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FEATURED ARTICLE

Non-coding variants in *MYH11*, *FZD3*, and *SORCS3* are associated with dementia in women

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Abstract

Introduction: Recent studies suggest that both sex-specific genetic risk factors and those shared between dementia and stroke are involved in dementia pathogenesis.

Methods: We performed both single-variant and gene-based genome-wide association studies of >11,000 whole genome sequences from the Women's Health Initiative cohort to discover loci associated with dementia, with adjustment for age, ethnicity, stroke, and venous thromboembolism status. Evidence for prior evidence of association and differential gene expression in dementia-related tissues and samples was gathered for each locus.

Results: Our multiethnic studies identified significant associations between variants within *APOE*, *MYH11*, *FZD3*, *SORCS3*, and *GOLGA8B* and risk of dementia. Ten genes implicated by these loci, including *MYH11*, *FZD3*, *SORCS3*, and *GOLGA8B*, were differentially expressed in the context of Alzheimer's disease.

Discussion: Our association of *MYH11*, *FZD3*, *SORCS3*, and *GOLGA8B* with dementia is supported by independent functional studies in human subjects, model systems, and associations with shared risk factors for stroke and dementia.

KEYWORDS
dementia, sex-specific, stroke, whole-genome sequence, women

1 | BACKGROUND

Over 20 years ago, the apolipoprotein E (*APOE*) ε4 allele was identified as a major genetic risk factor for late-onset Alzheimer's disease (AD) and dementia.[1,2] Genome-wide association studies (GWAS) have identified >30 additional loci contributing to AD risk, with several more identified by exome-based studies.[3] A substantial proportion of dementia risk remains unexplained. This may be because GWAS are typically underpowered for detecting associations with rare variants. Dementia also exhibits considerable phenotypic heterogeneity, and it is often difficult to distinguishing AD from vascular or other subtypes of dementia.[4–6]

There is a complex relationship between vascular risk factors and dementia. Both AD and cerebrovascular disease increase in prevalence with age and share risk factors like hypertension, *APOE* genotype, smoking, and diabetes mellitus.[6] Stroke and dementia are each risk factors for the other, and there is accumulating evidence that they share susceptibility genes and pathways.[7] There may also be sex-specific or hormonal differences that influence genetic susceptibility to AD or dementia.[8]

This analysis of >11,000 postmenopausal women from the Women's Health Initiative (WHI) study enriched for vascular disease aims to discover new genetic loci associated with dementia. Our analysis of whole genome sequence (WGS) data assesses variation across the allele frequency spectrum, including both coding and non-coding variants. We find strong association between dementia and *APOE*, as well as novel loci involving *MYH11*, *FZD3*, *SORCS3*, and *GOLGA8B*. Independent transcriptomic studies reveal that these loci are also associated with gene expression in the brain and that some of those genes are differentially expressed in AD and dementia.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors performed a literature review encompassing pre-prints and published articles and abstracts investigating the relationship between stroke, sex, and dementia. Previous studies provided evidence for shared risk factors between stroke and dementia, and inconsistent evidence for sex-specific effects on dementia risk.
2. **Interpretation**: Genome scans revealed significant associations between genetic variation in *APOE*, *FZD3*, *GOLGA8B*, *MYH11*, and *SORCS3* and dementia risk. Excluding the well-established apolipoprotein (*APOE*) locus, these loci have not been widely associated with Alzheimer's disease (AD) risk, but they have been associated with cognitive traits, shared risk factors for dementia and stroke, and/or differential gene expression in the brain between AD cases and controls. They also find evidence for an interaction between hormone therapy, *FZD3* genotype, and dementia risk.
3. **Future directions**: Further studies across diverse populations, stratified by sex, and enriched for known risk factors for dementia may reveal new genetic pathways influencing dementia.

2 | METHODS

2.1 | The women's health initiative

The WHI is a prospective study of postmenopausal women representing a socio-demographically diverse population, recruiting 161,808 women between 1993 and 1998 (Supplemental Methods).[9] The WHI included an Observational Study (WHI-OS) and randomized Clinical Trials (WHI-CT), including Hormone Therapy Trials (HT). Both the WHI-CT and WHI-OS cohorts have been actively followed for >25 years. WGS data were collected for 11,085 WHI participants through the Trans-Omics for Precision Medicine (TOPMed) project sponsored by the National Heart, Lung and Blood Institute using a centralized, rigorous approach (https://www.nhlbiwgs.org/topmed-whole-genome-sequencing-methods-freeze-8). Freeze 8 of the TOPMed data were aligned to the GRCh38 human reference and cleaned as previously described (Supplemental Methods).[10]

The WHI TOPMed participants included all eligible and consenting women with incident stroke (N = 4852) or venous thromboembolism (VTE; N = 1162), women with coronary heart disease (CHD; N = 1797), and 4216 controls matched on age and ethnicity. *APOE* ε2/ε3/ε4 genotypes were defined using WGS genotypes at rs7412 (avg. read depth [DP] = 39) and rs429358 (DP = 40). In total 1608 cases of dementia were identified by self-report, medical history updates, and/or death certificate information (Supplemental Methods). Comparisons with dementia status adjudicated by an expert panel suggest that the classification of dementia in this sample has high specificity, but likely under-reports the true number of dementia cases. Although the majority of dementia cases in the United States are affected by AD (60%-80%), cerebrovascular disease, Lewy body disease, and frontotemporal dementia (FTD); each represent the cause of dementia in 5% to 10% of cases and up to 50% of dementia cases show mixed pathology.[11]

2.2 | Statistical analyses

Single-variant association testing between dementia and single nucleotide variants (SNVs) and short insertions/deletions was performed using Scalable and Accurate Implementation of Generalized mixed model (SAIGE)[12] implemented in Encore (https://encore.sph.umich.edu/), controlling type 1 error by adjusting for relatedness and sample size imbalances (Supplemental Methods). Tests were restricted to variants with minor allele frequency (MAF) >0.1% (N = 877,506,482). Covariates included age at enrollment, self-reported ethnicity, stroke and VTE status, assignment in WHI-CT versus WHI-OS, randomization arm for those in the HT trial, and principal components (PCs) 1-10 to control for population stratification. Genome-wide significance was defined as $P < 5 \times 10^{-8}$, and

lead variants as those with the smallest *P* value at a locus significantly associated with dementia. For any loci with novel associations, we performed sensitivity analyses stratified by stroke status, *APOE* status, history of HT at baseline, and reported ancestry.

Aggregation tests improve the statistical power to identify associations driven by rare variants and can aid interpretation when variants are aggregated by biological features like genes. We applied the optimal unified sequence kernal association test (SKAT-O)[13] which allows for different variants within the same gene to have opposing effects. For variants with MAF ≤5%, we performed gene-based testing using the same covariates as the single-variant GWAS, where the "gene set" included all non-synonymous and splice junction variants within a gene. The genome-wide significance threshold was determined with a Bonferroni correction for the number of tested genes (N = 18,750, $P < 2.67 \times 10^{-6}$).

2.3 | Variant annotation

Variants were annotated Variant Effect Predictor (VEP; release 100)[14] and Ensembl Regulatory Build (release 97)[15] to identify their consequences in coding regions and regulatory features. Variants were intersected with published GWAS hits; expression quantitative trait loci (eQTL); transcription factor binding site (TFBS) motifs; and chromatin, histone, CCCTC-binding factor (CTCF) binding site, and DNAseI hypersensitivity sites (DHS) marks using HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php). The genomic context of variants associated with dementia was plotted using LocusZoom (http://my.locuszoom.org).

2.4 | Evidence for validation from GWAS

Our study design, a secondary analysis of WGS and phenotype data collected for other purposes, prohibits true replication:[16] No data sets share many of the study's attributes and no GWAS share the same covariates. Because prior studies have shown a strong genetic correlation between clinically defined AD and family history of AD or dementia,[3] we assembled evidence of association between the genes containing our association signals and AD-related phenotypes in different populations and under different statistical models using GenomicsDB (v.40beta; https://beta.niagads.org/genomics/app), which provides summary statistics from AD-related studies from the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS)[17] and the National Human Genome Research Institute-European Bioinformatics Institute GWAS catalog.[18]

2.5 | Evidence for validation from expression studies

We hypothesize that the variants identified by our GWAS may influence dementia risk by altering gene expression; if so, we would expect to see evidence for differential gene expression between AD cases and controls in the appropriate tissues or cells. Lead variants from our GWAS were extracted from AD-specific eQTL studies to nominate genes whose expression they may influence. We then determined if these genes were differentially expressed between those with and without dementia or AD within several recent studies of gene expression.

Evidence for eQTLs was collected from an Accelerating Medical Partnerships for Alzheimer's Disease (AMP-AD) consortium meta-analysis of RNA-sequencing (RNA-seq) data of brain tissues (N = 2051) collected from the Mayo study,[19] the Religious Orders Study (ROS) and Rush Memory and Aging (MAP) study,[20] and the Mount Sinai Brain Bank study[21,22] (https://www.synapse.org/#!Synapse:syn17015233). Differentially expressed genes (DEGs) were identified in the AMP-AD RNA-seq data by a sex-stratified meta-analysis comparing AD cases and controls (N = 2114)[23] (https://www.synapse.org/#!Synapse:syn11914606). AMP-AD eQTLs and DEGs were defined using the reported false discovery rate (FDR) <0.05 thresholds. DEGs from a study of single-cell RNA-seq data collected from three groups of ROS samples, those with little to no AD pathology, early-stage AD pathology, or late-stage AD pathology (N = 48),[24] were defined by an FDR-adjusted $P < .01$ and absolute $\log_2$ fold change ($\log_2$FC) > 0.25. Expression microarray data from the frontal cortex were used to identify DEGs for AD, vascular dementia (VaD), and FTD versus controls (N = 140),[5] with DEGs defined as those with a $\log_2$FC ≥1.2 and $P \leq .05$. Additional details for each of these studies are provided in Supplemental Methods.

3 | RESULTS

3.1 | Sample summary

Table 1 describes the characteristics of the WHI sample, stratified by dementia status. These 11,085 women have a mean age at baseline of 62 years, reporting non-Hispanic white (81%), African American (13%), Hispanic (3%), Asian/Pacific Islander (2%), Native American/Alaskan (0.5%), or other (0.7%) ancestry. Compared to women without dementia, those with dementia were older, less likely to be current smokers, and more likely to have had an incident stroke during follow-up. As expected, the *APOE* ε4 (rs429358) carrier frequency was higher among dementia cases than controls (33% vs 22%), who more closely resembled reference populations (26%; non-Finnish Europeans).[25] Similarly, the frequency of *APOE* ε2 (rs7412) was higher among controls and these reference samples (14% and 15%) than dementia cases (11%).

3.2 | Single variant association testing

The missense variant defining the *APOE* ε4 allele was strongly associated with dementia (rs429358: odds ratio [OR] = 1.89, 95% confidence interval [CI] 1.68-2.12, $P = 7.69 \times 10^{-27}$), along with 30 additional variants with $P < 5 \times 10^{-8}$ (Figure S1; Table 2). We also observe

TABLE 1 Summary statistics and sample description for the WHI data set

Characteristic	No dementia	Dementia
N	9477	1608
Age in years (SD)	66.2 (6.9)	68.4 (5.2)
Race/ethnicity (%)		
White	81	84
Black	13	11
Hispanic	3	2
Asian	2	1
Other	1	1
Current smoker (%)	8.1	5.8
Body mass index (kg/m^2)	28.9	28.0
Incident stroke (%)	43	50
Incident venous thromboembolism (%)	11	10
Diabetes (%)	6.8	6.2
Systolic blood pressure (mmHg)	132	132
Diastolic blood pressure (mmHg)	76	75
Treated hypertension (%)	45.3	44.3
APOE ε2 carrier (%)	14	11
APOE ε4 carrier (%)	22	33

significant evidence of association between three additional loci and dementia: an SNV at the *MYH11* locus, nine SNVs at the *FZD3* locus, and an SNV at the *SORCS3* locus. Within intron 8 of *MYH11*, rs10852375 (16:15778040, A >T, DP = 34, MAF = 0.41) is significantly associated with an increased risk of dementia (OR = 1.27, 95% CI: 1.17-1.37, $P = 1.70 \times 10^{-9}$). The association at *FZD3* is led by a downstream variant, rs352214 (8:28577124, C > G, DP = 35, MAF = 0.41), significantly associated with reduced risk of dementia (OR = 0.81, 95% CI: 0.75-0.87, $P = 4.15 \times 10^{-8}$, MAF = 0.41). Within intron 14 of *SORCS3*, rs76590698 (10:105189362, G > C, DP = 36, MAF = 0.0062) is associated with a sharply increased risk of dementia (OR = 4.36, 95% CI: 2.57-7.40, $P = 4.91 \times 10^{-8}$).

For the two common SNVs associated with dementia outside the *APOE* region, rs10852375 and rs352214, we performed additional analyses stratified by *APOE* ε4 carrier status, stroke status, prior use of hormone therapy (past or current vs never), and reported ancestry (Tables S1 to S4). We observed no evidence of an interaction with either *APOE* ε4 carrier or stroke status ($P > .05$, Supplemental Tables 1 and 3), although there was significant evidence of an interaction between rs352214 and hormone therapy status ($P = .041$, Supplemental Table 2), where the minor allele was more strongly associated with reduced risk of dementia among hormone therapy users (OR = 0.82, 95% CI: 0.75-0.89; $P < .0001$) than non-users (OR = 0.92, 95% CI: 0.84-1.00; $P = .04$). For both rs10852375 and rs352214, the direction of effect was consistent across ancestry groups. rs1085375 was significantly associated with dementia in the European (OR = 1.27, 95% CI: 1.16-1.39, $P < 1E-05$), African (OR = 1.29, 95% CI: 1.02-1.63, $P = .0360$) and Hispanic Americans (OR = 2.16, 95% CI: 1.22-3.83, $P = .0090$), whereas rs352214 was associated with dementia in both the European American (OR = 0.79, 95% CI: 0.72-0.87, $P < 1E-05$), and Other (OR = 0.47, 95% CI: 0.23-0.99, $P = .0460$) subsets (Supplemental Table 4).

3.3 | Gene-based association testing

An association between *GOLGA8B* and dementia ($P = 1.22 \times 10^{-6}$) reached the genome-wide significance threshold and was driven by eight rare coding changes. These rare variants have a maximum alternate allele count of two, five of which were unique to cases (Supplemental Table 5). Most variants observed in cases were either frameshift or in-frame deletions, whereas most variants observed in controls were base-pair substitutions. None of the genes at the single-variant GWAS loci exhibited association with dementia in the gene-based analyses: *P*-values for *APOE*, *MYH11*, *FZD3*, and *SORCS3* were 0.36, 0.60, 0.23, and 0.08, respectively.

3.4 | Variant annotation

rs10852375 falls within intron 8 of *MYH11* (Figure 1A) and both a CTCF binding site and a TFBS active in bipolar neurons and ≥12 cell/tissue types. rs10852375 occurs at a high information position across seven TFBS motifs and is a known eQTL for *NDE1* and *MYH11* in lymphoblastic cell lines, for *MYH11* in whole blood, *NPIPA5* in the thyroid, and *AF001548.5* in the brain and other cell types. rs352214 falls within a large linkage disequilibrium block 2.9 kb 3′ of *FZD3* (Figure 1B) and enhancer histone marks in five cell/tissue types including derived neurospheres. rs352214 is predicted to alter five TFBS motifs and is a known eQTL for *FZD3* in testis. Finally, the rare variant rs76590698 falls within intron 14 of *SORCS3* (Figure 1C), and a promoter flanking region active in seven cell/tissue types including astrocytes, has enhancer-like histone marks in 10 tissue types including brain, and is at a high information position for four TFBS motifs. These features suggest that the functional consequences of our lead SNVs are likely to be regulatory and influence gene expression rather than protein structure.

3.5 | Evidence for validation from GWAS

Variants within *FZD3*, *MYH11*, *SORCS3*, and *GOLGA8B* have prior evidence for association with AD-related traits. Genetic variants in *SORCS3* are significantly associated with AD,[26,27] although large GWAS have not identified significant evidence of association between *MYH11*, *FZD3*, or *GOLGA8B* and AD (Supplemental Table 6). We do observe nominally significant evidence ($P < .001$) for association between *FZD3* variants and AD in Europeans[28] and African Americans,[29] between *MYH11* and AD in studies representing samples with European[30] or trans-ethnic ancestry,[31] and between *GOLGA8B* variants and the presence of neuritic plaques characteristic of AD.[32]

TABLE 2 Variants significantly associated with dementia in single-variant association tests

Locus	CHR	POS	A1	A2	A2 freq	B	SE(β)	OR	P
FZD3	8	28498654	C	T	0.5848	0.2130	0.0388	0.8082	4.17E-08
	8	28524903	G	T	0.5917	0.2132	0.0390	0.8080	4.77E-08
	8	28540845	T	C	0.5917	0.2129	0.0390	0.8083	4.96E-08
	8	28560229	T	TC	0.5940	0.2135	0.0391	0.8078	4.84E-08
	8	28567614	A	G	0.5937	0.2140	0.0391	0.8073	4.45E-08
	8	28567992	A	C	0.5938	0.2138	0.0391	0.8075	4.62E-08
	8	28568746	G	A	0.5937	0.2140	0.0391	0.8073	4.45E-08
	8	28570481	T	C	0.5941	0.2139	0.0391	0.8074	4.53E-08
	8	**28577124**	**C**	**G**	**0.5911**	**0.2141**	**0.0390**	**0.8073**	**4.15E-08**
SORCS3	**10**	**105189362**	**G**	**C**	**0.0062**	**1.4726**	**0.2700**	**4.3605**	**4.91E-08**
MYH11	**16**	**15778040**	**A**	**T**	**0.4127**	**0.2363**	**0.0393**	**1.2666**	**1.75E-09**
APOE	19	44883210	G	GTAA	0.1161	0.4800	0.0620	1.6160	9.94E-15
	19	44884202	C	G	0.1163	0.4750	0.0617	1.6080	1.37E-14
	19	44884339	G	A	0.1163	0.4760	0.0617	1.6096	1.23E-14
	19	44884873	G	A	0.1213	0.4597	0.0606	1.5835	3.24E-14
	19	44885243	A	G	0.2298	0.3365	0.0474	1.4000	1.28E-12
	19	44887076	A	G	0.2365	0.3476	0.0475	1.4156	2.62E-13
	19	44888997	C	T	0.1384	0.4982	0.0579	1.6457	7.32E-18
	19	44891079	T	C	0.1181	0.4743	0.0615	1.6069	1.21E-14
	19	44891712	T	G	0.2322	0.3632	0.0477	1.4380	2.60E-14
	19	44892362	A	G	0.1274	0.4677	0.0593	1.5964	2.99E-15
	19	44892457	T	C	0.2363	0.3428	0.0475	1.4090	5.42E-13
	19	44892587	G	A	0.0890	0.4428	0.0690	1.5571	1.43E-10
	19	44892652	C	G	0.1230	0.4859	0.0603	1.6257	7.71E-16
	19	44892887	C	T	0.1248	0.4767	0.0599	1.6108	1.66E-15
	19	44892962	C	T	0.2338	0.3485	0.0478	1.4169	3.18E-13
	19	44893408	G	T	0.2046	0.3383	0.0489	1.4025	4.64E-12
	19	44903416	G	A	0.2793	0.2717	0.0433	1.3123	3.34E-10
	19	44906745	G	A	0.0915	0.6185	0.0698	1.8562	7.53E-19
	19	**44908684**	**T**	**C**	**0.1365**	**0.6367**	**0.0594**	**1.8903**	**7.69E-27**
	19	44912456	G	A	0.1142	0.4912	0.0632	1.6342	7.43E-15
	19	44912678	G	T	0.1143	0.4896	0.0631	1.6317	8.71E-15
	19	44912921	G	T	0.2397	0.2972	0.0465	1.3460	1.70E-10
	19	44913484	C	T	0.2435	0.3108	0.0465	1.3645	2.39E-11
	19	44915533	T	C	0.2197	0.2892	0.0471	1.3353	8.62E-10
	19	44916825	A	C	0.1034	0.5508	0.0660	1.7347	7.31E-17
	19	44917997	G	A	0.1210	0.4450	0.0605	1.5605	1.92E-13
	19	44918903	C	G	0.1514	0.5068	0.0557	1.6600	9.60E-20
	19	44919589	G	A	0.1662	0.4569	0.0535	1.5791	1.43E-17
	19	44919689	A	G	0.1670	0.4615	0.0535	1.5865	5.95E-18
	19	44923868	T	A	0.1222	0.4409	0.0603	1.5541	2.60E-13
	19	44924977	G	A	0.1347	0.3856	0.0576	1.4706	2.21E-11

Lead SNVs are defined by the smallest *P* value within an associated locus and are highlighted in bold font.

Abbreviations: A1, allele 1; A2 freq, frequency of the A2 allele; A2, allele 2; CHR, chromosome; OR, odds ratio for minor allele; POS, hg38 sequence position; SE, standard error; *β*, beta coefficient from analysis model.

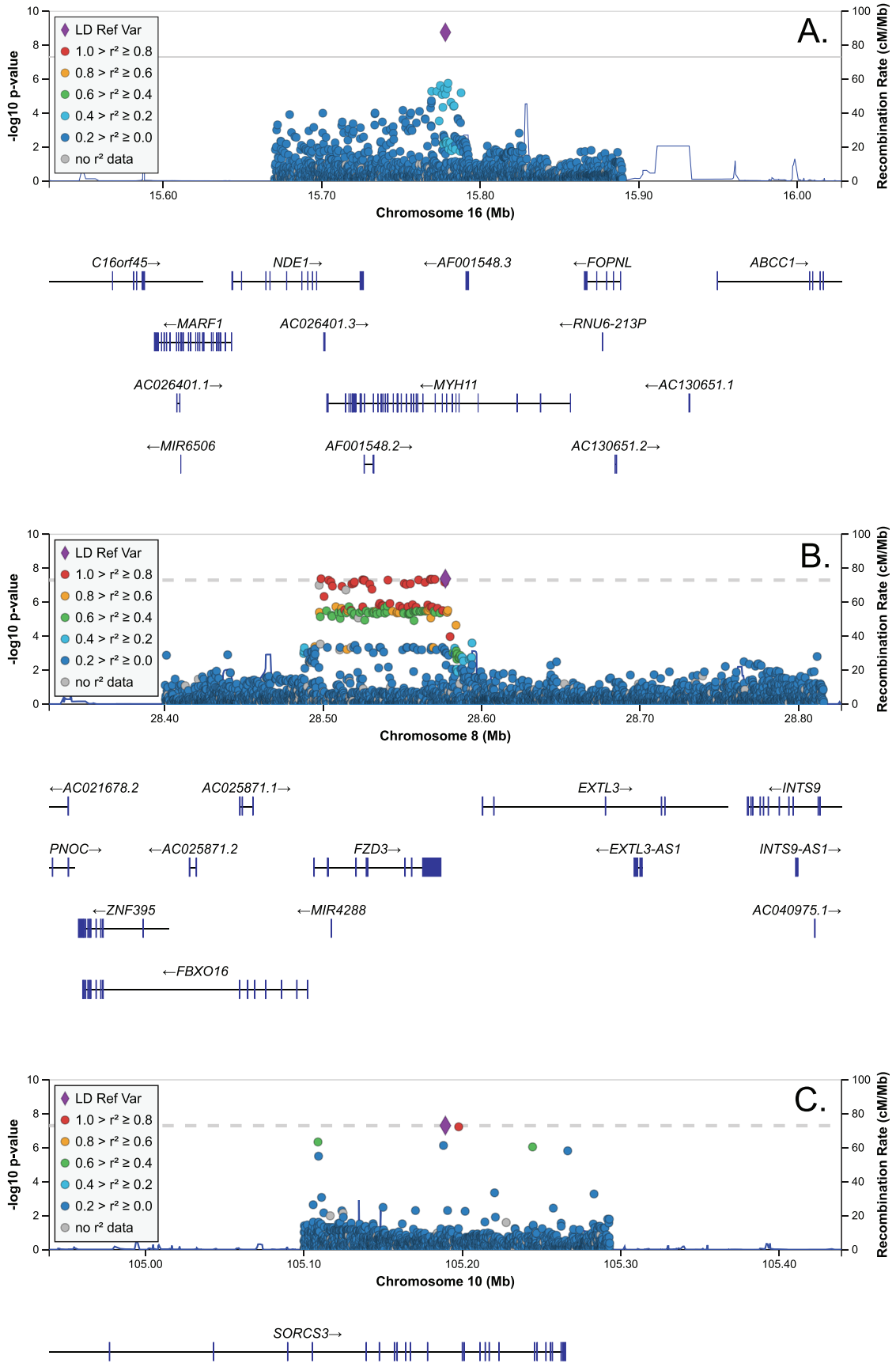

FIGURE 1 **LocusZoom plots for rs10852375 (A) and rs352214 (B).** Chromosomal positions are given with respect to the hg38 genome reference

TABLE 3 Evidence rs10852375 and rs352214 are eQTLs in brain tissues

Tissue	rsID	GENE	SYMBOL	A1	A2	β	P	FDR
TCX	rs352214	ENSG00000259366	.	C	G	−0.2201	1.02E-02	3.23E-01
TCX	rs352214	ENSG00000279302	*MIR3622A*	C	G	−0.1821	4.32E-02	5.78E-01
DLPFC	**rs352214**	**ENSG00000147419**	***CCDC25***	**C**	**G**	**−0.2001**	**6.15E-04**	**1.51E-02**
DLPFC	**rs352214**	**ENSG00000120875**	***DUSP4***	**C**	**G**	**−0.1877**	**1.65E-03**	**3.44E-02**
DLPFC	**rs352214**	**ENSG00000104290**	***FZD3***	**C**	**G**	**−0.7323**	**1.65E-38**	**2.10E-35**
DLPFC	rs352214	ENSG00000279302	*MIR3622A*	C	G	−0.1268	3.85E-02	3.24E-01
CER	rs10852375	ENSG00000261819	.	A	T	−0.2354	6.41E-03	2.51E-01
CER	rs10852375	ENSG00000091262	*ABCC6*	A	T	0.1835	3.33E-02	5.33E-01
CER	rs10852375	ENSG00000133393	*FOPNL*	A	T	−0.1877	2.92E-02	5.10E-01
CER	rs10852375	ENSG00000179889	*PDXDC1*	A	T	−0.1998	2.05E-02	4.44E-01
TCX	rs10852375	ENSG00000085721	*RRN3*	A	T	−0.1831	3.36E-02	5.83E-01
DLPFC	rs10852375	ENSG00000270580	.	A	T	−0.1260	3.42E-02	3.61E-01
DLPFC	**rs10852375**	**ENSG00000227827**	***AC138969.2***	**A**	**T**	**0.1915**	**1.20E-03**	**3.50E-02**
DLPFC	**rs10852375**	**ENSG00000183426**	***NPIPA1***	**A**	**T**	**−0.1833**	**1.79E-03**	**4.87E-02**
DLPFC	**rs10852375**	**ENSG00000183793**	***NPIPA5***	**A**	**T**	**0.2798**	**2.54E-06**	**1.60E-04**
DLPFC	rs10852375	ENSG00000179889	*PDXDC1*	A	T	−0.1736	3.63E-03	8.42E-02

All results from the AMP-AD study where the evidence for an eQTL was nominally significant ($P < .05$; https://www.synapse.org/#!Synapse:syn17015233). Results with FDR < 0.05 are highlighted in bold font.
Abbreviations: A1, allele 1; A2, allele 2; CER, cerebellum from Mayo study; DLPFC, dorsolateral prefrontal cortex from ROSMAP study; FDR, false discovery rate; TCX, temporal cortex from Mayo study. *ββ*, beta coefficient from regression model.

TABLE 4 Evidence our candidate genes are differentially expressed in brain between AD cases and controls

Symbol	Sex stratum	Fixed effects model		
		Z	P	FDR
AC138969.2	**FEMALE**	**−2.4354**	**1.49E-02**	**4.98E-02**
CCDC25	FEMALE	−2.3297	1.98E-02	6.18E-02
DUSP4	**FEMALE**	**−5.7706**	**7.90E-09**	**8.26E-07**
DUSP4	**MALE**	**−3.5100**	**4.00E-04**	**3.50E-03**
GOLGA8B	**FEMALE**	**−5.5125**	**3.54E-08**	**2.58E-06**
GOLGA8B	**MALE**	**−3.0663**	**2.17E-03**	**1.16E-02**
NDE1	**FEMALE**	**3.8782**	**1.00E-04**	**1.10E-03**
NPIPA1	**MALE**	**−2.9887**	**2.80E-03**	**1.41E-02**
SORCS3	**FEMALE**	**−5.9265**	**3.10E-09**	**4.31E-07**

Results from the AMP-AD meta-analysis where $P < 0.05$ (https://www.synapse.org/#!Synapse:syn11914606). Results with FDR < 0.05 are highlighted in bold. Abbreviations: FDR, false discovery rate; *P*, *P* value, Z: Z statistic value. Results were comparable in the random effects model, with slightly weaker *P* values (data not shown).

3.6 | Evidence for validation in expression studies

Both rs10852375 and rs352214 are significant eQTLs, whereas the gene implicated by the rare variant rs76590698 is differentially expressed in the AMP-AD study (Tables 3 and 4). Although rs76590698 was not observed in the AMP-AD eQTL data, both rs10852375 and rs352214 were significant eQTLs in the larger ROSMAP dorsolateral prefrontal cortex (DLPFC) sample and were nominally significant eQTLs in the smaller Mayo cerebellum and temporal cortex cohorts (CER, TCX; $P < .05$, Table 3). rs10852375 was a significant eQTL for *NPIPA1* ($\beta = -0.1833$, FDR = 0.0487), *NPIPA5* ($\beta = 0.2798$, FDR = 1.60×10^{-4}), and an unprocessed pseudogene *AC138969.2* ($\beta = 0.1915$, FDR = 0.0350) in the DLPFC, whereas rs352214 was a significant eQTL for *FZD3* ($\beta = -0.7323$, FDR = 2.10E-35), *CCDC25* ($\beta = -0.2001$, FDR = 0.0151), and *DUSP4* ($\beta = -0.1877$, FDR = 0.0344). These brain-specific results are consistent with those in other tissue types (above) and identify new genes whose expression is associated with either common SNV.

We investigated the evidence for differential gene expression within AD-related analyses for 11 genes implicated by our genome scans either directly (*MYH11*, *FZD3*, *GOLGA8B*, *SORCS3*) or by eQTLs (*AC138969.2*, *AF001548.5*, *CCDC25*, *DUSP4*, *FZD3*, *MYH11*, *NDE1*, *NPIPA1*, *NPIPA5*). Within the microarray study of frontal cortex, *MYH11* was differentially expressed in both AD (avg. $\log_2$FC = 1.31, min $P = .0005$) and FTD ($\log_2$FC = 1.51, $P = .0434$), while *DUSP4* was differentially expressed in VaD ($\log_2$FC = −1.86, $P = .0049$). Seven of the 11 genes were significant DEGs in the AMP-AD meta-analysis (*AC138969.2*, *CCDC25*, *DUSP4*, *GOLGA8B*, *NDE1*, *NPIPA1*, *SORCS3*; Table 4). Five of these significant results were in the female-specific analysis. In each case, the association pattern was similar but slightly weaker in the random effects model (not shown). Nine of the 11 genes were significant DEGs in neurons (FDR < 0.05; Table 5). Among the excitatory neurons, *DUSP4*, *MYH11*, and *NPIPA5* were significant DEGs

TABLE 5 Evidence our candidate genes are differentially expressed between samples with varying levels of AD pathology in neurons[24]

Excitatory neurons							Inhibitory neurons					
	absent vs present		absent vs early		early vs late		absent vs present		absent vs early		early vs late	
	FDR	log_2FC	FDR	log_2FC	FDR	log_2FC	FDR	log_2FC	FDR	log_2FC	FDR	log_2FC
CCDC25	6.18E-56	−0.23	**2.20E-72**	**−0.37**	**1.22E-20**	**0.38**	6.88E-05	−0.11	2.39E-08	−0.06	2.62E-05	−0.15
DUSP4	**8.70E-14**	**−0.58**	**6.19E-16**	**−0.84**	**2.66E-04**	**0.66**	**2.18E-04**	**−0.36**	2.96E-02	−0.02	1.13E-02	−1.27
FZD3	9.58E-26	0.08	5.34E-48	0.02	7.71E-28	0.18	5.43E-03	0.11	1.33E-09	0.01	**7.27E-13**	**0.27**
GOLGA8B	1.25E-51	−0.08	1.12E-38	0.03	8.36E-01	−0.37	3.76E-03	0.01	2.03E-03	0.12	3.33E-01	−0.35
MYH11	**5.26E-09**	**−0.52**	**2.28E-10**	**−0.47**	7.19E-03	−0.17	**3.09E-04**	**−0.31**	2.51E-03	−0.19	7.26E-01	−0.36
NDE1	1.09E-02	0.24	1.04E-06	0.19	1.90E-08	0.16	1.87E-01	−0.12	1.27E-02	−0.11	1.10E-02	−0.04
NPIPA1	5.88E-14	0.14	1.31E-26	0.07	2.53E-18	0.18	1.47E-01	0.08	7.44E-03	0.14	7.89E-03	−0.17
NPIPA5	**2.15E-03**	**0.33**	4.06E-01	0.58	**1.72E-05**	**−0.91**	4.57E-02	0.19	3.87E-01	0.61	3.96E-02	−1.78
SORCS3	1.60E-87	−0.17	1.43E-74	−0.11	4.27E-02	−0.18	4.74E-08	−0.04	4.40E-06	0.12	7.09E-01	−0.50

Abbreviations: FDR, false discovery rate-adjusted *P*-value from two-sided Wilcoxon-rank-sum test; log_2FC, log_2 fold change between comparison groups. Bold indicates when the FDR-adjusted *P*-value is < .01 and the absolute value of $log_2FC > 0.25$. Pathology refers to evidence of Alzheimer's disease related pathology in postmortem brain.

when those with and without AD pathology were compared, *CCDC25*, *DUSP4*, and *MYH11* were significant DEGs when those with early-stage AD pathology were compared with those without AD pathology, and *CCDC25*, *DUSP4*, and *NPIPA5* were significant DEGs when those with early-stage and late-stage AD pathology were compared. In the inhibitory neurons, *DUSP4* and *MYH11* were significant DEGs in comparisons of those with and without AD pathology, and *FZD3* was a significant DEG when those with early-stage versus late-stage AD pathology were compared. Across the expression studies, validation support was observed for all but *AF001548.5*, with *DUSP4*, *MYH11*, *CCDC25*, *GOLGA8B*, and *NPIPA5* having support from multiple sources.

4 | DISCUSSION

Variants within *APOE*, *MYH11*, *FZD3*, and *SORCS3* were associated with dementia in the WHI. Two of these non-coding SNVs are common and associated with allele-specific differences in gene expression and appear to fall within regulatory elements. Evidence for differential gene expression between AD cases and controls supported the potential role for *MYH11*, *FZD3*, *GOLGA8B*, and *SORCS3* in AD pathogenesis, along with *AC138969.2*, *CCDC25*, *DUSP4*, *NDE1*, and *NPIPA1*, and *NPIPA5*. Expression array studies of brain also supported a role for *DUSP4* in VaD, and for *MYH11* in FTD. Several of these genes are differentially expressed between those with varying levels of AD pathology in neurons. Gene-based tests detected significant association between dementia and rare coding changes in *GOLGA8B*, a gene whose expression differed significantly in the brain between AD cases and controls.

Our association of *FZD3*, *MYH11*, *SORCS3*, and *GOLGA8B* with dementia is supported by functional studies. Both *MYH11* and *FZD3* are differentially expressed in AD brain[33,34], and upregulation of *FZD3* relieves the phenotype in mouse models of AD.[35] *SORCS3* is differentially expressed in AD brain and is involved in APP processing.[26] Mouse models of *SORCS3* have shown that it is downregulated after amyloid beta (Aβ) plaque formation[36] and plays important roles in memory formation and synaptic plasticity.[37] Finally, *GOLGA8B* is significantly downregulated in the TCX in AD.[38] The genes identified by brain-based eQTL analyses of our lead variants also have biological ties to AD. *DUSP4* is differentially expressed in AD hippocampus,[39] and knock-out mice have impaired working memory and hippocampal function.[40] *NDE1* expression levels in blood is a potential biomarker for AD,[33] and *CCDC25* is differentially expressed in the entorhinal cortex of mice with *APOE* ε3/ε4 versus ε3/ε3 genotypes.[41]

Prior GWAS of AD have not implicated *FZD3*, *MYH11*, or *GOLGA8B*, possibly for reasons explained by our study design. The ascertainment for vascular disease in our sample has enriched for variants associated with both dementia and vascular disease. We observe variants within *MYH11*, *FZD3*, and *SORCS3* are associated with shared risk factors for stroke and dementia, including smoking, hypertension, and diabetes-related traits,[6,7,42–46] although there was no evidence that the lead SNVs at *MYH11* or *FZD3* were significantly associated with smoking, BMI, blood pressure, diabetes, low-density lipoprotein, stroke, VTE, or CHD in WHI (data not shown). We note a recent AD GWAS identified significant associations unique to those with or without hypertension,[47] suggesting that GWAS stratified by different AD risk factors may find novel results. Similarly, recent studies highlight shared genetic architecture and pathways between AD and other causes of dementia;[4,5] GWAS for dementia as defined in our study may enrich for those features shared across causes of dementia rather than those specific to AD. The WHI cohort is also exclusively female. Although the evidence for a significant sex effect on risk of AD is inconsistent,[8] there is evidence for sex differences in the effect of *APOE* ε4, hypertension, and diabetes on risk of AD. In older WHI participants, hormone therapy was previously associated with cognitive impairment, persisting for

years after medication use was terminated.[48] We observed a significant interaction between rs352214 and hormone therapy, where the protective effect on dementia risk was strongest among hormone therapy users. FZD3 is a receptor within the WNT/beta-catenin signaling pathway, playing a role in both neurodegeneration and estrogen biosynthesis.[49,50] Together, these results suggest that alternative study designs may identify additional loci associated with dementia not captured by AD-specific GWAS.

Our study has limitations that likely reduced its power. Our phenotype definition is based upon self-report data and medical records rather than a systematic evaluation by neurologists or neuropathology data. Our dementia phenotype may under-report cases and our cases likely represent several forms of dementia. Phenotypic heterogeneity, as well as difficulty sequencing *APOE*, may explain the weaker estimated effect size at rs429358 in our study compared to typical AD GWAS.[2] Our study was restricted to postmenopausal women, and therefore results may not be generalizable to men. Similarly, the scarcity of comparable data sets or GWAS with similar diagnoses, exposures, and covariates for replication analyses makes it more challenging to generalize our results to other populations. Functional studies are needed to determine whether the variants associated with dementia in our study directly influence gene expression, alone or in combination with other variation. Molecular or cellular studies are also needed to assess the consequences of our *GOLGA8B* variants on the protein's function.

We have demonstrated the importance of large and diverse WGS data sets to identify genetic risk factors for dementia. We identified a strong association between rs76590698 within *SORCS3* and dementia, with large odds ratios for AD comparable to *APOE* ε4 and *TREM2* R47H. Both rs76590698 and the *TREM2* variant share both similar effect sizes (OR ≈4) and allele frequencies in non-Finnish Europeans (0.5% vs 0.2%).[25] However, rs76590698 is an intronic variant with annotations suggesting a potential effect on gene regulation, whereas *TREM2* R47H is a loss-of-function variant. Furthermore, rs76590698 is much more common in Latino and East Asian populations (4.2%–5%),[25] highlighting the importance of studying diverse populations when searching for genetic variants influencing disease risk.

In conclusion, this study has shown that genetic variation significantly associated with risk of dementia among postmenopausal women selected for a study of stroke implicate genes, which are differentially expressed between AD cases and controls. These loci have previously been associated with shared risk factors for dementia and stroke. Future studies are needed to further investigate the associations between these loci and dementia; the roles the implicated genes may play in AD pathogenesis; and the potential influence of sex, stroke, hormone therapy, and ancestry on dementia risk.

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CONFLICTS OF INTEREST

The authors declare no competing interests.

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SUPPORTING INFORMATION

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