Original Investigation

Rarity of the Alzheimer Disease–Protective *APP* A673T Variant in the United States

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IMPORTANCE Recently, a rare variant in the amyloid precursor protein gene (*APP*) was described in a population from Iceland. This variant, in which alanine is replaced by threonine at position 673 (A673T), appears to protect against late-onset Alzheimer disease (AD). We evaluated the frequency of this variant in AD cases and cognitively normal controls to determine whether this variant will significantly contribute to risk assessment in individuals in the United States.

OBJECTIVE To determine the frequency of the *APP* A673T variant in a large group of elderly cognitively normal controls and AD cases from the United States and in 2 case-control cohorts from Sweden.

DESIGN, SETTING, AND PARTICIPANTS Case-control association analysis of variant *APP* A673T in US and Swedish white individuals comparing AD cases with cognitively intact elderly controls. Participants were ascertained at multiple university-associated medical centers and clinics across the United States and Sweden by study-specific sampling methods. They were from case-control studies, community-based prospective cohort studies, and studies that ascertained multiplex families from multiple sources.

MAIN OUTCOMES AND MEASURES Genotypes for the *APP* A673T variant were determined using the Infinium HumanExome V1 Beadchip (Illumina, Inc) and by TaqMan genotyping (Life Technologies).

RESULTS The A673T variant genotypes were evaluated in 8943 US AD cases, 10 480 US cognitively normal controls, 862 Swedish AD cases, and 707 Swedish cognitively normal controls. We identified 3 US individuals heterozygous for A673T, including 1 AD case (age at onset, 89 years) and 2 controls (age at last examination, 82 and 77 years). The remaining US samples were homozygous for the alanine (A673) allele. In the Swedish samples, 3 controls were heterozygous for A673T and all AD cases were homozygous for the A673 allele. We also genotyped a US family previously reported to harbor the A673T variant and found a mother-daughter pair, both cognitively normal at ages 72 and 84 years, respectively, who were both heterozygous for A673T; however, all individuals with AD in the family were homozygous for A673.

CONCLUSIONS AND RELEVANCE The A673T variant is extremely rare in US cohorts and does not play a substantial role in risk for AD in this population. This variant may be primarily restricted to Icelandic and Scandinavian populations.

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The amyloid precursor protein gene (*APP*; GenBank NC_011512) encodes a transmembrane protein of unknown normal function. In the normal processing of the APP protein, proteolytic cleavage yields a 39- to 43-amino acid peptide called β-amyloid (Aβ). Release of Aβ from APP is catalyzed by the β-site APP cleaving enzyme 1 (BACE1) that cleaves APP at the N-terminal end of Aβ and by the γ-secretase complex that cleaves at the C-terminal end.[1] Together, these 2 proteases generate the Aβ peptide. In Alzheimer disease (AD), Aβ accumulates in extracellular amyloid plaques that are characteristic of this disease. Mutations in *APP* cluster around the N-terminal and C-terminal sequences that encode Aβ and cause early-onset AD. Likewise, early-onset AD is also caused by mutations in the presenilin 1 gene (*PSEN1*) and presenilin 2 gene (*PSEN2*), which encode protease subunits of the γ-secretase complex.[1] Genetic studies and a large body of functional evidence convincingly show that Aβ is a toxic molecule critical to the pathogenesis of AD. As a result, multiple drug trials are in progress designed to stimulate Aβ clearance using immunological approaches or to inhibit Aβ production using small-molecule inhibitors of γ-secretase or BACE1.[2-5]

Recently, Jonsson et al[6] reported that the *APP* coding mutation A673T, in which alanine is replaced by threonine at position 673, is protective against late-onset AD. This rare variant was enriched in Icelandic elderly controls compared with AD cases from the same population. The frequency was 0.13% in AD cases and ranged from 0.45% to 0.79% in controls, depending on age. The A673T variant was also observed in an individual with ischemic cerebrovascular disease but not AD[7] and in a 104-year-old patient with dementia who had hippocampal sclerosis and little Aβ accumulation.[8] The A673T variant is located at position 2 of Aβ and thus is immediately downstream of the BACE1 cleavage site. Ex vivo and in vitro experiments show that this variant inhibits BACE1 cleavage and results in reduced Aβ production. Another mutation at this site, A673V, enhances BACE1 cleavage activity[9,10] and is a recessive mutation causing early-onset AD. Likewise, the K670N/M671L mutation that affects the 2 amino acids immediately upstream of the BACE1 cleavage site also enhances BACE1 cleavage, increases Aβ production, and causes early-onset AD.[11] Thus, multiple mutations in close proximity to the BACE1 cleavage site influence risk for AD and Aβ production.

We genotyped a large number of AD cases and controls to determine whether the A673T mutation is an important protective variant in cognitively intact elderly US white individuals and in patients with AD from the same population. We found that this variant is extremely rare and does not have a discernible impact on AD risk in the US population.

Methods

Genotyping

We genotyped the samples listed in **Table 1** using the Infinium HumanExome V1 Beadchip (Illumina, Inc). Genotyping was performed for 8410 individuals at the Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Medical Research, Manhasset, New York, 1990 individuals at the John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida, and 6166 individuals at the Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. Genotypes were initially called using the default clustering profile from Illumina and recalled using clustering profiles generated by Genentech using data from 30 000 samples. We also genotyped the individuals listed in **Table 2** for single-nucleotide polymorphism rs63750847 using the TaqMan assay C_89522366_10 (Life Technologies) and a 384-well plate format. Each plate contained samples from 2 heterozygotes from the exome array experiments. For both the exome array assay and the TaqMan assay, manual inspection of clustering indicated both were valid assays (eFigure 1 in the Supplement).

Participants

The National Institute on Aging Alzheimer's Disease Centers case-control sample, the University of Toronto/GlaxoSmithKline (also called Gen ADA) case-control sample, the Vanderbilt/Miami/Mount Sinai case-control sample, the National Institute on Aging–Late-Onset Alzheimer's Disease multiplex family-based sample, the National Cell Repository for Alzheimer's Disease multiplex family-based sample, the Multi-institutional Research in Alzheimer's Genetic Epidemiology family-based sample, and the Adult Changes in Thought (ACT) prospective cohort were described previously.[12,13] The Genetics Differences cohort is a population-based prevalent case-control study from the same population as the ACT study.[14] The Washington Heights-Inwood Columbia Aging Project sample is a multiethnic prospective cohort[15]; for this study, only white individuals were genotyped. The Washington University cohort is a white case-control cohort.[13] The Miami multiplex families and the National Institute of Mental Health multiplex families were as previously described.[16-18] The Cache County Study on Memory Health and Aging is a population-based study with 4 assessments of cognitive function since 1994.[19] The Swedish cohorts are case-control studies recruited from neuropsychiatric clinics in Sweden as described previously.[20] For the family-based sample, we genotyped a single affected individual from each kindred. All studies were approved by institutional review boards at the respective universities involved in each study, and the overall study was approved by the University of Pennsylvania institutional review board. The participants provided written informed consent.

Analysis

The exome chip genotyping data (16 525 samples total) were first preprocessed using quality check steps adapted from Naj et al.[13] Briefly, we excluded 881 samples and markers with a missing call rate higher than 2%, samples with genotype-imputed or reported sex mismatch, and markers significant ($P < 10^{-6}$) in either Hardy-Weinberg or informative missingness tests. We pruned 969 samples by relatedness test ($\hat{\pi} > 0.4$ using 15 086 linkage disequilibrium-pruned autosomal markers with a minor allele frequency >0.1) and compared samples with HapMap 3 data to exclude nonwhite individuals. We checked population substructure in 15 644 samples with good call rates using 5848 single-nucleotide polymorphisms that

Table 1. Samples Genotyped for A673T (rs63750847) With the Exome Array That Passed Quality Checking

Characteristic	Cohort											
	ADC[a]	University of Toronto/ GSK[b]	Miami[c]	NIMH[b]	NIA-LOAD[b]	NCRAD[b]	MIRAGE[b]	Genetic Differences[b]	ACT[b]	WHICAP[b]	Washington University[d]	Total
Samples, No. (A673T heterozygotes, No.)												
Cases	3930 (0)	152 (0)	936 (0)	354 (0)	749 (0)	395 (0)	576 (0)	239 (0)	282 (1)	54 (0)	554 (0)	8221 (1)
Controls	2326 (0)	0	995 (0)	0	458 (0)	0	12 (0)	216 (0)	1445 (1)	322 (0)	360 (0)	6134 (1)
Total	6256 (0)	152 (0)	1931 (0)	354 (0)	1207 (0)	395 (0)	588 (0)	455 (0)	1727 (2)	376 (0)	914 (0)	14 355 (2)
Male, %	43.6	46.1	38.5	28.0	39.4	31.9	38.4	35.8	43.4	39.9	40.4	41.1
Case age at onset												
Mean (SD), y	72.4 (9.3)	77.8 (6.8)	72.6 (7.1)	71.6 (8.1)	73.8 (7.2)	71.0 (8.5)	68.6 (8.7)	76.4 (6.2)	83.7 (4.7)	84.5 (7.2)	79.8 (9.7)	73.4 (9.1)
No.	3930	152	885	354	749	393	572	239	282	54	554	6130
Control age at last examination												
Mean (SD), y	77.2 (9.3)	NA	73.5 (7.9)	NA	79.6 (8.7)	NA	76.1 (7.8)	80.8 (6.6)	81.6 (6.1)	81.0 (6.1)	74.6 (8.7)	78.0 (8.6)
No.	2326	NA	991	NA	458	NA	12	216	1445	322	360	8164
Cohort type	Case-control	Case-control	Case-control	Multiplex families	Multiplex families	Multiplex families	Multiplex families	Population-based incident cases with matched controls	Prospective cohort	Prospective cohort	Case-control	

Abbreviations: ACT, Adult Changes in Thought; ADC, Alzheimer's Disease Centers; GSK, GlaxoSmithKline; MIRAGE, Multi-institutional Research in Alzheimer's Genetic Epidemiology; NA, not applicable; NCRAD, National Cell Repository for Alzheimer's Disease; NIA-LOAD, National Institute on Aging–Late-Onset Alzheimer's Disease; NIMH, National Institute of Mental Health; WHICAP, Washington Heights–Inwood Columbia Aging Project.

[a] In this cohort, 3640 cases and 2223 controls were genotyped at the Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Medical Research, Manhasset, New York (as 2 batches) and 282 cases and 103 controls were genotyped at the Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

[b] Genotyped at the Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

[c] Genotyped at the John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida.

[d] Genotyped at the Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Medical Research.

were present on both the exome array and in the HapMap 3 data set. Forty-nine individuals were likely to be from nonwhite or admixed populations. Two hundred seventy-three individuals were excluded owing to incomplete diagnosis information. In all, 14 355 individuals (8221 cases and 6134 controls) passed quality check. Five hundred eighty-five individuals were younger than 60 years at onset (512 AD cases) or at last visit (34 controls); 61 samples lacked age information.

Genotypes for rs63750847 (A673T; c.G2017>A) were ascertained via the exm1563596 marker (major/minor allele: G/A, 100% call rate after quality check). One sample with the A/A genotype was excluded owing to a very high missing call rate (20.84%). Two samples passing quality check carried the A/G genotype.

Results

A total of 8221 AD cases and 6134 elderly cognitively normal controls were genotyped using Illumina exome arrays (Table 1). These arrays have single-nucleotide polymorphism assays for more than 240 000 exonic variants that are nonsynonymous, nonsense, or splice-site variants. The exome array has an assay for rs63750847, which is the A673T variant discussed earlier (eFigure 2 in the Supplement). We identified 2 heterozygotes, one in a sample from an AD case (minor allele frequency = 0.0061%) of Russian ancestry who had onset of AD symptoms at age 89 years and an *APOE* genotype of ε3/ε3 and the second in a sample from a cognitively intact 82-year-old control (minor allele frequency = 0.0082%) born in Iceland with an *APOE* genotype of ε3/ε3 (**Table 3**). Both were from the ACT study based in Seattle, Washington. Population principal components showed both to be of northern European ancestry when compared with HapMap 3 samples (eFigure 2 in the Supplement).

To validate the array genotyping results, we used a TaqMan assay to regenotype 1610 of the same samples, including the 2 heterozygotes. We also genotyped 983 additional samples from the ACT study (Table 2). All genotypes derived from the exome array genotyping were confirmed by the TaqMan assay, including the 2 heterozygotes initially observed. All additional ACT samples were homozygous for the normal A673 allele. TaqMan genotyping was also used to survey 506 AD cases, 383 individuals with other dementias, and 3838 controls from the Cache County Study on Memory Health and Aging. All dementia cases were homozygous for the normal A673 allele. One of the 3838 individuals without dementia carried the A673T allele (Table 2). This individual was aged 77 years at last assessment, had an *APOE* genotype of ε3/ε4, and had ancestors from Denmark, Ireland, Scotland, and England (Table 3). Because the minor allele of the A673T variant was observed in a Swedish

Table 2. Samples Genotyped for A673T (rs63750847) by TaqMan Assay[a]

Characteristic	Cohort					
	United States			Sweden		
	ACT[b]	Cache County Study on Memory Health and Aging	Total White Individuals	Cohort 1	Cohort 2	Total Swedish Individuals
Samples, No. (A673T heterozygotes, No.)						
Cases	498 (1)	506 (0)	1004 (1)	298 (0)	564 (0)	862 (0)
Controls	1953 (1)	3838 (1)	5791 (2)	220 (0)	487 (3)	707 (3)
Dementia, other[c]	138 (0)	383 (0)	521 (0)	0	0	0
Total	2589 (2)	4727 (1)	7313 (3)	518 (0)	1051 (3)	1569 (3)
Male, No. (%)						
Cases	34.2	32.3		36.9	41.7	
Controls	43.5	41.7		25.0	72.1	
Age, mean (SD), y						
At onset for cases	84.1 (5.6)	82.4 (6.9)		75.7 (12.9)		
At sampling for cases					76.4 (10.7)	
At last examination for controls	81.2 (7.0)	79.8 (6.3)		98.0 (1.5)		
At sampling for controls					62.7 (10.7)	
Cohort type	Prospective cohort	Prospective cohort		Case-control	Case-control	

Abbreviation: ACT, Adult Changes in Thought.

[a] Life Technologies.

[b] Includes ACT samples genotyped using the exome array and an additional 364 cases, 1344 controls, and 117 other dementias. The two A673T variants are the same as in Table 1.

[c] Includes vascular dementia, mixed dementias, and other rare forms of dementia.

sample at a frequency of 0.42%,[2] we also genotyped 862 AD cases and 707 cognitively normal controls from Sweden (Table 2). Three controls were heterozygous for A673T. All AD cases were homozygous for the common A673 allele.

Previous work reported that an affected individual in a small family with late-onset AD was heterozygous for A673T.[21] Because an affected individual from the same family was genotyped using the exome array as one of the individuals from the National Institute on Aging–Late-Onset AD sample, we genotyped all other available family members for the A673T variant. This included 6 AD cases, 4 married-in spouses, and 7 blood relatives of affected individuals. We observed 1 spouse and the child of that spouse as heterozygous for A673T. The child is a blood relative of affected individuals in the family. Both the child and parent were unaffected individuals (ages at last visit, 84 and 72 years, respectively). The heterozygous individual originally reported as an AD case was actually the unaffected child described here. This family is from the United States with a Scandinavian background.

Discussion

The *APP* A673T variant is overrepresented in Icelandic controls when compared with Icelandic AD cases.[6] Therefore, like the *APOE* ε2 allele,[22] the A673T variant appears to protect against late-onset AD, defined as disease onset after age 60 years. Studies on the functional consequences of the A673T substitution showed that this amino acid substitution inhibited BACE1 cleavage of APP, potentially reducing or eliminating the production of Aβ peptide from APP encoded by this allele.[6] That this allele appears to be protective provides additional genetic evidence that Aβ is a critical toxic molecule contributing to AD. Overproduction of Aβ (eg, from the *APP* K670N/M671L mutation) causes early-onset AD, and a variant associated with reduced Aβ production, A673T, protects against AD. Amino acid 673 appears to be critical for BACE1 cleavage since a different allele at the same amino acid (an alanine change to a valine, A673V) enhances Aβ production and causes recessive early-onset dementia.[9] However, the A673T variant is exceedingly rare in the white individuals tested here (carrier frequency = 0.011% in US individuals with AD and 0.018% in cognitively normal controls), so it could not have a substantial role in risk for AD in the US population. The frequency in Swedish controls tested here was somewhat higher (0.42%) and is in line with the frequency in the Icelandic population. The effect size (Fisher exact test 99% CI, 3.97-∞) is weaker than in the Icelandic population (odds ratio = 5.29), although this observation is suggestive and a larger sample size is needed.

The protective effect of A673T against late-onset AD reported in the Icelandic study[6] supports the hypothesis that Aβ not only plays a critical role in early-onset familial AD but also is important for late-onset AD. This hypothesis is also supported by earlier work showing that the *APOE* ε4 allele not only increases risk for late-onset AD and lowers the age at onset[23] but similarly also modifies AD risk in carriers of *PSEN1*[24] and *PSEN2*[25] mutations. Mutations in *PSEN1* and *PSEN2* alter the C-terminal cleavage γ-secretase site and thus cause AD by an Aβ-related mechanism. The fact that *APOE* genotype influences age at onset of this Aβ-driven process suggests that late-onset AD and early-onset familial AD share at least 1 common mechanism. The age cutoff distinguishing early- and late-

Table 3. Heterozygotes for A673T

Cohort and Participant	Age, y[a]	*APOE* Genotype
ACT		
Case	89	ε3/ε3
Control	77	ε3/ε4
Cache County Study on Memory Health and Aging control	82	ε3/ε4
Swedish cohort 2		
Control 1	72	ε3/ε3
Control 2	55	ε4/ε4
Control 3	59	ε3/ε3
Family 1		
Control, mother	72	ε3/ε3
Control, daughter	84	ε3/ε3

Abbreviation: ACT, Adult Changes in Thought.

[a] Age indicates age at onset for the ACT case, age at last examination for the ACT, Cache County Study on Memory Health and Aging, and family 1 controls, and age at sampling for the 3 Swedish controls.

onset disease is also blurred by the observation that *PSEN2* mutations occur in early- and late-onset AD cases.[26,27]

Jonsson et al[6] reported that in Icelandic individuals, the A673T allele frequencies were 0.13% in AD cases and 0.45% to 0.79% in controls. They also reported frequencies of 0.21%, 0.51%, and 0.42% in Norwegian, Finnish, and Swedish controls, respectively. In our Swedish cohort, we observed 3 controls who were heterozygous for A673T (age at sampling, 72, 55, and 59 years). Two of these controls are too young to definitively conclude they will not develop AD in the future. In fact, 1 control (aged 55 years) has an *APOE* genotype of ε4/ε4, suggesting increased risk for late-onset AD. In our US sample, we observed much lower frequencies in cases and controls, and 1 of our 3 carriers was born in Iceland. While our results are inconclusive regarding whether A673T is an AD-protective allele, they do indicate that this allele has little influence on risk in white individuals living in the United States. Our findings and the absence of the A673T allele in a large Chinese sample (n = 8721)[28] suggest the *APP* A673T allele may have an appreciable effect on AD risk only in Scandinavian and Icelandic populations.

Conclusions

We show that the *APP* A673T allele is extremely rare in US white populations and thus does not play a substantial role in risk of developing AD in this group. Our study of a Swedish cohort showed a higher carrier frequency of *APP* A673T, and thus this variant appears primarily present in Icelandic and Scandinavian populations. Our results are consistent with this mutation being protective because carriers in our study were mostly controls. However, because of the rarity of this mutation in our populations, we could not independently verify that *APP* A673T is a protective allele.

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REFERENCES

1. Schellenberg GD, Montine TJ. The genetics and neuropathology of Alzheimer's disease. *Acta Neuropathol*. 2012;124(3):305-323.

2. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. *Cell*. 2012;148(6):1204-1222.

3. Ghosh AK, Brindisi M, Tang J. Developing β-secretase inhibitors for treatment of Alzheimer's disease. *J Neurochem*. 2012;120(suppl 1):71-83.

4. De Strooper B, Vassar R, Golde T. The secretases: enzymes with therapeutic potential in Alzheimer disease. *Nat Rev Neurol*. 2010;6(2):99-107.

5. Delrieu J, Ousset PJ, Caillaud C, Vellas B. "Clinical trials in Alzheimer's disease": immunotherapy approaches. *J Neurochem*. 2012;120(suppl 1):186-193.

6. Jonsson T, Atwal JK, Steinberg S, et al. A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline. *Nature*. 2012;488(7409):96-99.

7. Peacock ML, Warren JT Jr, Roses AD, Fink JK. Novel polymorphism in the A4 region of the amyloid precursor protein gene in a patient without Alzheimer's disease. *Neurology*. 1993;43(6):1254-1256.

8. Kero M, Paetau A, Polvikoski T, et al. Amyloid precursor protein (*APP*) A673T mutation in the elderly Finnish population. *Neurobiol Aging*. 2013; 34(5):e1-e3.

9. Di Fede G, Catania M, Morbin M, et al. A recessive mutation in the APP gene with dominant-negative effect on amyloidogenesis. *Science*. 2009;323(5920):1473-1477.

10. Giliberto L, Borghi R, Piccini A, et al. Mutant presenilin 1 increases the expression and activity of BACE1. *J Biol Chem*. 2009;284(14):9027-9038.

11. Mullan M, Crawford F, Axelman K, et al. A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid. *Nat Genet*. 1992;1(5):345-347.

12. Jun G, Naj AC, Beecham GW, et al; Alzheimer's Disease Genetics Consortium. Meta-analysis confirms *CR1*, *CLU*, and *PICALM* as Alzheimer disease risk loci and reveals interactions with *APOE* genotypes. *Arch Neurol*. 2010;67(12):1473-1484.

13. Naj AC, Jun G, Beecham GW, et al. Common variants at *MS4A4/MS4A6E*, *CD2AP*, *CD33* and *EPHA1* are associated with late-onset Alzheimer's disease. *Nat Genet*. 2011;43(5):436-441.

14. Kukull WA, Schellenberg GD, Bowen JD, et al. Apolipoprotein E in Alzheimer's disease risk and case detection: a case-control study. *J Clin Epidemiol*. 1996;49(10):1143-1148.

15. Tang MX, Stern Y, Marder K, et al. The *APOE*-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. *JAMA*. 1998;279(10):751-755.

16. Blacker D, Haines JL, Rodes L, et al. ApoE-4 and age at onset of Alzheimer's disease: the NIMH genetics initiative. *Neurology*. 1997;48(1):139-147.

17. Naj AC, Beecham GW, Martin ER, et al. Dementia revealed: novel chromosome 6 locus for late-onset Alzheimer disease provides genetic evidence for folate-pathway abnormalities. *PLoS Genet*. 2010;6(9):e1001130.

18. Beecham GW, Martin ER, Li YJ, et al. Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. *Am J Hum Genet*. 2009;84(1):35-43.

19. Breitner JCS, Wyse BW, Anthony JC, et al. *APOE*-epsilon4 count predicts age when prevalence of AD increases, then declines: the Cache County Study. *Neurology*. 1999;53(2):321-331.

20. Zetterberg M, Landgren S, Andersson ME, et al. Association of complement factor H Y402H gene polymorphism with Alzheimer's disease. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(6):720-726.

21. Cruchaga C, Haller G, Chakraverty S, et al; NIA-LOAD/NCRAD Family Study Consortium. Rare variants in *APP*, *PSEN1* and *PSEN2* increase risk for AD in late-onset Alzheimer's disease families. *PLoS One*. 2012;7(2):e31039.

22. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet*. 1994;7 (2):180-184.

23. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261(5123):921-923.

24. Lendon CL, Martinez A, Behrens IM, et al. E280A PS-1 mutation causes Alzheimer's disease but age of onset is not modified by ApoE alleles. *Hum Mutat*. 1997;10(3):186-195.

25. Wijsman EM, Daw EW, Yu X, et al. APOE and other loci affect age-at-onset in Alzheimer's disease families with PS2 mutation. *Am J Med Genet B Neuropsychiatr Genet*. 2005;132B(1):14-20.

26. Levy-Lahad E, Wijsman EM, Nemens E, et al. A familial Alzheimer's disease locus on chromosome 1. *Science*. 1995;269(5226):970-973.

27. Levy-Lahad E, Wasco W, Poorkaj P, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science*. 1995;269 (5226):973-977.

28. Ting SK, Chong MS, Kandiah N, et al. Absence of A673T amyloid-β precursor protein variant in Alzheimer's disease and other neurological diseases. *Neurobiol Aging*. 2013;34(10):e7-e8.