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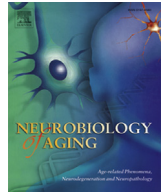
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Negative results

Failure of replicating the association between hippocampal volume and 3 single-nucleotide polymorphisms identified from the European genome-wide association study in Asian populations



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ABSTRACT

Hippocampal volume is a key brain structure for learning ability and memory process, and hippocampal atrophy is a recognized biological marker of Alzheimer's disease. However, the genetic bases of hippocampal volume are still unclear although it is a heritable trait. Genome-wide association studies (GWASs) on hippocampal volume have implicated several significantly associated genetic variants in Europeans. Here, to test the contributions of these GWASs identified genetic variants to hippocampal volume in different ethnic populations, we screened the GWAS-identified candidate single-nucleotide polymorphisms in 3 independent healthy Asian brain imaging samples (a total of 990 subjects). The results showed that none of these single-nucleotide polymorphisms were associated with hippocampal volume in either individual or combined Asian samples. The replication results suggested a complexity of genetic architecture for hippocampal volume and potential genetic heterogeneity between different ethnic populations.

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1. Introduction

Hippocampal volume, a heritable trait associated with cognition in humans, is considered to be a suitable endophenotype for aging-related physiological processes and presymptomatic diseases, such

as Alzheimer's disease. However, the genetic basis of hippocampal volume is still unclear.

Recently, the Cohorts for Heart and Aging Research in Genomic Epidemiology and the Enhancing Neuro Imaging Genetics through Meta-Analysis consortia have performed independent genome-wide association studies on hippocampal volume in different samples of European ancestry, and they identified 5 significantly associated genetic variants (rs17178006, rs6581612, rs6741949, rs7852872, and rs7294919) (Bis et al., 2012; Stein et al., 2012). Because the analyses were mostly conducted in Europeans, and the associations in other populations are yet to be tested.

2. Methods

We recruited a total of 990 healthy Asian subjects from 3 locations: 294 Chinese individuals from Kunming in southwestern China, 331 Chinese individuals from Beijing in northern China, and 365 Japanese subjects from Osaka, Japan. Among the 5 candidate

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Table 1
Replications of GWAS-identified SNPs on mean bilateral hippocampal volume in Asian populations

Locus	SNP	Populations	Sample size	Effect allele	Frequency	β (mm ³)	SE (mm ³)	<i>p</i> -value
2q24.3	rs6741949	Chinese (Kunming)	288	G	0.903	35.85	57.27	0.53
		Chinese (Beijing)	331	G	0.929	16.97	55.99	0.76
		Japanese (Osaka)	363	G	0.934	−49.30	41.82	0.24
		Combined Asians	982	G	0.923	−9.91	28.92	0.73
9q33.1	rs7852872	Chinese (Kunming)	288	C	0.427	34.37	31.90	0.28
		Japanese (Osaka)	361	C	0.431	−6.76	21.21	0.75
		Combined Asians	649	C	0.429	5.85	17.66	0.74
		Chinese (Kunming)	288	C	0.161	−32.40	46.02	0.48
12q24.22	rs7294919	Chinese (Beijing)	331	C	0.239	−1.98	35.19	0.96
		Japanese (Osaka)	365	C	0.203	−24.33	26.05	0.35
		Combined Asians	984	C	0.203	−19.16	19.06	0.31

Frequency, the frequency of the effect allele. β represents the difference in hippocampal volumes per copy increase of effect allele. Sex, age, age², sex \times age, sex \times age², and total intracranial volume (ICV) were included as covariates.

The combined sample and their results were marked in bold.

Key: GWAS, genome-wide association study; SE, standard error; SNPs, single-nucleotide polymorphisms.

single-nucleotide polymorphisms (SNPs) from genome-wide association studies, 2 of them (rs17178006 and rs6581612) are monomorphic in Asians according to the data from the 1000-Human-Genome (1000 Genomes Project Consortium et al., 2012); therefore, only the other 3 SNPs (rs6741949, rs7852872, and rs7294919) were included for further analysis. The effects of the 3 SNPs on mean bilateral hippocampal volume (as well as left and right hippocampal volume, separately) were analyzed using linear regression with sex, age, age², sex \times age, sex \times age², intracranial volume, and multidimensional scaling components (optional) as covariates, and dummy variables for different scanners or acquisition sequences were also included as covariates when analyzing the combined samples. Details about sample information, structural magnetic resonance imaging acquisition, image preprocessing, and statistical analyses were shown in [Supplementary Material](#) and [Supplementary Table 1](#).

3. Results

Our primary replication results were shown in [Table 1](#). None of the candidate SNPs were associated with mean bilateral hippocampal volumes in either individual sample or combined samples. We also assessed the associations by altering covariates (such as removing intracranial volume or including multidimensional scaling components), and the results remained nonsignificant ([Supplementary Tables 2 and 3](#)). The associations for left or right hippocampal volume were both not significant ([Supplementary Tables 4 and 5](#)). In addition, these SNPs were not associated with intracranial volume ([Supplementary Table 6](#)) or other factors (e.g., sex, age and so forth) either, excluding the possibility of the negative results caused by these factors.

We performed power analysis based on our sample size (a total of 990 subjects) using the genetic power calculator, and the analyses showed that we had over 80.0% power to detect risk variants with effect size of 2% of the variance, suggesting that our results are reliable.

4. Discussion

Our results did not show evidence of associations for the SNPs in our Asian samples. We performed the power calculation on our sample size and it is of enough power to identify true variants showing nominal significant associations ($p < 0.05$). Effect size

(β) is a measure of the strength of a phenomenon such as hippocampal volume variation; if an SNP contributes to hippocampal volume variation equally in different populations, the effect size should be the same between samples, but the *p*-value and standard error will vary because of differences in sample size; therefore, we also compared the effect sizes (β) of the SNPs between our Asian samples and Europeans. We found the effect sizes (β) in Asians were closer to zero compared with the results in Europeans (−9.91 mm³ vs. −52.80 mm³ for rs6741949-G; 5.85 mm³ vs. −47.70 mm³ for rs7852872-C; −19.16 mm³ vs. 47.58 mm³ for rs7294919-C), and the directions of β varied among the Asian samples ([Table 1](#)), indicating these SNPs unlikely contribute to large effects to hippocampal volume variation in Asians.

Notably, the genetic bases of hippocampal volume are very complex, likely with many involved variants of small effects. Although our imaging samples have been shown to be effective for the detection of genetic effects on hippocampal volumes extracted from the magnetic resonance imaging data ([Li et al., 2013](#); [Zhu et al., 2013](#)), we are still unable to detect extremely weak effect variants. More importantly, the most likely reason for the failure of replication is the well-known genetic divergences between European and Asian populations, which are common in genetic analyses of complex traits and disorders in world populations.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neurobiolaging.2014.07.015>.