

. ApoE E2, E3, E4 가 mma - secretase gamma - sec -
가 , E4 가 sporadic 65 retase (Wolfe 1999 ; De Strooper
(mitochondria) PS1 , C. elegans Notch signalling
cytochrome C oxidase 가 , ApoE ,
E2, E3, E4 가 0.078,
, APP, PS ApoE 0.770, 0.152 가 . 가
가 E4/E4>E3/E4>E2/E4>E3/E3>E2/E3>
, APP 가 E2/E2 가 . ApoE4
neurite outgrowth가 가
APP 가 , APP 가
neurite outgrowth가
, APP가 (extracellular matrix)
(heparan sulfate proteoglycan),
(entantin)

알쯔하이머치매의 유전자 전이 생쥐 모형

APP 가 . , APP
, 가 1991 ,
(beta - secretase gamma - secretase hallmark ,
) ApoE4
oxidative stress , APP PS
(microglia) 가
(neuron) (1).
RAGE(receptor for advanced glycation end prod- Games (1995)
uct) . Platelet derived growth factor
, RAGE (PDGF) beta promotor가 가
(Yan 1996)가 . (APP 717 valine pheny -
PS1 PS2 가 , PS1 lalanine) 가 human APP minigene
S182 PS2 . , construct APP intron 6,7,8 가 , exon 7,8
STM2 , C. elegans (alternative splicing) , APP
sel 12 spe - 4 (transcript) 가 APP 770, APP 751, APP
PS1 가 45 50kDa , 27 695 .
28kDa N- (NTF) 17 19 kDa C- (CTF) human APP mRNA가
, PS - 2 가 53 human APP 가
55kDa , 35kDa NTF 17 19kDa . PDGF - human APP construct human APP intron
CTF , endoproteolysis 6,7 8 ,
, 가 human APP 770 hu -
man APP 751 human APP 695
APP processing trafficking , 42 AD
. PS1 , APP ga - (astrocytosis) (microgliosis)

Table 1. Transgenic mice models of Alzheimer's disease

Construct(gene/promotor)	Changes in neuropathology, electrophysiology & behavior	Authors
Human APP minigene V717F/ PDGF-beta	Amyloid plaques, gliotic changes	D. Games et al.
Human APP 695 cDNA/PrP	Amyloid change, gliotic change and behavioral changes	K. Hsiao et al.
Human PS-1/PDGF-beta	A-beta 1-42 increase	K. Duff et al.
Human APP CTF 104/NF-L	Amyloid change, gliotic changes, behavioral changes, and LTP deficits	J. Nalbantoglu et al.

Theuring Table 1 .

AD . Nalbantoglu (1997) , - L(neurofilament - lig - Hsiao (1996) ht) APP C 104 (가 (Lys670Asn, Met671 591 695 가 human APP cDNA fra - Leu ; APP 770) 가 human APP 695 cDNA gment) prion promotor water maze (long - term potentiation) , APP 695 APP KPI(Kunitz - type protease inhi - bitor) , , (gliosis) (2 8 11 13) (1 40 peptide) 5 가 (p=0.03, rank sum test) (1 42/43 (Pearson Choi peptide) 14 가(p=0.03, rank sum test) 1993 ; Quon 1991 ; Lamb 1993 ; Zheng 1995 ; Re - aume 1996 ; Citron 1997) , water maze Y - maze(가) 가 AD 결론 Duff (1996) PDGF beta2 promotor가 가 PS1 . Construct PS1 (motif VRSG , ATG AD , TAG 1.4kb) , exon 3 exon 12 , PS1 2.4kb 가 , intron 4가 exon 4 exon5 , 224bp PS1 , PS1 exon5 가 Met146Leu Met146Val 가

PS1 mRNA가 , 참고문헌 (splicing) 46kDa PS1 (holoprotein) Citron M, Westaway D, Xia W, Carlson G, Diehl T, Levesque G, Johnson-Wood K, Lee M, Seubert P, Davis A, Kholodenko D, Motter R, Sherrington R, Perry B, Yao H, Strome R, Lieberburg I, Rommens J, Kim S, Schenk D, Fraser P, St George-Hyslop P, Selkoe DJ(1997) : Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid beta-protein in both transfected cells and transgenic mice. *Nat Med* 3 : 67-72 De Strooper B, Annert W, Cupers P, Saftig P, Craessaerts K, Mumm JS, Schroeter EH, Schrijvers V, Wolfe MS, Ray WJ, Go

- ate A, Kopan R(1999) : *A presenilin-1-dependent gamma-secretase-like protease release of Notch intracellular domain. Nature 398 : 518-522*
- Duff K, Eckman C, Zehr C, Yu X, Prada C-M, Perez-Tur J, Hutton M, Buee L, Harigaya Y, Yager D, Morgan D, Gordon MN, Holcomb L, Refolo L, Zenk B, Hardy J, Younkin S(1996) : *Increased amyloid-beta42 (43) in brains of mice expressing mutant presenilin 1. Nature 383 : 710-713*
- Games D, Adams D, Alessandrini R, Barbour R, Berthelette P, Blackwell C, Carr T, James C, Donaldson T, Gillespie F, Guido T, Hagopian S, Johnson-Wood K, Khan K, Lee M, Lelbowitz P, Lieberburg I, Littie S, Masliah E, McConlogue L, Montoya-Zavala M, Mucke L, Paganini L, Penniman E, Power M, Schenk D, Seubert P, Snyder B, Sorlano F, Tan H, Vitalis J, Wadsworth S, Wolozin B, Zhao J(1995) : *Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. Nature 373 : 523-527*
- Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G(1996) : *Correlative memory deficits, A-beta elevation, and amyloid plaques in transgenic mice. Science 274 : 99-102*
- Iqbal K, Swaab DF, Winblad B, Wisniewski HM(1999) : *Alzheimer's disease and related disorders. West Sussex, John Wiley and Sons Ltd*
- Lamb BT, Sisodia SS, Lawler AM, Slunt HH, Kitt CA, Kearns WG, Pearson PL, Price DL, Gearhart JD(1993) : *Introduction and expression of the 400 kilobase precursor amyloid protein gene in transgenic mice. Nat Genet 5 : 22-30*
- Nalbantoglu J, Tirado-Santiago G, Lahsaini A, Poirer J, Goncalves O, Verge G, Momoli F, Welner SA, Massicotte G, Julien J-P, Shapiro ML(1997) : *Impaired learning and LTP in mice expressing the carboxy terminus of the Alzheimer Amyloid protein. Nature 387 : 500-505*
- Pearson PE, Choi TK(1993) : *Expression of the human beta-amyloid precursor protein gene from a yeast artificial chromosome in transgenic mice. Proc Natl Acad Sci USA 90 : 10578-10582*
- Quon D, Wang Y, Catalano R, Scardina JM, Murakami K, Cordell B(1991) : *Formation of beta-amyloid protein deposits in brains of transgenic mice. Nature 352 : 239-241*
- Reaume AG, Howland DS, Trusko SP, Savage MJ, Lang DM, Greenberg BD, Siman R, Scott RW(1996) : *Enhanced amyloidogenic processing of the beta-amyloid precursor protein in gene-targeted mice bearing the Swedish familial Alzheimer's disease mutations and a "humanized" A-beta sequence. J Biol Chem 271 : 23380-23388*
- Theuring F, Thunecke M, Kosciessa U, Turner JDI(1997) : *Transgenic animals as models of neurodegenerative diseases in humans. Tibtech August 15 : 320-325*
- Wolfe MS, Xia W, Ostaszewski BL, Diehl TS, Kimberly WT, Selkoe DJ(1999) : *Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity. Nature 398 : 513-517*
- Yan SD, Chen X, Fu J, Chen M, Zhu H, Roher A, Slattery T, Zhao L, Nagashima M, Moser J, Migheli A, Nawroth P, Stern D, Schmidt AM(1996) : *RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. Nature 382 : 685-691*
- Zheng H, Jiang M, Trumbauer ME, Sirinathsinghji DJS, Hopkins R, Smith DW, Heavens RP, Dawson GR, Boyce S, Conner MW, Stevens KA, Slunt HH, Sisodia SS, Chen HY, Van der Ploeg LHT(1995) : *Beta-amyloid precursor protein deficient mice show reactive gliosis and decreases locomotor activity. Cell 81 : 525-531*