Identification of the gene encoding Brain Cell Membrane Protein 1 (BCMP1), a putative four-transmembrane protein distantly related to the Peripheral Myelin Protein 22 / Epithelial Membrane Proteins and the Claudins

ABSTRACT

We have identified the existence in several mammalian species of a gene encoding a putative four-transmembrane protein, BCMP1, wich defines a novel subclass in this family of proteins. In dog at least, the corresponding mRNA is highly present in brain cells. The chromosomal localization of the gene in man makes of it a likely candidate gene for X-linked mental retardation.

INTRODUCTION

Background We recently developped a screening procedure for the selection of sequences encoding proteins targeted to the cell nucleus. Our method relies on the expression in transfected cells of enhanced green fluorescent protein (EGFP) fusion proteins from cDNA library constructs. The selected clones encode EGFP fusion proteins that accumulate in the cell nucleus. Many of them were shown to harbor cDNA sequences corresponding to nuclear proteins that were translated in frame with the EGFP coding sequence. However, in nearly half of the selected clones the production of a fusion protein able to accumulate in the nucleus was shown to result from out of frame translation of the cDNA sequence fused to the EGFP coding region. On the average indeed, only one out of three cDNAs was positionned in frame with the EGFP coding sequence in the starting library. It was not expected that functional nuclear localization sequences would be generated at random (i.e. by out of frame translation of cDNA sequences) as often as was observed. One clone, called "C60", that was isolated in this approach exhibited a significant DNA sequence similarity with a mouse EST sequence present in the EMBL/GenBank database (clone MNCb-0941, accession #: AU035837). No open reading frame (ORF) had been identified in this sequence yet, but the comparison of our dog sequence with the one from mouse identified a putative ORF on the basis that in the 385 bp-long region of similarity most of the differences occurred at the third position of base triplets in frame with a starting ATG codon. However, both sequences diverged before the stop codon was reached. Assuming that this was the correct reading frame, the cDNA portion in our EGFP fusion construct was translated out of frame (frame +2). This out of frame translation generated a 201aa-long sequence presenting several neighbouring clusters of arginine residues, which somehow resembled basic type nuclear localization signals. Although it could explain why this cDNA was isolated in the screening, it did not allow us to conclude whether the protein normally encoded by the cDNA is a nuclear protein or not. To further characterize the protein encoded by the cloned sequences we decided to isolate a complete copy of the corresponding mRNA.

CONCLUSION

Conclusions We have described here the identification of the gene encoding a novel protein, called Brain Cell Membrane Protein 1 (BCMP1), which belongs to the large family of four-transmembrane proteins and appears to be highly expressed in the brain. The gene seems to be conserved on chromosome X within mammals, in close association with the DMD locus in man, rat and dog at least. The encoded BCMP1 protein

shares significant ressemblances with both PMP22/EMPs and the claudins, but exhibits distinct features, notably a predicted intracellular amino-terminal extension, which distinguishes it from the other known members of the family. PMP22/EMPs are integral membrane proteins that seems to be implicated in various cellular processes, such as cellular differentiation, control of proliferation, and apoptosis. PMP22 has been shown to play a critical role in peripheral nerves, where it is involved in the assembly of peripheral nerve myelin and in the regulation of proliferation and differentiation of Schwann cells. The claudins also constitute integral membrane proteins which are localized exclusively at tight junctions. Claudin-1, -2 and -3 have been shown to present calcium-independent cell-adhesion activity. Alterations in the PMP22 gene are responsible for hereditary motor and sensory neuropathies in human and rodents, known as Charcot-Marie-Tooth type 1A (CMT1A) disease and Trembler (Tr) mouse respectively. Individuals presenting nonsyndromic recessive deafness (autosomal recessive deafness DFNB29) were recently shown to harbor mutations in the gene encoding claudin-14. The Xp11.4 region of the human genome which comprises the BCMP1 gene has been linked to several forms of syndromic X-linked mental retardation, such as MRXS-2, -4, -6 and -10, and to a number of nonsyndromic MRX cases. The TM4SF2 gene which apparently encodes another member of the superfamily of four transmembrane proteins, a tetraspanin more distantly related to BCMP1 than are PMP22/EMPs and the claudins, is located very close to the BCMP1 gene in man. Mutations in the TM4SF2 gene and gene inactivation resulting from chromosomal translocation have been shown to be involved in several cases of X-linked mental retardation. Whether the BCMP1 gene is also involved in such genetic disorders and what is the function of the encoded protein thus constitute the obvious questions which will support our future investigations.