A cDNA specifying the human amyloid β precursor protein (ABPP) encodes a 95-kDa polypeptide

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Submitted August 5, 1988

Accession no. X12613

Although the ABPP gene gives rise to multiple mRNAs (1-3), the primary translation product of this gene is unknown. The longest published cDNA sequences (1-4) predict a 770-aa polypeptide of 87 kDa. However, in immunoblots, ABPP migrated as a single species of >92 kDa in rat brain (5), and in humans, as a species of 95-100 kDa in non-membrane-bound form (S. Younkin and D. Selkoe, personal communication), as multiple species of 110-135 kDa in membrane-associated form (6), and as a 130-kDa species in fibroblasts (7; P. and L. Gambetti, personal communication). The sizes of these larger species relative to the MW of ABPP predicted from the cDNA sequences have been attributed to posttranslational modification. However, we have isolated a cDNA (AHAP2) from a human fetal muscle λ gt11 cDNA library encoding an 843-aa polypeptide with a deduced MW of 94,642. This cDNA contains both exons encoding the protease inhibitor domains (1-3), and is 79 nt longer at the 5' end than the sequence of Kang et al. (4) (sequence "K"). Primer extension analysis indicates that the 5' terminus of this cDNA is 14 nt from a transcriptional start site. The 5' end of our cDNA (sequence "M") shows a G at nt 151 (reported as an A at nt 49 in sequence "P", of Ponte et al. [1]), an extra G (asterisk) at nt 130 relative to published sequences (1,4) (nt -97 in sequence "K"; nt 28 in sequence "P"), and an ATG triplet at nt 8. The "extra" G places the upstream ATG in frame with the deduced aa sequence of ABPP (1,4), and increases its length by 73 aa. This cDNA, encoding the longest ABPP described to date, may explain some of the observations on the sizes of tissue-derived ABPP noted above.

M: [EcoRI linker]GGAGGATATGAAGTCCATCTTCACTTCAGAGATCTCTCTCC (40)

M K S I F T S E I S S
[1] [10]

K: [Okayama-Berg 5' end]AGTTTCTCTCGGCAGC (-107)

M: GTCTTGATATTGTCAACCCAGAACCTGGTCGAGTGGTCAGTTTCTCTCGGCAGC (94)

V L I F V N P E P G R V V S F L G S
[20]

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P: [EcoRI linker]CGCGGAGCAGCGTGC CGGGG-CCCCGGGAGACGGCGGCG (46)

K: GGTAGGCGAGAGCACGCGGAGGAGCGTGC CGGGG-CCCCGGGAGACGGCGGCG (-79)

M: GGTAGGCGAGAGCACGCGGAGGAGCGTGC CGGGGCCCCGGGAGACGGCGGCG (148)

G R R E H A E E R A R G P R E T A A
[30] [40]

P: GTAGCGGCGCGGCGAGAGCAAGGACGCGGCGGATCCCACTCGCACAGCAGCGCA (100)

K: GTGGCGGCGCGGCGAGAGCAAGGACGCGGCGGATCCCACTCGCACAGCAGCGCA (-25)

M: GTGGCGGCGCGGCGAGAGCAAGGACGCGGCGGATCCCACTCGCACAGCAGCGCA (202)

V A A R A E Q G R G G S H S S A
[50] [60]

P: CTCGGTGCCCCGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTGCTCCTGCTG (154)

K: CTCGGTGCCCCGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTGCTCCTGCTG (30)

M: CTCGGTGCCCCGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTGCTCCTGCTG (256)

L G A P R R V A M L P G L A L L L L
[70] [80]

ACKNOWLEDGEMENTS Supported by grants from the Aaron Diamond Foundation, the Charles A. Dana Foundation, the Muscular Dystrophy Association, and the National Institutes of Health.

REFERENCES: (1) Ponte et al. (1988) *Nature* 331:525; (2) Tanzi et al. (1988) *Nature* 331:528; (3) Kitaguchi et al. (1988) *Nature* 331:530; (4) Kang et al. (1987) *Nature* 325:733; (5) Shivers et al. (1988), *EMBO J* 7:1365; (6) Selkoe et al. (1988) *PNAS*, in press; (7) Tabaton et al. (1988) *J Neuropathol Exp Neurol* 47:336.