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Alzheimer's disease risk variants show association with cerebrospinal fluid amyloid beta

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Abstract

The use of quantitative endophenotypes in genetic studies may provide greater power, allowing for the use of powerful statistical methods and a biological model for the effects of the disease-associated

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genetic variation. Cerebrospinal fluid (CSF) amyloid beta (Aβ) levels are promising endophenotypes for late-onset Alzheimer's disease (LOAD) and show correlation with LOAD status and Aβ deposition. In this study, we investigated 29 single nucleotide polymorphisms (SNPs) positive in AlzGene (http://www.alzgene.org) meta-analyses, for association with CSF Aβ levels in 313 individuals. This study design makes it possible to replicate reported LOAD risk alleles while contributing novel information about the mechanism by which they might affect that risk. Alleles in *ACE*, *APOE*, *BDNF*, *DAPK1*, and *TF* are significantly associated with CSF Aβ levels. In vitro analysis of the *TF* SNP showed a change in secreted Aβ consistent with the CSF phenotype and known Alzheimer's disease variants, demonstrating the utility of this approach in identifying SNPs that influence risk for disease via an Aβ-related mechanism.

Keywords

Amyloid beta; Alzheimer's disease; Genetics; Association; Transferrin

Introduction

Late-onset Alzheimer's disease (LOAD) is the most common neurodegenerative disorder affecting more than five million people in the USA alone. With the exception of apolipoprotein E epsilon 4 (*APOE* ε4), no polymorphism has shown consistent and replicated association with LOAD. Current case-control approaches may not have the statistical power to detect the small effect sizes expected in a complex disease like LOAD. Statistical power is further degraded by the inherent heterogeneity of samples ascertained using clinical exams [1-4]. An endophenotype-based approach may help alleviate the issues of heterogeneity and statistical power. Continuous traits allow for the use of quantitative statistical methods and may provide a biological model of disease and the possible effects of the disease-associated genetic variation. Cerebrospinal fluid (CSF) amyloid beta (Aβ) levels have emerged as promising endophenotypes for LOAD. Recent studies have shown that CSF levels of 42 amino acid Aβ (Aβ42) are correlated with LOAD status and Aβ deposition [5-7]. The creators of AlzGene, a publicly available online database, have used meta-analyses of published genetic association studies as one way to address the problem of small sample sizes [8]. Several single nucleotide polymorphisms (SNPs) show significant effects on LOAD risk across multiple independent studies in the AlzGene meta-analyses [8]. In this study, we successfully genotyped 29 such SNPs from 26 genes (from the AlzGene database on December 1, 2007) in 313 individuals for whom CSF biomarkers have been measured. This novel approach is designed to provide information about the possible biological mechanisms by which these variants modulate risk for disease.

Materials and methods

Samples

CSF was collected from 313 individuals by lumbar puncture after fasting as described previously [6]. Age at lumbar puncture in these samples ranges from 43 to 91 years. Seventy-two percent of these individuals were non-demented at the time of the CSF draw, 63% are women, and 42% carry at least one *APOE* ε4 allele (Table 1). CSF collection, processing, and 40 amino acid Aβ (Aβ40) and Aβ42 measurements were performed as described previously [6].

SNP selection and association analysis

We selected 29 SNPs from 26 genes that show significant association with LOAD in the AlzGene meta-analyses (on December 1, 2007; Table 2). SNPs were genotyped using

Sequenom genotyping technology [9]. Significant covariates were identified using stepwise discriminant analysis. Age, CDR and APOE *ε4* were significantly associated with CSF Aβ42/Aβ40 ratio; gender was significantly associated with total Aβ levels. In order to adjust for these significant covariates, genotypes were tested for association with normalized Aβ42/Aβ40 ratio and total Aβ levels after adjustment for their respective significant covariates using analysis of covariance. To validate the CDR adjustment, we tested each significant SNP for association in the nondemented samples only; in each case, we detected association of similar direction, magnitude, and probability. Dominant and recessive models were tested for polymorphisms that were significant in the additive model, had a minor allele frequency (MAF) less that 20%, or when indicated by published reports. All associations showed similar direction and magnitude when analyzed only in the non-demented or demented stratum. In the absence of specific prior hypotheses supported by previous studies and/or known biology (e.g., *APOE ε4* allele is known to increase Aβ42 deposition [10], leading to a decrease in the ratio of soluble Aβ42/Aβ40), elevated Aβ42/Aβ40 ratio (phenotype observed with most familial AD mutations[7]) and decreased total Aβ levels (driven by decreased Aβ40) are hypothesized to be associated with increased risk for AD [11,12]. Because these SNPs show strong evidence for association in previous studies (see AlzGene.org) and are associated with specific prior hypotheses for disease risk and Aβ effects (described above), we have not applied a multiple test correction. Haplotype analyses were performed using the default settings for a quantitative trait in UNPHASED [13].

Transfection and Aβ measurement

The QuickChange II site-directed mutagenesis kit (Stratagene, Cedar Creek, TX, USA) was used to introduce the P589S point mutation into a wild-type *TF* (TF-WT) complementary DNA (cDNA) construct (Origene, Rockville, MD, USA). The construct was confirmed by sequence analysis. HEK cells were transiently co-transfected with APPΔNL and GFP, TF-WT, or TF-P589S constructs. Conditioned medium was collected and secreted Aβ40 and Aβ42 were measured by enzyme-linked immunosorbent assay as described previously [14]. Six independent transfections were performed. A comparison of secreted Aβ levels between cells transfected with TF-WT and TF-P589S was performed using a *t* test.

Results

Seven polymorphisms were significantly associated with CSF Aβ levels in our sample, including two in *APOE*(Table 2). Aβ42/Aβ40 ratio was significantly decreased with increasing number of *APOEε4* alleles in our sample (p=0.0001). Rs405509 is located just 5′ of the *APOE* gene; the minor allele “G” (which is protective in the AlzGene meta-analysis) showed significant association with higher total Aβ (total Aβ, p=0.030). Within *ACE*, the Alzgene risk allele of rs1800764 “T” has a frequency of 0.49 and is associated with a higher Aβ42/Aβ40 ratio (p=0.0141). To follow up previous reports, we genotyped rs4343 then used rs1800764, rs4291, and rs4343 to define the A, B, and C clades [15,16]. Individuals with a clade C haplotype have significantly higher Aβ42/Aβ40 ratio than individuals with a “protective” clade A haplotype (p=0.028). Rs6265 is an amino acid substitution in brain-derived neurotrophic factor (*BDNF*). The Alzgene risk allele “A” is associated with decreased CSF total Aβ (p=0.034), which is driven by a significant decrease in Aβ40. The minor allele of rs4878104 (protective effect; “A”) in the death-associated protein kinase 1 (*DAPK1*) gene is associated with increased total Aβ levels driven by increased Aβ40 (p=0.0062). The Alzgene risk allele of rs190938 (in hCG2039140) is associated with decreased Aβ42/Aβ40 ratio. The minor allele “T” of rs1049296 results in a proline to serine substitution at codon 589 in transferrin (*TF*). This allele is associated with an increased Aβ42/Aβ40 ratio in our sample (p=0.030). To determine whether the *P589S* variant affects Aβ42/Aβ40 ratio in vitro, we transfected HEK cells with cDNA encoding wild type or *P589S TF*. Consistent with the genetic data, the Aβ42/

Aβ40 ratio was significantly higher in media from cells expressing the *P589S* variant when compared to media from cells expressing wild-type *TF* (p=0.0035; Fig. 1).

Discussion

These results indicate that several of the risk alleles from the AlzGene meta-analysis also show association with CSF Aβ levels. The observation of decreased Aβ42/Aβ40 ratio with the *APOE ε4* allele is consistent with a previous report showing a significant reduction in CSF Aβ42 with little change in Aβ40 levels [17]. In transgenic models, *APOE* ε4 increases Aβ deposition and the formation of fibrillar Aβ [10], leading to a reduction in soluble CSF Aβ42; this is consistent with the decrease in Aβ42/Aβ40 ratio observed in our data. The protective allele of rs405509 shows association with increased total Aβ levels. Aβ40 inhibits Aβ deposition in mouse models, suggesting that increased Aβ40 may be protective [11]. Our observation of an increase in total Aβ levels with this allele is consistent with its "protective" association with LOAD in AlzGene. The association of rs405509 with total Aβ levels, but not Aβ42/Aβ40 ratio, is in contrast to the *APOE ε4* allele, which is associated with Aβ42/Aβ40 ratio but not total Aβ levels. This difference suggests the possibility of additional risk alleles in the *APOE* region and is consistent with a recent report suggesting that regulatory region polymorphisms in *APOE* may affect the rate of cognitive decline in LOAD patients independently of the *APOE* ε4 allele [18].

Rs1800764 is within the 5′ promoter region of angiotensin-converting enzyme (*ACE*). The association of the risk allele with increased Aβ42/Aβ40 ratio is consistent with the predicted effect of a LOAD risk allele. Haplotype analyses in *ACE* have identified three major clades (A, B, and C) and suggest that the C clade is associated with higher plasma levels of ACE [15] and increased CSF Aβ42 [16]. The association of clade C from our haplotype analysis with increased Aβ42/Aβ40 ratio is consistent with these reports, reports that clade C is over-transmitted in LOAD cases [23] and with biological evidence that ACE functions to degrade Aβ and may alter risk for AD by modulating the aggregation of Aβ into plaques [19].

The risk alleles of both rs6265 and rs4878104 are associated with decreased total Aβ levels (driven by reduction in Aβ40). As mentioned previously, increased Aβ40 may inhibit Aβ deposition [11], making these associations consistent with risk for disease. Our data for rs4878104 are also consistent with our previous report that this SNP is associated with risk for LOAD and changes in *DAPK1* expression [20]. To our knowledge, there is no published data suggesting a link between *DAPK1* function and Aβ. The association observed with rs190938 is difficult to interpret, as hCG2039140 has no known function.

The association of rs1049296 with CSF Aβ42/Aβ40 is consistent with the meta-analysis results suggesting that the minor allele is associated with increased risk for AD. The association of the minor allele with risk for disease has also been confirmed in a large family-based association study [23]. We have also shown that cell lines overexpressing a *TF* cDNA containing the minor allele of rs1049296 have a significantly higher Aβ42/Aβ40 ratio then those overexpressing wild-type *TF* cDNA. TF transports both iron and aluminum to proliferating cells. Results from a study of posttranslational regulation and processing of amyloid precursor protein (APP) suggest that altered iron distribution affects APP holoprotein expression as well as Aβ production [21]. It has also been shown that treatment of human neuroblastoma cells with (-)-epigallocatechin-3-gallate (EGCG) results in increased expression of TF and decreased levels of APP. EGCG treatment of Chinese hamster ovary cells expressing the APP "Swedish" mutation (Lsy670/Asn, Met671/Leu) resulted in a reduction of Aβ secretion [22]. Together, these data suggest that rs1049296 affects risk for LOAD by modulating Aβ.

While the associations we observe between CSF Aβ and genetic variants in *APOE, ACE, BDNF, DAPK1*, and *TF* display modest significance and are not corrected for multiple tests,

they are consistent with the known biology of these genes and prior hypotheses of LOAD risk (from the AlzGene meta-analyses). Our failure to detect association with other SNPs could be due to limited statistical power or the possibility that they influence risk through a mechanism other than modulating Aβ levels (e.g., CHRNB2, which may affect synaptic transmission but probably does not affect APP metabolism). Our findings in *ACE* and *TF* are of particular interest, as genetic variation in *ACE* and *TF* were recently confirmed to be associated with risk for LOAD in a family-based sample [23]. Schjeide et al. tested nearly the same set of SNPs selected in a very similar way and found several significant results including three variants that were significant in our study (APOE ε4, ACE clade C, and rs1049296). The probability of finding three or more SNPs that are significant in both of these independent studies by chance is 0.020 (empirical *p* value from simulations).

In addition to this independent replication, our in vitro data show that media from cell lines overexpressing a *TF* cDNA containing the minor allele of rs1049296 have a significantly higher Aβ42/Aβ40 ratio, which is consistent with the effects of variants in the *Presenilins* and *β amyloid precursor protein* that cause familial Alzheimer's disease [12], further supporting our genetic findings. These data indicate that several putative risk factors for LOAD observed in the AlzGene meta-analysis may affect risk via an Aβ-related mechanism, providing support for the relevance of the amyloid hypothesis to LOAD pathogenesis. Our findings highlight the potential of this endophenotype-based approach to provide valuable information about the genetic etiology of LOAD.

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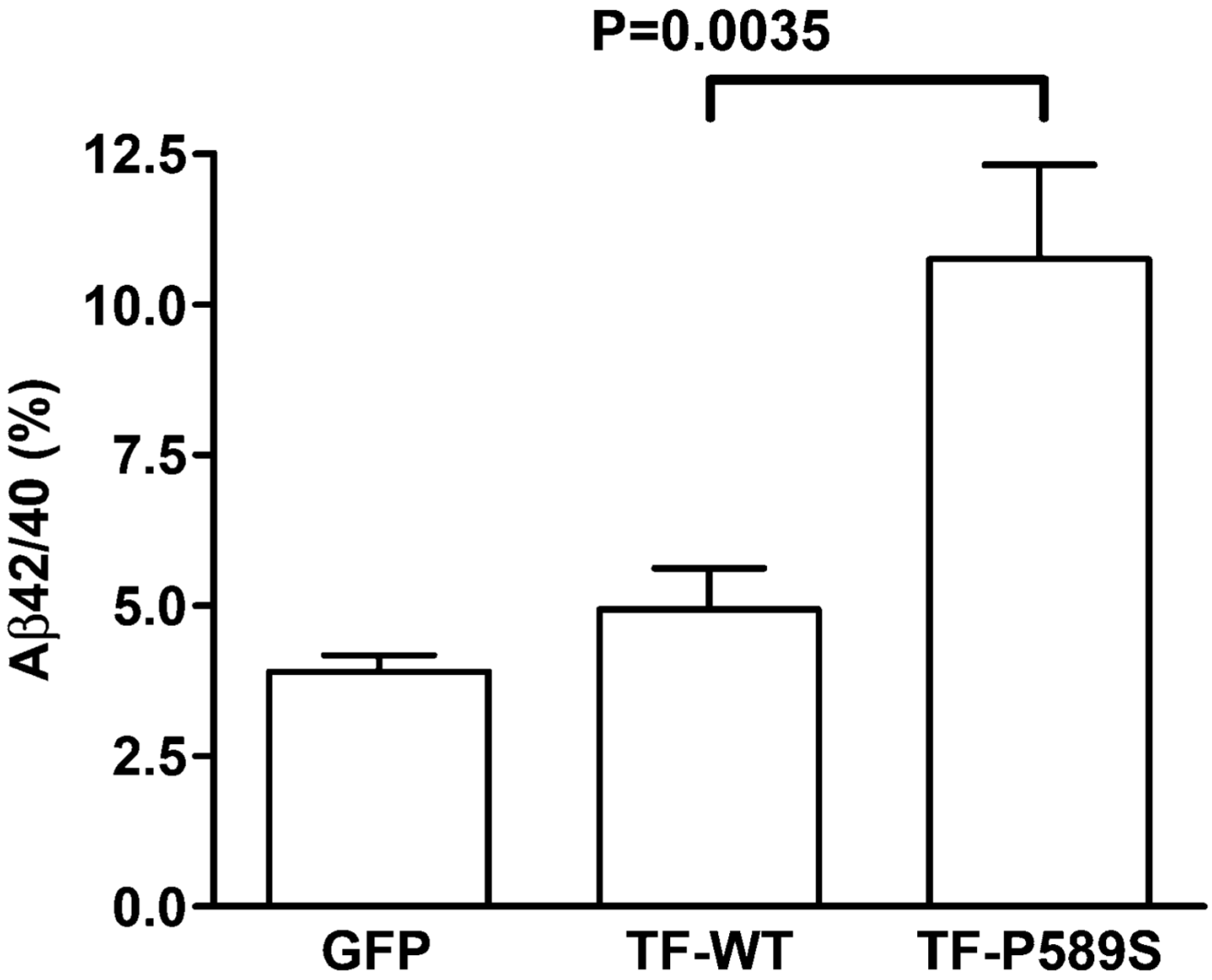

Fig. 1.

Ratio of Aβ42 to Aβ40 in the media of wild-type *TF* vs. P589S HEK cells. Data are from six independent transfections. Error bars represent SEM. The *y*-axis represents Aβ42 as a percentage of Aβ40 levels. *P* value is for a *t* test contrasting *TF-WT* and TF-P589S

Table 1

Characteristics of Washington University CSF sample

	Sample
N	313
Age in years mean (range, SD)	67.5 (43-91,11.5)
%female	63
%APOE4+	42
CDR	0=72%, 0.5=20%, 1=8%
Aβ42 mean (range, SD, pg/ml)	564 (175-1295, 244)
Aβ40 mean (range, SD, pg/ml)	10,463 (2,355-24,899, 3,900)

Sample size (*N*), age, percent of females, percent of APOE ε4 allele carriers, clinical dementia rating (CDR), Aβ42 and Aβ40 (pg/ml)

Table 2

P values from ANCOVA analyses of polymorphisms from the AlzGene meta-analyses for association with normalized Aβ42/Aβ40 ratio (adjusted for CDR and *APOE ε4*) and total Aβ (adjusted for gender) levels

Variant	Gene	MAF	Aβ42/Aβ40	Total Aβ	AD allele (OR)[a]
APOE ε4[a]	*APOE*	0.20	0.0001	0.16	E4 (3.68; 3.31, 4.11)
rs1800764	*ACE*	0.49	0.014[b]	0.82[b]	C (0.83; 0.72, 0.95)
rs4291	ACE	0.37	0.22	0.32	T (0.82; 0.70, 0.96)
rs4343	ACE	0.48	0.22	0.32	G (1.08; 0.69, 1.68)
rs405509	*APOE*	0.48	0.094	0.030	G (0.75; 0.70, 0.08)
rs440446	*APOE*	0.30	0.092	0.12	C (0.58; 0.5, 0.68)
rs6265	BDNF	0.18	0.90	0.022	A (1.09; 1.00, 1.17)
rs13500	*CH25H*	0.09	0.72	0.50	T (1.44; 1.08, 1.93)
rs4845378	*CHRNB2*	0.13	0.39	0.88	T (0.67; 0.5, 0.9)
rs4878104	*DAPK1*	0.35	0.42[c]	0.0062[c]	A (0.87; 0.79, 0.95)
rs3745833	GALP	0.32	0.41	0.42	C (1.21; 1.1, 1.33)
rs1903908	hCG2039140	0.13	0.034	0.086	T (1.23; 1.06, 1.44)
rs1143634	*IL1B*	0.22	0.055	0.76	T (1.18; 1.03, 1.34)
rs498055	*LOC439999*	0.50	0.67	0.98	G (1.15; 1.03, 1.29)
rs6907175	LOC651924	0.44	0.36	0.49	A (0.86; 0.77, 0.96)
rs2471738	*MAPT*	0.19	0.46	0.65	T (1.3; 1.01, 1.67)
rs1801131	MTHFR	0.34	0.86	0.19	C (0.94; 0.73, 1.16)
rs2074877	MYH13	0.38	0.25	0.83	C (1.12; 1, 1.25)
rs8192708	PCK1	0.10	0.19	0.44	A (1.28; 1.11, 1.47)
rs3800324	PGBD1	0.05	0.075	0.092	A (1.42; 1.13, 1.8)
rs1799990	*PRNP*	0.32	0.82	0.49	G (0.89; 0.83, 0.99)
rs165932	*PSEN1*	0.40	0.96	0.46	G (0.93; 0.86, 1.01)
rs600879	SORCS1	0.11	0.34	0.46	minor (1.24; 1.04, 1.48)
rs1010159	*SORL1*	0.35	0.66	0.084	C (1.06; 0.99, 1.14)
rs1049296	*TF*	0.16	0.030[b]	0.17[b]	T (1.18; 1.04, 1.33)
rs2306604	*TFAM*	0.46	0.36	0.086	G (0.78; 0.67, 0.91)
rs1554948	TNK1	0.44	0.62	0.43	A (0.84; 0.76, 0.93)
rs157581	*TOMM40*	0.29	0.25	0.79	C (2.75; 2.4, 3.15)
rs11622883	WGA_14q32.13	0.44	0.28	0.33	A (0.84; 0.77,0.93)

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Variant	Gene	MAF	Aβ42/Aβ40	Total Aβ	AD allele (OR)[a]
rs1859849	WGA_7p15.2	0.24	0.26	0.61	C (1.16; 1, 1.36)

For each SNP, the gene, minor allele frequency (MAF), *p* value for Aβ42/Aβ40 ratio and total Aβ, and the LOAD-associated allele and odds ratio (OR) from AlzGene are shown.

P values are not corrected for multiple tests.

[a] We tested association with the number of *APOE ε4* alleles.

[b] *P* values from a dominant model

[c] *P* values from a recessive model.