Neurobiology of Aging 36 (2015) 2909.e1–2909.e4

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

The APP A673T frequency differs between Nordic countries

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ARTICLE INFO

Article history:
Received 26 June 2015
Accepted 5 July 2015
Available online 11 July 2015

Keywords:
Alzheimers
Aging
Dementia
Amyloid beta
Cognition

ABSTRACT

A coding gene variant A673T (rs63750847) in the *APP* gene has recently been recognized as a protective variant of late-onset Alzheimer's Disease in a large Icelandic population and has been observed recurrently in populations from Nordic countries. The variant also was related to longevity in the Icelandic population. However, because of the extreme rarity of A673T in non-Nordic populations, the association with Alzheimer's disease has not yet been formally replicated. Because the variant has not been reported among the Danes, we aimed to study its frequency among healthy middle-age twins and oldest-old singletons and explore the possible effects on longevity and cognitive abilities. Surprisingly, only 1 of 3487 unrelated Danes carried the A673T variant, (0.014% [95% CI 0.000–0.080]), which was significantly lower than in the other Nordic countries averaging to 0.43% (95% CI 0.40–0.46). In conclusion, the A673T variant is rarer in Danes than other Nordic countries, thus precluding assessment of association with longevity or cognitive functioning.

1. Introduction

Accumulated amyloid plaques are a central pathological feature of Alzheimer's disease (AD), and the main proteinaceous components are amyloid-beta (Aβ) peptides. Aβ peptide is formed through sequential proteolytic processing of the amyloid beta (A4) precursor protein (APP) by the b-site APP cleaving enzyme 1 and the g-secretases, thus leading to formation of Aβ (Zhang et al., 2011). When present in large contents, these peptides form oligomers and gradually polymerize into amyloid plaques.

Genetic studies and a large body of functional studies convincingly show that Aβ is a toxic molecule critical to the pathogenesis of AD, although Aβ especially as polypeptides is also naturally accumulating with age (Jansen et al., 2015). To date, approximately 40 missense mutations in the *APP* gene have been identified in over 80 AD families. Most of these are located near processing sites or within the Aβ coding sequence, in most cases resulting in autosomal dominant early-onset AD (Kutoku et al., 2015). Recently, an *APP* gene variant rs63750847-A, which results in an alanine to threonine substitution at position 673 in APP (A673T) was found to be significantly more common in an Icelandic control group than in AD patients suggesting that this variant protects against late-onset AD. The large Icelandic study also revealed an enrichment of the APP 674T allele in elderly and thus suggests this as a longevity gene variant. Additionally, the A673T carriers in the control group had a higher cognitive level than noncarriers supporting the relevance for cognition (Jonsson et al., 2012). The variant has subsequently been found in several Nordic countries, and was also observed in an individual with ischemic cerebrovascular disease (Peacock et al., 1993), and in a 104-year-old patient with dementia who had hippocampal sclerosis and little Aβ accumulation (Kero et al., 2013). Whereas other, pathogenic, variants in *APP* increases Aβ production (Kero et al., 2013), the A673T variant has by means of in vivo and in vitro studies, been shown to be protective by inhibiting b-site cleaving enzyme 1 cleavage and reducing Aβ production and even decreasing Aβ aggregation (Kero et al., 2013; Maloney et al., 2014).

In this study, we aimed to investigate whether the A673T variant is related to longevity and cognitive functioning among Danes. We used four Danish study populations including middle-aged Danish twins aged 46–55 years and three cohorts of oldest-olds aged 92–100 years.

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0197-4580/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2015.07.011

2. Materials and methods

2.1. Subjects

The participants included in this study were drawn from four population-based nationwide surveys conducted at the University of Southern Denmark: The Danish 1905-Birth Cohort Study (Nybo et al., 2001), the Danish 1910-Birth Cohort Study (Vestergaard et al., In press), the Danish 1915-Birth Cohort Study (Christensen et al., 2013), and a study of the middle-aged Danish twins (Skytthe et al., 2013).

The Danish 1905-Birth Cohort Study is a prospective investigation of an entire Danish birth cohort. The survey was initiated in 1998, when the participants were 92–93 years old and followed by three follow-up studies of the participating survivors in 2000, 2003, and 2005. Of the 3600 individuals still alive at intake, 2262 participated and 1651 provided either a blood-spot sample or a cheek swap at their first assessment in 1998. The Danish 1910 and 1915 birth cohort studies include Danes born in 1910 and 1915, respectively, who were alive and living in Denmark on September 1st, 2010. Among 400 invited participants from the 1910-Birth Cohort Study, 273 participated and 176 provided blood samples. In the 1915-Birth Cohort Study, 2509 individuals were identified as eligible participants when they were 95 years old, 1584 individuals participated and 1165 individuals provided biological samples (Christensen et al., 2013). Each of the surveys in the cohort studies comprises multidimensional face-to-face interviews and assessments of cognitive and physical functioning. The middle-aged Danish twins were aged 46–67 years when the study was initiated in 1998 (Gaist et al., 2000). A total of 40 monozygotic twin pairs, 40 dizygotic twin pairs, and 40 twin pairs of opposite sex for each birth year between 1931 and 1952 were included in the cohort. The participants were revisited from 2008 to 2011 and blood was donated during the 10–14 year later reassessment (Skytthe et al., 2013). Only one individual from each twin pair was included in the genotyping of the middle-aged participants, who represented younger controls in this study. The middle-aged Danish twins were assessed by a battery of cognitive tests and physical evaluations. Among the tests were a cognitive composite score of working memory and speed, a depression score (Cambridge Mental Disorders of the Elderly Examination), self-rated health, and a grip strength assessment, as described in details elsewhere (Vestergaard et al., 2015). Written informed consents were obtained from all participants and all four surveys were approved by the Regional Scientific Ethical Committees for Southern Denmark.

2.2. Genotyping and quality control

DNA was extracted either from blood spots cards using the QIAamp DNA Mini and Micro Kit (Qiagen, Hilden, Germany) or from whole blood using a salting out method as previously described (Deelen et al., 2014; Miller et al., 1988). DNA was genotyped for the variant rs63750847 (A673T) by allelic discrimination using the predesigned Taqman single nucleotide polymorphism genotyping assay C_89522366_10 (Life Technologies). Reactions were conducted as recommended by the manufacturer. Polymerase chain reaction was performed in the StepOnePlus Real-Time PCR system and genotypes called using the StepOne software version 2.1 (Life Technologies). DNA from two previously identified APP A673T heterozygous carriers were used as positive controls for technical validation of the methodology. The presence of the APP A673T variant was confirmed in an independent DNA sample by Sanger sequencing according to the previous protocol (Kero et al., 2013).

2.3. Statistically analyses

Statistical analyses were performed using STATA 10.1 (StataCorp, TX, USA). Allelic frequencies were estimated from data in six of eigth previous articles found by searching the NCBI (PubMed) database for the terms A673T and APP. Two articles were excluded as they did not contain population data. Data from Finland available at http://exac.broadinstitute.org/variant/21-27269932-C-T was included in the frequency estimation. *p* Values for comparison of allele frequencies were obtained using Fisher's exact test and binominal confidence intervals were calculated for allele frequencies.

3. Results

3.1. Rarity of the APP A673T variant

The study included participants from three cohorts of oldest-old born in 1905, 1910, or 1915 and a younger population of unrelated middle-age twins (aged 46–55 years). The APP 673T variant was found in only 1 of 744 unrelated individuals in the middle-aged group, while none of the oldest-old from the 1905 cohort (N = 1462, aged 92–93 years) or the 1910 and 1915 cohorts (N = 1281, aged 95+ years) carried the variant. No association with longevity was found in the cross-sectional design (Fisher's exact *p*-value: 0.21), but it is clear that this analysis is not powerful enough to make any

Table 1
Population frequencies of the APP A673T variant by country

Country	Allelic frequency, %	Population size	Difference in frequency from the Danes, %	Fisher exact, *p*-value	Reference
Denmark	0.014	3.487	—	—	Present work
Iceland	0.44	82.296	0.43	<0.001	Jonsson et al., 2012
Norway	0.21	712	0.20	0.017	Jonsson et al., 2012
Sweden	0.42	390	0.41	<0.001	Jonsson et al., 2012
	0.10	1.569	0.09	0.09	Wang et al., 2015
				0.004[a]	
Finland	0.52	590	0.50	<0.001	Jonsson et al., 2012
	0.10	515	0.09	0.24	Kero et al., 2013
	0.27	3307	0.26	<0.001	http://exac.broadinstitute.org/variant/21-27269932-C-T
				0.001[a]	
USA	0.007	14.355	−0.007	0.48	Wang et al., 2015
	0	4.318	−0.014	0.45	Bamne et al., 2014
				0.40[a]	
China	0	8.721	−0.014	0.29	Ting et al., 2013
	0	2.641	−0.014	0.57	Liu et al., 2014
				0.24[a]	

Frequencies are compared to the Danish combined cohort.
[a] Combined test by country.

conclusions. We reviewed the existing literature on APP 673T and population data that display differences between countries (Table 1). Interestingly, the allelic frequency in the Danes of 0.014% (95% CI 0.000%; 0.080%) was lower than those of the other Nordic countries, which was averaged to 0.42% (95% CI 0.39%; 0.46%) but slightly higher than in more geographically distant populations from North America and China.

3.2. Twins heterozygous of the APP A673T variant

We tested the genotype for the twin partner of the only APP 673T heterozygote found in the sample of middle-aged individuals. As both of these male twins were heterozygous, their cognitive as well as physical performances were evaluated against the remaining study sample of similar age as the twins were three years older than the average age of the group. On the cognitive tests none of the twins showed signs of dementia (Cognitive composite score: 10.2; +1.5 standard deviation [SD] and Cognitive composite score: 4.1; −0.4 SD) or depression, as they were among the 36% of the participants who performed best on the Cambridge Mental Disorders of the Elderly Examination. Also, both twins rated their own health as "very good" such as 42% of the cohort participants, and their physical performances were slightly better than the average male (grip strength: 55, +0.6 SD and 55, +0.6 SD).

4. Discussion

Among the middle-age Danes, we observed an allelic frequency of 0.014% for the APP A673T variant, which is significantly lower than the frequencies previously reported in the other Nordic countries. Surprisingly none of the genotyped 2743 oldest-old Danes carried the allele. The rarity of this variant in Danes precludes any conclusions on its association with longevity.

The Nordic allelic frequencies were initially demonstrated to range from 0.44% (95% CI 0.41%; 0.47%) in Iceland to 0.21% (95% CI 0.04%; 0.62%) in Norway (Jonsson et al., 2012). Later studies, however, reported slightly lower frequencies in Nordic populations but these were not as low as the frequency seen in the Danes in the present work (Kero et al., 2013; Wang et al., 2015). However, more geographically distant population, that is, Northern Americans and Chinese reported even lower frequencies than in the Danes (Bamne et al., 2014; Liu et al., 2014; Ting et al., 2013).

In the study by Jonsson et al., an enrichment of the APP 674T allele in elderly was observed and they estimated that the odds for rs63750847-A carriers of reaching age 85 years was 1.47-fold the odds of noncarriers when unadjusted for cohort differences (Jonsson et al., 2012). However, we could not confirm this finding in the present work because of the rarity of the allele, as was also the case in a Chinese longevity study (Liu et al., 2014). If the estimated risk protection against Alzheimer (1/odds ratio of approximately 5) for the APP A674T variant is true as previously suggested (Jonsson et al., 2012; Wang et al., 2015), then it is on an individual level numerically as important as, or even more important, than that of the apolipoprotein e4 allele (Alzgene database).

The low APP A674T allelic frequency among the Danes is surprising, given that, the Nordic populations are usually considered highly genetically similar, but at this state, we have no obvious explanation for the dissimilarity. It can be speculated that the higher frequency in the northern part of the Nordic countries than in the southern part is due to genetic drift, although we can not rule out that other hypothesis such as natural selection is an option. Yet other genetic difference, that is, apolipoprotein e2 and e4 alleles are known to vary in frequency between European countries with higher frequencies in the northern European countries and even between Nordic countries differences have been reported (Ewbank, 2004; Gerdes et al., 2000). Furthermore, recent fine-scale genetic structures have likewise demonstrated genetic differences between Nordic countries (Leslie et al., 2015).

In conclusion, we showed that the APP A673T variant is rarer in Denmark than other Nordic countries. In light of the rarity, we found no signs of association with longevity or cognitive function.

Disclosure statement

The authors have no conflicts of interest to disclose.

Acknowledgements

The authors thank Lilja Jansson and Steen Gregersen for technical assistance. The study was supported by a grant from the US National Institutes of Health/National Institute on Aging, Grant No. P01 AG08761; by a grant from The Danish Agency for Science, Technology and Innovation, Grant No. 09–070081, the INTERREG 4 A programme Syddanmark-Schleswig-K.E.R.N, the European Union's Seventh Framework Programme (FP7/2007–2011) under grant agreement n° 259679 and by grants from the Brødrene Hartmanns, Hørslev Fonden, A.P. Møller og Hustru Chastine MC-kinney Møllers foundations, and the Helsinki University Central Hospital. The Danish Aging Research Center is supported by a grant from the VELUX Foundation.

References

Bamne, M.N., Demirci, F.Y., Berman, S., Snitz, B.E., Rosenthal, S.L., Wang, X., Lopez, O.L., Kamboh, M.I., 2014. Investigation of an amyloid precursor protein protective mutation (A673T) in a North American case-control sample of late-onset Alzheimer's disease. Neurobiol. Aging 35, 1779.e15–1779.e16.

Christensen, K., Thinggaard, M., Oksuzyan, A., Steenstrup, T., Andersen-Ranberg, K., Jeune, B., McGue, M., Vaupel, J.W., 2013. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. Lancet 382, 1507–1513.

Deelen, J., Beekman, M., Uh, H.W., Broer, L., Ayers, K.L., Tan, Q., Kamatani, Y., Bennet, A.M., Tamm, R., Trompet, S., Guethbjartsson, D.F., Flachsbart, F., Rose, G., Viktorin, A., Fischer, K., Nygaard, M., Cordell, H.J., Crocco, P., van den Akker, E.B., Bohringer, S., Helmer, Q., Nelson, C.P., Saunders, G.I., Alver, M., Andersen-Ranberg, K., Breen, M.E., van der Breggen, R., Caliebe, A., Capri, M., Cevenini, E., Collerton, J.C., Dato, S., Davies, K., Ford, I., Gampe, J., Garagnani, P., de Geus, E.J., Harrow, J., van Heemst, D., Heijmans, B.T., Heinsen, F.A., Hottenga, J.J., Hofman, A., Jeune, B., Jonsson, P.V., Lathrop, M., Lechner, D., Martin-Ruiz, C., McNerlan, S.E., Mihailov, E., Montesanto, A., Mooijaart, S.P., Murphy, A., Nohr, E.A., Paternoster, L., Postmus, I., Rivadeneira, F., Ross, O.A., Salvioli, S., Sattar, N., Schreiber, S., Stefansson, H., Stott, D.J., Tiemeier, H., Uitterlinden, A.G., Westendorp, R.G., Willemsen, G., Samani, N.J., Galan, P., Sorensen, T.I., Boomsma, D.I., Jukema, J.W., Rea, I.M., Passarino, G., de Craen, A.J., Christensen, K., Nebel, A., Stefansson, K., Metspalu, A., Magnusson, P., Blanche, H., Christiansen, L., Kirkwood, T.B., van Duijn, C.M., Franceschi, C., Houwing-Duistermaat, J.J., Slagboom, P.E., 2014. Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age. Hum. Mol. Genet. 23, 4420–4432.

Ewbank, D.C., 2004. The APOE gene and differences in life expectancy in Europe. J. Gerontol. A Biol. Sci. Med. Sci. 59, 16–20.

Gaist, D., Bathum, L., Skytthe, A., Jensen, T.K., McGue, M., Vaupel, J.W., Christensen, K., 2000. Strength and anthropometric measures in identical and fraternal twins: no evidence of masculinization of females with male co-twins. Epidemiology 11, 340–343.

Gerdes, L.U., Jeune, B., Ranberg, K.A., Nybo, H., Vaupel, J.W., 2000. Estimation of apolipoprotein E genotype-specific relative mortality risks from the distribution of genotypes in centenarians and middle-aged men: apolipoprotein E gene is a "frailty gene," not a "longevity gene". Genet. Epidemiol. 19, 202–210.

Jansen, W.J., Ossenkoppele, R., Knol, D.L., Tijms, B.M., Scheltens, P., Verhey, F.R., Visser, P.J., Amyloid Biomarker Study, G, Aalten, P., Aarsland, D., Alcolea, D., Alexander, M., Almdahl, I.S., Arnold, S.E., Baldeiras, I., Barthel, H., van Berckel, B.N., Bibeau, K., Blennow, K., Brooks, D.J., van Buchem, M.A., Camus, V., Cavedo, E., Chen, K., Chetelat, G., Cohen, A.D., Drzezga, A., Engelborghs, S., Fagan, A.M., Fladby, T., Fleisher, A.S., van der Flier, W.M., Ford, L., Forster, S., Fortea, J., Foskett, N., Frederiksen, K.S., Freund-Levi, Y., Frisoni, G.B., Froelich, L., Gabryelewicz, T., Gill, K.D., Gkatzima, O., Gomez-Tortosa, E., Gordon, M.F., Grimmer, T., Hampel, H., Hausner, L., Hellwig, S., Herukka, S.K., Hildebrandt, H., Ishihara, L., Ivanoiu, A., Jagust, W.J., Johannsen, P., Kandimalla, R., Kapaki, E., Klimkowicz-Mrowiec, A., Klunk, W.E., Kohler, S., Koglin, N., Kornhuber, J.,

Kramberger, M.G., Van Laere, K., Landau, S.M., Lee, D.Y., de Leon, M., Lisetti, V., Lleo, A., Madsen, K., Maier, W., Marcusson, J., Mattsson, N., de Mendonca, A., Meulenbroek, O., Meyer, P.T., Mintun, M.A., Mok, V., Molinuevo, J.L., Mollergard, H.M., Morris, J.C., Mroczko, B., Van der Mussele, S., Na, D.L., Newberg, A., Nordberg, A., Nordlund, A., Novak, G.P., Paraskevas, G.P., Parnetti, L., Perera, G., Peters, O., Popp, J., Prabhakar, S., Rabinovici, G.D., Ramakers, I.H., Rami, L., Resende de Oliveira, C., Rinne, J.O., Rodrigue, K.M., Rodriguez-Rodriguez, E., Roe, C.M., Rot, U., Rowe, C.C., Ruther, E., Sabri, O., Sanchez-Juan, P., Santana, I., Sarazin, M., Schroder, J., Schutte, C., Seo, S.W., Soetewey, F., Soininen, H., Spiru, L., Struyfs, H., Teunissen, C.E., Tsolaki, M., Vandenberghe, R., Verbeek, M.M., Villemagne, V.L., Vos, S.J., van Waalwijk van Doorn, L.J., Waldemar, G., Wallin, A., Wallin, A.K., Wiltfang, J., Wolk, D.A., Zboch, M., Zetterberg, H., 2015. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 313, 1924–1938.

Jonsson, T., Atwal, J.K., Steinberg, S., Snaedal, J., Jonsson, P.V., Bjornsson, S., Stefansson, H., Sulem, P., Gudbjartsson, D., Maloney, J., Hoyte, K., Gustafson, A., Liu, Y., Lu, Y., Bhangale, T., Graham, R.R., Huttenlocher, J., Bjornsdottir, G., Andreassen, O.A., Jonsson, E.G., Palotie, A., Behrens, T.W., Magnusson, O.T., Kong, A., Thorsteinsdottir, U., Watts, R.J., Stefansson, K., 2012. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 488, 96–99.

Kero, M., Paetau, A., Polvikoski, T., Tanskanen, M., Sulkava, R., Jansson, L., Myllykangas, L., Tienari, P.J., 2013. Amyloid precursor protein (APP) A673T mutation in the elderly Finnish population. Neurobiol. Aging 34, 1518.e1–1518.e3.

Kutoku, Y., Ohsawa, Y., Kuwano, R., Ikeuchi, T., Inoue, H., Ataka, S., Shimada, H., Mori, H., Sunada, Y., 2015. A second pedigree with amyloid-less familial Alzheimer's disease harboring an identical mutation in the amyloid precursor protein gene (E693delta). Intern. Med. 54, 205–208.

Leslie, S., Winney, B., Hellenthal, G., Davison, D., Boumertit, A., Day, T., Hutnik, K., Royrvik, E.C., Cunliffe, B., Wellcome Trust Case Control, C., International Multiple Sclerosis Genetics, C., Lawson, D.J., Falush, D., Freeman, C., Pirinen, M., Myers, S., Robinson, M., Donnelly, P., Bodmer, W., 2015. The fine-scale genetic structure of the British population. Nature 519, 309–314.

Liu, Y.W., He, Y.H., Zhang, Y.X., Cai, W.W., Yang, L.Q., Xu, L.Y., Kong, Q.P., 2014. Absence of A673T variant in APP gene indicates an alternative protective mechanism contributing to longevity in Chinese individuals. Neurobiol. Aging 35, 935.e11–935.e12.

Maloney, J.A., Bainbridge, T., Gustafson, A., Zhang, S., Kyauk, R., Steiner, P., van der Brug, M., Liu, Y., Ernst, J.A., Watts, R.J., Atwal, J.K., 2014. Molecular mechanisms of Alzheimer disease protection by the A673T allele of amyloid precursor protein. J. Biol. Chem. 289, 30990–31000.

Miller, S.A., Dykes, D.D., Polesky, H.F., 1988. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 16, 1215.

Nybo, H., Gaist, D., Jeune, B., Bathum, L., McGue, M., Vaupel, J.W., Christensen, K., 2001. The Danish 1905 cohort: a genetic-epidemiological nationwide survey. J. Aging Health 13, 32–46.

Peacock, M.L., Warren Jr., J.T., Roses, A.D., Fink, J.K., 1993. Novel polymorphism in the A4 region of the amyloid precursor protein gene in a patient without Alzheimer's disease. Neurology 43, 1254–1256.

Skytthe, A., Christiansen, L., Kyvik, K.O., Bodker, F.L., Hvidberg, L., Petersen, I., Nielsen, M.M., Bingley, P., Hjelmborg, J., Tan, Q., Holm, N.V., Vaupel, J.W., McGue, M., Christensen, K., 2013. The Danish Twin Registry: linking surveys, national registers, and biological information. Twin Res. Hum. Genet. 16, 104–111.

Ting, S.K., Chong, M.S., Kandiah, N., Hameed, S., Tan, L., Au, W.L., Prakash, K.M., Pavanni, R., Lee, T.S., Foo, J.N., Bei, J.X., Yu, X.Q., Liu, J.J., Zhao, Y., Lee, W.L., Tan, E.K., 2013. Absence of A673T amyloid-beta precursor protein variant in Alzheimer's disease and other neurological diseases. Neurobiol. Aging 34, 2441.e7–2441.e8.

Vestergaard S, A.-R.K., Skytthe A, Christensen K, Robine J-M., Jeune, B. In press. Health and function assessments in two adjacent Danish birth cohorts of centenarians: impact of design and methodology. Eur. J. Ageing.

Vestergaard, S., Thinggaard, M., Jeune, B., Vaupel, J.W., McGue, M., Christensen, K., 2015. Physical and mental decline and yet rather happy? A study of Danes aged 45 and older. Aging Ment. Health 19, 400–408.

Wang, L.S., Naj, A.C., Graham, R.R., Crane, P.K., Kunkle, B.W., Cruchaga, C., Murcia, J.D., Cannon-Albright, L., Baldwin, C.T., Zetterberg, H., Blennow, K., Kukull, W.A., Faber, K.M., Schupf, N., Norton, M.C., Tschanz, J.T., Munger, R.G., Corcoran, C.D., Rogaeva, E., Lin, C.F., Dombroski, B.A., Cantwell, L.B., Partch, A., Valladares, O., Hakonarson, H., St George-Hyslop, P., Green, R.C., Goate, A.M., Foroud, T.M., Carney, R.M., Larson, E.B., Behrens, T.W., Kauwe, J.S., Haines, J.L., Farrer, L.A., Pericak-Vance, M.A., Mayeux, R., Schellenberg, G.D., National Institute on Aging-Late-Onset Alzheimer's Disease Family, S., Alzheimer's Disease Genetics, C., Albert, M.S., Albin, R.L., Apostolova, L.G., Arnold, S.E., Barber, R., Barmada, M.M., Barnes, L.L., Beach, T.G., Becker, J.T., Beecham, G.W., Beekly, D., Bennett, D.A., Bigio, E.H., Bird, T.D., Blacker, D., Boeve, B.F., Bowen, J.D., Boxer, A., Burke, J.R., Buxbaum, J.D., Cairns, N.J., Cao, C., Carlson, C.S., Carroll, S.L., Chui, H.C., Clark, D.G., Cribbs, D.H., Crocco, E.A., DeCarli, C., DeKosky, S.T., Demirci, F.Y., Dick, M., Dickson, D.W., Duara, R., Ertekin-Taner, N., Fallon, K.B., Farlow, M.R., Ferris, S., Frosch, M.P., Galasko, D.R., Ganguli, M., Gearing, M., Geschwind, D.H., Ghetti, B., Gilbert, J.R., Glass, J.D., Graff-Radford, N.R., Growdon, J.H., Hamilton, R.L., Hamilton-Nelson, K.L., Harrell, L.E., Head, E., Honig, L.S., Hulette, C.M., Hyman, B.T., Jarvik, G.P., Jicha, G.A., Jin, L.W., Jun, G., Kamboh, M.I., Karydas, A., Kaye, J.A., Kim, R., Koo, E.H., Kowall, N.W., Kramer, J.H., Kramer, P., LaFerla, F.M., Lah, J.J., Leverenz, J.B., Levey, A.I., Li, G., Lieberman, A.P., Lopez, O.L., Lunetta, K.L., Lyketsos, C.G., Mack, W.J., Marson, D.C., Martin, E.R., Martiniuk, F., Mash, D.C., Masliah, E., McCormick, W.C., McCurry, S.M., McDavid, A.N., McKee, A.C., Mesulam, M.M., Miller, B.L., Miller, C.A., Miller, J.W., Montine, T.J., Morris, J.C., Murrell, J.R., Olichney, J.M., Parisi, J.E., Perry, W., Peskind, E., Petersen, R.C., Pierce, A., Poon, W.W., Potter, H., Quinn, J.F., Raj, A., Raskind, M., Reiman, E.M., Reisberg, B., Reitz, C., Ringman, J.M., Roberson, E.D., Rosen, H.J., Rosenberg, R.N., Sano, M., Saykin, A.J., Schneider, J.A., Schneider, L.S., Seeley, W.W., Smith, A.G., Sonnen, J.A., Spina, S., Stern, R.A., Tanzi, R.E., Thornton-Wells, T.A., Trojanowski, J.Q., Troncoso, J.C., Tsuang, D.W., Van Deerlin, V.M., Van Eldik, L.J., Vardarajan, B.N., Vinters, H.V., Vonsattel, J.P., Weintraub, S., Welsh-Bohmer, K.A., Williamson, J., Wishnek, S., Woltjer, R.L., Wright, C.B., Younkin, S.G., Yu, C.E., Yu, L., 2015. Rarity of the Alzheimer disease-protective APP A673T variant in the United States. JAMA Neurol. 72, 209–216.

Zhang, Y.W., Thompson, R., Zhang, H., Xu, H., 2011. APP processing in Alzheimer's disease. Mol. Brain 4, 3.