



Associations of *ARHGAP26* Polymorphisms with Alzheimer's Disease and Cardiovascular Disease

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Abstract

The Rho GTPase activating protein 26 (*ARHGAP26*) gene has been reported to be associated with neuropsychiatric diseases and neurodegenerative diseases including Parkinson's disease. We examined whether the *ARHGAP26* gene is associated with Alzheimer's disease (AD) and/or cardiovascular disease (CVD). Multivariable logistic regression model was used to examine the associations of 154 single nucleotide polymorphisms (SNPs) within the *ARHGAP26* gene with AD and CVD using the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI-1) cohort. Fourteen SNPs were associated with AD (top SNP rs3776362 with $p = 3.43 \times 10^{-3}$), while 37 SNPs revealed associations with CVD (top SNP rs415235 with $p = 2.06 \times 10^{-4}$). Interestingly, 13 SNPs were associated with both AD and CVD. SNP rs3776362 was associated with CVD, Functional Activities Questionnaire (FAQ), and Clinical Dementia Rating Sum of Boxes (CDR-SB). A replication study using a Caribbean Hispanics sample showed that 17 SNPs revealed associations with AD, and 12 SNPs were associated with CVD. The third sample using a family-based study design showed that 9 SNPs were associated with AD, and 3 SNPs were associated with CVD. SNP rs6836509 within the *ARHGAP10* gene (an important paralogon of *ARHGAP26*) was associated with AD and cerebrospinal fluid total tau (t-tau) level in the ADNI sample. Several SNPs were functionally important using the RegulomeDB, while a number of SNPs were associated with significant expression quantitative trait loci (eQTLs) using Genotype-Tissue Expression (GTEx) databases. In conclusion, genetic variants within *ARHGAP26* were associated with AD and CVD. These findings add important new insights into the potentially shared pathogenesis of AD and CVD.

Keywords Alzheimer disease · Cardiovascular disease · *ARHGAP26* · Single nucleotide polymorphism · RegulomeDB · eQTLs

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Introduction

Alzheimer's disease (AD) and cardiovascular diseases (CVDs) including atherosclerosis, strokes, hypertension, myocardial infarction, coronary heart disease, and

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congestive heart failure, are common in aging, especially among adults aged 65 years and older, which constitute increasing public health problems (Carter et al. 2017; de la Torre 2012; Gong et al. 2018; Justin et al. 2013; Tini et al. 2020). AD, the most common form of neurodegenerative diseases and dementia, has a substantial genetic component with heritability of 58 to 79% (Gatz et al. 2006). Ninety-five percent of all people who have AD are late-onset AD with occurrence in the eighth or ninth decade of life (American Psychiatric Association 2013; Bettens et al. 2010; Guerreiro et al. 2010). As for CVD, the heritability ranges from 0.30 to 0.50 for various quantitative CVD measures (O'Donnell and Nabel 2008), and the narrow-sense heritability of CAD is estimated to be about 40% (McPherson and Tybjaerg-Hansen 2016; Peden and Farrall 2011).

The co-occurrence of AD and CVD has been suggested due to shared risk factors between AD and CVDs, as well as due to a direct causal association. For example, cardiac diseases cause hypoperfusion and microemboli, which have been implicated in the etiology of AD (Attems and Jellinger 2014; de Bruijn and Ikram 2014; de la Torre 2012; Justin et al. 2013; Tini et al. 2020). It has been reported that CVD and cardiovascular risk factors are associated with an increased risk of AD and mild cognitive impairment (MCI) (de Bruijn and Ikram 2014; Gorelick et al. 2011; Tini et al. 2020). Furthermore, AD and CVD share similar genetic and biochemical profiles and common triggers (Mur et al. 2020; Tini et al. 2020). Several genes have been linked to AD and CVD including apolipoprotein E (*APOE*), *MTHFR*, *HFE*, and *FTO* (Eriksson et al. 2010; Kotze and van Rensburg 2012; Mahley 2016; Mansoori et al. 2012; Mur et al. 2020; Ray et al. 2008). Individuals who carry AD-associated *APOE-ε4* allele usually have higher cholesterol levels (de Bruijn and Ikram 2014) and display a more marked association between the extent of CVD and the density of cardinal neuropathological lesions of AD than subjects who do not carry this *APOE-ε4* allele (Tini et al. 2020). Recently, one study identified 90 single nucleotide polymorphisms (SNPs) on 19 different chromosomes that jointly conferred increased risk for AD and cardiovascular outcomes (Broce et al. 2019).

Among the suggested candidate genes for AD and CVD, the Rho GTPase activating protein 26 (*ARHGAP26*) gene (also known *GRAF*, *GRAF1*, *OPHNIL*, *OPHNIL1*) is located at 5q31.3 (Borkhardt et al. 2000; Ishikawa et al. 1998). GAP (GTPase-activating protein), one of the modulators of Rho GTPase family, is involved in oxidative stress contributing to vascular disease (Strassheim et al. 2019) and neuroplasticity changes in AD and other brain diseases (Guiler et al. 2021; Lefort 2015). For example, the *ARHGAP26* gene was reported to be associated with neuropsychiatric diseases (Dahm et al. 2014), while another study found that *ARHGAP26* was significantly upregulated in Parkinson disease (PD), a neurodegenerative disorder, when compared with controls (Jiang et al. 2019). AD is the most

common form of age-related neurodegenerative disorder with dementia featured by progressive memory loss and cognitive decline (Lane et al. 2018; Lipnicki et al. 2017). It has been demonstrated that AD shares genetic, epigenetic, and environmental risk factors with PD (Cacabelos 2020; Desikan et al. 2015; Kelly et al. 2020; Ramanan and Saykin 2013). However, no study has investigated the associations of the *ARHGAP26* gene with AD and/or CVD. This study aimed to investigate the association of *ARHGAP26* gene with the risk of AD and CVD by using a case–control sample, followed by a replication using additional case–control study. A third sample of a family-based study design was also used for replication and confirmation of the current findings in this study. In addition, the associations of *ARHGAP10* gene (also known *GRAF2*; *PSGAP*; *PS-GAP*), an important paralogon of *ARHGAP26* (Katoh and Katoh 2004), with AD and CVD were examined in the present study.

Materials and Methods

Subjects

ADNI Sample

The Alzheimer's Disease Neuroimaging Initiative (ADNI) (adni.loni.usc.edu) was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. The ADNI study began in 2004 as a multicenter that provides services in the United States and Canada. The ADNI is an ongoing, longitudinal, multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD. In the present study, the merged data was used from several components of ADNI. There was an Institutional Review Board (IRB) exemption for the current study due to secondary data analysis.

Data of 800 individuals, 200 patients with early AD, 400 with MCI, and 200 with cognitive normal (CN) as controls were extracted from the ADNI cohort 1. Social-demographic factors included gender, age, race, and educational level. Gender was self-reported as either male or female. Age and years of education were considered as continuous variables. Race consisted of four subgroups: non-Hispanic White, non-Hispanic African American, Hispanic, and others. CVD was defined as Yes (with the cardiovascular disease history) or No (without cardiovascular disease history) with a total of 521 patients with CVD. Cerebrospinal fluid

(CSF) biomarker included the total tau (t-tau). The Functional Activities Questionnaire (FAQ) was used to measure the activities of daily living, and the higher total scores represent increased disability (Pfeffer et al. 1982). The Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) was utilized to examine the global cognition of participants. A higher CDR-SB score indicates a more severe degree of cognitive deficits (Morris 1993).

Genotyping was conducted using the Affymetrix technique. A total of 154 SNPs within the *ARHGAP26* gene and 63 SNPs within the *ARHGAP10* gene located at 4q31.23 were available in the ADNI sample. *APOE-ε4* carriers were defined as individuals with at least one $\epsilon 4$ allele while non-carriers were defined as individuals with no $\epsilon 4$ allele (*APOE-ε4-0*) (Table 1).

The Caribbean Hispanics Sample

To validate the association of *ARHGAP26* gene, we used data from The Columbia University Study of Caribbean Hispanics with Familial and Sporadic Late Onset Alzheimer's disease-dbGaP Study Accession: phs000496.v1.p1 (Lee et al. 2011). Gender was self-reported as either male or female, while age and years of education were considered as continuous variables. All individuals are Hispanic.

CVD was defined as Yes (with the history of heart disease) or No (without history of heart disease).

Genotyping was conducted using the Illumina technique. A total of 249 SNPs within the *ARHGAP26* gene and 89 SNPs within the *ARHGAP10* gene were available. *APOE-ε4* carriers were defined as individuals with at least one $\epsilon 4$ allele while non-carriers were defined as individuals with no $\epsilon 4$ allele (*APOE-ε4-0*) (Table 1).

NIA-LOAD Family Study

Three thousand seven individuals were available from the National Institute on Aging-Late Onset Alzheimer's Disease (NIA-LOAD) Family Study: Genome-Wide Association Study for Susceptibility Loci—Study Accession: phs000168.v2.p2. The details about these subjects were described elsewhere (Lee et al. 2008). Genotyping was conducted by the Center for Inherited Disease Research (CIDR) using the Illumina Infinium II assay protocol. A total of 1266 AD cases and 1279 non-AD individuals from 1386 pedigree (including 589 nuclear families) (Table 1) were included. A total of 351 individuals with CVD and 1553 without CVD was available. A total of 155 SNPs within the *ARHGAP26* gene and 62 SNPs within the *ARHGAP10* gene were available.

Table 1 Descriptive statistics

	ADNI sample	Caribbean Hispanics sample	Family Study (NIA sample)
Variable	<i>N</i> (%) or mean \pm SD	<i>N</i> (%) or mean \pm SD	<i>N</i> (%) or mean \pm SD
Sample	755	2307	2545
Gender (% female)	308 (40.8%)	1559 (67.6%)	1644 (64.6%)
<i>APOE-ε4</i> (% $\epsilon 4$)	374 (49.5%)	744 (32.3%)	—
Age (year)	75.20 \pm 6.72	76.13 \pm 8.99	75.53 \pm 8.15
Education (year)	15.55 \pm 3.05	6.53 \pm 5.08	—
Race			
White	684 (90.6%)	—	2271 (89.2%)
Hispanic	17 (2.3%)	2307 (100%)	—
African American	36 (4.8%)	—	—
Other	18 (2.4%)	—	274 (10.8%)
Diagnosis			
CN	214 (28.3%)	1412 (61.2%)	1279 (51.3%)
AD	173 (22.9%)	864 (37.5%)	1266 (49.7%)
MCI	368 (48.8%)	—	—
CVD (% yes)	521 (70.5%)	430 (18.7%)	351 (13.8%)
FAQ	4.94 \pm 6.54	—	—
CRD-SB	1.78 \pm 1.84	—	—
t-tau	301.39 \pm 131.55	—	—

CN cognitive normal; AD Alzheimer disease; MCI mild cognitive impairment; CVD cardiovascular disease; FAQ Functional Activities Questionnaire; CDR-SB Clinical Dementia Rating Sum of Boxes; SD standard deviation

Statistical Methods

Genotype Quality Control

The Golden Helix Software (https://www.goldenhelix.com/products/SNP_Variation/index.html) was used to assess control genotype data for conformity with Hardy–Weinberg equilibrium (HWE). To deal with population stratification, the principal-component analysis approach (Price et al. 2006) in HelixTree was used to obtain first three principal components (PCs) for both data. Call rate and minor allele frequency (MAF) was determined for each SNP using The Golden Helix Software. SNPs with MAF < 1%, and/or call rate < 95%, and/or HWE < 10^{-4} were removed for further association analyses.

Multivariable Logistic/Linear Regression Models in PLINK Software

For the case–control designs, the multivariable logistic regression analyses of risk of AD and CVD as binary traits, adjusted for gender, age, education, racial group, *APOE-ε4* genotype, and first three PCs were performed. The asymptotic *p*-values for the logistic regression models were observed while the odds ratio (OR) and its 95% confidence interval were estimated. For continuous outcomes such as FAQ, CDR-SB, and t-tau, the multivariable linear regression analyses, adjusted for gender, age, education, racial group, *APOE-ε4* genotype, and first three PCs, were performed. The multivariable logistic/linear regression models were performed using PLINKv1.9 (www.cog-genomics.org/plink/1.9/) (Chang et al. 2015). To deal with multiple testing, Bonferroni correction was used for statistical significance.

Haplotype Analysis in the ADNI Sample

Pairwise linkage disequilibrium (LD) statistics (*D'*) were assessed for controls, and haplotype blocks were constructed using HAPLOVIEW software (Barrett et al. 2005). Haplotype analysis of AD and CVD was performed using the multivariate logistic model using the PLINK v1.07 (Purcell et al. 2007). The asymptotic *p*-values for the logistic regression models were observed while the OR and its standard error were estimated using PLINK v1.07.

Family-Based Association Study

A family-based association analysis for AD and CVD was performed using the PLINK v1.07 (Purcell et al. 2007). The DFAM procedure in PLINK implements the sib-transmission disequilibrium test (TDT) and also allows for unrelated individuals to be included. This test can be used to combine discordant

sibship data, parent–offspring trio data, and unrelated case/control data in a single analysis.

Functional Analysis In Silico

Functional annotation of SNPs was performed using three online functional prediction websites: SNPinfo (<https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html>), RegulomeDB (<http://regulomedb.org/>), and the Genotype-Tissue Expression (GTEx) (www.gtexportal.org). First, the associated SNPs were examined for microRNA binding sites, splicing sites, regulatory gene regions, and species-conserved regions using NIH-SNP Function Prediction (<http://snpinfo.niehs.nih.gov/cgi-bin/snpinfo/snpfunc.cgi>). Second, the potential functional consequences of associated SNPs were accessed using RegulomeDB (Boyle et al. 2012), which has a self-developed score system with a score ranging from 1 to 7, where a higher score indicates less functional significance. Third, the expression quantitative trait loci (eQTLs) of associated SNPs were assessed by the GTEx database.

Data Availability Statement

The datasets used during the current study are available in the (Alzheimer's Disease Neuroimaging Initiative (ADNI) repository, (<http://adni.loni.usc.edu/data-samples/access-data/>), (dbGaP:phs000496.v1.p1 Columbia University Study of Caribbean Hispanics and Late Onset Alzheimer's disease) repository, (<https://www.ncbi.nlm.nih.gov/gap/?term=phs000496.v1.p1>), and (National Institute on Aging—Late Onset Alzheimer's Disease Family Study: Genome-Wide Association Study for Susceptibility Loci dbGaP Study Accession: phs000168.v2.p2) repository, (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000168.v2.p2).

Results

Genotype Quality Control and Descriptive Statistics

The characteristics of participants of the three samples are presented in Table 1. After merging SNPs and phenotypes, 755 individuals in the ADNI sample kept in the study include 173 individuals with AD, 368 with MCI, and 214 with CN, while 2307 individuals in the Caribbean Hispanics sample were remained including 864 individuals with AD and 1412 with CN. The mean ages were 75.20 years, 76.13 years, and 75.53 years for ADNI sample, Caribbean Hispanics sample, and NIA family-based study, respectively. There were slightly more males (59.2%) than females in the ADNI sample, and more females than males in the

Caribbean Hispanics sample (67.6%) and the NIA family-based study (64.6%).

Single Marker Association Analysis in the ADNI Sample

A total of 14 SNPs within the *ARHGAP26* gene were associated with AD ($p < 0.05$) in the ADNI sample, and the best associated SNP was rs3776362 ($p = 3.43 \times 10^{-3}$). Furthermore, 37 SNPs revealed associations with CVD (top SNP rs415235 with $p = 2.06 \times 10^{-4}$). Interestingly, 13 SNPs were associated with both AD and CVD (top 3 SNPs for AD rs3776362, rs245852, and rs35291 with

$p = 3.43 \times 10^{-3}$, 9.47×10^{-3} , and 9.996×10^{-3} , respectively, and $p = 8.66 \times 10^{-3}$, 2.91×10^{-3} , and 4.16×10^{-3} for CVD, respectively). The SNPs with $p < 0.05$ with AD or CVD are presented in Table S1. The top 10 SNPs associated with AD or CVD are presented in Table 2. The top two SNPs (rs415235 and rs1370982) showing significant associations with CVD remained significant after a Bonferroni correction ($p < 0.05/137 = 3.65 \times 10^{-4}$). The best AD-associated SNP, rs3776362, was further associated with FAQ, and CDR-SB ($p = 0.0229$ and 0.0411 , respectively). Within the *ARHGAP10* gene, four SNPs were associated with AD (top SNP rs6836509 with $p = 0.0278$), but no SNP was found to be associated with CVD. Interestingly, rs6836509 in the ADNI

Table 2 SNPs of *ARHGAP26* and *ARHGAP10* genes associated with AD and CVD in the ADNI sample

CHR	SNP	Position	DB ^a	MA ^b	MAF ^c	HW ^d	OR_AD ^e	p_AD ^f	OR_CVD ^g	p_CVD ^h	p_CDR ⁱ	p_FAQ ^j	p_tau ^k
4	rs6836509	148,874,101	4	T	0.16	0.001	1.84	0.0278	0.87	0.4321	0.4233	0.3637	4.63E-04
4	rs4027115	149,059,167	6	A	0.03	0.005	3.09	0.0373	2.02	0.1588	0.0527	0.1763	0.6776
4	rs12331287	149,176,271	4	G	0.15	0.603	0.60	0.0381	1.04	0.8061	0.3197	0.5093	0.8641
4	rs17475681	148,919,478	2b	C	0.08	0.243	0.48	0.0413	0.89	0.6023	0.0311	0.0152	0.428
5	rs3776362	142,379,050	2b	G	0.16	0.454	1.97	3.42E-03	1.57	8.66E-03	0.0229	0.0411	0.4567
5	rs245852	142,374,573	5	C	0.20	0.363	1.75	9.47E-03	1.62	2.91E-03	0.0558	0.0618	0.6881
5	rs35291	142,329,249	5	G	0.32	0.992	1.60	9.99E-03	1.46	4.16E-03	0.0504	0.2232	0.7157
5	rs712178	142,299,485	6	G	0.32	0.876	1.59	0.0113	1.49	2.60E-03	0.4321	0.1755	0.5789
5	rs27779	142,239,267	7	T	0.32	0.186	1.55	0.0149	1.57	7.17E-04	0.37	0.2283	0.9639
5	rs463717	142,231,074	3a	A	0.36	0.012	1.52	0.0183	1.33	0.0236	0.6292	0.3751	0.917
5	rs1347813	142,379,487	3a	A	0.22	0.512	1.60	0.0193	1.70	7.32E-04	0.1076	0.1092	0.9363
5	rs153170	142,257,435	7	T	0.35	0.137	1.48	0.0284	1.54	9.15E-04	0.7642	0.3049	0.7386
5	rs153169	142,257,316	5	A	0.23	0.438	1.53	0.0347	1.57	2.69E-03	0.2986	0.227	0.8167
5	rs37212	142,313,187	5	G	0.22	0.317	1.54	0.0365	1.54	4.73E-03	0.2451	0.2037	0.6573
5	rs37210	142,316,372	7	C	0.22	0.368	1.54	0.0386	1.53	5.21E-03	0.2947	0.2169	0.5906
5	rs415235	142,266,140	6	G	0.31	0.901	1.32	0.1342	1.68	2.06E-04	0.9165	0.4034	0.7032
5	rs1370982	142,361,277	4	C	0.34	0.066	1.333	0.1039	1.64	2.91E-04	0.6238	0.3595	0.5824
5	rs35294	142,339,220	5	G	0.32	0.107	1.39	0.0698	1.60	5.62E-04	0.7166	0.337	0.5083
5	rs153166	142,282,801	4	T	0.39	0.197	1.32	0.1156	1.53	7.70E-04	0.7263	0.728	0.826
5	rs830302	142,295,675	4	G	0.37	0.281	1.43	0.0444	1.54	8.39E-04	0.9842	0.3944	0.9787
5	rs409509	142,269,057	5	C	0.24	0.564	1.50	0.0416	1.62	1.39E-03	0.3476	0.2503	0.7965

AD Alzheimer disease; CVD cardiovascular disease; FAQ Functional Activities Questionnaire; CDR Clinical Dementia Rating Sum of Boxes; 2b Likely to affect binding (TF binding+any motif+DNase footprint+DNase peak); 3a Less likely to affect binding (TF binding+any motif+DNase peak)

^aRegulomeDB score

^bMinor allele

^cMinor allele frequency

^dHardy-Weinberg equilibrium p-value

^eOdd ratios based on logistic regression for AD

^fp-value based on logistic regression for AD

^gOdd ratios based on logistic regression for CVD

^hp-value based on logistic regression for CVD

ⁱp-value based on linear regression for CDR-SB

^jp-value based on linear regression for FAQ

^kp-value based on linear regression for t-tau

sample was associated with t-tau protein ($p=4.63 \times 10^{-4}$), and rs17475681 was associated with FAQ and CRD-SB and FAQ ($p=0.0311$ and 0.0152 , respectively).

Haplotype Analyses in the ADNI Sample

Using HAPLOVIEW software, we identified three haplotype blocks including top AD-associated and CVD-associated SNPs within the *ARHGAP26* gene in the ADNI sample. Figure 1 shows the LD (D') structure. The G-C haplotype from rs13161500 and rs1370982 ($D'=0.85$) revealed significant associations with AD and CVD ($p=0.0126$ and 1.27×10^{-4} , respectively) (Table 3). The G-A haplotype from rs3776362 and rs1347813 ($D'=1.00$) revealed significant associations with AD and CVD ($p=3.42 \times 10^{-3}$ and 8.43×10^{-3} , respectively).

Association Analysis in Caribbean Hispanics Sample

Single marker analysis showed that 17 SNPs within the *ARHGAP26* gene were associated with AD ($p < 0.05$) and the best associated SNP was rs2107622 with $p=5.59 \times 10^{-4}$. Furthermore, 12 SNPs were associated with CVD (top SNP

rs6580265 with $p=2.91 \times 10^{-3}$). Interestingly, two SNPs (rs2107622 and rs245828) were associated with both AD and CVD ($p=5.59 \times 10^{-4}$ and 2.50×10^{-2} for AD and $p=2.35 \times 10^{-2}$ and 2.92×10^{-2} for CVD, respectively). The SNPs with $p < 0.05$ with AD or CVD in Caribbean Hispanics sample are presented in Table S2. The top 10 SNPs associated with AD or CVD are presented in Table 4. Within the *ARHGAP10* gene, two SNPs (rs6845865 and rs10003349) were associated with AD, and several SNPs were associated with CVD.

Association Analysis in NIA Sample Using a Family-Based Study Design

A family-based study showed that nine SNPs within the *ARHGAP26* gene were associated with AD and three SNPs were associated with CVD in the NIA sample (Table 5). Four AD-associated SNPs (rs245852, rs37212, rs3776362, and rs37210) within the *ARHGAP26* gene from the NIA sample were also associated with AD and CVD in the ADNI sample (Table 2). Within the *ARHGAP10* gene, four SNPs were associated with AD, but no SNP was associated with CVD.

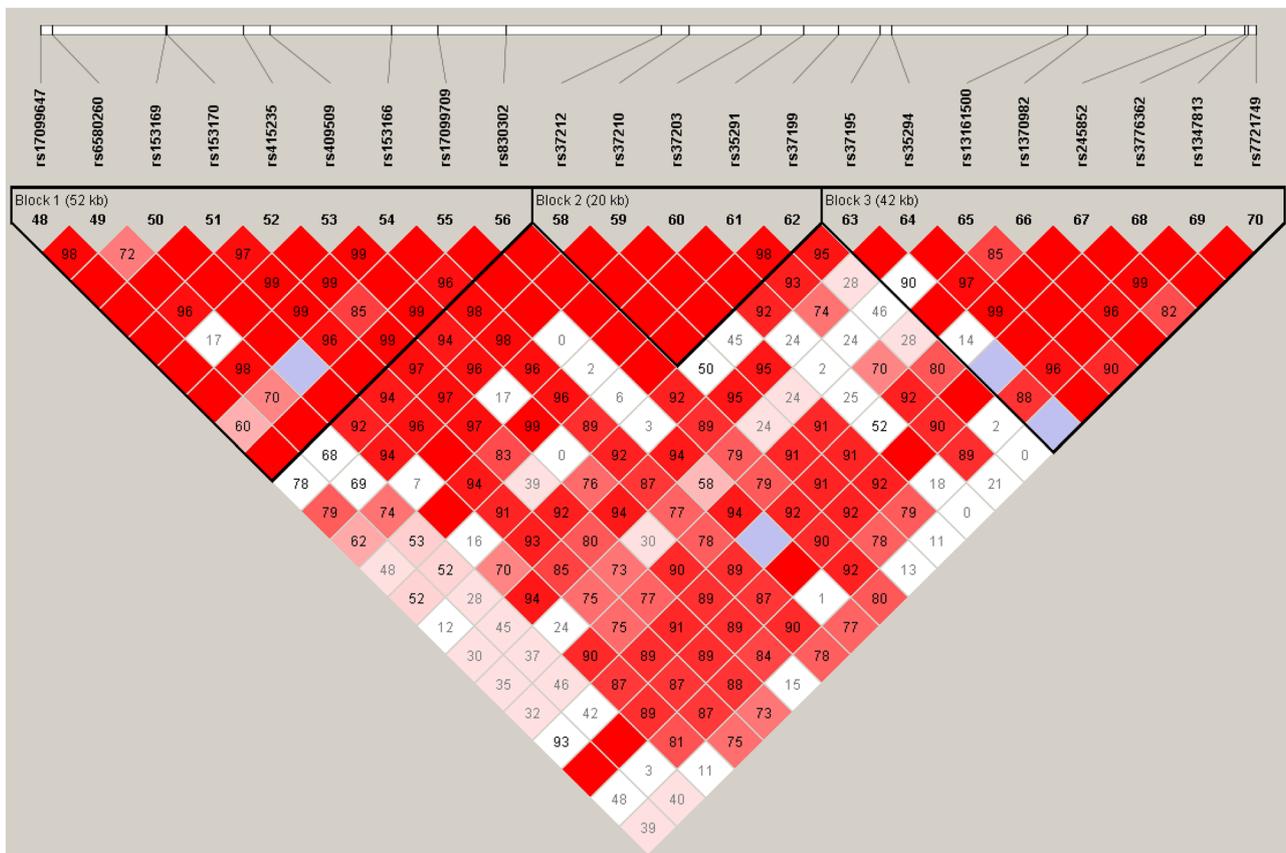


Fig. 1 Haplotype structure (D') of SNPs within *ARHGAP26* at 5q31.3 including the top SNPs with AD and CVD

Table 3 Haplotypes of *ARHGAP26* associated with AD and CVD in the ADNI sample

SNPs	Haplotype ^a	Freq ^b	OR_AD ^c	χ^2 ^d	p_AD ^e	OR_CVD ^f	χ^2 ^g	p_CVD ^h
rs13161500-rs1370982	A-C	0.0561	0.573	2.22	0.136	0.988	0.00204	0.964
	G-C	0.283	1.6	6.22	0.0126	1.75	14.7	1.27E-04
	G-T	0.655	0.752	2.61	0.106	0.588	15	1.05E-04
rs1370982-rs245852	C-C	0.195	1.75	6.73	9.47E-03	1.62	8.86	2.91E-03
	C-T	0.144	0.822	0.585	0.444	1.35	2.43	0.119
	T-T	0.661	0.75	2.64	0.104	0.61	13.1	2.91E-04
rs245852-rs3776362	C-G	0.157	1.97	8.57	3.42E-03	1.57	6.89	8.66E-03
	G-T	0.0377	0.815	0.166	0.684	1.5	1.2	0.273
	T-T	0.805	0.58	6.43	0.0112	0.619	8.72	3.15E-03
rs3776362-rs1347813	G-A	0.158	1.97	8.57	3.42E-03	1.58	6.98	8.23E-03
	T-A	0.0636	0.839	0.229	0.632	1.72	3.24	0.0717
	T-G	0.779	0.63	5.23	0.0223	0.592	11.2	7.97E-04

AD Alzheimer disease; CVD cardiovascular disease

^aHaplotype inferred from 2 SNPs

^bHaplotype frequency

^cOdds ratio based on logistic regression for AD

^d χ^2 value based on logistic regression for AD

^ep-value based on logistic regression for AD

^fOdds ratio based on logistic regression for CVD

^g χ^2 value based on logistic regression for CVD

^hp-value based on logistic regression for CVD

In Silico Analysis

In the ADNI sample, rs3776362 associated with both AD and CVD was located at the gene regulatory region, and rs415235 associated with CVD was located at the species-conserved region. In the Caribbean Hispanics sample, rs7727006 associated with CVD was located at the gene regulatory region, and rs11167807 associated with AD was located at the species-conserved region.

RegulomeDB returned score of ≤ 3 is considered functionally important. Within the *ARHGAP26* gene, three SNPs, rs3776362 (with 2b), rs463717 (3a), and rs1347813 (3a), associated with AD and CVD are functionally important in the ADNI sample (Table 2). Four SNPs, rs258764 (3a), rs11167807 (3a), and rs6894946 (2b) associated with AD, and rs17707291 (3a), associated with CVD are functionally important in the Caribbean Hispanics sample (Table 4). Two SNPs, rs3776362 (2b) and rs3776309 (2b), associated with AD are functionally important in the family-based study (Table 5).

Within the *ARHGAP26* gene, a total of 14 SNPs in Table 2, 9 SNPs in Table 4, and 4 SNPs in Table 5 had significant eQTLs. Within the *ARHGAP10* gene, a total of 2 SNPs in Tables 2, 3 SNPs in Table 4, and 4 SNPs in Table 5 had significant eQTLs. A more comprehensive list of SNPs with eQTLs is presented in supplementary Table S3.

Discussion

The present study examined the associations of the *ARHGAP26* gene polymorphisms with AD and CVD using three datasets. In the ADNI sample, there were 13 SNPs within the *ARHGAP26* gene associated with both AD and CVD, while in the replication sample using a case-control sample, there were 2 SNPs associated with both AD and CVD. The results of an additional sample using a family-based study showed that nine SNPs were associated with AD, and three SNPs were associated with CVD. The top SNP rs3776362 associated with AD in the ADNI sample was associated with cognitive phenotypes (FAQ and CDR-SB). Haplotype analysis further supported the single marker of the *ARHGAP26* gene in associations with AD and CVD in the ADNI sample. Several SNPs of this gene are functionally important using the RegulomeDB data. Within the *ARHGAP10* gene, top SNP rs6836509 associated with AD and t-tau protein level in the ADNI sample. Additionally, over 20 SNPs of *ARHGAP26* and *ARHGAP10* genes had eQTLs using the GTEx database.

The *ARHGAP26* (also known as *GRAF*) gene is a protein coding gene. Previous studies have shown that *GRAF* mRNA is expressed in a variety of avian tissues and is particularly abundant in brain and liver (Hildebrand et al. 1996; Lucken-Ardjomande Hasler et al. 2014). *GRAF* may be a regulator of the Rho family of small GTP-binding proteins

Table 4 SNPs of *ARHGAP26* and *ARHGAP10* genes associated with AD and CVD in the Caribbean Hispanics sample

CHR	SNP	Position	DB ^a	MA ^b	MAF ^c	HW ^d	OR_AD ^e	p_AD ^f	OR_CVD ^g	p_CVD ^h
4	rs6845865	148,974,602	4	G	0.29	0.003	1.18	0.0264	0.93	0.429
4	rs10003349	148,928,213	7	G	0.45	0.989	1.16	0.0304	1.12	0.149
4	rs13129809	148,903,388	7	A	0.40	0.044	0.96	0.5333	0.78	1.86E-03
4	rs10857228	148,979,700	4	A	0.38	0.683	0.91	0.1564	1.28	2.09E-03
4	rs2575582	148,875,302	7	A	0.20	0.086	1.01	0.9497	1.34	3.14E-03
4	rs12650033	148,987,187	7	A	0.34	0.036	0.93	0.2906	1.24	0.0106
5	rs2107622	142,551,397	4	A	0.15	0.438	0.71	5.59E-04	1.28	0.0235
5	rs258791	142,541,417	4	G	0.17	0.050	0.76	2.83E-03	1.08	0.4343
5	rs10073449	142,074,634	4	A	0.14	0.597	0.75	3.52E-03	1.18	0.1342
5	rs853160	142,559,092	5	A	0.32	0.147	1.20	0.0118	1.07	0.4329
5	rs258764	142,576,453	3a	A	0.31	0.119	1.20	0.0126	1.12	0.1627
5	rs11167807	142,579,907	3a	G	0.14	0.332	0.78	0.0133	1.11	0.3245
5	rs245828	142,414,146	5	G	0.49	0.011	1.16	0.0250	0.84	0.0292
5	rs2074637	142,586,382	4	G	0.17	0.813	0.81	0.0252	1.09	0.4089
5	rs6894946	142,555,732	2b	A	0.34	0.076	1.17	0.0283	0.94	0.4953
5	rs2398617	142,587,812	4	C	0.28	0.124	0.86	0.0284	1.01	0.9527
5	rs6580265	142,433,727	5	A	0.23	0.980	0.96	0.5839	1.30	2.91E-03
5	rs10057800	142,438,222	5	A	0.23	0.894	0.96	0.6373	1.30	3.41E-03
5	rs17100148	142,584,654	4	A	0.07	0.408	0.98	0.8644	0.65	0.0119
5	rs17707291	142,463,668	3a	G	0.10	0.256	1.15	0.2283	0.69	0.0124
5	rs7727006	142,465,816	7	C	0.12	0.151	1.10	0.3419	0.74	0.0164
5	rs258747	142,656,813	5	G	0.43	0.914	1.06	0.3600	0.84	0.0312
5	rs10044036	142,238,119	5	A	0.22	0.110	1.00	0.9889	1.21	0.0365
5	rs258770	142,561,515	4	G	0.27	0.129	1.06	0.4332	0.83	0.0391

AD Alzheimer disease; CVD cardiovascular disease; 2b likely to affect binding (TF binding + any motif + DNase footprint + DNase peak); 3a likely to affect binding (TF binding + any motif + DNase peak)

^aRegulomeDB score

^bMinor allele

^cMinor allele frequency

^dHardy-Weinberg equilibrium *p*-value

^eOdd ratios based on logistic regression for AD

^f*p*-value based on logistic regression for AD

^gOdd ratios based on logistic regression for CVD

^h*p*-value based on logistic regression for CVD

that exhibit binding to a protein tyrosine kinase (Hildebrand et al. 1996; Shibata et al. 2001). Indeed, the *GRAF* gene is involved in leukemia (Bojesen et al. 2006; Borkhardt et al. 2000; Hildebrand et al. 1996), human brain cancer (Wang et al. 2013), gastric cancer (Wangxia et al. 2019), and ovarian cancer (Chen et al. 2019). *ARHGAP26* is also critical for muscle development and may be involved in RhoA activity and progressive muscle degeneration (Doherty et al. 2011; Li et al. 2019). In addition, *ARHGAP26* might be involved in the pathogenesis of mental retardation (Barresi et al. 2010) and neuropsychiatric diseases (Dahm et al. 2014). Interestingly, one recent study suggested that *ARHGAP26* is involved in the development of dyslexia, a heritable neurodevelopmental disorder characterized by difficulties

in reading and writing (Naskar et al. 2018). The patients with dyslexia are similar to patients with dementia who have language deficiencies with significantly lower results in the area of verbal expression, hearing comprehension, repetition, reading, and writing (Banovic et al. 2018). In the present study, we found *ARHGAP26* gene polymorphisms were associated with AD and CVD. Especially, in the ADNI sample, there were 13 SNPs of the *ARHGAP26* gene associated with both AD and CVD, while in the replication sample using a case-control sample, there were 2 SNPs associated with both AD and CVD. Additionally, four SNPs (rs245852, rs37212, rs3776362, and rs37210) were associated with AD both in ADNI and the family-based study. These findings suggest a shared genetic susceptibility among AD and CVD.

Table 5 SNPs of *ARHGAP26* and *ARHGAP10* genes associated with AD and CVD in the NIA sample

CHR	SNP	Position	DB ^a	MA ^b	MAF ^c	HW ^d	Fam#_AD ^e	p_AD ^f	Fam#_CVD ^g	p_CVD ^h
4	rs10027921	148,931,585	7	A	0.11	0.271	73	0.0250	48	0.3848
4	rs964170	148,915,406	5	A	0.11	0.281	73	0.0258	49	0.4652
4	rs12645249	148,916,117	3a	A	0.11	0.281	73	0.0258	49	0.4652
4	rs11729081	148,916,367	5	A	0.11	0.281	73	0.0258	49	0.4652
5	rs1370982	142,361,277	4	A	0.30	0.104	301	0.0154	196	0.5617
5	rs245852	142,374,573	5	G	0.17	0.895	197	0.0229	132	0.2592
5	rs258799	142,510,153	6	G	0.42	0.175	389	0.0263	264	0.9244
5	rs37212	142,313,187	5	G	0.19	0.794	226	0.0286	145	0.5877
5	rs35294	142,339,220	5	A	0.27	0.015	286	0.0329	189	0.9821
5	rs3776362	142,379,050	2b	C	0.13	0.566	172	0.0380	109	0.5981
5	rs3776309	142,468,337	2b	A	0.10	0.793	75	0.0397	62	0.634
5	rs37210	142,316,372	7	A	0.19	0.698	225	0.0410	145	0.3952
5	rs17099403	142,080,538	4	G	0.03	0.440	32	0.0446	17	0.3982
5	rs7726056	142,225,189	5	G	0.10	0.301	91	0.2779	48	0.0141
5	rs245853	142,375,143	4	G	0.02	0.144	15	0.6455	6	0.0202
5	rs37195	142,337,942	4	C	0.02	0.048	14	0.6442	6	0.0458

AD Alzheimer Disease; CVD cardiovascular disease; 2b Likely to affect binding (TF binding + any motif + DNase footprint + DNase peak); 3a Less likely to affect binding (TF binding + any motif + DNase peak)

^aRegulomeDB score

^bMinor allele

^cMinor allele frequency

^dHardy-Weinberg equilibrium *p*-value

^eThe number of informative families for analysis of AD

^f*p*-value based on family-based association study for AD

^gThe number of informative families for analysis of CVD

^h*p*-value based on family-based association study for CVD

To our knowledge, this is the first study that investigates the associations of *ARHGAP26* gene polymorphisms with AD and CVD.

AD is the most common form of age-related neurodegenerative disorder with dementia (Lane et al. 2018; Lipnicki et al. 2017). Both AD and PD are neurodegenerative disorders and may share genetic, epigenetic, and environmental risk factors (Cacabelos 2020; Cifelli et al. 2019; Desikan et al. 2015; Jabir et al. 2015; Kelly et al. 2020; Ramanan and Saykin 2013; Ray et al. 2008). Although AD, vascular dementia (VD), and PD exert increasingly lethal or disabling effects, the associations among these diseases at the molecular level remain unclear (Chen et al. 2021). Interestingly, one recent study found that *ARHGAP26* mRNA was significantly upregulated in PD, suggesting that the gene *ARHGAP26* may be associated with PD (Jiang et al. 2019). Furthermore, it is suggested that common molecular mechanisms underlie the development of AD, PD, and cancer (Aliev et al. 2013; Driver et al. 2012; Forés-Martos et al. 2021; Jabir et al. 2015; Roe et al. 2010, Sharma et al. 2020). Previous findings and the current study suggest that *ARHGAP26* may be one of the mechanisms to link AD, CVD, cancer, and PD;

however, a confirmation study and a gene functional analysis are needed.

We also examined the association of the *ARHGAP10* gene with AD and CVD. The *ARHGAP10* gene, an important paralogon of *ARHGAP26*, is located at 4q31.23 (Kato and Kato 2004; Koeppl et al. 2004; Shibata et al. 2001). *ARHGAP10* mRNA is expressed in the brain, heart, skeletal muscle, and testis (Ren et al. 2001; Shibata et al. 2001). Recently, *ARHGAP10* gene mutations have been found to play a pathophysiologic and pathogenic role in schizophrenia (Hada et al. 2021; Sekiguchi et al. 2020). However, no study has focused on the effect of *ARHGAP10* gene on AD and CVD. The present study showed that several SNPs in each of the three samples were associated with AD. Interestingly, rs6836509 in the ADNI sample was also associated with t-tau protein, and rs17475681 was associated with CRD-SB and FAQ. Additionally, several SNPs were found to be associated with CVD only in the Hispanic sample. These findings may suggest that *ARHGAP10* gene may play a role in AD and related cognitive functions, but no SNPs on this gene have been found to be associated with both AD and CVD.

Previous studies have shown that the co-occurrence of AD and CVD might be due to shared risk factors between AD and CVDs, but there might also be a direct causal association of CVD and cardiovascular risk factors with AD (de la Torre 2012; Justin et al. 2013; Attems and Jellinger 2014; de Bruijn and Ikram 2014; Jabir et al. 2015; Monte and Vondriska 2014; Tini et al. 2020). AD and CVDs may also share genetic factors (Carter et al. 2017; Moreira et al. 2005; Mur et al. 2020; Nicot et al. 2007; Tan et al. 2013; Tini et al. 2020). Genome-wide association study also found that there may be a link between AD and CVDs using pathway analysis (Liu et al. 2014). A recent study identified 90 SNPs on 19 different chromosomes that jointly conferred increased risk for AD and cardiovascular outcomes (Broce et al. 2019). Our current findings and previous reports suggest three possible scenarios for genetic variants shared by AD and CVD: (1) genetic variants influence cardiovascular risk factors and AD independently, or (2) genetic variants influence AD through multiple cardiovascular risk factors (Broce et al. 2019), and/or (3) those disease-associated variants involved in common biology pathways result in the disease development. However, some genes could interact with cardiovascular risk factors in the development of AD (Bessi et al. 2020). Additionally, epigenetic influence at cellular and molecular levels in cancer, metabolic and cardiovascular complications are also involved in the development of neurological (psychosis) and neurodegenerative disorders such as AD and PD (Sharma et al. 2020).

There are several strengths of this study. First, we used a total of three samples: a population-based case control (ADNI) sample, a case control Caribbean Hispanic sample, and a family-based sample. A family study offers several advantages and has long been the favored approach for genetic study because of (1) reducing the type 1 error rate arising from population stratification and the NIA family-based study confirmed the results of the ADNI sample; (2) possessing several advantageous features for linkage and association tests compared with using samples of related subjects; (3) remaining a powerful and advantageous approach in complex trait genetics; and (4) reducing heterogeneity for the study due to related family members who tend to share similar lifestyles and genetic factors for a trait. Second, three samples revealed that several common genetic variants were associated with both AD and CVD, while top AD-associated SNP rs3776362 in the ADNI sample was also associated with cognitive phenotypes such as FAQ and CDR-SB. In addition, we performed functional analyses and found several SNPs with eQTLs.

There are a number of limitations in this study. The three samples may have ethnic heterogeneity even though there is a small proportion of Hispanic population representation in the ADNI sample. The majority in the ADNI sample and the NIA-LOAD family-based sample are non-Hispanic

White; however, the Caribbean Hispanic sample is a genetic heterogeneous population. Furthermore, different genotyping platforms may lead to a limited overlap of the SNPs in three sets of samples. Finally, the results in the present study might be spurious or subject to type I error due to the large number of analyses performed in this study.

Conclusion

ARHGAP26 genetic variants are significantly associated with the risks of AD and CVD in three independent samples. A number of SNPs within the *ARHGAP26* gene associated AD and CVD are functionally important or have had significant eQTLs based on in silico analysis. Furthermore, one AD-associated SNP rs3776362 in the ADNI sample was also associated with cognitive phenotypes. In addition, several *ARHGAP10* genetic variants are significantly associated with the risks of AD in these independent samples. Within the *ARHGAP10* gene, top SNP rs6836509 associated with AD in the ADNI sample was associated with t-tau protein. These results suggest a potential role of *ARHGAP26* and *ARHGAP10* in the pathogenesis of AD and/or CVD. Future functional study of these two genes may help to better characterize the genetic architecture of AD and CVD.

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Author Contribution KW and CX contributed to design, data management, and statistical analysis, drafted and reviewed statistical methods. YL, DFM, and DX managed the literature searches, added references, and drafted part of the manuscript. All authors were involved in a substantive review of the manuscript. All authors read and approved the manuscript.

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Availability of Data and Materials The datasets generated during and/or analyzed during the current study are available in the (Alzheimer's Disease Neuroimaging Initiative (ADNI) repository, (<http://adni.loni.usc.edu/data-samples/access-data/>), and (dbGaP:phs000496.v1.p1 Columbia University Study of Caribbean Hispanics and Late Onset Alzheimer's disease) repository, (<https://www.ncbi.nlm.nih.gov/gap/?term=phs000496.v1.p1>).

Declarations

Ethics Approval and Consent to Participate All participants signed informed consent in the original studies. There was an Institutional Review Board exemption for current study due to secondary data analysis.

Consent for Publication Consent for publication was obtained from the participants in the original studies.

Competing Interests The authors declare no competing interests.

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