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J Alzheimers Dis. 2016 ; 52(1): 373–383. doi:10.3233/JAD-160077.**Hippocampal Sclerosis of Aging, a Common Alzheimer's Disease 'Mimic': Risk Genotypes are Associated with Brain Atrophy Outside the Temporal Lobe****Kwangsik Nho^{a,c,d,*}, Andrew J. Saykin^{a,b,c,d}, Alzheimer's Disease Neuroimaging Initiative¹, and Peter T. Nelson^{e,*}**^aCenter for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA^bDepartment of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA^cCenter for Computational Biology and Bioinformatics, Indiana University School of Medicine, Indianapolis, IN, USA^dIndiana Alzheimer Disease Center, Indiana University School of Medicine, Indianapolis, IN, USA^eUniversity of Kentucky, Sanders-Brown Center on Aging and Pathology Department, University of Kentucky, Lexington, KY, USA**Abstract**

Hippocampal sclerosis of aging (HS-Aging) is a common brain disease in older adults with a clinical course that is similar to Alzheimer's disease. Four single-nucleotide polymorphisms (SNPs) have previously shown association with HS-Aging. The present study investigated structural brain changes associated with these SNPs using surface-based analysis. Participants from the Alzheimer's Disease Neuroimaging Initiative cohort (ADNI; $n = 1,239$), with both MRI scans and genotype data, were used to assess the association between brain atrophy and previously identified HS-Aging risk SNPs in the following genes: *GRN*, *TMEM106B*, *ABCC9*, and *KCNMB2* (minor allele frequency for each is $>30\%$). A fifth SNP (near the *ABCC9* gene) was evaluated in *post-hoc* analysis. The *GRN* risk SNP (rs5848_T) was associated with a pattern of atrophy in the dorsomedial frontal lobes bilaterally, remarkable since *GRN* is a risk factor for frontotemporal dementia. The *ABCC9* risk SNP (rs704180_A) was associated with multifocal atrophy whereas a SNP (rs7488080_A) nearby (~ 50 kb upstream) *ABCC9* was associated with atrophy in the right entorhinal cortex. Neither *TMEM106B* (rs1990622_T), *KCNMB2*

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SUPPLEMENTARY MATERIAL

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(rs9637454_A), nor any of the non-risk alleles were associated with brain atrophy. When all four previously identified HS-Aging risk SNPs were summed into a polygenic risk score, there was a pattern of associated multifocal brain atrophy in a predominately frontal pattern. We conclude that common SNPs previously linked to HS-Aging pathology were associated with a distinct pattern of anterior cortical atrophy. Genetic variation associated with HS-Aging pathology may represent a non-Alzheimer's disease contribution to atrophy outside of the hippocampus in older adults.

Keywords

Arteriosclerosis; dementia; KATP; progranulin; rs5848; rs704180; rs1990622; rs9637454; SUR2; TDP-43

INTRODUCTION

There is accumulating evidence of a common brain disease that mimics Alzheimer's disease (AD) clinically, and which has been classified using the term "hippocampal sclerosis" based on pathologic observations [1–11]. This disease affects up to 25% of the "oldest-old" [1, 12–14] and is associated with substantial disease-specific cognitive impairment [7–9, 13–17]. We apply the term "hippocampal sclerosis of aging" (HS-Aging) [1], to differentiate this disease from other conditions referred to as "hippocampal sclerosis", because the latter designation refers to a pathologic phenomenon observed in many different brain disorders [13, 18–20]. HS-Aging is distinguished by the advanced age of the affected individuals, by the usual lack of either seizure disorder or frontotemporal dementia symptoms clinically, and by the presence of hippocampal TDP-43 pathology at autopsy [1, 2, 21–24]. HS-Aging is generally misdiagnosed in live individuals as AD [9, 16]; put another way, a relatively large proportion of what is considered "Alzheimer's disease" clinically is actually HS-Aging. Despite rapid progress from multiple research centers, much remains to be learned about HS-Aging pathoetiology.

One promising approach for better understanding HS-Aging is through the study of genetics and specifically genotype-phenotype correlations. HS-Aging pathology has been linked with single-nucleotide polymorphisms (SNPs) within or near four different genes: *GRN*, *TMEM106B*, *ABCC9*, and *KCNMB2*. Two of the putative HS-Aging risk SNPs were previously associated with risk for frontotemporal lobar degeneration (FTLD), namely rs5848 (*GRN*) and rs1990622 (near *TMEM106B*) [25–28]. Genome-wide association studies (GWAS) implicated the other two SNPs—rs704180 (*ABCC9*) and rs9637454 (*KCNMB2*)—in genes that encode potassium channel regulators [29, 30]. All four SNPs are relatively common, with minor allele frequencies of ~30%–50% in most populations. In terms of the disease phenotype, the study of multiple large cohorts indicated that HS-Aging, although diagnosed at autopsy according to the signal feature of hippocampal sclerosis, also affects brain areas outside of the hippocampus, including the frontal neocortex [31–33].

Collectively, these prior findings indicate that multiple genes can cause or exacerbate a disease (which we refer to currently as HS-Aging) that affects brain regions outside of the hippocampus. More specifically, we hypothesized that HS-Aging risk SNPs in older adults would be associated with brain structural variance detectable with brain neuroimaging, both

within and outside the temporal lobe. To test this hypothesis, we evaluated data including magnetic resonance imaging (MRI) and genetic information, from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. These analyses indicated that the HS-Aging risk gene variants are associated with relatively widespread brain atrophy in older adults.

MATERIALS AND METHODS

Subjects

All individuals included in this report were participants in the ADNI cohort and aged 55–90 years at the time of scan. The ADNI initial phase (ADNI-1) was launched in 2003 to test whether serial MRIs, other biological markers, and clinical and neuropsychological assessment could be combined to measure the progression of mild cognitive impairment (MCI) and early AD. The ADNI-1 participants were recruited from 59 sites across the U.S. and Canada and included approximately 200 cognitively normal older individuals (HC), 400 patients diagnosed with MCI, and 200 patients diagnosed with early probable AD aged 55–90 years. ADNI-1 has been extended in subsequent phases (ADNI-GO and ADNI-2) for follow-up of existing participants and additional new enrollments. Inclusion and exclusion criteria, clinical and neuroimaging protocols, and other information about ADNI have been published previously [34] and can be found at <http://www.adni-info.org>. Demographic information, raw scan data, *APOE* and whole-genome genotyping data, neuropsychological test scores, and diagnostic information are publicly available from the ADNI data repository (<http://www.loni.usc.edu/ADNI/>). Written informed consent was obtained at the time of enrollment and/or genetic sample collection and protocols were approved by each participating study and sites' Institutional Review Board. We only included non-Hispanic Caucasians in order to limit the impact of population stratification on association analysis (removing 140 participants).

Genotyping and imputation

Genotyping was performed using the Illumina Human610-Quad BeadChip for the ADNI-1 participants, and the Illumina HumanOmni Express BeadChip and the Illumina Omni2.5M BeadChip for participants initially enrolled in ADNI-GO or ADNI-2. *APOE* genotyping was separately obtained using standard methods to yield the *APOE* $\epsilon 4$ allele defining SNPs (rs429358, rs7412). rs5848 (*GRN*) was genotyped only in the Illumina HumanOmni Express BeadChip and other SNPs (rs704180, rs7488080, rs1990622, and rs9637454) were not genotyped in any genotyping platforms. The un-genotyped SNPs were imputed separately in each phase as the ADNI cohort used different genotyping platforms. Before the imputation, we performed standard sample and SNP quality control procedures as described previously [35]. Furthermore, in order to prevent spurious association due to population stratification, we selected only non-Hispanic Caucasian participants that clustered with HapMap CEU or TSI populations using multidimensional scaling analysis (<http://www.hapmap.org>). Imputation was performed using MACH and minimac in a two-stage procedure as described previously [36]. The pilot 1 data of the 1000 Genomes Project were used as a reference panels for inferring missing genotypes. Minimac produced the posterior probabilities of the imputed genotypes at un-genotyped marker loci for each individual. In order to assess the

quality of imputation, an r^2 value equal to 0.30 was imposed as the threshold to accept the imputed genotypes.

Imaging processing

T₁-weighted brain MRI scans at baseline were acquired using a sagittal 3D MP-RAGE sequence following the ADNI MRI protocol [37]. As detailed in previous studies [38], a widely employed automated MRI analysis technique was used to process MRI scans: FreeSurfer V5.1 software (<http://surfer.nmr.mgh.harvard.edu/>). FreeSurfer was used to process and extract brain-wide target MRI imaging phenotypes (region volume and cortical thickness) by automated segmentation and parcellation. The cortical surface was reconstructed to measure thickness at each vertex on the surface. The cortical thickness was calculated by taking the Euclidean distance between the grey/white boundary and the grey/cerebrospinal fluid (CSF) boundary at each vertex on surface. For surface-based comparison of the cortical thickness, all individual cortical surfaces were registered to a common surface template, which was an average created from all cognitively normal control subjects. The cortical thickness was smoothed with 10 mm FWHM Gaussian kernel to improve the signal-to-noise ratio and statistical power. The common surface template is a triangle mesh consisting of 327,684 vertices with a cortical thickness value at each vertex on surface. In order to assess relative size of significant clusters on surface, we identified the number of vertices belonging to the significant clusters in a 100 vertices unit.

Imaging genetics analysis

The SurfStat software package (<http://www.math.mcgill.ca/keith/surfstat/>) was employed to perform surface-based analysis using a general linear model (GLM) approach. GLMs were developed using age at scan, gender, years of education, intracranial volume (ICV), diagnosis at baseline, MRI field strength, and SNP as independent variables. Following analysis of cortical thickness to examine the association between candidate SNPs and localizable cortical thickness measures, correction for multiple comparisons was performed using the random field theory (RFT) correction method at a 0.05 level of significance.

RESULTS

The main research question was whether candidate SNPs previously associated with HS-Aging pathology are associated with brain atrophy detectable by structural MRI in older adults from the ADNI cohort. Detailed information about the SNPs, stratified by demographics and other parameters, is presented in Table 1. In the 1,239 included participants, the average age at scan was 73.8, average educational level was 15.9, percentage of participants with *APOE* $\epsilon 4$ allele was 46.0%, and percentage of participants that were female was 42.7%. The genes (SNPs) studied here were *GRN*(rs5848), *TMEM106B* (rs1990622), *ABCC9* (rs704180), and *KCNMB2* (rs9637454). The assumed models of mode of inheritance were derived from the published literature [29, 39]. We did not observe any associations with the non-risk alleles of these SNPs at the same statistical threshold (data not shown). For the SNPs showing an association ($p < 0.05$) with cortical thickness variance (following correction for multiple comparisons), tabular data about localization of atrophy and corrected p -values are presented in Table 2.

None of the four SNPs previously identified to be associated with HS-Aging pathology showed associations with medial temporal lobe atrophy in the ADNI cohort. Two SNPs (rs5848 and rs1990622) previously linked to risk for both FTLD with TDP43-positive inclusions (FTLD-TDP) and HS-Aging showed different results. For *GRN*/rs5848 (Fig. 1; dominant model), the atrophy significantly associated with the risk allele was localized to the medial dorsal frontal cortex, roughly corresponding to Brodmann Area 9. Participants having at least one risk allele have decreased cortical thickness compared to those with no risk allele. As was the case for all SNPs tested, the non-risk SNPs did not show any significant spatial clusters (data not shown). For *TMEM106B*/rs1990622 (a dominant model was used), there was no area of MRI-detected atrophy (data not shown).

SNPs in two other genes were assessed that previously were linked to HS-Aging pathology: *ABCC9* and *KCNMB2*. For *ABCC9*/rs704180, (Fig. 2; recessive model), the atrophy was multifocal with the largest area showing association to the SNP appearing in the right frontal lobe (Table 2). By contrast, for *KCNMB2*/rs9637454 (recessive model), we found no evidence of atrophy associated with the risk allele (data not shown).

In a *post-hoc* analyses, we also evaluated two SNPs that were intergenic, between *ABCC9* and *CMAS* on chromosome 12p (Fig. 3). A prior study showed that rs10743430 is associated with entorhinal thinning [40], a neuroimaging phenotype that could be a proxy for HS-Aging pathology. We identified another SNP (rs7488080) that is closer to *ABCC9* on chromosome 12p than rs10743430, and tested its association with brain atrophy in the ADNI cohort. These two SNPs are in strong linkage disequilibrium (LD) with each other ($r^2 = 0.87$, $D' = 0.99$). We confirmed that in this sample (larger than in the prior study, but not an independent sample since Furney et al. [40] analyzed ADNI-1; see Discussion below), both rs10743430 and rs7488080 were associated with right entorhinal thinning.

When the *APOE* $\epsilon 4$ status was added as a covariate, the results were not changed (Supplementary Material).

We investigated whether the four common variants (rs5848, rs1990622, rs704180, and rs9637454) previously associated with risk of HS-Aging may also collectively underlie brain atrophy using cumulative genetic risk scores or polygenic risk scores to model the aggregate effect. Note that the intergenic SNPs described above were not included in this analysis. A polygenic score for each subject was constructed by summing the number of risk alleles across the four risk SNPs without considering their effect sizes. Figure 4(A) showed the distribution of the polygenic risk scores for each diagnosis group. The association analysis between polygenic risk scores and cortical thickness identified significant regional differences in thickness including multiple, predominately frontal, neocortical areas.

DISCUSSION

Here we report that gene variants previously associated with risk of HS-Aging pathology are also associated with brain atrophy outside the temporal lobe. The *GRN* risk locus (rs5848) was associated with atrophy in the frontal cortex bilaterally, whereas the other risk locus also associated with FTLD, rs1990622 (*TMEM106B*), was not associated with cortical atrophy

in this sample. *ABCC9* gene variants (rs704180 and rs7488080) were associated with more multifocal, or generalized, atrophy. The only evaluated SNP that showed association with medial temporal structural changes (entorhinal cortex) in this dataset was rs7488080 which is ~50 kb upstream the *ABCC9* gene. When the risk alleles were combined, they were related to a frontal cortex predominant pattern of brain atrophy. These data indicate that gene variants associated with HS-Aging pathology are also associated with vulnerability to neurodegeneration outside the hippocampal formation proper.

There are limitations to this study. The ADNI dataset is enriched for individuals at risk for AD and the present study relates to a disease (HS-Aging) which is similar but not identical to AD clinically [16, 41], so, the study findings may best relate to the subset of individuals with HS-Aging related genotype that have an “AD-like” phenotype. From a technical standpoint, the medial and more variable brain regions can be challenging to assess confidently across individuals using structural MRI. Further, the average age of the included subjects at the time of their MRI scan was not extremely old (73.8 years) in comparison to the ages of the individuals with autopsy-proven HS-Aging (often over 85 years at death) [1, 2, 6, 7, 9, 12, 16, 17, 31, 42]. However, the current study also lacks some of the sources of bias that affect most autopsy studies (for examples, see [43, 44]). It should be noted that the observations made on the ADNI research subjects could provide important insights about the structural brain changes that occur earlier in the disease course.

An assumption underlying the current study is that neuropathologic classification is continuously evolving and fails to capture the full complexity of the aged human brain. The term “sclerosis” means “hardening” in Greek, and lacks a specific connotation in terms of molecular pathogenesis. Hippocampal sclerosis in aged individuals is diagnosed at autopsy, according to consensus-based criteria [45], when neuron loss and astrocytosis are observed in the hippocampal formation, out of proportion to AD-type plaques and tangles in the same structure. However, the actual anatomical localization of HS-Aging related pathologic changes are not confined to the hippocampal formation [1, 31, 32] and the applied nomenclature for the disease is heterogeneous [13, 19]. Even at academic centers specializing in neurodegenerative disease, HS-Aging tends to be misdiagnosed as AD clinically because of overlapping symptoms and imperfectly understood biomarkers [1, 16, 41]. Hence the disease nosology, and even the awareness of its existence, should be recognized as being currently in a state of rapid change.

As described above, genetic risk factors for HS-Aging have provided insights into potential disease mechanisms. For example, *APOE* gene variants are not associated with altered risk for HS-Aging [1, 12, 16, 41, 46] and including *APOE* genotype in our models did not alter our results in terms of the genotype associations. These findings provide strong support for the hypothesis that HS-Aging is a separate disease entity from AD.

In the present study we found that the pattern of brain atrophy associated with different candidate HS-Aging risk alleles was not the same for each gene, and that atrophy was localized to regions mostly outside of the hippocampus. For *GRN*(rs5848), the atrophy associated with the risk genotype was localized to the dorsal and (mostly) medial frontal cortex. There was a striking bilaterally symmetric pattern that seemed to correspond to or

near Brodmann Area 9. This is intriguing because *GRN* mutations lead to a frontotemporal dementia (FTD, a clinical term) that is associated with a pathologic diagnosis of FTLD-TDP. Remarkably, there was no apparent atrophy signal related to rs5848 and the anterior temporal lobe such as occurs in FTLD-TDP. In addition to HS-Aging pathology, rs5848 has also been linked to multiple other brain disorders [47–49]. It is thus possible that the rs5848-associated structural changes that were elucidated in the current study were due to brain conditions other than HS-Aging.

Another gene that was associated with brain atrophy in the ADNI cohort and previously associated with the HS-Aging pathology is *ABCC9*. The risk SNP, rs704180, was also associated with brain atrophy in the ADNI cohort but the statistically significant atrophy (controlling for multiple comparisons) is outside of the hippocampal formation. A SNP near *ABCC9* (rs7488080) was associated with entorhinal cortex atrophy in the ADNI cohort. This SNP is <50 kb upstream of the *ABCC9* start site, the next closest gene is *CMAS*. Also noteworthy is that rs10743430, in strong linkage disequilibrium ($R^2 = 0.87$) with rs7488080, but not rs704180, was previously found to be the second strongest SNP in association with the endophenotype of entorhinal thinning in the ADNI-1 and AddNeuroMed cohorts [40]. At the time of that prior study, only 939 participants were evaluated for entorhinal thickness whereas the current study included 1,239 participants. Notably, entorhinal cortical atrophy may be a strong proxy for HS-Aging in a MRI study since the entorhinal cortex appears involved even early in the disease process [50].

The *KCNMB2* and *TMEM106B* variants, when assessed individually, did not show significant association signals with cerebral atrophy in the ADNI dataset. However, prior evidence suggests that risk of HS-Aging pathology is increased when risk alleles are present in combination [39]. We therefore tested for potential interactions and found that frontal cortical atrophy may be associated with a polygenic combination of HS-Aging risk SNPs.

The present results can be reconciled with prior studies to help refine our expectations about a prevalent and high-morbidity brain disease that mimics AD. A directly relevant recent study from Rush University found that in elderly individuals that died with eventually autopsy-proven HS, premortem neuroimaging showed extensive brain atrophy on MRI, especially in the frontal lobes [32]. We previously reported evidence for brain pathology outside the hippocampal formation (specifically in the frontal cortex) in patients with comorbid HS-Aging [31], and multiple lines of evidence point to a multi-domain cognitive deficit in patients affected by the disease [1, 16]. The hypothesis that HS-Aging is actually a diffuse or multifocal disease that is often comorbid with brain arteriosclerosis pathology rather than one localized to medial temporal lobe structures, is quite credible given the prior reports [13, 16, 31, 33, 50–52]. We conclude that the present study adds additional evidence to support a role for genetic variation in brain pathologies, and to the appreciation that this is a multi-factorial condition that can impact brain areas well beyond the hippocampus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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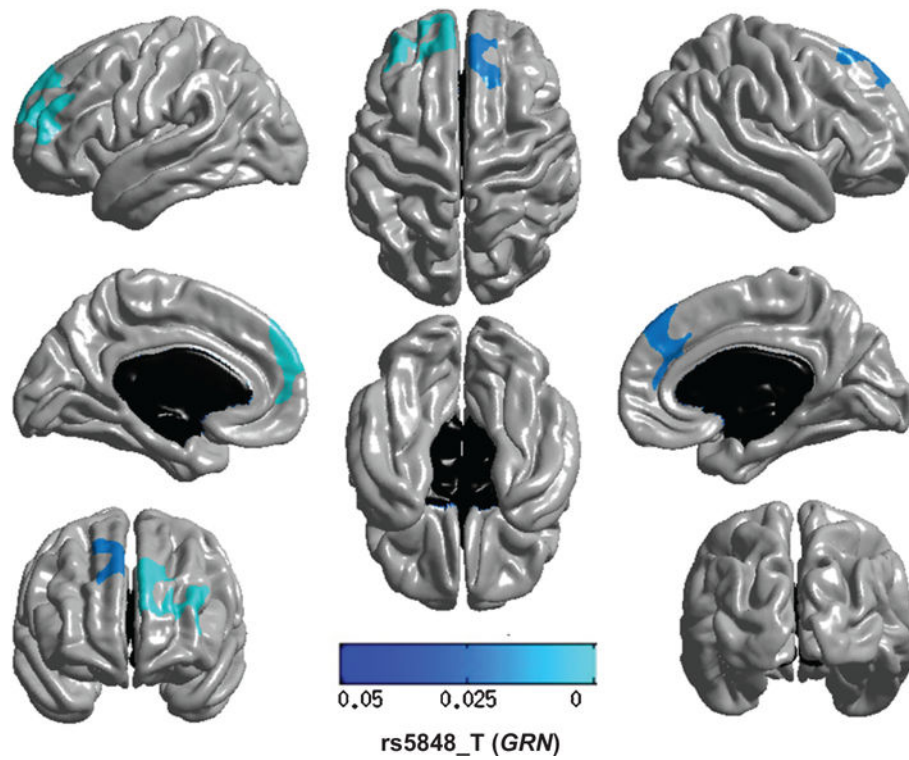


Fig. 1. Regional brain atrophy associated with variation in *GRN*/rs5858. *GRN* encodes progranulin, a potent growth factor that plays important roles in wound healing and angiogenesis. Note that the *GRN*/rs5848_T allele is associated with atrophy that localizes on both sides to the dorsal and medial frontal neocortex. This is remarkable since *GRN* is a risk gene for frontotemporal dementia. The multi-tone blue tab indicates *p* value.

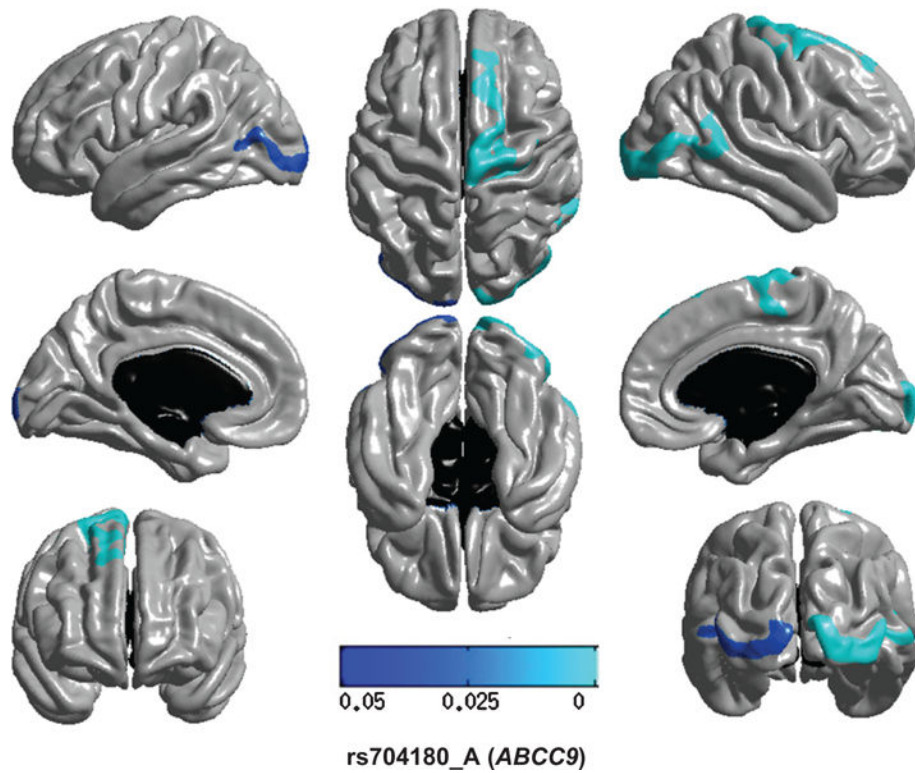


Fig. 2. Regional brain atrophy associated with variation in *ABCC9*/rs704180. *ABCC9* encodes SUR2 (sulfonylurea receptor 2), a protein that acts as a metabolic sensor important in brain's responses to hypoxia and other stressors. The regions of the brain where atrophy is associated with the presence of the *ABCC9*/rs704180 risk allele were scattered throughout the brain, mostly outside of the temporal lobe. The multi-tone blue tab indicates p value.

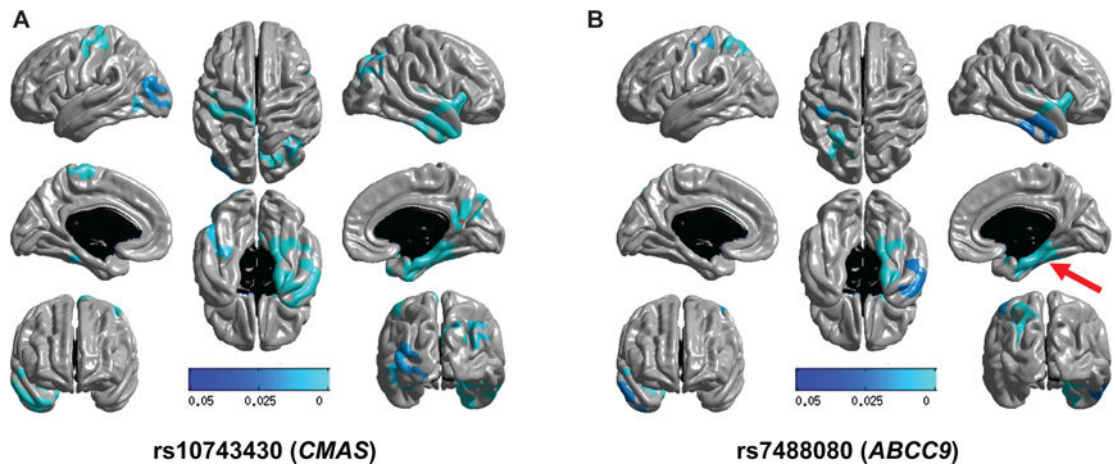


Fig. 3.

A prior study [40] identified an intergenic SNP between genes *ABCC9* and *CMAS* on human chromosome 12p that is strongly associated with entorhinal cortical thinning in the ADNI and AddNeuroMed datasets ($p < 1e^{-6}$). Here are shown results from that SNP ([A]; rs10743430; dominant model) and also a nearby SNP ([B]; rs7488080; dominant model) that is in close linkage disequilibrium ($r^2 = 0.87$, $D' = 0.99$). Note that for both SNPs, the risk allele is associated with right-sided entorhinal cortex atrophy (red arrow, panel B), as well as atrophy in other regions. The multi-tone blue tab indicates p value.

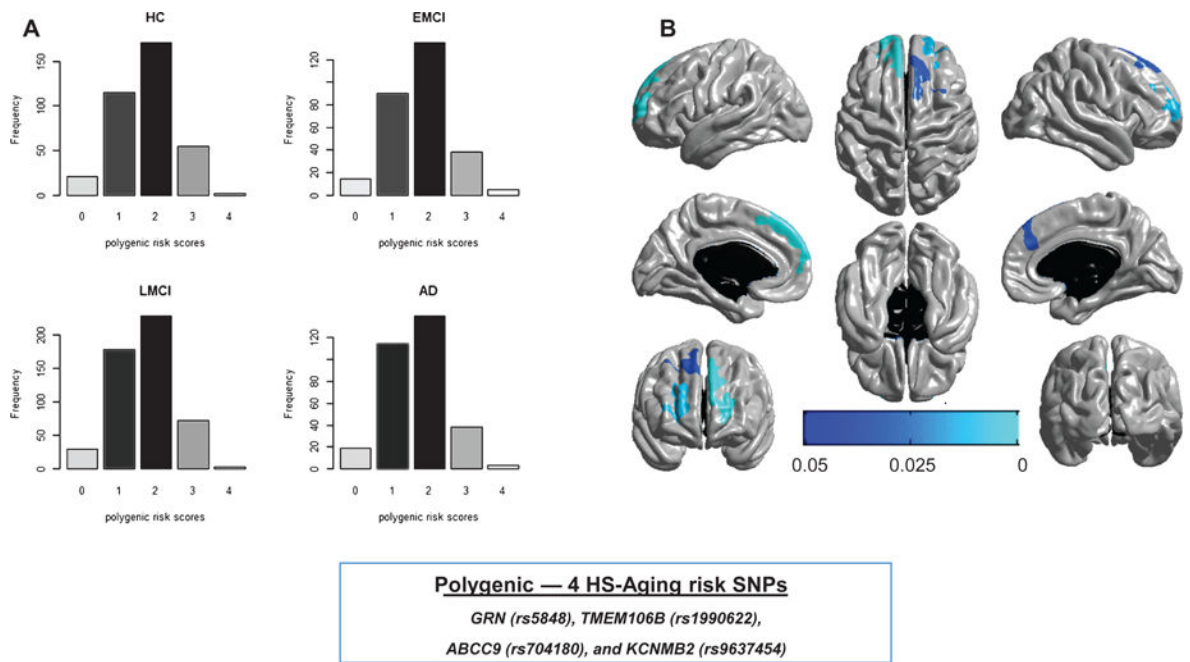


Fig. 4. Distribution (A) of polygenic risk scores for each diagnosis group—cognitively normal control (HC), early MCI (EMCI), late MCI (LMCI), and Alzheimer’s disease (AD) by clinical impression—and regional brain atrophy (B) associated with polygenic risk scores. The polygenic risk scores were used to investigate the possibility of overlapping genetic factors. Those scores reflect a combined effect of four risk alleles for HS-Aging. The polygenic risk scores are associated with cortical thickness in multifocal brain atrophy including multiple areas of the neocortex, predominately in the frontal lobes. The multi-tone blue tab indicates *p* value.

Genes and SNPs assessed in the current study, with additional information related to genotype, demographics, clinical diagnosis, and the MRI field strength (putative risk genotype shown in the leftward columns).

Table 1

Gene/SNP-> Genotype->	GRN/rs848			ABCC9/rs704180			ABCC9/rs7488080			TMEM106B/rs19906722			KCNMB2/rs9637454		
	TT/TC	CC	AA	AA	GG/GA	AA/AG	GG	TT/CT	CC	AA	GG/AG	CC	AA	GG/AG	
N	668	571	335	335	904	135	1,104	1,022	217	89	1,150	217	89	1,150	
Sex (M/F)	384/284	326/245	189/146	189/146	521/383	75/60	635/469	594/428	116/101	48/41	662/488	116/101	48/41	662/488	
APOE ε4 status (presence/absence)	291/377	284/287	170/165	170/165	405/499	63/72	512/592	472/550	103/114	46/43	529/621	103/114	46/43	529/621	
Age (Mean ± SD)	73.92 ± 7.29	73.75 ± 6.97	73.72 ± 7.41	73.72 ± 7.41	73.89 ± 7.05	73.34 ± 7.47	73.90 ± 7.11	73.95 ± 7.17	73.33 ± 7.02	73.62 ± 7.70	73.86 ± 7.10	73.33 ± 7.02	73.62 ± 7.70	73.86 ± 7.10	
Diagnosis (HC/EMCI/LMCI/AD)	195/116/245/112	151/102/207/111	93/66/121/55	93/66/121/55	253/152/331/168	34/30/49/22	312/188/403/201	286/187/364/185	60/31/88/38	24/17/35/13	322/201/417/210	60/31/88/38	24/17/35/13	322/201/417/210	
Magnetic field strength (1.5T/3T)	392/276	353/218	178/157	178/157	567/337	79/56	666/438	603/419	142/75	54/35	691/459	142/75	54/35	691/459	

Table 2

Gene variants associated with MRI detected brain atrophy: anatomic localization, size, and corrected p values of significant clusters

<i>Gene (SNP)</i>	Cluster	Anatomic localization	Cluster size*	Corrected p-value
<i>GRN</i> (rs5848)	1	Left frontal lobe	33.4	4.0×10^{-5}
	2	Right frontal lobe	19.2	0.020
<i>ABCC9</i> (rs7488080)	1	Right frontal and temporal lobes	45.9	1.91×10^{-5}
	2	Left parietal lobe	31.8	6.42×10^{-4}
	3	Right temporal lobe including entorhinal cortex	33.9	7.60×10^{-4}
	4	Left frontal and parietal lobes	26.7	0.013
	5	Right temporal lobe	19.8	0.020
<i>ABCC9</i> (rs704180)	1	Right frontal lobe	61.6	7.13×10^{-8}
	2	Right temporal and occipital lobes	38.3	2.50×10^{-5}
	3	Left occipital lobe	19.4	0.032

* See text for calculation method.