-1 cDNA was cloned, was at the low levels found in other tissues.

DISCUSSION

In this report we present the complete amino acid sequence of the human VACM-1 gene and analyze the expression of this gene in 16 tissues. We identified the *Hs-VACM-1* gene while searching for the gene for ataxia telangiectasia on chromosome 11q22–23 and have since mapped it (Stankovic et al. 1997) to a location immediately centromeric to the gene for mitochondrial acetoacetyl coenzyme A thiolase (*ACAT*) and, according to the *NotI* restriction map developed by Arai et al. (1996), a minimum of 8.5 Mb centromeric to the mixed lineage leukemia gene *MLL*. The amino acid sequence of the human VACM-1 protein was identical to that of its rabbit counterpart with the exception of 7 of the 780 amino acids that comprise each protein. Interestingly, 4 of the 7 residues that differ in the human protein are conserved in the nematode CUL-5 cullin protein, in agreement with an earlier report in which the rabbit VACM-1 protein was found to be most closely related to the CUL-5 protein (Kipreos et al. 1996). The hypothetical transmembrane region identified in the rabbit protein is also completely conserved in the human gene. However, the significance of a single transmembrane motif has been questioned and the possibility that VACM-1 does not have a membrane-spanning domain has been raised (Kipreos et al. 1996). Common biochemical properties have been suggested for all cullin proteins on the basis of a conserved primary structure, and it has been claimed that all members of the family, including VACM-1, act intracellularly. Whether the putative nuclear localization motif is instrumental in directing CUL-1 protein to the

Figure 2 Analysis of *Hs-VACM-1* mRNA transcription in human tissues. (A,B) Nylon membranes containing electrophoretically separated poly(A)⁺ RNA (2 μ g) from the indicated tissues that were hybridized with [α -³²P]dCTP-labeled *Hs-VACM-1* cDNA. C and D are the same membranes that were used in A and B, respectively; but hybridized with radiolabeled β -actin DNA; the orders of the tissues are the same as shown in A and B. Size markers shown at the left of A and B are in kilobases.

nucleus or some other cellular compartment is unknown. If the cullin family of proteins do have common biochemical properties, the lack of conservation of the nuclear localization motif in CUL-5 and the VACM-1 proteins suggests that this motif is not required for these functions.

Contrary to the assumption, on the basis of statistical sampling of expressed sequence tag (EST) libraries, that expression of the *VACM-1* genes is restricted to certain tissues or stages of development (Kipreos et al. 1996), our analysis suggests that the human *VACM-1* gene is transcribed in all tissues, albeit at a low level. The major transcript is at least 3 kb bigger than the *Hs-VACM-1* cDNA sequence that we have assembled. A similar observation was made in the rabbit by Burnatowska-Hledin et al. (1995), who found strong hybridization to an mRNA of ~6.5 kb. Our study indicates that there is

little if any additional sequence remaining to be discovered at the 5' end of the cDNA, suggesting that the outstanding sequence would most likely be from the 3' end. We have already found >700 bp more 3' untranslated sequence than was identified in the rabbit *VACM-1* cDNA, and it has become apparent that there are many poly(A) sequences in this sequence. Priming at these sites during cDNA synthesis may give an artificially low estimate of the length of the *VACM-1* mRNA transcript.

The finding that the *Hs-VACM-1* gene is transcribed in all tissues indicates that a role for this gene in tumor progression should be considered, as highlighted for the cullin family in general by Kipreos et al. (1996). Our localization of the *Hs-VACM-1* gene to human chromosome 11q22-23 is intriguing in the light of the loss of heterozygosity observed in breast cancer tumor samples at 11q22-23 (Carter et al. 1994; Hampton et al. 1994; Gudmundsson et al. 1995; Negrini et al. 1995; Tomlinson et al.

1995; Winqvist et al. 1995). Markers within the locus for the ataxia telangiectasia gene *ATM* have recently been associated with this loss of heterozygosity, but no evidence was found of mutations in the remaining allele (Vorechovsky et al. 1996). Because this region of loss of heterozygosity extends centromeric to the *ATM* gene and includes the region to which we have mapped the *Hs-VACM-1* gene, this gene should now be considered as a possible tumor suppressor gene associated with breast cancer.

METHODS

Construction of the *Hs-VACM-1* cDNA Sequence

A human fetal thymus cDNA library cloned in λ MAX (Clontech) was arrayed and pooled in a 96-well format for screening by PCR. An arrayed human frontal cortex cDNA library was also used in PCR screening. Clones specific to exons that were

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trapped from cosmids derived from the AT region were identified and partially purified by PCR of the arrayed thymus and frontal cortex cDNA libraries, and isolated in a final hybridization step. Additional overlapping cDNA clones were obtained from a human embryonic brain cDNA library and by hybridization selection (Morgan et al. 1992; Futreal et al. 1994) from a human lymphoblastoid cell line, using sequences derived from AT gene region cosmids and YACs.

DNA Sequencing

The sequence of the *Hs-VACM-1* cDNA was determined by direct sequencing of cDNA clones and by a vectorette sequencing strategy described previously (Byrd et al. 1996). cDNA clones and gel-purified, agarased PCR products were sequenced using an Applied Biosystems 373A DNA sequencer, and sequence assembly and analysis were performed using applications of the GCG program as described previously (Byrd et al. 1996).

Analysis of *Hs-VACM-1* Expression

Multiple tissue Northern blots (Clontech) were hybridized with the complete *Hs-VACM-1* cDNA sequence and washed according to the manufacturers recommendations. Hybridization signals were detected using Kodak X-OMAT AR film; exposures for up to 15 days were required to detect the weakest signals.

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