Available online at www.sciencedirect.com
ScienceDirect
Neuroscience Letters 406 (2006) 265–269
Neuroscience Letters
www.elsevier.com/locate/neulet

Lack of association of 5 SNPs in the vicinity of the insulin-degrading enzyme (IDE) gene with late-onset Alzheimer's disease

Ayla Ozturk [a,1], Steven T. DeKosky [b], M. Ilyas Kamboh [a,*]

[a] *Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, Pittsburgh, PA 15261, USA*
[b] *Department of Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15261, USA*

Received 7 April 2006; received in revised form 27 June 2006; accepted 21 July 2006

Abstract

Insulin-degrading enzyme (IDE) is a strong biological and positional candidate gene for Alzheimer's disease (AD). Previously some studies have examined the role of common variation in the IDE gene with AD risk but the results have been inconsistent. In this study we examined the role of 5 SNPs that define a linkage disequilibrium (LD) block spanning 276 kb around IDE. Our sample comprised up to 1012 late-onset AD (LOAD) cases and 771 older white controls. In addition, we also examined the association of these SNPs with quantitative measures of AD progression, namely age-at-onset (AAO), disease duration and Mini-Mental State Examination (MMSE) score. None of the SNPs examined in this fairly large case-control sample revealed significant association with AD risk. These SNPs also showed no significant association with AD quantitative traits.

Keywords: Genetics; Polymorphisms; Chromosome 10

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive deposition of β-amyloid (Aβ) peptide in extracellular senile plaques. Rare mutations in amyloid precursor protein (APP) and presenilin 1 and 2 genes are associated with increased production of Aβ [22]. Although the increased production of Aβ is a key step for peptide accumulation, its impaired clearance also defines the steady-state level of this peptide. Insulin-degrading enzyme (IDE) is one of several enzymes linked to Aβ degradation [20]. IDE deficiency has been shown to promote significant net increase in Aβ deposition in mouse brain [10,14] and also preventing Aβ toxicity [15]. Neuron-specific overexpression of IDE or neprilysin in mice significantly reduced brain Aβ levels [11], suggesting a potential role of IDE in AD treatment. Moreover, IDE is located on chromosome 10q q23–q25 between two regions showing linkage to LOAD [2,4,9,16,17].

Despite the linkage data and biological relevance of IDE with AD, several case-control studies did not provide convincing evidence of association of IDE with AD [1,6,9,18,21]. However, in a comprehensive study by Prince et al. [19], significant associations with the severity of disease, as measured by quantitative traits such as MMSE score, protein tau levels in cerebral spinal fluid, AAO, and degree of brain pathology was found. Prince et al. [19] concluded that the effect of IDE might be in the severity of the disease rather than on disease risk. A recent study by Ertekin-Taner et al. [8] replicated the results of Prince et al. [19] in case-control series and also found significant association of IDE haplotypes with plasma Aβ42. One study reported a possible association of IDE with AD risk among non-*APOE*4* carriers [7], but the sample size was too small for a meaningful interpretation. Although IDE is an excellent biological and positional candidate for AD, its association with AD is yet to be established.

To evaluate the potential influence of genetic variation in IDE on AD risk and correlated quantitative traits, we examined five single nucleotide polymorphisms (SNPs) located in and around the IDE gene in a large Caucasian case-control cohort. The physical locations of these SNPs, as taken from Prince et al. [19], are: IGS6 (rs967878), IDE7 (rs2251101), IDE8 (rs551266), IDE14 (rs1832196), HHEX23 (rs1544210) from pter (94.31 Mb) to qter (94.62 Mb) along chromosome 10. IDE7, IDE8 and IDE14 SNPs are located within the IDE gene and they are flanked by the IGS6 SNP located in an intergenic region and the HHEX23 SNP located in the hematopoetically-expressed homeobox (HHEX)

* Corresponding author. Tel.: +1 412 624 3066; fax: +1 412 383 7844.
E-mail address: ikamboh@hgen.pitt.edu (M.I. Kamboh).
[1] Current address: Department of Periodontology, School of Dental Medicine, Ondokuz Mayis University, Samsun 55139, Turkey.

0304-3940/$ – see front matter © 2006 Published by Elsevier Ireland Ltd.
doi:10.1016/j.neulet.2006.07.054

gene. The IDE7, IDE14, and HHEX23 were haplotype tagging SNPs that capture the common variation (>5%) in the 276.5 kb genomic region harboring the IDE, kynesin like 1 (KNSLI), and HHEX genes [19]. The IGS6 and IDE8 SNPs have been found to be associated with AD risk [8,19]. The same 5 SNPs have also been typed by Ertekin-Taner et al. [8]. Thus, all the tested SNPs have shown to be associated with AD risk in at least one study. The purpose of the present study was either to confirm or refute the published findings in a well powered case-control sample.

The study sample compromised 1012 white LOAD sporadic subjects and 771 white control subjects. The LOAD (≥60) cases (66.7 % female, 25.8% autopsy-confirmed) were from the University of Pittsburgh Alzheimer's Disease Research Center (ADRC). The mean age of patients was 76.57 ± [S.D.] 5.7 years with a mean AAO of 72.29 ± 6.33 years. Clinical diagnoses of the patients were made according to the NINCDS/ADRDA criteria [13]. The ADRC follows a standard evaluation protocol, which includes medical history, general medical and neurological examinations, a psychiatric interview, neuropsychological testing and a MRI scan. The controls (61.50% female, mean age 75.20 ± 5.63 years) were recruited from the same Western Pennsylvania region as the cases, and were determined to be cognitively intact following extensive clinical examination (see Wang et al. [23] for details). This study was approved by the University of Pittsburgh Institutional Review Board.

Genotyping was performed using pyrosequencing. Sequences for the PCR (F,R) and sequencing (S) primers for these 5 SNPs are: IDE7-rs2251101; F:AGATCGCACGACTGCACTGTAG (biotinylated) R:TGAGTCCCTCCATGTATCATGAAT S:GGGGGACCTGCTG; IDE8-rs551266; F:ACACTGCTAGGTACACGGCAAA R:TGAATCCAACTGCTAGATAAATTATAAGTAGG (biotinylated) S:AATGCTCAATAAATGAGAGA; IDE14-rs1832196; F:ATGTGACCATTTTGGGTTAGTG R:CCATTTTGCCTAGGCTAGTCTCAA (biotinylated) S:TTGGCACGCTGTTG; HHEX23-rs1544210; F:GGCCTGGGATTTTACTGTACTATCA (biotinylated) R:TTCCTGCATTTTGATTTTCTTCTTG S:GCTACTGTTTTCCTGCA; IGS6-rs967878; F:TGGTATCCGTGGGTTACAGACA (biotinylated) R:CCTGCTCCTGGGTTCTCCTTTCATC S:ATCCAGGACTTGCTGA. Allele frequencies were calculated by the allele counting method. Goodness of fit to Hardy–Weinberg expected proportions was examined by chi-square test. The differences in genotype frequencies between cases and controls were tested by chi-square tests. The pair-wise linkage disequilibrium (LD) between markers was estimated using the D' method [12]. Multiple logistic regression models were used to examine the association of each genetic marker with AD. The estimated odds ratios (ORs) were adjusted for the effects of significant covariates such as age, sex and APOE. The mean AAO between different genotype groups were compared using one-way analysis of variance (ANOVA) and adjusted for the effects of sex and APOE. Kaplan–Maier survival analysis was also used to compare the AAO between genotypes. The disease duration was estimated by subtracting the AAO from the age at death and then mean disease duration was compared between genotypes after adjusting for the effects of sex and APOE genotype. Data on disease duration were available on 157 AD patients. Mean disease duration was 9.73 ± 0.27 years. All computations were performed using R statistical 2.0.0 program http://www.maths.lth.se/help/R/.R/doc/html/index.html). The haplotype frequencies were estimated using the expectation-maximization algorithm in the EH software program (http://linkage.rockefeller.edu/ott/eh.htm).

The distribution of allele and genotype frequencies of the 5 SNPs is presented in Table 1. The frequencies of all SNPs were in Hardy–Weinberg equilibrium in AD patients and controls. We found no differences in the allelic or genotypic frequencies between AD patients for any of the SNPs. Stratifying the data by *APOE*4* and non-*APOE*4* did not change the results. In addition to single site analysis we also performed 5-site haplotype

Table 1
Distribution of polymorphisms in and around IDE in LOAD cases and controls

Polymorphisms	*n*	Genotype			Allele frequency	*p*-value genotype (allele)
		(%)*n*	(%)*n*	(%)*n*		
IGS6/G → T (rs967878)		AA	CA	CC		
AD cases	910	17.69 (161)	50.33 (458)	31.98 (291)	42.9/57.1	0.14 (0.07)
Controls	744	14.65 (109)	50.27 (374)	35.08 (261)	39.8/60.2	
IDE7/T → C (rs2251101)		GG	AG	AA		
AD cases	966	10.56 (102)	39.75 (384)	49.69 (480)	30.4/69.6	0.62 (0.45)
Controls	732	9.29 (68)	39.75 (291)	50.96 (373)	29.2/70.8	
IDE8/T → C (rs551266)		CC	TC	TT		
AD cases	871	3.1 (27)	30.88 (269)	66.02 (575)	18.5/81.5	0.59 (0.13)
Controls	735	4.76 (35)	31.16 (229)	64.08 (471)	16.4/83.6	
IDE14/C → T (rs1832196)		TT	CT	CC		
AD cases	1012	1.78 (18)	24.11 (244)	74.11 (750)	13.8/86.2	0.85 (0.80)
Controls	698	1.72 (12)	23.5 (164)	74.79 (522)	13.5/86.5	
HHEX G → A (rs1544210)		TT	CT	TT		
AD cases	892	24.44 (218)	49.33 (440)	26.23 (234)	49.1/50.9	0.71 (0.95)
Controls	771	24.51 (189)	49.29 (380)	26.2 (202)	49.2/50.8	

analysis, including all 5 SNPs or 3-site haplotype analysis using the tagSNPs. The overall 5-site ($p = 0.60$) or 3-site ($p = 0.80$) analyses were not significant.

We also examined the association of IDE and surrounding chromosome 10 markers with quantitative traits related to AD, namely disease duration, AAO, and measures of cognitive function such as MMSE scores at baseline and during the last phase of the study (Table 2). No association was observed with any of the 5 SNPs and AAO, disease duration or MMSE scores at the baseline. The only significant association observed was between the IDE14 SNP and MMSE scores measured during the last phase of the study after adjusting for sex, APOE gene and cohort ($p = 0.03$). The homozygous TT carriers had higher cognitive scores (21.08 ± 1.53) than both CT and CC genotypes (19.05 ± 0.32 and 19.89 ± 0.18, respectively). Since, we observed a modest association after multiple comparisons only in last phase of MMSE, this should be interpreted with caution because this could be a chance observation.

A number of studies have examined the role of IDE genetic variants with AD risk, but results are not consistent. The first study that examined the IDE gene looked at the common genetic variation (>5%) in this gene covering all the coding and 5′ region in relation to AD risk and found no significant association [1]. Later, meta analysis stratified by APOE status yielded a possible association among non-*APOE*4* carriers [7]. Studies of IDE variants in different ethnic groups yielded variable results. While IDE was associated with AD risk in an *APOE*4*-dependent fashion in Han Chinese [3], no association was found in Japanese [21] and French [6] cohorts. An additional study examined a large 276-kb region harboring the IDE gene in relation to AD risk and quantitative traits associated with AD risk [19]. While no association was observed with AD risk, several significant associations with AD quantitative traits, including MMSE scores, microtubule-associated protein tau levels in cerebral spinal fluid, AAO, and the degree of brain pathology were found. It should be emphasized, however, that as opposed to the AAO, which is static over time and provides meaningful genetic association data, the initial association of genotype and severity of disease may be difficult to interpret unless it is confirmed in independent studies. Recently, Ertekin-Taner et al. [8] analyzed the same IDE markers previously shown to be associated with quantitative traits [19] and two additional markers, and found significant associations with Aβ42 levels and LOAD. A follow-up of the original study [19] has also reported association of one IDE SNP with Aβ deposition [5]. Thus, additional studies in independent samples are important in clarifying the role of IDE genetic variation in relation to quantitative traits associated with AD.

In our study we examined 5 SNPs extending locally around IDE in a large Caucasian case-control cohort. In our study, neither variant was associated with LOAD risk or AAO when replication was sought up to 1012 LOAD cases and 771 controls. Likewise, there was no difference between the cases and controls

Table 2
Mean quantitative traits (±S.D.) among genotypes in LOAD

Polymorphisms	Genotype			*p*-value
IGS6/G → T (rs967878)	AA	AC	CC	
AAO*	71.79 ± 0.51 (149)	72.54 ± 0.31 (421)	72.11 ± 0.38 (261)	0.52
Disease duration**	9.47 ± 0.72 (35)	9.61 ± 0.41 (98)	10.41 ± 0.50 (61)	0.39
MMSE baseline†	22.43 ± 0.30 (219)	22.03 ± 0.18 (694)	21.72 ± 0.21 (473)	0.17
MMSE last†	19.99 ± 0.42 (186)	19.77 ± 0.22 (613)	19.62 ± 0.26 (411)	0.72
IDE7/T → C (rs2251101)	GG	GA	AA	
AAO*	72.65 ± 0.60 (97)	72.05 ± 0.32 (356)	72.54 ± 0.30 (446)	0.63
Disease duration**	7.71 ± 1.23 (13)	9.06 ± 0.40 (77)	9.94 ± 0.43 (88)	0.12
MMSE baseline†	22.10 ± 0.40 (146)	21.98 ± 0.20 (566)	22.09 ± 0.17 (708)	0.91
MMSE last†	20.29 ± 0.46 (127)	19.78 ± 0.24 (497)	19.68 ± 0.22 (624)	0.53
IDE8/T → C (rs551266)	CC	TC	TT	
AAO*	73.15 ± 1.02 (26)	72.16 ± 0.39 (233)	72.83 ± 0.27 (516)	0.35
Disease duration**	11.68 ± 2.31 (4)	10.52 ± 0.70 (42)	9.64 ± 0.34 (102)	0.43
MMSE baseline†	22.97 ± 0.76 (37)	21.95 ± 0.24 (386)	22.22 ± 0.15 (878)	0.36
MMSE last†	21.34 ± 0.73 (32)	19.63 ± 0.29 (341)	19.78 ± 0.20 (776)	0.24
IDE14/C → T (rs1832196)	TT	TC	CC	
AAO*	72.85 ± 1.91 (16)	72.51 ± 0.38 (220)	71.31 ± 0.24 (665)	0.55
Disease duration**	6.81 ± 2.81 (2)	9.80 ± 0.55 (53)	9.80 ± 0.32 (155)	0.59
MMSE baseline†	22.31 ± 1.07 (26)	21.54 ± 0.25 (354)	22.13 ± 0.14 (1068)	0.12
MMSE last†	21.08 ± 1.53 (22)	19.05 ± 0.32 (310)	19.89 ± 0.18 (941)	0.03
HHEX G → A (rs1544210)	TT	CT	CC	
AAO*	71.48 ± 0.48 (190)	72.68 ± 0.30 (396)	73.04 ± 0.43 (206)	0.07
Disease duration**	10.32 ± 0.73 (35)	9.90 ± 0.48 (70)	9.03 ± 0.45 (49)	0.37
MMSE baseline†	21.98 ± 0.23 (346)	22.15 ± 0.18 (703)	22.26 ± 0.22 (363)	0.70
MMSE last†	19.78 ± 0.29 (303)	19.86 ± 0.22 (615)	19.71 ± 0.29 (322)	0.93

* Adjusted for gender and *APOE*4*.
** Adjusted for gender, *APOE*4* and AAO.
† Adjusted for age (controls), AAO (cases), disease status, gender and *APOE*4*.

after stratifying the data by APOE status. Haplotype analysis revealed no significant association. Similar to our results, Nowotny et al. [18] did not find any significant association in a large case control cohort consisting of 1217 cases and 1257 controls from four different series. They examined the same tagSNPs (IDE7, IDE14, and HHEX23) and additional 15 markers in and around the IDE. Although they found significant association of the IDE7 SNP in two samples ($p = 0.0066$, and $p = 0.026$), this result was not replicated in the other two series.

Inconsistency in reported AD association studies has been attributed to several factors, including among others, genotyping errors, ascertainment bias in patient selection (autopsy-confirmed AD cases versus clinically assessed AD cases), population stratification, differences in the pattern of linkage disequilibrium between population groups, relative effect size of a marker and locus heterogeneity [23]. Potential genotyping error was not a major confounding factor in our sample as we repeated 10% of the genotypes for each SNP to confirm the validity of the genotyping systems. About 26% of our AD cases were autopsy-confirmed and thus clinically least ambiguous. However, we found no significant difference in genotype frequencies between our autopsy-confirmed and clinically-assessed AD cases. Our sample size was sufficiently large to detect modest effect sizes. Although the results of our large study do not support the role of common genetic variation in the IDE gene with LOAD, we cannot exclude a minor role of this gene in the etiology of AD because we did not examine the entire common variation, and more importantly rare variants in this gene. We also did not evaluate the role of IDE genetic variation with Aβ levels because this trait is not available in our sample. It is possible that the effect of the IDE on AD risk is mediated through modulating Aβ levels, as shown by others [5,8].

Acknowledgement

This study was supported by the National Institutes on Aging grants AG 13672 and AG 05133.

References

[1] R. Abraham, A. Myers, F. Wavrant-DeVrieze, M.L. Hamshere, H.V. Thomas, H. Marshall, D. Compton, G. Spurlock, D. Turic, B. Hoogendoorn, J.M. Kwon, R.C. Petersen, E. Tangalos, J. Norton, J.C. Morris, R. Bullock, D. Liolitsa, S. Lovestone, J. Hardy, A. Goate, M. O'Donovan, J. Williams, M.J. Owen, L. Jones, Substantial linkage disequilibrium across the insulin-degrading enzyme locus but no association with late-onset Alzheimer's disease, Hum. Genet. 109 (2001) 646–652.

[2] L. Bertram, D. Blacker, K. Mullin, D. Keeney, J. Jones, S. Basu, S. Yhu, M.G. McInnis, R.C. Go, K. Vekrellis, K. Vekrellis, D.J. Selkoe, A.J. Saunders, R.E. Tanzi, Evidence for genetic linkage of Alzheimer's disease to chromosome 10q, Science 290 (2000) 2302–2303.

[3] L. Bian, J.D. Yang, T.W. Guo, Y. Sun, S.W. Duan, W.Y. Chen, Y.X. Pan, G.Y. Feng, L. He, Insulin-degrading enzyme and Alzheimer disease: a genetic association study in the Han Chinese, Neurology 63 (2004) 241–245.

[4] D. Blacker, L. Bertram, A.J. Saunders, T.J. Moscarillo, M.S. Albert, H. Wiener, R.T. Perry, J.S. Collins, L.E. Harrell, R.C. Go, A. Mahoney, T. Beaty, M.D. Fallin, D. Avramopoulos, G.A. Chase, M.F. Folstein, M.G. McInnis, S.S. Bassett, K.J. Doheny, E.W. Pugh, R.E. Tanzi, Results of a high resolution genome screen of 437 Alzheimer's disease families, Hum. Mol. Genet. 12 (2003) 23–32.

[5] M.E. Blomqvist, K. Chalmers, N. Andreasen, N. Bogdanovic, G.K. Wilcock, N.J. Cairns, L. Feuk, A.J. Brookes, S. Love, K. Blennow, P.G. Kehoe, J.A. Prince, Sequence variants of IDE are associated with the extent of beta-amyloid deposition in the Alzheimer's disease brain, Neurobiol. Aging 26 (2005) 795–802.

[6] M. Boussaha, D. Hannequin, P. Verpillat, A. Brice, T. Frebourg, D. Campion, Polymorphisms of insulin degrading enzyme gene are not associated with Alzheimer's disease, Neurosci. Lett. 329 (2002) 121–123.

[7] S.D. Edland, F. Wavrant-De Vriese, D. Compton, G.E. Smith, R. Ivnik, B.F. Boeve, E.G. Tangalos, R.D. Petersen, Insulin degrading enzyme (IDE) genetic variants and risk of Alzheimer's disease: evidence of effect modification by apolipoprotein E (APOE), Neurosci. Lett. 345 (2003) 21–24.

[8] N. Ertekin-Taner, M. Allen, D. Fadale, L. Scanlin, L. Younkin, R.C. Petersen, N. Graff-Radford, S.G. Younkin, Genetic variants in a haplotype block spanning IDE are significantly associated with plasma Abeta42 levels and risk for Alzheimer disease, Hum. Mutat. 23 (2004) 334–342.

[9] N. Ertekin-Taner, N. Graff-Radford, L.H. Younkin, C. Eckman, M. Baker, J. Adamson, J. Ronald, J. Blangero, M. Hutton, S.G. Younkin, Linkage of plasma Abeta42 to a quantitative locus on chromosome 10 in late-onset Alzheimer's disease pedigrees, Science 290 (2000) 2303–2304.

[10] W. Farris, S. Mansourian, Y. Chang, L. Lindsley, E.A. Eckman, M.P. Frosch, C.B. Eckman, R.E. Tanzi, D.J. Selkoe, S. Guenette, Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo, Proc. Natl. Acad. Sci. 100 (2003) 4162–4167.

[11] M.A. Leissring, W. Farris, X. Wu, D.C. Christodoulou, M.C. Haigis, L. Guarente, D.J. Selkoe, Enhanced proteolysis of beta-amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death, Neuron 40 (2003) 1087–1093.

[12] R.C. Lewontin, The interaction of selection and linkage. ii. Optimum models, Genetics 50 (1964) 757–782.

[13] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, E.M. Stadlan, Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease, Neurology 34 (1984) 939–944.

[14] B.C. Miller, E.A. Eckman, K. Sambamurti, N. Dobbs, K.M. Chow, C.B. Eckman, L.B. Hersh, D.L. Thiele, Amyloid-beta peptide levels in brain are inversely correlated with insulin activity levels in vivo, Proc. Natl. Acad. Sci. 100 (2003) 6221–6226.

[15] A. Mukherjee, E. Song, M. Kihiko-Ehmann, J.P. Goodman, J.S. Pyrek, S. Estus, L.B. Hersh, Insulin hydrolyzes amyloid beta peptides to products that are neither neurotoxic nor deposit on amyloid plaques, J. Neurosci. 20 (2000) 8745–8749.

[16] A. Myers, P. Holmans, H. Marshall, J. Kwon, D. Meyer, D. Ramic, S. Shears, J. Booth, F.W. DeVrieze, R. Crook, M. Hamshere, R. Abraham, N. Tunstall, F. Rice, S. Carty, S. Lillystone, P. Kehoe, V. Rudrasingham, L. Jones, S. Lovestone, J. Perez-Tur, J. Williams, M.J. Owen, J. Hardy, A.M. Goate, Susceptibility locus for Alzheimer's disease on chromosome 10, Science 290 (2000) 2304–2305.

[17] A. Myers, F. Wavrant De-Vrieze, P. Holmans, M. Hamshere, R. Crook, D. Compton, H. Marshall, D. Meyer, S. Shears, J. Booth, D. Ramic, H. Knowles, J.C. Morris, N. Williams, N. Norton, R. Abraham, P. Kehoe, H. Williams, V. Rudrasingham, F. Rice, P. Giles, N. Tunstall, L. Jones, S. Lovestone, J. Williams, M.J. Owen, J. Hardy, A. Goate, Full genome screen for Alzheimer disease: stage II analysis, Am. J. Med. Genet. (Neuropsychiatr. Genet.) 114 (2002) 235–244.

[18] P. Nowotny, A.L. Hinrichs, S. Smemo, J.S. Kauwe, T. Maxwell, P. Holmans, M. Hamshere, D. Turic, L. Jehu, P. Hollingworth, P. Moore, L. Bryden, A. Myers, L.M. Doil, K.M. Tacey, A.M. Gibson, I.G. McKeith, R.H. Perry, C.M. Morris, L. Thal, J.C. Morris, M.C. O'Donovan, S. Lovestone, A. Grupe, J. Hardy, M.J. Owen, J. Williams, A. Goate, Association studies between risk for late-onset Alzheimer's disease and variants in insulin degrading enzyme, Am. J. Med. Genet. (Neuropsychiatr. Genet.) 136 (2005) 62–68.

[19] J.A. Prince, L. Feuk, H.F. Gu, B. Johansson, M. Gatz, K. Blennow, A.J. Brookes, Genetic variation in a haplotype block spanning IDE influences Alzheimer disease, Hum. Mutat. 22 (2003) 363–371.

[20] W.Q. Qiu, D.M. Walsh, Z. Ye, K. Vekrellis, J. Zhang, M.B. Podlisny, M.R. Rosner, A. Safavi, L.B. Hersh, D.J. Selkoe, Insulin-degrading enzyme regulates extracellular levels of amyloid β-protein by degradation, J. Biol. Chem. 273 (1998) 32730–32738.

[21] A. Sakai, H. Ujike, K. Nakata, Y. Takehisa, T. Imamura, N. Uchida, A. Kanzaki, M. Yamamoto, Y. Fujisawa, K. Okumura, S. Kuroda, No association between the insulin degrading enzymegene and Alzheimer's disease in a Japanese population, Am. J. Med. Genet. (Neuropsychiatr. Genet.) 125 (2004) 87–91.

[22] D. Scheuner, C. Eckman, M. Jensen, X. Song, M. Citron, N. Suzuki, T.D. Bird, J. Hardy, M. Hutton, W. Kukull, E. Larson, E. Levy-Lahad, M. Viitanen, E. Peskind, P. Poorkaj, G. Schellenberg, R. Tanzi, W. Wasco, L. Lannfelt, D. Selkoe, S. Younkin, Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease, Nat. Med. 2 (1996) 864–870.

[23] X. Wang, S. DeKosky, E. Luedecking-Zimmer, M. Ganguli, M.I. Kamboh, Genetic variation in alpha-1 antichymotrypsin and its association with Alzheimer's disease, Hum. Genet. 110 (2002) 6–65.