REST rs3796529 variant does not influence human subcortical brain structures

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Nho et al. identified the minor allele T of REST missense variant rs3796529 confers a protective effect on right hippocampal loss with corrected p = 0.061 using 315 samples (including n= 135 mild cognitive impairment (MCI) cases) [1]. Meta-analysis of the four remaining cohorts indicate a marginal association of rs3796529 with right hippocampal volume (p = 0.063) [1]. Nho et al. used the Fisher's method to combine 0.061 and 0.063, and got the combined p = 0.025 based on the five independent cohorts (n = 923) [1]. Nho et al. further investigated the association between rs3796529 and hippocampal volume using imaging data of 1566 samples including MCI, Alzheimer's disease (AD) and cognitively normal individuals from Alzheimer's Disease Neuroimaging Initiative (ADNI) [2]. They identified the minor allele T of rs3796529 confers a protective effect on hippocampal loss in both MCI and AD participants, but not the cognitively normal individuals [2]. Nho et al. described that this issue deserves further investigation [2-3].

In previous study, Lu et al. found that induction of REST is a universal feature of normal ageing in human cortical and hippocampal neurons [3]. Here, we investigate if rs3796529 variant affects the structure of these brain regions using seven genome-wide association studies (GWAS) datasets about the volumes of seven subcortical regions (nucleus accumbens, caudate, putamen, pallidum, amygdala, hippocampus and thalamus) from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium (n = 30,717) [4]. The results show that the rs3796529 variant T allele does not significantly influence human subcortical brain structures in these seven subcortical regions (Table 1).

Table 1, rs3796529 variant T allele and volumes of seven subcortical regions

Brain regions	Effect_Beta	SE	*P* value	Number of samples
Hippocampus	-8.5167	5.8208	0.1434	13163
Accumbens	-0.0667	1.3557	0.9608	13112
Amygdala	-1.5668	2.9339	0.5933	13160
Caudate	5.2224	6.0745	0.3899	13171
Pallidum	1.7307	2.3721	0.4656	13142
Putamen	-1.4257	7.4333	0.8479	13145
Thalamus	-3.938	7.7855	0.613	13193

Beta is the overall estimated effect size for the effect (minor) allele T; Beta >0 and Beta <0 mean that this SNP increases and reduces the volume, respectively. SE: overall standard error for effect size estimate;

Taken together, our findings from large-scale samples show that rs3796529 variant neither confers a significant effect on hippocampal loss, nor effect on volumes of other six subcortical regions. Following studies are required to investigate our findings.

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Conflict of interest statements

The authors reported no potential conflicts of interest.

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