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Association between *WWOX/MAF* variants and dementia-related neuropathologic endophenotypes

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Abstract

The genetic locus containing the *WWOX* and *MAF* genes was implicated as a clinical Alzheimer's disease (AD) risk locus in two recent large meta-analytic genome wide association studies (GWAS). In a prior GWAS, we identified a variant in *WWOX* as a suggestive risk

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allele for hippocampal sclerosis (HS). We hypothesized that the *WWOX/MAF* locus may be preferentially associated with non-plaque- and non-tau-related neuropathological changes (NC). Data from research participants with GWAS and autopsy measures from the National Alzheimer's Coordinating Center (NACC) and the Religious Orders Study and the Rush Memory and Aging Project (ROSMAP) were meta-analyzed. Notably, no variants in the locus were significantly associated with ADNC. However, several *WWOX/MAF* variants had significant adjusted associations with limbic-predominant age-related TDP-43 encephalopathy NC (LATE-NC), HS, and brain arteriolosclerosis. These associations remained largely unchanged after adjustment for ADNC (operationalized with standard semiquantitative staging), suggesting that these associations are independent of ADNC. Thus, WWOX genetic variants associated with clinical AD-type dementia phenotype were associated pathologically with LATE-NC related brain changes, not ADNC.

Keywords

ADRD; Human; Hippocampus; ADNC; SNV; SNP

Introduction

The human WW domain-containing oxidoreductase *(WWOX)* and MAF bZIP transcription factor (*MAF*) genes are situated close to each other on chromosome 16q23. The normal functions of these genes are incompletely characterized. WWOX protein plays roles in transcription regulation, glucose metabolism, and central nervous system development (Kośla et al. 2019), while the protein encoded by the *MAF* gene is a transcription factor that regulates cellular processes including T-cell susceptibility to apoptosis.

This locus has been implicated in human disease. *WWOX* has been hypothesized to play a role in neurodegenerative disease, particularly Alzheimer's disease (AD) (Chang et al. 2014; Dourlen et al. 2019; Sze et al. 2004). A large genome-wide association study (GWAS) of clinical AD suggested that *WWOX* confers AD risk in non-Hispanic White individuals (Kunkle et al. 2019) and a follow-up GWAS in African American individuals nominally replicated this association (Kunkle et al. 2020). More recently, the largest AD GWAS to date also found an association between AD and *MAF*, the gene just downstream of *WWOX* (Bellenguez et al. 2020). In addition to AD, *WWOX* has also shown suggestive linkage with autism and schizophrenia (Bacchelli et al. 2020; McClay et al. 2011) and *MAF* has been associated with thyroid-related diseases, such as Graves' disease and Hashimoto's disease (Campbell et al. 2016). Nonetheless, the neurochemistry of WWOX and MAF in the human brain, and in human disease, is still poorly understood.

It has become increasingly clear that AD and AD-related dementias (AD-ADRD) are highly complex at both the individual level (multiple pathologies per person) and in a population (many different combinations of mixed pathologies). Thus, multiple neuropathological changes are associated with the AD clinical syndrome and these neurodegenerative diseases often co-occur, especially in older age (Rahimi and Kovacs 2014; Nelson et al. 2019). A recent community-based cohort study looking at the prevalence of multiple proteinopathies

in older adults found that all individuals had the presence of at least one of tau, amyloid-β (Aβ), α-synuclein, or TAR-DNA binding protein 43 (TDP-43) pathologies at autopsy and only 6.4% of individuals presented with only a single proteinopathy (Karanth et al. 2020).

A previous GWAS found *WWOX* to be a gene suggestive for association with hippocampal sclerosis (HS) pathology (Nelson et al. 2014). The brain conditions which were previously referred to as "HS-Aging" and "HS dementia" are now subsumed under a broader disease category, and are characterized by the presence of comorbid TDP-43 proteinopathy, which is a more sensitive and specific feature. The condition was recently classified with the term limbic-predominant age-related TDP-43 encephalopathy (LATE) (Nelson et al. 2019). The presence of the neuropathological changes underlying LATE (LATE-NC) is associated with a dementia syndrome similar to AD (Nelson et al. 2019).

Given that we had found a suggestive link between *WWOX* variants and HS, and others found an association between the *WWOX/MAF* locus and clinical AD, we hypothesized that a more definitive conclusion could be reached via a pathology-based study of separate cohorts with both genetic and pathologic information (including TDP-43 proteinopathy) available. We investigated whether the *WWOX/MAF* AD association could be due to neuropathological changes other than AD-type pathological hallmarks, amyloid plaques and neurofibrillary tangles. GWAS data and autopsy-confirmed neuropathological endophenotypes were gathered from the National Alzheimer's Coordinating Center (NACC) and from the Religious Orders Study and the Rush Memory and Aging Project (ROSMAP), to resolve novel associations between pathological findings and *WWOX/MAF* genetic variation.

Material and Methods

Study Participants

Phenotypic data from NACC (March 2021 data freeze) were linked with genotype data from the Alzheimer's Disease Genetics Consortium (ADGC). Individuals who died at age 65 years or older were included in this study. Similar to other studies using NACC data (Katsumata et al. 2020; Dugan et al. 2021), individuals were excluded from the NACC cohort if at least one of 19 rare brain diseases were diagnosed (Supplemental Table 1) or if they were missing any adjustment variables or all of the endophenotypes under study.

The ROSMAP study has been described in detail elsewhere (Mahoney et al. 2019). Briefly, data were acquired from two well-characterized cohort studies of aging and dementia. The Religious Orders Study (ROS), begun in 1994, and the Rush Memory and Aging Project (MAP), begun in 1997, involve older adults who enrolled without dementia, agreed to annual clinical evaluations and organ donation at death, and signed an Anatomical Gift Act for brain donation. Written informed consent was obtained from participants, and research was carried out in accordance with Institutional Review Board (IRB)-approved protocols. ROSMAP data are available online at the Rush Alzheimer's Disease Center Resource Sharing Hub (https://www.radc.rush.edu/), as well as on the Accelerating Medicines Partnership-Alzheimer's Disease (AMP-AD) Knowledge Portal (syn3219045).

Neuropathological Endophenotype Definitions

In the NACC Neuropathology (NP) dataset, LATE-NC was defined as either present or absent using the “distribution of TDP-43 immunoreactive inclusions” variables indicating if TDP-43 proteinopathy was observed in either the hippocampus (NPTDPC NACC field), entorhinal/inferior temporal cortex (NPTDPD), or neocortex (NPTDPE) in a case lacking overall diagnosis of frontotemporal lobar degeneration (FTLD)-TDP. HS was defined as either present or absent based on the “hippocampal sclerosis of CA1 and/or subiculum” (NPHIPSCL) variable using the “unilateral,” “bilateral,” and “present but laterality not assessed” response categories. Arteriolosclerosis was defined similarly using the “arteriolosclerosis” (NACCARTE) variable and collapsing the “moderate” and “severe” response categories. Presence of neurofibrillary tangles was also defined dichotomously using the “Braak stage for neurofibrillary degeneration (B score)” (NACCBRAA) variable and collapsing the “stage V (B3)” and “stage VI (B3)” response categories. Presence of neuritic plaques was defined dichotomously using the “frequent neuritic plaques (C3)” response category of the “density of neocortical neuritic plaques (CERAD score) (C score)” (NACCNEUR) variable.

In ROSMAP, LATE-NC was defined dichotomously using the “TDP-43 stage” (tdp_st4) variable and collapsing the 2nd and 3rd stages in cases lacking FTLD-TDP. HS was defined dichotomously by the “hippocampal sclerosis was rated as definitely present with CA1 region affected” response category of the “definite presence of typical hippocampal sclerosis” (hspath_typ) variable. Arteriolosclerosis was defined dichotomously using the “arteriolosclerosis” (arteriol_scler) variable and collapsing the “moderate” and “severe” response categories. Presence of neurofibrillary tangles was defined dichotomously using the “semiquantitative measure of neurofibrillary tangles” (braaksc) variable and collapsing the “V” and “VI” response categories. Presence of neuritic plaques was defined dichotomously by the “definite” response category of the “semiquantitative measure of neuritic plaques” (ceradsc) variable.

Quality Control of Genotype Data

For NACC participants, genomic data from the ADGC imputed using the Haplotype Reference Consortium (ADGC-HRC) were used (McCarthy et al. 2016). The genetic data for ROSMAP was also imputed using the HRC and the methods have been described in detail elsewhere (Dumitrescu et al. 2020). Standard GWAS quality control (QC) procedures were performed separately on the ADGC and ROSMAP genotype data using PLINK1.9 (Marees et al. 2018; Purcell et al. 2007). Variants were excluded if they were missing in more than 5% of samples, if they had a minor allele frequency less than 1%, or if they had Hardy-Weinberg Equilibrium (HWE) p-values $< 1\times10^{-6}$ among AD controls. Individuals were excluded if they were missing more than 5% of genotypes. Two individuals were considered related if they had an identity by descent measure of at least 0.25, which indicates that they are second-degree relatives. For related pairs, the individual with the lowest call rate was excluded.

NACC and ROSMAP genotype data were separately merged with 1000 Genomes data Phase 3. Principal components (PCs) were calculated for the merged data sets using the

"pca" procedure in PLINK1.9, and the first two PCs were plotted. The ADGC-HRC and ROSMAP individuals with first and second PCs that overlapped with those of the 1000 Genomes individuals of known European ancestry were identified and all other individuals were excluded from the analysis.

Variant-Level Associations

All statistical analyses were conducted in R programming language, version 4.1.1 (R Core Team 2021). The gene boundaries of *WWOX* and *MAF* were defined based on the canonical transcripts (*WWOX*: 78,133,309 – 79,246,564; *MAF*: 79,627,744 – 79,634,622) using the GRCh37/hg19 gene range list from PLINK (https://www.cog-genomics.org/plink/1.9/resources). Since both of the genome-wide significant *WWOX/MAF* AD variants (rs62039712 from Kunkle *et al.* and rs450674 from Bellenguez *et al.*) were in the intergenic region between the *WWOX* and *MAF* genes, we defined the *WWOX/MAF* locus to be from 78,133,309 to 79,634,622 +/− 250kb of flanking.

Associations between each endophenotype and each variant were tested separately in the NACC and ROSMAP datasets using binary logistic regression models assuming each of the three most commonly used modes of inheritance (MOI): additive, dominant, and recessive. Variants were excluded from the analyses if they were multiallelic, if there were fewer than 15 minor alleles present across all participants, or if the logistic regression analysis resulted in complete or quasi-complete separation. All regression models adjusted for age at death, sex, ADGC data selection round (for NACC data) or ROS/MAP study (for ROSMAP data), and the first three genetic PCs. Odds ratios (OR) were calculated for each variant by exponentiating the variant's beta estimate. Since some endophenotypes were only available in a subset of participants, PCs were calculated separately for each endophenotype using the "pca" procedure in PLINK1.9. NACC and ROSMAP variant-level results were meta-analyzed using a fixed-effect, inverse-variance meta-analysis via the metagen function from the meta R package, version 4.18–0 (Balduzzi, Rücker, and Schwarzer 2019). Random-effect meta-analysis is appropriate, in general, for combining studies with varying studying designs but can result in problems concerning power and heterogeneity estimates, especially when few studies are combined (Jackson and Turner 2017; von Hippel 2015; Gavaghan, Moore, and McQuay 2000). We, thus, chose to employ fixed-effect meta-analysis. Plots of study-specific and meta-analyzed variant-level p-values were created using LocusZoom Standalone, version 1.4 (https://genome.sph.umich.edu/wiki/LocusZoom_Standalone) (Pruim et al. 2010). Linkage disequilibrium estimates were computed using LDlink assuming a CEU population (https://ldlink.nci.nih.gov/) (Machiela and Chanock 2015).

Variant Prioritization and Downstream Analyses

Statistically significant variants were identified using a Bonferroni-corrected threshold for significance that accounts for the effective number of independent tests in the *WWOX*/*MAF* +/− 250kb region. The effective number of independent tests in the region was calculated for each endophenotype subset using the method of Gao *et al.* (Gao, Starmer, and Martin 2008). Briefly, Pearson's correlation coefficient was calculated for all pairs of variants and these coefficients were placed in a square matrix. The eigenvalues of the matrix were then

computed and ordered from largest to smallest and the effective number of independent tests was defined to be the smallest number of ordered eigenvalues that account for 99.5% of the sum of all eigenvalues. The Bonferroni-corrected threshold for identifying prioritized variants for an endophenotype was defined as a variant-level p-value less than 0.05 divided by the effective number of independent tests in the region for the endophenotype.

Prioritized variants were investigated for expression quantitative trait loci (eQTL) and splicing quantitative trait loci (sQTL) associations using the Genotype-Tissue Expression (GTEx) Project's V8 public data (Consortium 2013) and the BRAINEAC Brain eQTL Almanac (http://braineac.org/) (Ramasamy et al. 2014). Prioritized variants were also investigated for associations with other molecular mechanisms using the INFERring the molecular mechanisms of NOncoding genetic variants (INFERNO) software assuming a threshold on r^2 of 0.5 and a threshold on linkage disequilibrium (LD) block size of 500 kb (http://inferno.lisanwanglab.org/index.php) (Amlie-Wolf et al. 2018). Prioritized variants were also investigated for association with clinical AD using two large data sources: the Phase 3 summary statistics from the clinical AD GWAS of Jansen *et al.* (Jansen et al. 2019) and the ADGC-HRC data.

Sensitivity Analyses

The dependency of the study's results on several analytic choices were investigated. In addition to including 250kb of flanking on both sides of the *WWOX/MAF* locus, all analyses were conducted assuming no flanking and 25kb of flanking. Since some neurodegenerative diseases are more pronounced at later ages and some variant effects may be age-dependent or only affect the age of onset, all analyses were also conducted on the subset of individuals with ages of death of 75 years or older. Finally, to determine if significant variant-level results were independent of ADNC, all analyses were also conducted while adjusting for the presence of neurofibrillary tangles and, separately, for the presence of neuritic plaques.

Results

In the NACC data set, n=3,749 individuals had available data for at least one of the endophenotypes along with GWAS data. In ROSMAP, a total of n=1,390 individuals had available data for at least one of the endophenotypes along with GWAS data. Table 1 shows a summary of individual characteristics and endophenotypes for both NACC and ROSMAP participants. NACC participants with neurofibrillary tangles ($p<0.001$), neuritic plaques ($p<0.001$), and brain arteriolosclerosis ($p<0.001$) tended to be younger at death. Conversely, ROSMAP participants with an endophenotype present tended to be older at death and were less likely to be male (all $p<0.05$).

Variant-Level Associations

A total of 9,492 genetic variants in the *WWOX/MAF* locus passed QC in NACC and 8,953 variants passed QC in ROSMAP. A total of 8,256 variants were shared between NACC and ROSMAP and were included in the meta-analysis. Notably, rs62039712, the top *WWOX/MAF* variant from the Kunkle *et al.* clinical AD GWAS (Kunkle et al. 2019), did

not pass QC in either data set because it was missing in greater than 5% of individuals. No variants were in high enough linkage disequilibrium with rs62039712 in a CEU populations in LDlink to serve as proxies (no variants with R^2 >0.4 within 500kb of rs62039712).

The *WWOX* variant previously found to be genome-wide suggestive for HS with a recessive MOI, rs55751884 (Nelson et al. 2014), had nominally significant adjusted associations with HS (OR=5.53, 95% CI: (1.51, 19.51), p=0.01133) in NACC and neuritic plaques in both NACC and ROSMAP (NACC: OR=2.38, 95% CI: (1.32, 4.57), p=0.00330; ROSMAP: OR=0.32, 95% CI: (0.07, 0.93), p=0.03506) assuming a recessive MOI (Table 2). However, while the NACC and ROSMAP odds ratios for rs55751884 on neuritic plaques were of similar magnitude, they did not point in the same direction despite having the same minor allele (NACC: OR=2.38; ROSMAP: OR=0.32) and the adjusted meta-analytic p-value did not reach nominal significance (OR=1.58, 95% CI: (0.91, 2.74), p=0.10566). Notably, the adjusted meta-analytic association between rs55751884 and HS remained nominally significant when restricted to participants not included in the 2014 HS GWAS (meta-analysis: OR=2.97, 95% CI: (1.13, 7.83), p=0.02748) representing a nominal replication of that HS association (Supplemental Table 2). When additive and dominant MOIs were assumed, additional adjusted associations reached nominal statistical significance including brain arteriolosclerosis in NACC (dominant MOI: OR=0.82, 95% CI: (0.69, 0.98), p=0.03008) (Supplemental Table 2).

The recently identified genome-wide significant clinical AD risk variant near the *MAF* gene, rs450674 which is between *WWOX* and *MAF* approximately 53kb away from *MAF*'s 3' end (Bellenguez et al. 2020), had a nominally significant adjusted association with neuritic plaques in NACC (OR=0.86, 95% CI: (0.78, 0.96), p=0.00637) and in the meta-analysis of NACC and ROSMAP (OR=0.90, 95% CI: (0.82, 0.99), p=0.03227) assuming an additive MOI (Table 2). No additional adjusted associations were found to be nominally significant when assuming a recessive or dominant MOI (Supplemental Table 2).

Variant Prioritization and Downstream Analyses

The largest estimate of the effective number of independent tests for the *WWOX/MAF* locus ± 250kb was 1,364 in NACC and 804 in ROSMAP. The larger of these two estimates was used to compute the Bonferroni-corrected threshold for the *WWOX/MAF* locus +/− 250kb of 3.67×10^{-5} (0.05/1,364). Variants with p-values less than this threshold were prioritized for further investigation. Associations with ADNC endophenotypes were notably absent for the recently identified clinical AD loci of rs62039712 and rs450674 (Figure 1). Several loci in the *WWOX*/*MAF* region contained variants that approached the Bonferroni-corrected threshold for significance in NACC but none surpassed it (Supplemental Figure 1).

Eight thousand two hundred and fifty-six variants were shared between NACC and ROSMAP in the *WWOX/MAF* locus ± 250kb and were meta-analyzed across NACC and ROSMAP. Five variants had meta-analytic p-values that met the Bonferroni-corrected significance threshold for the *WWOX/MAF* region ± 250kb for at least one endophenotype and one MOI. Two of these variants, rs6564590 and rs7404901, were associated with LATE-NC assuming an additive MOI (OR=1.43, 95% CI: (1.22, 1.68), $p=1.07\times10^{-5}$ and OR=1.44, 95% CI: (1.22, 1.69), $p=1.56\times10^{-5}$, respectively) and are in high LD with one another

(R^2=0.735 in LDlink). Two additional variants, rs9925100 and rs9930659, were associated with HS while assuming a recessive MOI (OR=2.44, 95% CI: (1.63, 3.61), $p=1.34\times10^{-5}$and OR=2.29, 95% CI: (1.57, 3.34), $p=1.82\times10^{-5}$, respectively). These two variants are also in high LD with one another (R^2 = 0.726 in LDlink) and are located approximately 947kb downstream from the previously identified *WWOX* HS locus, rs55751884. The remaining variant, rs4435266, was associated with brain arteriolosclerosis while assuming a dominant MOI (OR=0.74, 95% CI: (0.64, 0.85), $p=2.02\times10^{-5}$) (Table 3 and Figure 2). While the other endophenotypes were associated with variants in either the NACC-only or the ROSMAP-only analyses, they did not have any associations with meta-analytic p-values that met the Bonferroni-corrected significance threshold (Supplemental Figure 2).

None of the prioritized meta-analytic variants were found to be associated with eQTLs or sQTLs for *WWOX*, *MAF*, or any other proximal genes in GTEx. However, all five variants were found to have notable associations in BRAINEAC. The two HS variants, rs9925100 and rs9930659, had nominally significant eQTL associations for *WWOX* (both brain tissue-wide p-values $< 3.9\times10^{-3}$) with the hippocampus and putamen regions having the strongest single-tissue associations. Both of the LATE-NC variants, rs6564590 and rs7404901, had nominally significant eQTL associations with *MAF* (brain tissue-wide p=0.040 and p=0.012, respectively), with the thalmus region having the strongest single-tissue association for rs6564590 (p=0.0096) and the frontal cortex region having the strongest single-tissue association for rs7404901 (p=0.0036). The brain arteriolosclerosis variant, rs4435266, also had a nominally significant eQTL association with MAF (brain tissue-wide p=0.019) with the cerebellum region having the strongest single-tissue association (p=0.0088). Additionally, in INFERNO the LATE-NC variants were found to be eQTLs for Roadmap enhancers in the blood and immune organ tissues, the brain arteriolosclerosis variant was found to be an eQTL for Roadmap enhancers in blood and skeletal muscle tissues, and the HS variants were found to be eQTLs for both Roadmap and FANTOM5 enhancers in the blood and Roadmap enhancers in immune organ and skeletal muscle tissues. Of the five prioritized variants, only rs7404901 was nominally significant in the Jansen *et al.* GWAS of clinical AD (Jansen et al. 2019), though the effect was weak (n=426,823, OR=1.005, 95% CI: (1.000, 1.009), p=0.03818). Three of the prioritized variants – rs6564590, rs9925100, and rs9930659 – had nominally significant marginal associations with clinical AD status in ADGC-HRC and the corresponding effect estimates were also small (n=21,439, OR=1.05, 95% CI: (1.01, 1.09), p=0.01115; n=21,507, OR=0.96, 95% CI: (0.92, 1.00), p=0.04813; and n=20,865, OR=0.94, 95% CI: (0.91, 0.98), p=0.00521, respectively).

Sensitivity Analyses

Varying WWOX/MAF Flanking.—The Bonferroni-corrected threshold for the *WWOX/MAF* locus was estimated to be 3.12×10^{-5} (0.05/1,214) with 25kb of flanking and 4.19×10^{-5} (0.05/1,194) with 0kb of flanking. Not surprisingly, all five of the prioritized meta-analytic variants along with the majority of the NACC-only and ROSMAP-only variants identified in the primary analysis with 250kb of flanking were also identified when the flanking was reduced. The exception to this were several variants associated with neuritic plaques in the NACC-only analysis which were located just upstream of *WWOX* near the *CLEC3A* gene. Of the 12 neuritic plaque variants that surpassed the

Bonferroni-corrected threshold in the NACC-only analysis when the *WWOX/MAF* locus was flanked by 250kb, only one variant (rs79416778) remained with no flanking. This result highlights the specificity of the neuritic plaques association, not only with NACC, but with the *CLEC3A* gene specifically. See Supplemental Table 4 for the complete results.

Age of Death 75+: The odds ratio estimates for all five of the prioritized meta-analytic variants remained largely unchanged when the analyses were restricted to only those individuals with an age of death of 75 years of age or older. Additionally, the meta-analytic p-values for the associations between rs6564590 and LATE-NC (OR=1.42, 95% CI: (1.20, 1.66), $p=2.85\times10^{-5}$) and rs4435266 and brain arteriolosclerosis (OR=0.73, 95% CI: (0.63, 0.85), $p=3.07\times10^{-5}$) and remained below the Bonferroni-corrected threshold. The remaining associations were all nominally significant, but did not quite meet the Bonferroni-corrected threshold (all remaining p-values $\leq 6.12\times10^{-5}$). These findings suggest that age of death does not meaningfully impact the associations between the prioritized variants and the endophenotypes. See Supplemental Table 5 for the complete results.

Adjusting for ADNC.—The odds ratio estimates for all five of the prioritized meta-analytic variants remained largely unchanged when the analyses were adjusted for neurofibrillary tangles and, separately, neuritic plaques. Additionally, all of the meta-analytic p-values remained nominally significant after adjustment for neurofibrillary tangles and, separately, neuritic plaques. These findings suggest that the associations of the prioritized variants are independent of ADNC. See Supplemental Table 6 for the complete results.

Discussion

Using autopsy-confirmed neuropathologic endophenotypes, we evaluated the genetic associations between the *WWOX/MAF* locus and several neurodegenerative diseases using neuropathological changes to operationalize the presence and severity of the diseases. We found significant adjusted meta-analytic associations between *WWOX* variants and LATE-NC, HS, and brain arteriolosclerosis. While previous GWASs linked variants in the *WWOX/MAF* locus with HS and clinical AD, the associations with LATE-NC and brain arteriolosclerosis have never been reported. Furthermore, since these associations remained nominally significant after adjustment for AD-related neuropathological changes and none of the variants were robustly associated with clinical AD, it suggests that the LATE, HS, and brain arteriolosclerosis neuropathological changes associated with *WWOX/MAF* are independent of ADNC.

The novel neuritic plaque signal found in the NACC-only analyses near the *CLEC3A* gene is intriguing since other *CLEC* family genes have been linked to AD and inflammation (Wang, Liu, et al. 2020; Porcellini et al. 2010; Meng et al. 2020). Additionally, a recent genome-wide interaction analysis found evidence of variant-by-variant interactions for neurofibrillary tangles involving variants near *CLEC3A* and *WWOX* (Wang, Yang, et al. 2020). Further investigations into the influence of *CLEC3A* on neurodegenerative disease are warranted.

The previously identified AD-associated *WWOX/MAF* variant, rs62039712, did not pass QC in either dataset and did not have any proxy variants, and was only available in two of

the 12 Stage 1 GWAS cohorts from Kunkle *et al.* These factors indicate that rs62039712 was difficult to impute. The recently identified AD-associated *MAF* variant, rs450674 (Bellenguez et al. 2020), which is located approximately 362kb downstream of *WWOX* and is not in linkage disequilibrium with rs62039712, was found to have a nominally significant adjusted association with neuritic plaques in NACC (OR=0.86, 95% CI: (0.78, 0.96), p=0.00637) and in the meta-analysis of NACC and ROSMAP (OR=0.90, 95% CI: (0.82, 0.99), p=0.03227). However, since Kunkle *et al.*, Bellenguez *et al.*, and the present study have all utilized data from the ADGC – albeit using different, more specific phenotypes in the case of the current study – this region of the genome should be investigated further in other datasets to better understand its influence on AD risk.

We examined the associations of the genome-wide suggestive HS *WWOX* variant, rs55751884, with neuropathological endophenotypes. The rs55751884 variant was nominally significant in adjusted association tests for neuritic plaques in both NACC and ROSMAP (NACC: OR=2.38, 95% CI: (1.32, 4.57), p=0.00330; ROSMAP: OR=0.32, 95% CI: (0.07, 0.93), p=0.03506), HS in NACC (OR=5.53, 95% CI: (1.51, 19.51), p=0.01133), and borderline significant for neurofibrillary tangles in NACC (OR=1.66, 95% CI: (0.94, 3.07), p=0.08202). Even though the meta-analytic association between HS and rs55751884 did not reach the Bonferroni-corrected threshold for significance in our current study, that same region of *WWOX* had the strongest association with arteriolosclerosis in ROSMAP, which also merits additional investigation.

Given the abundant evidence that mixed pathologies are highly prevalent in elderly populations, the hypothesis that *WWOX* is associated with several neuropathological endophenotypes fits in with recent studies looking at genetic pleiotropy in neurological conditions (Chornenkyy, Fardo, and Nelson 2019). Pleiotropic effects have been found between AD and Parkinson's disease (Ibanez et al. 2018), AD and amyotrophic lateral sclerosis (Montibeller and de Belleroche 2018), early-onset AD and frontotemporal dementia (Cochran et al. 2020), AD-related psychosis and schizophrenia (Creese et al. 2019), LATE-NC and FTLD-TDP (Nelson et al. 2019), and, more recently, LATE-NC and HS (Dugan et al. 2021). A specific example is the *MAPT* gene which is a risk allele for many tauopathies, and also for Parkinson's disease (not a condition linked to tau pathology) (Lin and Farrer 2014). Pleiotropic effects have also been found between AD-related neuropathological changes like neuritic plaques, neurofibrillary tangles, and cerebral amyloid angiopathy (Chung et al. 2018). Further, it has been shown that brain arteriolosclerosis is linked to HS and LATE-NC (Blevins et al. 2020; Neltner et al. 2014). Our data indicate that the associations between the *WWOX/MAF* locus and LATE-NC, HS, and brain arteriolosclerosis were independent of ADNC. Thus, *WWOX* is apparently associated with more than one clinico-pathologic entity. Since *WWOX* is also known to play a role in molecular functions (Teng et al. 2013), autism spectrum disorder (Bacchelli et al. 2020), multiple sclerosis (Beecham et al. 2013), schizophrenia (McClay et al. 2011), and brain volume (Xia et al. 2017), it is a good target for additional follow-up studies.

There are limitations to our study. While the NACC and ROSMAP cohorts are quite different due to varying recruitment models, our primary results showed agreement between the two cohorts. For the five newly identified variants, the allele frequencies and effect

estimates were broadly consistent across NACC and ROSMAP, suggesting that these variants are similarly prevalent and associative in both cohorts (Table 3). The two studies did show some disagreement. When the *WWOX/MAF* variants previously reported were investigated in the present study, rs55751884 showed diverging results between NACC and ROSMAP for neurofibrillary tangles and neuritic plaques and differing effect sizes for HS and LATE-NC (Table 2). Additionally, the association between *CLEC3A* variants and neuritic plaques was seen only in the NACC cohort.

Because data come from studies employing variable study designs and are highly homogeneous, the degree to which findings are generalizable is unknown, especially concerning individuals of non-Caucasian ancestries. Additionally, while a random effects meta-analysis can be optimal for combining heterogeneous studies, we employed a fixed effects meta-analysis as we were only combining two studies and a random effects approach can be underpowered in such situations (Jackson and Turner 2017). These suggestive findings extend prior research in the field that linked the *WWOX/MAF* locus with neurodegenerative phenotypes. Yet these findings need corroborative evaluations in additional data sets to evaluate the relationships between genetics and neuropathologic data.

Conclusions

In conclusion, we showed using large genetic datasets and autopsy-derived endophenotypes that neuropathological endophenotypes related to LATE, HS, and brain arteriolsclerosis were associated with *WWOX/MAF* gene variants. While clinical diagnoses of AD may be helpful for discovering dementia-related genetic variation, our study adds to the growing body of literature highlighting the complexity of dementia phenotypes, and the benefit of leveraging autopsy-derived data for studies of aging-related brain disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AD	Alzheimer's disease
ADGC	Alzheimer's disease genetics consortium
ADNC	Alzheimer's disease neuropathological changes
ADRD	Alzheimer's disease-related dementias
AD-ADRD	Alzheimer's disease and Alzheimer's disease-related dementias
eQTL	expression quantitative trait loci
FTLD	frontotemporal lobar degeneration
GTEx	Genotype-Tissue Expression
GWAS	genome wide association study
HS	hippocampal sclerosis
HWE	Hardy-Weinberg equilibrium
LATE	limbic-predominant age-related TDP-43 encephalopathy
LATE-NC	limbic-predominant age-related TDP-43 encephalopathy neuropathological changes
LD	linkage disequilibrium
MOI	mode of inheritance
NACC	National Alzheimer's Coordinating Center
NP	neuropathology
OR	odds ratio
PC	principal component
QC	quality control
ROSMAP	Religious Orders Study and the Rush Memory and Aging Project
sQTL	splicing quantitative trait loci
TDP-43	TAR-DNA binding protein 43
WWOX	WW domain-containing oxidoreductase

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Article Highlights:

- The *WWOX/MAF* locus has been identified as a potentially harboring AD risk variants
- The present study failed to find associations with AD-related endophenotypes
- However, several other non-AD endophenotypes were associated with *WWOX/MAF* variants
- The novel associations were unchanged by adjustment for AD-related endophenotypes

Statement of Verification

The work under consideration here has not been published previously, is not under consideration for publication elsewhere, and its publication is approved by all authors and tacitly by the responsible authorities where the work was carried out. If accepted for publication, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

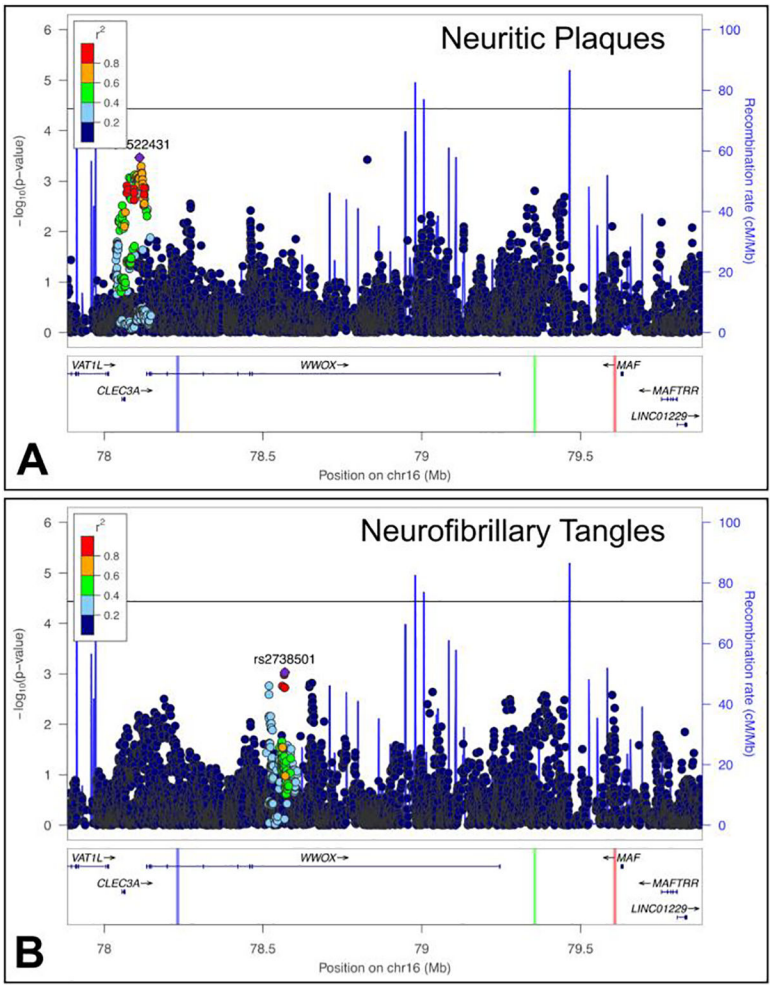

Figure 1:

LocusZoom plots of the *WWOX/MAF* region ± 250kb for **A** neuritic plaques and **B** neurofibrillary tangles, both assuming an additive MOI. Meta-analytic variant-level p-values were adjusted for age at death, sex, Alzheimer's Disease Genetics Consortium (ADGC) cohort or Religious Orders Study and Memory and Aging Project (ROSMAP) study, and first three genetic principal components and meta-analyzed across the NACC and ROSMAP cohorts. The horizontal line at 4.44 represents the Bonferroni-corrected threshold for significance for the *WWOX/MAF* locus ± 250kb. The blue region on the gene window highlights the location of rs55751884, the variant previously found to be genome-wide suggestive for HS; the green region on the gene window highlights the location of rs62039712, the variant previously found to be genome-wide significant for clinical AD; and the red region on the gene window highlights the location of rs450674, an *MAF* variant recently found to be associated with clinical AD.

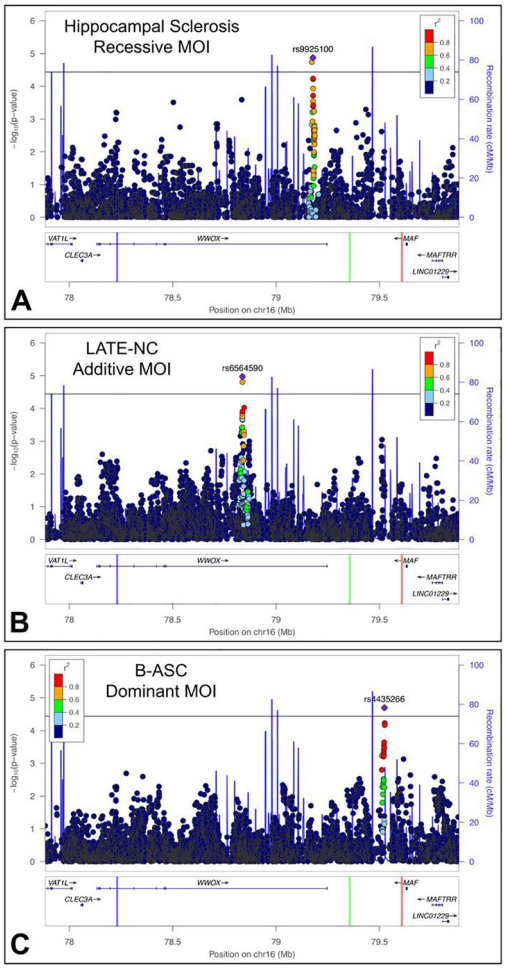

Figure 2:

LocusZoom plots of the *WWOX/MAF* region +/− 250kb for **A** hippocampal sclerosis (HS) assuming a recessive mode of inheritance (MOI), **B** limbic-predominant age-related TDP-43 encephalopathy neuropathological changes (LATE-NC) assuming an additive MOI, and **C** brain arteriolosclerosis assuming a dominant MOI. Variant-level p-values were adjusted for age at death, sex, Alzheimer's Disease Genetics Consortium (ADGC) cohort or Religious Orders Study and Memory and Aging Project (ROSMAP) study, and first three genetic principal components. The horizontal line at 4.44 represents the Bonferroni-corrected threshold for significance for the *WWOX/MAF* locus ± 250kb. The blue region on the gene window highlights the location of rs55751884, the variant previously found to be genome-wide suggestive for HS; the green region on the gene window highlights the location of rs62039712, the variant previously found to be genome-wide significant for clinical AD; and the red region on the gene window highlights the location of rs450674, an *MAF* variant recently found to be associated with clinical AD.

Table 1:

Individual characteristics stratified by endophenotype status for National Alzheimer's Coordinating Center (NACC) and Religious Orders Study and Rush Memory and Aging Project (ROSMAP) participants.

Endophenotype Status	NACC			ROSMAP		
	Number of Participants (%)	Age at Death, Mean (SD)	Female, N (%)	Number of Participants (%)	Age at Death, Mean (SD)	Female, N (%)
Hippocampal Sclerosis	N=631	85.9 (8.3)	319 (50.6)	N=1200	89.6 (6.5)	812 (67.7)
Absent	542 (85.9)	85.9 (8.4)	270 (49.8)	1091 (90.9)	89.3 (6.5)	729 (66.8)
Present	89 (14.1)	86.0 (7.5)	49 (55.1)	109 (9.1)	92.4 (6.0)	83 (76.1)
LATE-NC	N=412	85.1 (7.9)	207 (50.2)	N=1130	89.8 (6.4)	775 (68.6)
Absent	291 (70.6)	84.9 (8.1)	138 (47.4)	733 (64.9)	88.8 (6.6)	471 (64.3)
Present	121 (29.4)	85.4 (7.3)	69 (57.0)	397 (35.1)	91.8 (5.6)	304 (76.6)
Neurofibrillary Tangles	N=3760	82.5 (8.2)	1939 (51.6)	N=1390	89.4 (6.5)	944 (67.9)
Braak Stage 0 to IV	1236 (32.9)	85.0 (8.4)	639 (51.7)	1046 (75.3)	88.9 (6.7)	679 (64.9)
Braak Stage V or VI	2524 (67.1)	81.2 (7.9)	1300 (51.5)	344 (24.7)	91.0 (5.6)	265 (77.0)
Neuritic Plaques	N=3764	82.5 (8.2)	1940 (51.5)	N=1222	89.5 (6.5)	825 (67.5)
None/Sparse/Moderate	1269 (33.7)	85.9 (8.3)	612 (48.2)	810 (66.3)	89.2 (6.8)	510 (63.0)
Frequent	2495 (66.3)	80.7 (7.6)	1328 (53.2)	412 (33.7)	90.2 (5.8)	315 (76.5)
Brain Arteriolosclerosis	N=2999	82.9 (8.3)	1514 (50.5)	N=1390	89.4 (6.5)	944 (67.9)
None/Mild	1720 (57.4)	81.9 (8.4)	832 (48.4)	1013 (72.9)	89.0 (6.4)	666 (65.7)
Moderate/Severe	1279 (42.6)	84.3 (8.0)	682 (53.3)	377 (27.1)	84.3 (8.0)	278 (73.7)

NACC = National Alzheimer’s Coordinating Center; ROSMAP = Religious Orders Study and Rush Memory and Aging Project; SD = standard deviation; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathological changes.

Table 2:

Adjusted results for previously published HS and clinical AD variants in the *WWOX/MAF* locus. All analyses adjusted for age at death, sex, Alzheimer's Disease Genetics Consortium (ADGC) cohort or Religious Orders Study and Memory and Aging Project (ROSMAP) study, and the first three genetic principal components. The rs55751884 results are reported assuming a recessive mode of inheritance (MOI) as that was the MOI with the strongest association in Nelson *et al.*, 2014. The rs450674 results are reported assuming an additive MOI as that was the MOI reported in Bellenguez *et al.*, 2020.

Variant	Effect Allele	MOI	Endophenotype	NACC			ROSMAP			Meta-Analysis		
				OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
rs55751884	C	Rec.	Hippocampal Sclerosis	5.53	1.51–19.51	0.01133	1.88	0.53–5.21	0.29671	3.04	1.32–6.97	0.00878
			LATE-NC	3.69	0.75–20.26	0.10571	1.21	0.48–2.92	0.67826	1.58	0.73–3.44	0.24823
			Neurofibrillary Tangles	1.66	0.94–3.07	0.08202	0.57	0.21–1.38	0.22405	1.23	0.75–2.02	0.41942
			Neuritic Plaques	2.38	1.32–4.57	0.00330	0.32	0.07–0.93	0.03506	1.58	0.91–2.74	0.10566
			Brain Arteriolosclerosis	1.24	0.73–2.08	0.42069	1.48	0.63–3.32	0.35418	1.30	0.84–2.02	0.23621
rs450674	C	Add.	Hippocampal Sclerosis	0.77	0.48–1.23	0.26429	1.29	0.85–2.00	0.23481	1.02	0.74–1.39	0.91268
			LATE-NC	1.05	0.76–1.46	0.75143	0.97	0.81–1.17	0.75133	0.99	0.84–1.16	0.90518
			Neurofibrillary Tangles	0.93	0.83–1.04	0.20840	0.95	0.79–1.13	0.56609	0.94	0.85–1.03	0.16999
			Neuritic Plaques	0.86	0.78–0.96	0.00637	1.05	0.87–1.27	0.62292	0.90	0.82–0.99	0.03227
			Brain Arteriolosclerosis	0.93	0.84–1.04	0.22636	1.04	0.87–1.25	0.66185	0.96	0.87–1.06	0.41977

NACC = National Alzheimer's Coordinating Center; ROSMAP = Religious Orders Study and Rush Memory and Aging Project; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathological changes; MOI = mode of inheritance; Rec. = recessive MOI; Add. = additive MOI; OR = odds ratio; and CI = confidence interval.

Table 3:

Variant-level results for variants with uncorrected meta-analytic p-values that met the Bonferroni-corrected threshold for significance for the *WWOX/MAF* locus ± 250kb. All analyses adjusted for age at death, sex, Alzheimer's Disease Genetics Consortium (ADGC) cohort or Religious Orders Study and Memory and Aging Project (ROSMAP) study, and the first three genetic principal components.

Endophenotype	Variant	Effect Allele	MOI	NACC				ROSMAP				Meta-Analysis		
				Allele Freq.	OR	95% CI	P-value	Allele Freq.	OR	95% CI	P-value	OR	95% CI	P-value
LATE-NC	rs6564590	G	Add.	0.428	2.09	1.50–2.94	8.65×10^{-6}	0.421	1.28	1.07–1.54	0.00783	1.43	1.22–1.68	1.07×10^{-5}
	rs7404901	C	Add.	0.349	1.94	1.38–2.74	0.00011	0.354	1.31	1.09–1.58	0.00435	1.44	1.22–1.69	1.56×10^{-5}
HS	rs9925100	C	Rec.	0.316	2.32	1.19–4.35	0.01481	0.328	2.49	1.48–4.07	0.00087	2.44	1.63–3.61	1.34×10^{-5}
	rs9930659	C	Rec.	0.350	2.87	1.54–5.20	0.00112	0.364	1.98	1.20–3.17	0.00829	2.29	1.57–3.34	1.82×10^{-5}
B-ASC	rs4435266	A	Dom.	0.182	0.75	0.64–0.88	0.00041	0.184	0.71	0.54–0.94	0.01447	0.74	0.64–0.85	2.02×10^{-5}

NACC = National Alzheimer's Coordinating Center; ROSMAP = Religious Orders Study and Rush Memory and Aging Project; HS = hippocampal sclerosis; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathological changes; B-ASC = brain arteriolosclerosis; MOI = mode of inheritance; Rec. = recessive MOI; Add. = additive MOI; Dom. = dominant MOI; OR = odds ratio; and CI = confidence interval.