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The APP A673T frequency differs between Nordic countries

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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 (AD) 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, due to the extreme rarity of A673T in non-Nordic populations the association with AD have not yet been formally replicated. Since 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 one out 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.

Keywords

Alzheimers; Aging; Dementia; Amyloid beta; Cognition

Introduction

Accumulated amyloid plaques are a central pathological feature of Alzheimer's Disease (AD) and the main proteinaceous components are amyloid-beta peptides. Amyloid-beta peptide (Aβ) is formed through sequential proteolytic processing of the amyloid beta (A4)

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precursor protein (APP) by the b-site APP cleaving enzyme 1 (BACE1) 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 poly-peptides 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. The majority 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 non-carriers 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 BACE1 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 46-55 year of age and three cohorts of oldest olds 92-100 year of age.

Materials and Methods

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 S and Jeune, 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 3,600 individuals still alive at intake, 2,262 participated, and 1,651 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, 2,509 individuals were identified as eligible participants when they were 95 years old, 1,584 individuals participated and 1,165 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 46-67 years of age 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 re-visited from 2008-2011 and blood was donated during the 10-14 years later re-assessment (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.

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 pre-designed Taqman® SNP genotyping assay C_89522366_10 (Life Technologies). Reactions were conducted as recommended by the manufacturer. PCR was performed in the Step One Plus™ Real-Time PCR system and genotypes called using the Step One™ 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).

Statistically analyses

Statistical analyses were performed using STATA 10.1 (StataCorp, Texas, USA). Allelic frequencies were estimated from data in six out of eight previous papers found by searching the NCBI (PubMed) database for the terms A673T and APP. Two papers 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.

Results

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 (46-55 years of age). 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, 92-93 years of age) or the 1910 and 1915 cohorts (N=1281, 95+ years of age) carried the variant. No association with longevity was found in the cross sectional design (fishers exact p-value: 0.21), but it is clear that this analysis is not powerful enough to make any 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.

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 (CCS: 10.2; +1.5 SD and CCS: 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” like 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).

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 i.e. 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 and co-worker 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 was 1.47-fold the odds of non-carriers when unadjusted for cohort differences (Jonsson, et al., 2012). However, we could not confirm this finding in the present work due to 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/OR 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 APOE 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 i.e. APOE 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.

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We investigated whether the A673T variant is related to longevity and cognitive functioning among Danes.

We used four Danish study populations including middle-aged Danish twins 46-55 year of age and three cohorts of oldest olds 92-100 year of age.

The A673T variant was significantly rarer in Danes than other Nordic countries.

No significant association with longevity or cognitive functioning was observed among Danes.

Table 1

Population frequencies of the APP A673T variant by country. Frequencies are compared to the Danish combined cohort.

	Allelic frequency	Population Size	Difference in frequency from the Danes	Fishers exact	Reference
Country				**p-value**	
Denmark	0.014%	3.487	-	-	Present work
Iceland	0.44%	82.296	0.43%	<0.001	Johnson *et al.* 2012
Norway	0.21%	712	0.20%	0.017	Johnson *et al.* 2012
Sweden	0.42%	390	0.41%	<0.001	Johnson *et al.* 2012
	0.10%	1.569	0.09%	0.09	Wang *et al.* 2015
				0.004*	
Finland	0.52%	590	0.50%	<0.001	Johnson *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*	
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*	
China	0%	8.721	-0.014%	0.29	Ting *et al.* 2013
	0%	2.641	-0.014%	0.57	Lui *et al.* 2014
				0.24*	

* combined test by country.