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Reassessment of Risk Genotypes (*GRN*, *TMEM106B*, and *ABCC9* Variants) Associated with Hippocampal Sclerosis of Aging Pathology

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Abstract

Hippocampal sclerosis of aging (HS-Aging) is a common, high morbidity-associated neurodegenerative condition in elderly persons. To understand risk factors for HS-Aging, we analyzed data from the Alzheimer's Disease Genetics Consortium and correlated the data with clinical and pathologic information from the National Alzheimer's Coordinating Center database. Overall, 268 research volunteers with HS-Aging and 2957 controls were included; detailed neuropathologic data were available for all. The study focused on single nucleotide polymorphisms previously associated with HS-Aging risk: rs5848 (*GRN*), rs1990622 (*TMEM106B*), and rs704180 (*ABCC9*). Analyses of a subsample that were not previously evaluated (51 HS-Aging cases and 561 controls) replicated the associations of previously identified HS-Aging risk alleles. To test for evidence of gene-gene interactions and genotype-

phenotype relationships, pooled data were analyzed. The risk for HS-Aging diagnosis associated with these genetic polymorphisms was not secondary to an association with either Alzheimer disease or dementia with Lewy bodies neuropathologic changes. The presence of multiple risk genotypes was associated with a trend for additive risk for HS-Aging pathology. We conclude that multiple genes play important roles in HS-Aging, which is a distinctive neurodegenerative disease of aging.

Keywords

Alzheimer disease; Hippocampal sclerosis; KATP; SUR2; Genome wide association study (GWAS); Progranulin; Frontotemporal lobar degeneration (FTLD)

INTRODUCTION

Hippocampal sclerosis of aging (HS-Aging) is diagnosed neuropathologically when neuron loss and astrogliosis are observed in the hippocampal formation, and are not considered attributable to Alzheimer disease (AD)-type plaques and tangles (1-3). Although there are other brain diseases with pathologic changes that are described as “hippocampal sclerosis,” HS-Aging is distinguished by the presence of TDP-43 pathology and the absence of severe symptoms or clinical signs of frontotemporal dementia (4-8). HS-Aging is a relatively common disease in elderly persons (2, 7, 9, 10) and is associated with substantial disease-specific cognitive impairment (11, 12). Even at state-of-the-art research institutions such as U.S. Alzheimer’s Disease Centers (ADCs), HS-Aging tends to be misdiagnosed as AD clinically because of overlapping manifestations (7, 12, 13), and therefore autopsy data are essential for accurate disease diagnosis.

There is no known disease-modifying treatment for HS-Aging. One factor impeding development of therapeutic strategies is that disease mechanisms are still incompletely understood. Vascular disease may contribute to HS-Aging pathology or, alternatively, pathogenetic factors may overlap with those of frontotemporal lobar degeneration (FTLD) (2, 10, 14, 15).

Genetic risk factors for HS-Aging have recently been characterized, yielding new insights into disease mechanisms. In contrast to AD, *APOE* gene variants are not associated with altered risk for HS-Aging (7, 9, 12, 13, 16). Here, we discuss “risk alleles” that are single nucleotide polymorphisms (SNPs), and risk genotypes (combinations of alleles), associated with altered manifestation of a phenotype. The association of a SNP with a specific phenotype (in the present study, autopsy-diagnosed HS-Aging pathology) is expressed commonly using 2 parameters: 1) odds ratio (OR), which represents the odds of HS-Aging pathology for individuals with the risk genotype relative to the odds for those without the risk genotype; and 2) probability (p value) of observing an OR at least as large as the one discovered, given the sample sizes, and assuming no underlying association between the SNP and the phenotype.

Hippocampal sclerosis pathology in AD cases was associated with SNPs previously associated with FTLD, namely rs5848 (*GRN*) and rs1990622 (near *TMEM106B*) (17-20). A

prior genome wide association study (GWAS) that focused on HS-Aging pathology as an endophenotype reported that 2 SNPs in near-perfect linkage disequilibrium with each other (rs704178 and rs704180) in *ABCC9* are associated with HS-Aging pathology, with OR = 2.1 and an overall p value = 1.4×10^{-9} when all the cohorts' data were combined (21). For practical reasons, we will refer only to rs704180 hereafter.

To learn more about genetic polymorphisms associated with HS-Aging pathology, we examined genomics data from the Alzheimer's Disease Genetics Consortium (ADGC), correlated with clinical and pathologic data from the National Alzheimer's Coordinating Center (NACC) database (22-24). Data were analyzed from ADC research volunteers who had been examined clinically with subsequent neuropathological evaluation, to test whether previously reported HS-Aging risk alleles (rs5848, rs1990622, and rs704180) can be replicated, and to evaluate gene-gene interactions. We also tested whether or not the association between those alleles and HS-Aging pathology is related to AD or dementia with Lewy bodies neuropathologic changes among genotyped subjects in the relatively large NACC autopsy cohort.

MATERIALS AND METHODS

Patient Subjects

The ADGC accrued genomics data from 29 different ADCs (more than 10 cases each from 26 ADCs, more than 100 cases each from 20 ADCs) with multiple iterations of SNP data (23, 25, 26), which were analyzed together with neuropathological and clinical data gathered through NACC (24). Research using NACC data was approved by the University of Washington Human Subjects Division; protocols at individual ADCs were approved of and regulated by local Institutional Review Boards. NACC data were obtained from the Minimum Data Set, Uniform Data Set, and Neuropathology Data Set (12, 24). The 3 allele identities were analyzed according to ADGC SNP nomenclature and were rs5848 (A/G); rs1990662 (A/G; note that other reports have used T/C for this allele, the "A" allele is analogous to "T" allele in other reports whereas the "G" allele we report is analogous to "C" allele); and rs704180 (this is an A/G allele in near-perfect linkage disequilibrium with rs704178, which is a G/C allele; G/C alleles are challenging because of reverse strand issues, so we recommend using rs704180 as the referent allele). Neuropathologic evaluations were performed according to center-specific protocols, including whether neuropathologists studied left, right, or bilateral hippocampi (12), and entered into a standardized format for NACC purposes. Only individuals who died after age 60 were included in this study. HS-Aging case/control operationalization in NACC were described previously (12, 21); details of the NACC parameter definitions are presented in the Supplemental Material. Relatively few persons with FTLN-TDP, FTLN-tau, other FTLN subtypes, or spongiform encephalopathy were genotyped in our available database (Supplemental Material). These subjects were excluded from the analyses because the subsample with FTLN and prion subtypes (together comprising 188 individuals, 24 with HS-Aging pathology) was underpowered for statistical comparisons.

After exclusions, data from a total of 2343 NACC/ADGC research subjects with genotype and autopsy information outside of UK-ADC data were available for analyses at the time of

our prior published HS-Aging GWAS (21). Some cases are included in the current study and not the HS-GWAS project because they met inclusion criteria as stated; however, these research subjects are not an independent cohort for the purpose of a replication experiment. Notably, the current study included patients who died before the year 2000. Subgroup analysis confirmed that the rate of HS diagnosis was lower before 2000 but this enabled a complete assessment of the NACC/ADGC data. Additional data from 612 research subjects with genotype and NACC autopsies were available for the present study that were not available for previous analyses and were not previously analyzed in our studies. These cases provided an independent subgroup to retest the association between putative risk alleles and HS-Aging pathology. The 612 cases comprising a replication cohort were accrued from 26 different ADCs; average number of cases per ADC was 23.5; median number of research subjects included for analyses per ADC was 21; and the maximum number of included research subjects from one ADC was 79. The main reason for these cases being now available for this study is that there was a round of database-wide quality control (QC) and imputation that was performed by the ADGC in the spring of 2014; this effort was completed after the dates the HS-Aging GWAS paper was submitted and reviewed. This QC/imputation refined the availability of genotyped NACC cases and enabled inclusion of research subjects that were previously excluded due to covariate coding that was suboptimal. For example, over 500 research subjects' data were excluded from the NACC/ADGC analyses previously because they were classified as having an inappropriate age parameter, although those cases were within the included age range. Further, and beyond the issues related to imputation and QC, the database analyzed in the current study included data from 122 research subjects whose genotyping data appeared in the database after the time-stamp of the database used for the HS-Aging GWAS. Additional QC were performed on all of the cases and found that the specific targeted SNP calls for rs5848, rs1990622, and rs704180 were of adequate technical quality but data from 6 additional research subjects were removed due to a first-degree relationship following KING-Robust analysis.

Neuropathology

Features of AD neuropathologic changes were operationalized as diffuse plaques (most of the autopsies predated the universal application of Thal A β staging), neuritic plaques, and neurofibrillary tangles (NFTs). Diffuse plaques were graded according to cortical density (frequent, moderate, sparse, or none operationalized with NACC parameter "NPDIFF"), Consortium to Establish a Registry for Alzheimer's Disease (CERAD) stages of neuritic plaque densities (frequent, moderate, sparse, or none) operationalized with NACC parameter "NPCERAD") (27), and NFTs according to Braak stages for neurofibrillary pathology (Stages 0-VI operationalized with NACC parameter "NPBRAAK") (28). Dementia with Lewy bodies (DLB) pathology was characterized according to established guidelines using NACC parameter "NPLEWY," which indicates whether pathology "is consistent with criteria of Consortium on Dementia with Lewy bodies for Lewy body pathology, brainstem predominant type," "Lewy body pathology, intermediate or transitional (limbic) type," or "Lewy body pathology, diffuse (neocortical) type" (29).

Clinical and Genomic Data

Clinical data including the Mini-Mental State Examination (MMSE) (30) were collected by trained clinicians and interviewers as previously described (12, 31). Genomic data from ADGC were transferred from PLINK format into Microsoft Excel spreadsheet for additional studies, with subsequent analyses performed using R 3.1.0 (32).

Statistics

Statistical methods included marginal logistic regression that was used to construct confidence intervals (CI) for odds ratios and to test for association between candidate SNPs and HS-Aging pathology. Three modes of inheritance (MOI) were examined for each SNP using conventional genotype transformations: additive MOI (number of risk alleles, i.e., 0, 1 or 2); dominant MOI (at least 1 risk allele = 1; 0 otherwise); and recessive MOI (2 risk alleles = 1; 0 otherwise). Contingency tables were used to calculate HS-Aging pathology odds ratios and supporting CI for combinations of risk genotypes (using recessive for *ABCC9* and dominant for *TMEM106B* and *GRN*). Chi-square and Fisher exact tests were used to compare HS-Aging pathology prevalence between individuals with both a *ABCC9* A_A genotype (for rs704180) and a *TMEM106B* A_A genotype (rs1990622) and others, for deaths occurring prior to 2000 and after, respectively. Similarly, MMSE between these 2 groups was examined with a 2-tailed Student t-test. Chi-square tests were used to compare differences in the prevalence of AD and DLB neuropathologic changes for each gene.

RESULTS

Patient demographic data and presence or absence of HS-Aging are summarized in Table 1. The genotyped research volunteers from NACC were predominantly patients with severe AD pathology (see below). More detailed information about HS-Aging pathology cases and controls in the NACC dataset without genomics data have been reported (12). Because of the more permissive inclusion criteria and the lack of GWAS-related screening exclusions, the number of subjects in the current study is larger than in the prior GWAS (21). From among the 268 pathologically verified HS-Aging cases and 2957 controls with genotype data now available for analyses, there were 51 HS-Aging cases and 561 controls that were not available for analyses in the previous GWAS study (21); these cases were not from the UK-ADC cohort. NACC and ADGC data also included 31 HS-Aging cases and 239 controls from the UK-ADC. DNA samples from these individuals were analyzed in the prior study using PCR-based SNP characterization (21). PCR data from UK-ADC cases agreed with the ADGC SNP data (not shown); therefore ADGC-derived SNP data were used for UK-ADC data in the analyses where all the data were pooled.

A focus of the present study was genetic polymorphisms that previously were associated with risk for developing HS-Aging pathology (Fig. 1). Of the 3225 individuals included in the study overall, 3210 (99.5%) had SNP calls for rs1990622 (*TMEM106B*), 3213 (99.6%) had SNP calls for rs704180 (*ABCC9*), and 2732 (84.7%) had SNP calls for rs5848 (*GRN*). The OR with 95% CIs for the 3 putative risk alleles assuming additive, dominant, and recessive MOIs are shown in Table 2. For all 3 SNPs, the same risk alleles (i.e. rs5848 “T”, rs1990622 “A”, and rs704180 “A” alleles) showed positive association with HS-Aging risk

as in prior published studies (17-21). Data from the entire cohort showing the proportion of individuals with HS-Aging pathology stratified by SNP genotype and age at death are shown in Figure 2, which conveys the descriptive trend with regard to their association with HS-Aging pathology. Note that unlike the case for the *GRN* and *TMEM106B* SNPs, patients who are heterozygous for the putative *ABCC9* risk allele show greater risk than those that are homozygous lacking the risk allele in the oldest age category, indicating a recessive MOI. The trend toward greater HS-Aging risk for individuals with both risk alleles spans a broad age range and, as expected, the overall HS-Aging prevalence is highest among the “oldest-old” (7, 14, 33). Among cases that were not analyzed previously (and with the caveat that the sample size was smaller than the previous study [21]), the OR for the association between HS-Aging pathology and rs1990622 suggested a strong association (Table 2). These data were compatible with prior studies in terms of the probable MOI for these SNPs; specifically, there was an apparent recessive MOI for rs704180, but more probably an additive or dominant MOI for rs5848 and rs1990622.

All the cases were analyzed together (n = 3225 total) to test for evidence of gene-gene interactions and genotype-phenotype effects. Individuals with more than 1 risk genotype had risk for HS-Aging pathology that trended higher than with either gene’s risk allele(s) alone, but the data indicated an additive effect rather than synergistic or superadditive effect (Fig. 3). For additional statistical information, p values for Figure 3 comparisons are provided in Supplemental Material.

A prior study showed that recognition of HS-Aging by neuropathologists at autopsy has increased over the past decade at ADCs (12). We hypothesized that as a consequence of under-diagnosis some patients who came to autopsy prior to 2000 would have the HS-Aging disease, despite no HS pathologic diagnosis having been made at that time. Thus, cases with the HS-Aging genetic risk alleles could have lower tested cognitive performance before death even without an HS diagnosis. Data presented in Figure 4 confirm that there was lower diagnostic rate of HS-Aging pathologic changes prior to vs. after 2000 (overall proportion of cases with HS pathologic diagnosis was 1.7% before 2000 and 11.7% after 2000, $p < 0.00001$). The MMSE score difference between persons with vs. without HS-Aging pathology among individuals who died after the year 2000 (mean final MMSE scores 23.0 vs. 18.1, $p < 0.0001$) is in agreement with prior studies about cognitive impairment associated with HS-Aging pathology (11, 12). Among patients lacking HS-Aging diagnosis and also without advanced AD pathology (Braak stages IV and lower) who died prior to 2000 (but not afterward when the pathologic diagnoses were presumably more accurate), the average final MMSE score for people with both risk alleles (rs1990622 A_A and rs704180 A_A) was lower than that of the other genotypes ($p = 0.03$). Among persons with advanced AD pathology (Braak stages V and VI), the average final MMSE scores were much lower; we assume that most of the cognitive impairment in those individuals was due to AD (not shown).

Although the gene polymorphisms we tested could cause or exacerbate HS-Aging pathology through direct mechanisms, a potential confounder is that *TMEM106B*, *ABCC9*, and/or *GRN* polymorphisms may be associated with altered AD or DLB pathology, which could lead to secondary brain changes that were subsequently diagnosed as hippocampal sclerosis at

autopsy. Indeed, it has been hypothesized that both *TMEM106B* and *GRN* play a pathogenic role in AD (34-36). The proportions of NACC cases with AD and DLB pathologies, stratified by risk allele genotype, are presented in Tables 3 and 4 (which essentially depict the percentages of cases in each category). The data do not support a role for these specific *TMEM106B*, *ABCC9*, or *GRN* alleles in AD pathogenesis because the risk SNPs are not associated with altered levels of AD-type plaques (“diffuse plaques” or “neuritic plaques” according to CERAD grading of plaque densities [27]) or NFTs (Braak staging [37]). Moreover, there is no evidence for increased risk of any DLB subtype in association with the HS-Aging risk alleles. There were insufficient numbers of genotyped FTLD cases available to test the link in those diseases; therefore, these cases were excluded (for details on exclusions see Supplemental Material).

DISCUSSION

In the large NACC autopsy dataset derived from multiple research centers, the risk of developing HS-Aging pathology showed variation that was associated with specific previously described polymorphisms in *TMEM106B*, *ABCC9*, and *GRN*. The current study constitutes the first replication of the previously described association between the *ABCC9* risk genotype and HS-Aging. Among persons with both risk-associated *TMEM106B* and *ABCC9* genotypes, there was higher-trending risk for being diagnosed with HS-Aging pathology than individuals with either of these risk genotypes by themselves. The HS-Aging associated gene polymorphisms are not associated with an increased risk for AD or DLB pathologic changes. These observations indicate that multiple genetic influences are important in the pathogenesis of HS-Aging.

There are limitations inherent to the study design. NACC data derive from ADC memory disorder clinics, comprising a pooled sample that imperfectly reflects characteristics of the broader population. For example, FTLD prevalence tends to be 5% or higher at memory disorder clinics, whereas in epidemiological samples FTLD prevalence is usually <1% of demented participants (21, 38, 39). However, in the present sample, the FTLD cases were minimal because these were not yet analyzed for GWAS among the available NACC/ADGC dataset. Also due to the cohort being derived from ADCs, there may be ascertainment bias toward sampling a subgroup of HS-Aging cases that clinically resemble AD (12). The paucity of HS pathologic diagnoses before 2000 indicates a change over time in diagnostic practices, and there are methodologic differences across ADCs that directly influence phenotype instantiation. For example, sampling half the brain leads to false-negatives because HS-Aging pathology is unilateral on hematoxylin and eosin stain in 40% to 55% of cases (7, 10). There also was inadequate sample size to determine conclusively the gene-gene interaction effects governing the 3 risk alleles. Despite these considerations, the NACC database represents a high-quality composite data source, extensively audited and sourced from state-of-the-art research centers, enabling the analyses of genomic determinants of human diseases.

For the understanding of genotype-phenotype correlations, this study, along with other recent scholarship (17, 20, 40-42), underscores the critical importance of using pathologic observations for diagnosis because clinicians may fail to detect specific underlying diseases.

Here we focused on particular SNPs that were previously associated with HS-Aging pathology. From our analyses, 3 salient issues emerged: first, the strong correlation between the *TMEM106B* SNP (rs1990622) and HS-Aging pathology; second, the replication of observable association between *ABCC9* SNP (rs704180) with HS-Aging pathology; and third, a reflection on how these SNPs may all contribute to a common disease characterized by TDP-43 pathology.

There was evidence for a strong role for *TMEM106B* in HS-Aging pathology in the current study. We note that in the prior HS-Aging genomics study (21), we used data from fewer volunteers (included here were 2343 research subjects, plus 612 new subjects, not counting UK-ADC subjects, versus a total of 1636 from the prior study). As expected, the inclusion of substantial numbers of additional research subjects produced slightly different results. However, the analytic outcomes of the current study were not outside the range of expectations. Specifically, the 95% CI of the odds ratios for *GRN*, *TMEM106B*, and *ABCC9* with regard to risk for HS-Aging pathology in the current study overlap with the 95% CI of the prior study. The *TMEM106B* SNP rs1990622 is a risk allele for FTLD, as determined by a GWAS (43). Subsequent studies have found that the same rs1990622 allele is associated with altered risk for amyotrophic lateral sclerosis and for neurodegeneration linked to *C9ORF72* repeat expansions (44, 45). Also, the same allele is associated with HS pathology in older individuals (17, 20), and a GWAS corroborated the association (21), as does the present study. There is some evidence that rs1990622 may also change risk for AD (34, 35), although we see no evidence for that in the NACC dataset.

Unlike *TMEM106B*, *ABCC9* is not known to be associated with FTLD nor with any other neurodegenerative diseases. However, *ABCC9* gain-of-function mutations do cause Cantu syndrome, in which neurovascular anomalies have been observed (21, 46, 47). Blood vessel pathology is relevant because *ABCC9* is physiologically involved in vasoregulation (46, 48, 49) and, autopsy-confirmed brain arteriolosclerosis is on average more severe in HS-Aging cases vs. controls (14, 50). An *ABCC9* SNP within the same intron and only 1152 base pairs away from rs704178 (which is in near-complete linkage disequilibrium with rs704180) has been associated with sleep duration and depressive symptoms (51, 52). *ABCC9* is a member of an evolutionarily conserved family of genes that encode large proteins with multiple membrane spanning domains, other family members having been implicated in human diseases. For example, *ABCC7* (also known as *CFTR*) is the susceptibility gene in cystic fibrosis, and *ABCC8* mutations cause congenital hyperinsulinism (53). The role of the *ABCC9* gene product, SUR2, is to modify "KATP" potassium channel function (46); therefore, it is notable that a new GWAS (published after primary review of the current study) has shown that *KCNMB2*, another potassium channel modulator, is also a possible risk allele for HS-Aging pathology (54). Additional work is needed to characterize more confidently the associations between potassium channel physiology and HS-Aging pathology.

In gathering experimental evidence about disease mechanisms, a critical clue is the pathologic biomarker, TDP-43 (4, 5). The "border-zone" between HS-Aging and hippocampal TDP-43 pathology is not clearly defined, either in the research community or in consensus-based neuropathologic diagnostic criteria (2). Recent studies from different

centers, however, have established that HS-Aging pathology and hippocampal TDP-43 pathology both tend to occur in the same brains, and both are correlated with cognitive impairment (8, 11, 12, 20, 55-58). HS-Aging may prove to be the most prevalent TDP-43 proteinopathic condition (2). The contradistinction from AD-type pathology is supported by the lack of association between HS-Aging pathology and *APOE* polymorphism (7, 9, 12, 16). By contrast, if *TMEM106B*, *ABCC9*, and *GRN* each contribute to HS-Aging pathogenetically, they may do so through a mechanism related to TDP-43 pathology. This was anticipated for *TMEM106B* and *GRN* polymorphisms (17, 59), because both of those genes are directly linked to risk for FTLTDP (43, 60, 61). The current study provides fresh information indicating additive risk among persons harboring a relatively common genotype that combines risk alleles. Approximately 20% of included subjects had the rs704180 “A_A” allele and at least one rs1990622 “A” allele. Interestingly, it has been reported that *ABCC9* protein is found in the “endosomal/lysosomal” compartment during ischemic stress conditions in cardiac myocytes (62), and this cellular compartment may be where TDP-43 pathology is intensified through *TMEM106B* and *GRN* mechanisms also (63-67).

In summary, we confirmed that specific *TMEM106B*, *ABCC9*, and *GRN* SNPs each are associated with HS-Aging pathology in the NACC cohort. None of the SNPs are exonic and the disease usually manifests among the “oldest-old” (7, 14), perhaps indicating relatively subtle dysregulation in concert with other factors that are yet to be elucidated. These results provide yet more indication that the human aged brain is an extremely complex system impacted simultaneously by diverse environmental stimuli, comorbid pathologies, and genetic vulnerabilities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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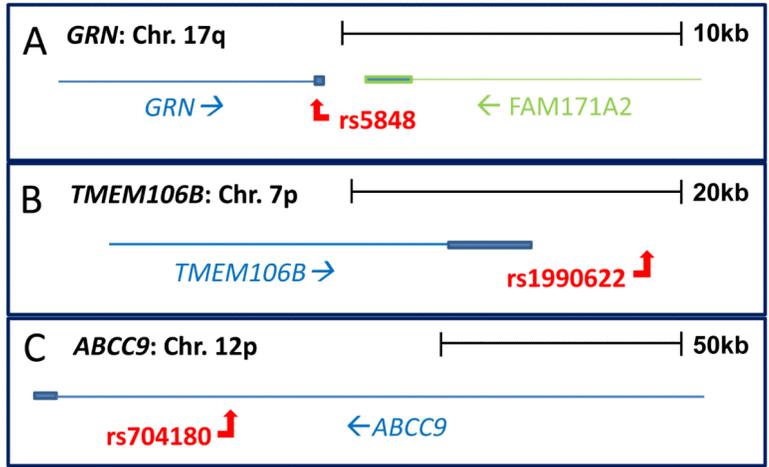


Figure 1. Genomic context for the 3 single nucleotide polymorphisms (SNPs) shown in the chronological order that they were discovered to be relevant to hippocampal sclerosis in aged populations (17, 18, 21, 43, 59). (A) rs5848 (annotated as a T/C SNP) resides in the proximal 3' untranslated region of the *GRN* gene on chromosome 17q. (B) rs1990622 (an A/G SNP) resides approximately 7 kb downstream from the annotated 3' untranslated region of the *TMEM106B* gene on chromosome 7p. (C) SNP rs704180 (an A/G SNP) resides within an intron in the *ABCC9* gene on chromosome 12p. Figures are derived from UCSC Genome Browser, genome.ucsc.edu, using human genome assembly GRCh37. SNP, single nucleotide polymorphism.

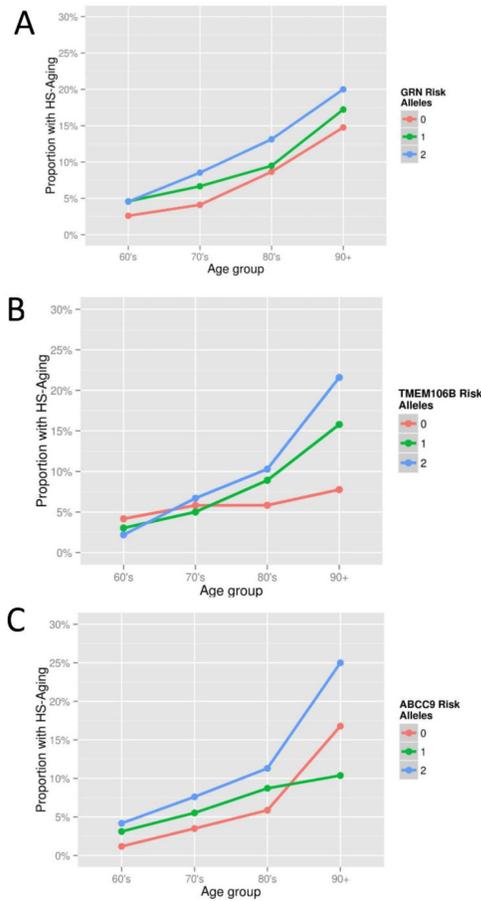


Figure 2.

Proportion of cases with Hippocampal sclerosis of aging (HS-Aging) pathology by age group at death and genotype. (A-C) Genotypes are shown for rs1990622 (*TMEM106B*; panel A); rs704180 (*ABCC9*; panel B); and rs5848 (*GRN*; panel C). These analyses factor in the results of all the cases (n = 3498 total), with case/control operationalizations as described in Methods. Note that HS-Aging pathology is most common in the “oldest-old”, and that the previously described risk genotypes (rs1990622 A_A; rs704180 A_A; and rs5848 T_T) have the highest risk for HS-Aging pathology across multiple age groups. For statistical analyses of relevant odds ratios, see Table 2.

One risk genotype only
Two risk genotypes combined
Three risk genotypes combined

	<i>ABCC9</i> <i>rs704180</i> (<i>rec MOI</i>)	<i>TMEM106B</i> <i>rs1990622</i> (<i>dom MOI</i>)	<i>GRN</i> <i>rs5848</i> (<i>dom MOI</i>)	
<i>ABCC9</i> <i>rs704180</i> (<i>rec MOI</i>)	77 1.78 (0.55-5.78) 79.1 (2001.8)	333 4.00 (1.76-9.05) 80.9 (2001.8)	60 4.51 (1.60-12.71) 80.6 (2003.9)	N OR (95% CI) Avg Death Age (Yr)
<i>TMEM106B</i> <i>rs1990622</i> (<i>dom MOI</i>)		856 1.69 (0.75-3.77) 80.4 (2001.5)	750 2.72 (1.23-6.00) 81.0 (2001.9)	N OR (95% CI) Avg Death Age (Yr)
<i>GRN</i> <i>rs5848</i> (<i>dom MOI</i>)			199 1.64 (0.63-4.26) 81.0 (2001.6)	N OR (95% CI) Avg Death Age (Yr)
			<i>All 3</i> <i>risk</i> <i>genotypes--></i> 248 3.39 (1.45-7.91) 80.5 (2002.6)	N OR (95% CI) Avg Death Age (Yr)

Figure 3. Genotype combinations and the risk of being diagnosed with HS-Aging pathology. Each case (total n = 2709) included here had genotype information for each risk allele (rs5848, rs1990622, and rs704180). For these data, odds ratio (OR) was assessed in comparison to the individuals that lacked all three risk alleles: rs5848 (T_T), rs1990622 (A_A), and rs704180 (A_A). In terms of potential confounders that might affect HS-Aging pathologic diagnosis (age and year of death), the control group had average age at death 80.1 years and average 2001.7 year of death. The number of persons in each group (N), average age at death, OR, and 95% confidence intervals (CI) are shown for each combinatorial subgroup. For a similar analysis that assumes a dominant mode of inheritance for *TMEM106B* and *GRN*, see Supplemental Materials. MOI, mode of inheritance; dom, dominant; rec, recessive.

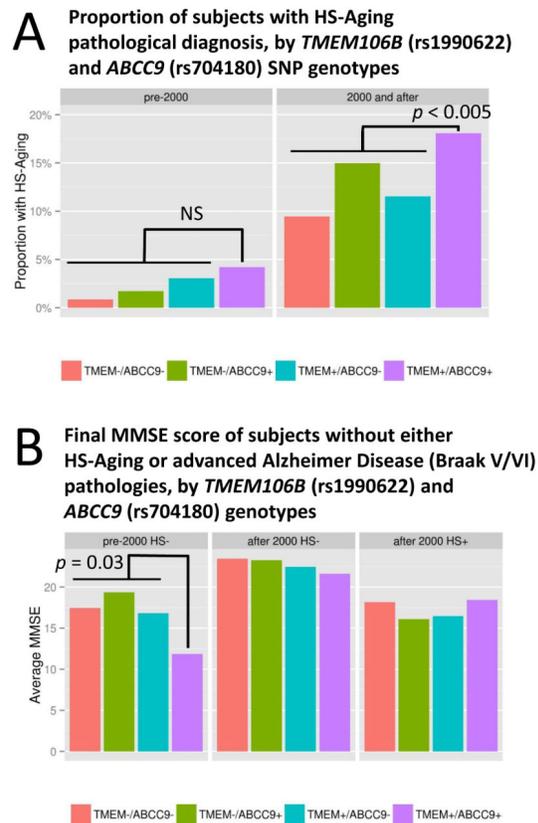


Figure 4.

Additional evidence of additive effects for *ABCC9* and *TMEM106B* SNPs in hippocampal sclerosis of aging (HS-Aging) pathology. In both panels, “ABCC9+” means rs704180 A_A and “ABCC9-” means rs704180 A_G or G_G; “TMEM+” means rs1990622 A_A and “TMEM-“ means rs1990622 A_G or G_G. (A) The proportion of individuals with HS-Aging by pathological diagnoses is shown, stratifying by *ABCC9* and *TMEM106B* genotypes. Note that as previously shown, the neuropathologic diagnosis of HS-Aging pathology was relatively unusual prior to 2000. In these pre-2000 cases, among a subset of patients without either diagnosis of HS-Aging or AD (Braak Stage \leq IV), neuropathologic changes, cases with both *TMEM106B* and *ABCC9* risk genotypes shows lower global cognitive status as indicated by final MMSE scores ($p = 0.03$), compatible with the hypothesis that a substantial proportion of these individuals had undiagnosed HS-Aging pathology. Statistical tests are Chi-square except for the pre-2000 HS-Aging pathologic evaluations for which there was a low cell count and the Fisher exact test was used. NS, not significant; MMSE, Mini-Mental State Examination; SNP, single nucleotide polymorphism.

Table 1**Demographic Data for 3255 Subjects**

NACC data outside UK-ADC available for use in prior study ¹ (n = 2343)				
Age group at death (y)	Male		Female	
	HS-	HS+	HS-	HS+
60's	120	6	77	4
70's	433	28	363	23
80's	422	36	491	48
>90	72	14	179	27
Total	1047	84	1110	102
NACC data unavailable for use in prior study (n = 612)				
Age group at death (y)	Male		Female	
	HS-	HS+	HS-	HS+
60's	117	0	88	1
70's	84	10	67	3
80's	65	10	77	8
>90	20	7	43	12
Total	286	27	275	24
Data from UK-ADC (n = 270)				
Age group at death	Male		Female	
	HS-	HS+	HS-	HS+
60's	11	1	12	0
70's	31	2	43	2
80's	46	3	60	9
>90	11	4	25	10
Total	99	10	140	21
Total HS-:	2957			
Total HS+:	268			

HS- or +, hippocampal sclerosis of aging absent or present; NACC, National Alzheimer's Coordinating Center; UK-ADC, University of Kentucky Alzheimer Disease Center¹ (21).

Table 2

Risk Alleles, p Values, and Odds Ratios, with 95% Confidence Intervals for National Alzheimer's Coordinating Center Datasets

NACC data available for use in prior study (n = 186 HS–Aging, 2157 controls)				
SNP	Risk allele*	Additive MOI Odds ratio (95% CI)	Dominant MOI Odds ratio (95% CI)	Recessive MOI Odds ratio (95% CI)
<i>ABCC9</i> (rs704180)	A	1.51 (1.22-1.89)	1.46 (0.99-2.17)	1.90 (1.40-2.60)
<i>TMEM106B</i> (rs 1990622)	A	1.16 (0.94-1.44)	1.18 (0.80-1.75)	1.24 (0.91-1.70)
GRN (rs5848)	T	1.25 (0.99-1.59)	1.33 (0.97-1.82)	1.35 (0.80-2.30)
NACC data unavailable for use in prior study (Replication cohort) (n = 51 HS–Aging, 561 controls)				
SNP	Risk allele*	Additive MOI Odds ratio (95% CI)	Dominant MOI Odds ratio (95% CI)	Recessive MOI Odds ratio (95% CI)
<i>ABCC9</i> (rs704180)	A	1.38 (0.93-2.05)	1.13 (0.59-2.18)	2.00 (1.10-3.60)
<i>TMEM106B</i> (rs 1990622)	A	1.86 (1.22-2.86)	2.70 (1.21-3.84)	2.14 (1.21-3.84)
GRN (rs5848)	T	1.74 (1.12-2.69)	2.24 (1.16-4.33)	1.92 (0.80-4.59)

HS–Aging, hippocampal sclerosis of aging; CI, confidence interval; MOI, mode of inheritance, SNP, single nucleotide polymorphisms.

Data are for the additive, dominant, and recessive models of MOI.

* See Materials and Methods for description of rationale for risk allele identification.

Table 3

Proportion of Research Subjects with Alzheimer Disease Neuropathologic Changes

Gene (SNP)	Number of risk alleles	Proportion of Subjects with Alzheimer Disease Neuropathologic Changes by Risk Allele			
		n*	Braak V or Braak VI NFTs	Severe CERAD neuritic amyloid plaque density	Severe diffuse amyloid plaque density
<i>GRN</i> (rs5848)	0	1463	0.71	0.79	0.64
	1	1041	0.72	0.80	0.64
	2	228	0.74	0.82	0.63
<i>TMEM</i> (rs 1990622)	0	638	0.71	0.81	0.65
	1	1517	0.71	0.78	0.65
	2	1053	0.70	0.80	0.62
<i>ABCC9</i> (rs704180)	0	780	0.73	0.80	0.64
	1	1584	0.71	0.80	0.65
	2	847	0.68	0.77	0.62

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; SNP, single nucleotide polymorphism. Neuropathologic changes are: advanced Braak stages, CERAD neuritic plaque densities, or diffuse amyloid plaque densities. According to SNP genotype: *GRN* (rs5848 "T" is risk allele), *TMEM106B* (rs1990662 "A" is risk allele), and *ABCC9* (rs704180 "A" is risk allele). None of the pathologic features differ between columns at $p < 0.05$. The sample size refers to those available with Braak staging; there was some variance between pathologic variables in pathologic variable missingness.

* This sample size refers specifically to cases with Braak staging and genotype data

Table 4

Proportion of Research Subjects with Lewy Body Neuropathologic Changes According to Single Nucleotide Polymorphism Genotype

Gene (SNP)	Number of Risk alleles	n	Proportion of Cases with Lewy Body Neuropathologic Changes by Risk Allele		
			Brainstem-predominant subtype	Intermediate-limbic subtype	Neocortical-diffuse subtype
<i>GRN</i> (rs5848)	0	1463	0.031	0.070	0.122
	1	1041	0.035	0.080	0.115
	2	228	0.039	0.079	0.105
<i>TMEM</i> (rs 1990622)	0	638	0.020	0.066	0.130
	1	1519	0.034	0.078	0.106
	2	1053	0.037	0.076	0.116
<i>ABCC9</i> (rs704180)	0	781	0.033	0.088	0.118
	1	1583	0.033	0.068	0.110
	2	848	0.031	0.075	0.116

Single nucleotide polymorphism (SNP) genotypes: *GRN* (rs5848 “T” is risk allele), *TMEM106B* (rs1990662 “A” is risk allele), and *ABCC9* (rs704180 “A” is risk allele). None of the pathologic features differ between columns at $p < 0.05$.