Peripheral blood gene expression correlates of cortical atrophy across in cognitively normal elderly and MCI

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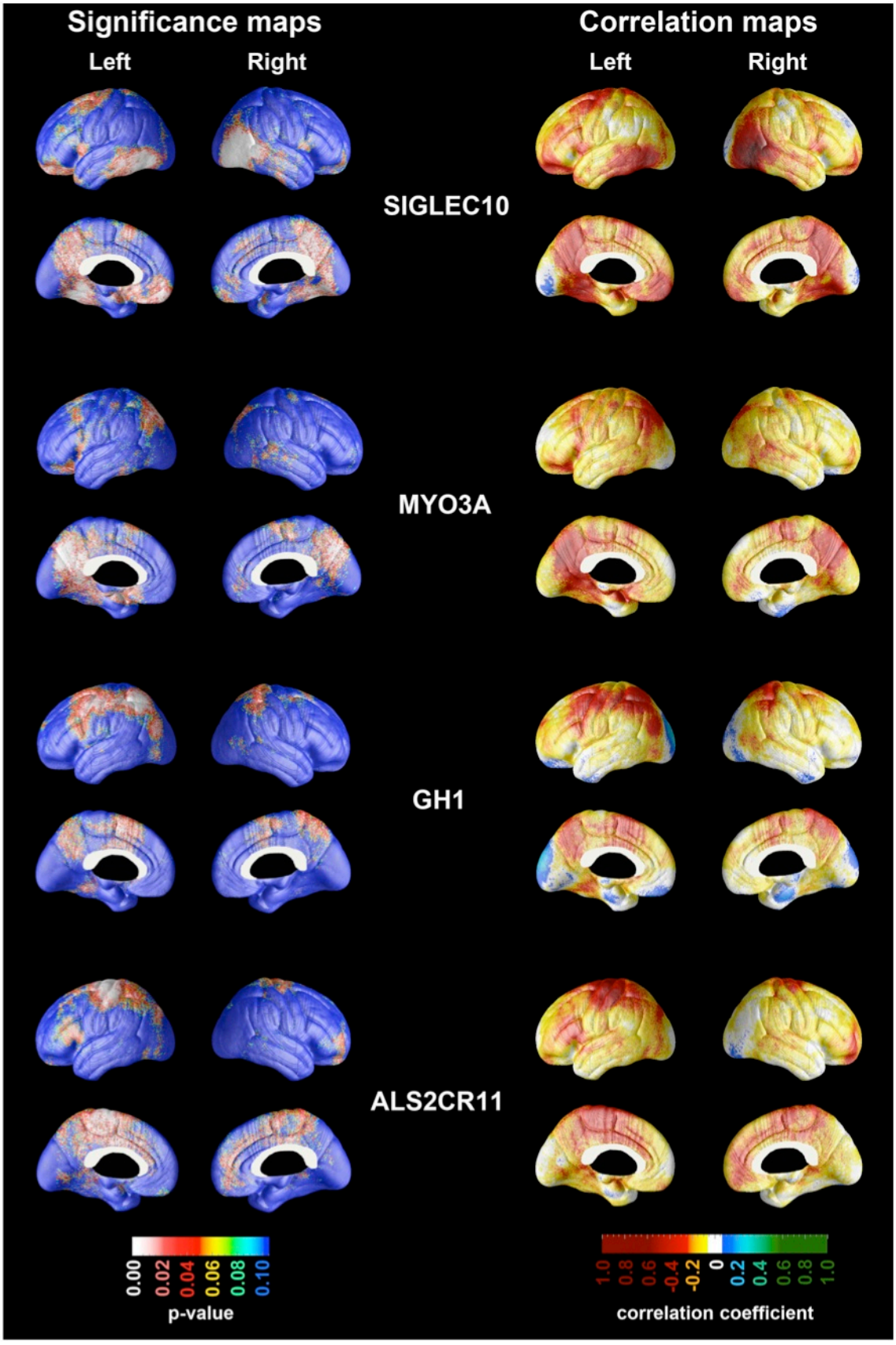
Background: Human genome-wide gene expression studies have generated important knowledge about the unique influences of multiple genes in health and disease. The complex interactions between gene expression and imaging biomarkers in Alzheimer's disease (AD) and the at-risk state of mild cognitive impairment (MCI) may yield important insights about the genetic influences and pathogenesis of AD.

Methods: We collected peripheral blood and 1.5T 3D MPRAGE T1-weighted brain MRI data from 38 cognitively normal (NC), 18 nonamnestic and 19 amnestic MCI subjects. Peripheral blood RNA was extracted using Paxgene tubes, amplified, labeled, and hybridized onto Illumina Human RefSeq-8 BeadChip arrays, querying the expression of ~24,000 RefSeq curated transcripts followed by quality control, quantile normalization with R and Bioconductor packages. The imaging data were analyzed with the cortical pattern matching and cortical thickness mapping techniques. Linear regression was used to examine the relationship between log2-transformed absolute gene expression levels and cortical thickness while adjusting for age and gender. For multiple comparison correction we used permutation tests with a threshold of $p<0.01$.

Results: Higher expression of Sialic acid binding lg-like lectin 10 (SIGLEC10), a gene associated with tissue damage-induced immune responses, showed associations with bilateral temporo-occipital, precuneal, posterior cingulate and inferior temporal cortical thinning (left hemisphere $p_{corrected}=0.032$; right hemisphere $p_{corrected}=0.043$). Higher expression of Myosin IIIA (MYO3A), a gene encoding the subtype of myosin that interacts with the GRINLIA glutamatergic receptor, while showing regionally similar associations with cortical thinning, also showed an association with the left lateral parietal cortex (left hemisphere $p_{corrected}=0.049$, right hemisphere $p=0.12$). Higher expression of growth hormone 1 (GH1), a regulator of neuronal survival via insulin-like growth factor, showed a pattern of association similar to that of MYO3A with trend-level significance on the left ($p_{corrected}=0.059$). Finally higher expression of Amyotrophic lateral sclerosis (ALS) 2 chromosome region 11 (ALS2CR11), a gene encoding a protein with calcium binding properties that has been implicated in the pathogenesis of ALS, correlated with bilateral cortical thinning of the sensorimotor strip, supplementary motor area and precuneus/posterior cingulate cortex as well as left inferior frontal and anterior cingulate cortex (left hemisphere $p_{corrected}=0.044$, right hemisphere $p=0.3$).

Conclusions: Altered peripheral blood gene expression is associated with cortical atrophy in the pre-dementia cognitive spectrum.


Significance maps
Left
Right
Correlation maps
Left
Right
SIGLEC10
MYO3A
GH1
ALS2CR11
0.00
0.02
0.04
0.06
0.08
0.10
p-value
1.0
0.8
0.6
0.4
0.2
0
0.2
0.4
0.6
0.8
1.0
correlation coefficient