Effect of *REST* on brain metabolism in the Alzheimer's disease continuum

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Recently, Nho and colleagues[1] showed that the minor allele of rs3796529, a non-synonymous polymorphism in the *REST* gene, was protective against medial temporal lobe (MTL) atrophy in *APOE* ε3/ε3 individuals across the Alzheimer's disease (AD) continuum and, specifically, in patients with mild cognitive impairment (MCI). However, the possible protective effect of this variant in healthy control individuals (CN) [2] or *APOE* ε4 carriers was not specifically assessed.

In order to investigate a possible effect of this genetic variant on brain glucose metabolism we analyzed the [18F] fluorodeoxyglucose-PET (FDG-PET) metabolism patterns[3] in all Alzheimer's Disease Neuroimaging Initiative participants with available whole genome sequencing (n=751). We compared the FDG uptake between carriers versus non-carriers of this *REST* variant in CN, MCI and AD patients, using age and gender as covariates (including both *APOE* ε4 and non-*APOE* ε4 individuals).

Figures A and B show that both CN and MCI subjects harboring at least one minor allele of rs3796529 (CN, n=91 and MCI, n=149) presented increased metabolism in MTL structures with respect to non-carriers (CN, n=167 and MCI, n=296; $p<0.005$). No significant differences in metabolism were observed in AD patients (21 carriers versus 27 non-carriers; data not shown). Stratification by *APOE* ε4 genotype did not alter these results (data not shown), suggesting that these effects are independent of *APOE* ε4 status.

REST levels correlated with cognitive preservation in healthy aging, but were diminished in neurodegeneration.[4] Nho et al[1] identified a protective variant for hippocampal atrophy in this gene by whole exome sequencing. The higher MTL metabolism in carriers of rs3796529 provides further evidence for the neuroprotective role of this *REST* variant in both healthy controls and MCI patients. Additional work is needed in order to elucidate if this common variant (minor allele frequency =0.20 in European non-Finnish individuals; exac.broadinstitute.org/), or any other genetic variant in linkage disequilibrium, is contributing to healthy aging and/or protecting against the AD pathophysiological process.

References

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Figure. **Group analysis between carriers versus non-carriers of the REST variant rs3796529 in CN (A) and MCI subjects (B)**. Areas in which the carrier group presents increased metabolism with respect to the non-carrier group are displayed. As illustrated, both CN and MCI carriers of this variant showed increased metabolism in medial temporal lobe structures. All results are presented at $p<0.005$ using an extent threshold of $k=50$ voxels. **CN=healthy controls; MCI= patients with mild cognitive impairment.**

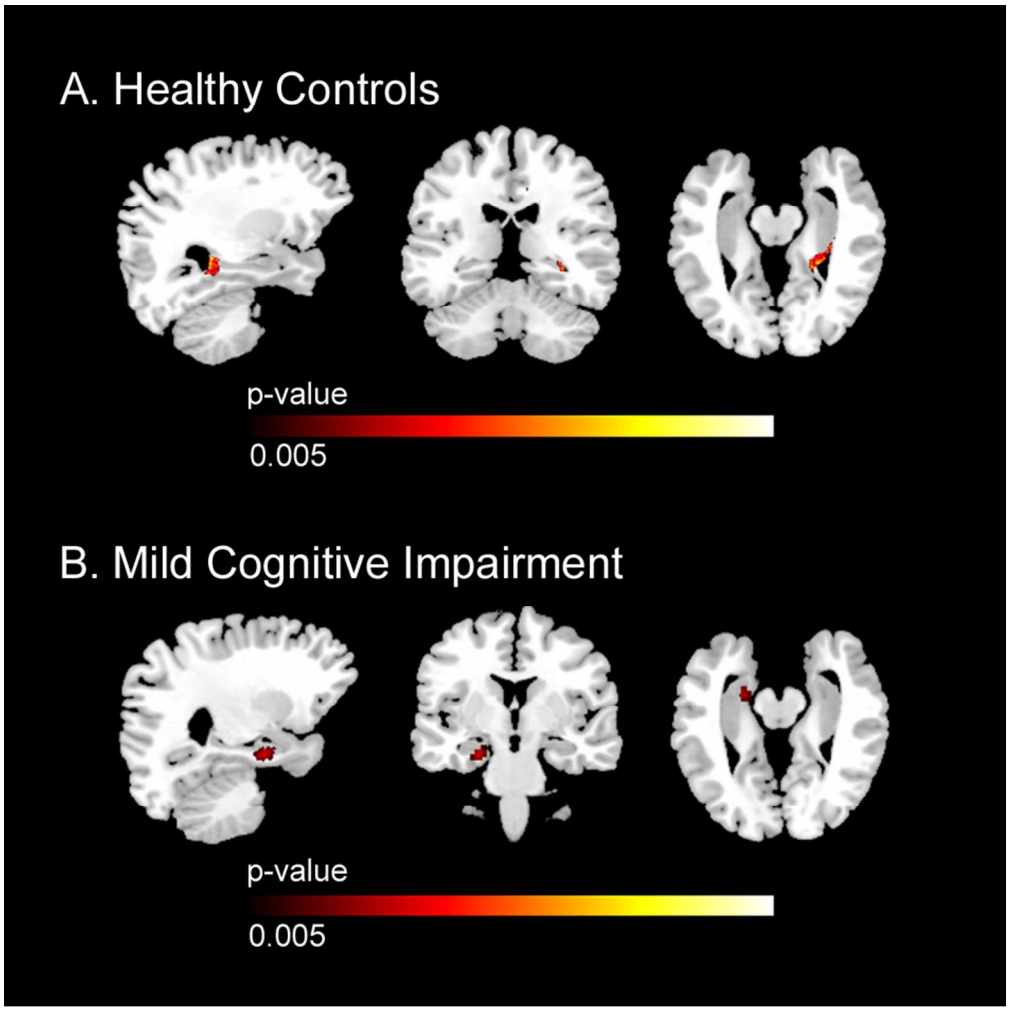

Figure. Group analysis between carriers versus non-carriers of the REST variant rs3796529 in CN (A) and MCI subjects (B). Areas in which the carrier group presents increased metabolism with respect to the non-carrier group are displayed. As illustrated, both CN and MCI carriers of this variant showed increased metabolism in medial temporal lobe structures. All results are presented at $p<0.005$ using an extent threshold of $k=50$ voxels. CN=healthy controls; MCI= patients with mild cognitive impairment.
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