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Brief communication

Genetic variants in a 'cAMP element binding protein' (CREB)-dependent histone acetylation pathway influence memory performance in cognitively healthy elderly individuals

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ABSTRACT

The molecular pathways underlying age-related memory changes remain unclear. There is a substantial genetic contribution to memory performance through life span. A recent study has implicated *RbAp48*, which mediates its effect on age-related memory decline by interacting with cyclic adenosine monophosphate responsive element binding protein *(CREB)1* binding protein and influencing this histone acetylation pathway. To validate these findings, we tested whether genetic variants in *RbAp48*, *CREB1*, and *CREBBP* are associated with memory performance in 3 independent data sets consisting of 2674 cognitively healthy elderly individuals. Genetic variant rs2526690 in the *CREBBP* gene was significantly associated with episodic memory performance ($p_{meta} = 3.7 \times 10^{-4}$) in a multivariate model adjusted for age, sex, and apolipoprotein E status. Identifying genetic variants that modulate mechanisms of cognitive aging will allow identifying valid targets for therapeutic intervention.

1. Introduction

Although there is substantial evidence that decline in cognitive performance occurs with normal aging, the neurobiological basis of these age-related cognitive changes remains unclear. Cross-sectional and longitudinal studies showed that across cognitive domains, memory performance undergoes significant decline with increasing age (Small et al., 1999). Heritability estimates from twin and family studies indicate that genetic variants strongly influence cognitive ability differences throughout the life span, including in old age (Harris and Deary, 2011). To date, however, most associations in or surrounding common variants are largely unreplicated, with the exception of the apolipoprotein E (*APOE*) gene (Wisdom et al., 2011) and have little biological support.

In our increasingly aging society, the population aged 60 years and older is set to rise 3-fold to 2 billion by 2050 (Publications, 2001), consequently the burden of age-related cognitive impairment will increase. Characterizing genetic factors accounting for the age-related memory deficits will identify valid targets for therapeutic intervention to ameliorate cognitive impairment in the elderly individuals.

Recently, gene expression analysis of human postmortem tissue harvested from the hippocampal formation identified a substantial age-related decline in the expression of the histone-binding protein *RbAp48* gene (Pavlopoulos et al., 2013). Inhibition of *RbAp48* in young genetically engineered mice caused memory deficits similar to those associated with aging, whereas increasing RbAp48 expression in old mice reversed age-related memory impairment.

Rbap48 gene is known to facilitate the action of the cyclic adenosine monophosphate responsive element binding protein *(CREB)1* gene's-binding protein *CREBBP*, which is acetylates histones and affects age-related memory loss. In the present study, we investigated whether genetic variants in these histone acetylation pathway genes (*RbAp48*, *CREBBP*, and *CREB1*) influence memory performance in cognitive healthy elderly individuals.

2. Methods

2.1. Study cohorts

2.1.1. The National Institute of Aging Late-Onset Alzheimer's Disease

The National Institute of Aging Late-Onset Alzheimer's Disease Family Study was described elsewhere (Wijsman et al., 2011). From

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the total cohort, 494 nondemented and unrelated healthy individuals were included in the present study. Episodic memory scores at the last cognitive assessment were computed as the average of the 2 standardized measures of Logical Memory IA and IIA (Wechsler, 1987). Genome-wide genotyping was performed using Illumina Human610Quadv1_B BeadChips (Illumina, San Diego, CA, USA) (Naj et al., 2011).

2.1.2. The Alzheimer's Disease Genetic Consortium

A total of 1744 cognitively normal elderly individuals from Alzheimer's Disease Genetic Consortium (ADGC) cohort consisting of 5 different independent NIA-funded Alzheimer's disease centers (Naj et al., 2011) were used to test the association of histone acetylation pathway genes and episodic memory performance. Episodic memory scores at the last cognitive assessment were computed as the average of the 2 standardized measures of Logical Memory IA and IIA (Wechsler, 1987). Genome-wide genotyping was performed using various genotyping arrays (Saykin et al., 2010). To test the possible association of the histone pathway genes and Alzheimer's disease, we additionally used a sample of 11,840 demented subjects from 15 different independent ADGC subcohorts.

2.1.3. The Washington Heights Aging Project

The Washington Heights Aging Project is a population-based study of elderly individuals residing in New York (Mayeux et al., 2001). The memory domain included the total and delayed recall of the Selective Reminding Test (Buschke and Fuld, 1974) and the recognition component of the Benton Visual Retention Test (Benton, 1955). The composite measure of memory was computed as the average of the standardized individual memory tests from the last cognitive assessment (Siedlecki et al., 2008). Our analysis was restricted to the White subsample consisting of 436 cognitively healthy elderly individuals. Genome-wide genotyping was done using the Omni Express platform by Illumina.

2.2. Statistical methods

2.2.1. Imputed genotype data

To significantly improve the single-nucleotide polymorphism (SNP) coverage of the genes analyzed based on the different genome-wide association studies platforms, we used the imputed genotype data available for each of the study cohorts.

Genome-wide imputation of allele dosages within each of the study cohorts was performed using the worldwide reference panel (v3, released March 2012) from 1000 Genomes for imputation of genotypes (build 37, http://www.1000genomes.org/announcements/updated-integrated-phase-1-release-calls-2012-03-16) and the IMPUTE2 (http://mathgen.stats.ox.ac.uk/impute/impute_v2.html) software applying strict pre-phasing, pre-imputation filtering, and variant position and strand alignment control. Only imputed SNP dosages with an imputation quality estimate of $R^2 \geq 0.30$ were included in the final SNP set for analysis.

2.3. Tagging SNPs

Using the tagger program implemented in Haploview 4.0 (Barrett et al., 2005), tag-SNPs across the 3 genes were selected on the basis of linkage disequilibrium patterns observed in the Caucasian samples from the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/). The tag-SNPs were selected within a 50-Kb region flanking either side of the gene to capture all alleles with a correlation coefficient $r^2 \geq 0.8$.

2.3.1. Single-marker tests of association

Regression models adjusted for sex, age, and education were conducted in the 3 different cohorts using PLINK (Purcell et al., 2007). In each of the cohorts, interaction analysis between SNP markers significant in single-marker association tests and the *APOE* locus (coded as 0 or 1 based on the absence or the presence of e4 allele) was performed using linear regression analyses which modeled the main effect of both loci, an interaction term of the SNP × APOE, and covariates (sex, age, and education).

2.3.2. Statistical significance

Multiple testing adjustment of the obtained *p*-values was carried out using The Genetic Type I error calculator tool (Li et al., 2012) to compute gene-specific thresholds of significance based on the number of SNPs used to tag (tag-SNPs) each of the analyzed genes: 37 tag-SNPs in CREB1 ($p \leq 0.001$), 98 tag-SNPs in CREBBP ($p \leq 5 \times 10^{-4}$), and 40 tag-SNPs in RBBP4 ($p \leq 0.001$).

2.3.3. Meta-analysis

SNP association with episodic memory performance was obtained from the 3 independent cohorts and combined by meta-analysis using METAL (Willer et al., 2010). Results obtained from SNP-*APOE* interaction models within each cohort were also meta-analyzed. Because of the known *APOE*-e4 association with impaired cognitive performance (Mayeux et al., 2001) and the suggestive interaction between the most significant SNP and *APOE* locus ($p_{meta} = 0.07$), we stratified our analysis by *APOE* classifying the cohort's participants as carriers of 1, 2, or no copies of *APOE*-e4 allele.

3. Results

The strongest genetic association with episodic memory performance was observed for intronic SNP rs2526690 in *CREBBP*, reaching statistical significance after adjusting for multiple testing ($p_{meta} = 3.7 \times 10^{-4}$). When comparing the estimates of the beta coefficient of the SNP based on the APOE-e4 status, the SNP effect size appeared to be driven by the noncarriers of *APOE*-e4 allele (all subjects: $\beta = 0.20$, standard error [SE] = 0.07; *APOE*-e4 noncarriers $\beta = 0.13$, SE = 0.08).

Although not reaching statistically significant thresholds, 3 additional SNPs in *CREBBP* (rsrs36099109, rs112455953, and rs112193373) showed nominal associations that were directionally consistent across cohorts among individuals lacking the *APOE*-e4 allele ($p_{meta} = 0.006$, $p_{meta} = 0.001$, and $p_{meta} = -0.002$, respectively).

Within *CREB1* gene proximity (39-Kb upstream the gene), SNP rs72954151 was found nominally associated with episodic memory ($p_{meta} = 0.008$) in the noncarriers of the *APOE*-e4 allele. SNP marker rs9660296 located 8-Kb upstream of *RBBP4* gene appeared nominally associated with episodic memory performance ($p_{meta} = 0.040$) among noncarriers of *APOE*-e4.

Table 1 summarizes all SNP associations with nominal *p*-values under any of the 3 *APOE* status models considered for analysis.

Analysis of the episodic memory associated SNPs in a cohort of 11,840 demented subjects from the ADGC did not identify any significant association (Table 2), reinforcing the hypothesis that the association is not related to Alzheimer's disease but age-related memory impairment.

4. Discussion

We examined whether genetic variants in members of the cell signaling pathway, *RbAp48*, *CREB1*, and *CREBBP*, are associated with episodic memory performance in cognitively healthy elderly subjects. We identified an SNP in *CREBBP* significantly associated with episodic memory in meta-analyses of 3 independent cohorts ($p_{meta} = 3.7 \times 10^{-4}$). Cognitively healthy elderly individuals carrying the G allele at SNP rs2526690 showed significantly

Table 1
Meta-analysis of SNP associations with episodic memory performance in 3 independent cohorts of cognitively healthy elderly individuals

Gene	SNP	bp	A1	All subjects			E4 carriers			Non-E4 carriers		
				Effect	p_{meta}	Direction	Effect	p_{meta}	Direction	Effect	p_{meta}	Direction
CREB1	rs80140096	208353957	G	0.05	0.034	−+−−−−−	−0.02	0.770	+++++−+	0.08	*0.009*	−+−−−−−
	rs72954151	208355330	G	0.04	0.066	++−+−−−	−0.04	0.439	++−++−−	0.07	*0.008*	−+−−−−−
	rs2042484	208363062	T	0.00	0.829	+−++−−+	0.08	*0.046*	+−+++−+	−0.02	0.286	−+−−−−
	rs74844716	208392215	T	0.04	0.188	+−++−++	−0.03	0.756	+−−−−++	0.09	*0.040*	+−++−++
	rs55834243	208443586	C	0.05	0.302	−+−+−−−	−0.10	0.256	−++++−+	0.11	*0.046*	−+−−+−−
CREBBP	rs79848897	3737375	C	0.04	0.151	−−−−−+−	−0.08	0.103	+++−+++	0.08	*0.011*	−−−−−+−
	rs2108430	3738078	T	0.02	0.751	−++−+−−	−0.10	*0.028*	−+−+−−−	0.06	0.063	+++−+−+
	rs72778151	3738286	T	0.04	0.157	+++++++	−0.10	0.114	−−+−−−−	0.08	*0.019*	+++++++
	rs36099109	3742348	T	0.04	0.149	+++++−−	−0.12	*0.043*	−−−−−−−	0.09	*0.006*	+++++++
	rs79213162	3744912	C	0.07	0.038	+−++−++	0.06	0.303	+−+++++	0.06	0.124	+−++−++
	rs75712687	3745273	A	0.04	0.212	++++++−	−0.10	0.106	−−−−−−−	0.09	*0.021*	+++++++
	rs75987714	3745883	G	0.07	0.113	−−−+−++	−0.02	0.734	+−−++++	0.10	*0.042*	−−−+−++
	rs6500550	3746241	T	0.01	0.931	−+−−+−−	−0.11	*0.018*	−−−++−−	0.05	0.121	+++−+−+
	rs1639150	3747204	C	0.05	0.044	−−−++−−	0.00	0.876	−+++−−−	0.06	*0.046*	−−−++−−
	rs112455953	3748679	T	0.06	0.059	++++++−	−0.12	0.063	−−−−−−−	0.11	*0.001*	+++++++
	rs112193373	3748761	A	0.05	0.107	++++++−	−0.13	*0.044*	−−−−−−−	0.11	*0.002*	+++++++
	rs39733	3773164	T	0.03	0.160	++++−++	0.12	*0.015*	++−++++	0.00	0.848	−+++−+−
	rs7199513	3773490	G	0.06	0.019	−−−−−−−	0.01	*0.020*	−−+−−−−	0.04	0.223	−−−−+−+
	rs130024	3834316	T	0.00	0.815	−−+−+−+	0.15	*0.038*	+−+−+++	−0.04	0.463	−−+−−−+
	rs7198381	3864502	A	0.19	0.001	+++++++	0.00	0.072	+−−++++	0.14	*0.030*	+++++++
	rs62039107	3890293	G	0.03	0.244	−+−−+−−	0.12	*0.019*	+−−−−−−	0.00	0.950	−+−−+−−
	rs2526690	3917531	G	0.20	**3.7 × 10^{-4}**	−−−−−−−	0.00	*0.018*	−++−−−+	0.13	*0.033*	−−−−−−−
	rs2386817	3938602	A	0.13	*0.010*	+−+++++	0.00	*0.046*	+−−+++−	0.07	0.173	+−+−+++
	rs58670576	3939457	C	0.15	*0.018*	−−−−−+−	0.08	0.428	−+−−−++	0.15	*0.028*	−−−−++−
	rs72760840	3951740	A	0.04	0.119	++−++++	0.15	*0.006*	+++++++	0.01	1.000	−+−+−+−
	rs2080248	3956074	G	0.13	*0.022*	−+−+−−−	0.00	0.553	−+−−−++	0.00	*0.032*	−+−+−−−
	rs73503973	3959437	C	0.17	*0.015*	−+−+−−−	0.00	0.451	−+−−−−−	0.00	*0.018*	−+−−−−−
	rs117150760	3971681	C	0.09	0.121	−+−−−+−	−0.08	0.618	−+++−++	0.14	*0.033*	−+−−−−−
RBBP4	rs180743675	33080061	A	0.98	0.328	++++++−	0.44	*0.016*	+++−+++	−0.09	0.472	+−+++−−
	rs9660296	33108400	T	1.70	0.089	+−++−++	0.05	0.779	−+++−−+	0.15	*0.040*	+−+−+++
	rs659867	33143896	C	1.94	0.053	−+−−+−−	0.00	0.202	+++−+−−	0.17	0.088	−+−−−−−

A1 corresponds to the allele reported as associated. Values highlighted in bold are meta-analysis *p*-values reaching significance after multiple testing adjustment. Values highlighted in cursive are nominally significant *p*-values.
Key: SNP, single-nucleotide polymorphism.

better average episodic memory scores when compared with carriers of the A allele($\beta = 0.20$, SE = 0.07 vs. $\beta = -0.20$, SE = 0.07). The effect size of the identified SNP is relatively small, in agreement with previous findings supporting the hypothesis that genetic contributions to cognitive phenotypes most likely involve multiple quantitative trait loci and environmental factors. Several other genetic variants in *RBBP4* and *CREB1* also showed nominal associations ($p_{meta} \leq 0.05$) with episodic memory performance. Consistent with the idea that this signaling pathway is defective in age-related memory loss, our results show that genetic variation in these genes might be associated with memory performance in cognitively healthy elderly subjects.

Table 2
Meta-analysis of the SNP associations with episodic memory performance in a sample of 11,840 demented individuals from the ADGC cohort

Gene	SNP	bp	A1	Effect	p_{meta}	Direction
CREB1	rs80140096	208353957	G	0.00	0.904	−++−++−−+−+?+−
	rs72954151	208355330	G	0.01	0.671	−++−−+−−−++−++−
	rs2042484	208363062	T	0.00	0.856	−++−+?−−−+++?+−
	rs74844716	208392215	T	0.06	0.106	+−−++?++−++??++
	rs55834243	208443586	C	0.09	0.155	−??−??−−?−?????
CREBBP	rs79848897	3737375	C	0.00	0.966	+−−−+?−−−+−+++−
	rs2108430	3738078	T	0.01	0.595	−+++−?+−+−+−−−+
	rs72778151	3738286	T	0.02	0.506	−−++−?+++−+−?−−
	rs36099109	3742348	T	0.02	0.409	−−++−?+++−++?−−
	rs79213162	3744912	C	−0.07	0.149	−−++−?−+−−+−?−−
	rs75712687	3745273	A	0.02	0.520	−−++−?+++−+−?−−
	rs75987714	3745883	G	0.03	0.585	++−?+?−????????
	rs6500550	3746241	T	0.04	0.068	−+++−?+−+−+−?++
	rs1639150	3747204	C	0.01	0.729	+−−−+?++−+???−−
	rs112455953	3748679	T	0.02	0.493	−−++−?+++−+−?−−
	rs112193373	3748761	A	0.02	0.493	−−++−?+++−+−?−−
	rs39733	3773164	T	0.11	0.081	??????????+??+?
	rs7199513	3773490	G	0.03	0.369	−−??+?−????????
	rs130024	3834316	T	0.14	0.141	???+?????????+?
	rs62039107	3890293	G	0.01	0.782	+−+++?−++−−+?−−
	rs2526690	3917531	G	−0.09	0.732	????????????−?

A1 corresponds to the allele reported as associated; SNPs not imputed or with poor imputation quality were not considered in the meta-analysis.
Key: ADGC, Alzheimer's Disease Genetic Consortium; SNP, single-nucleotide polymorphism.

Disclosure statement

The authors have no conflicts of interest to disclose.

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