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Population-based genome-wide association study of cognitive decline in older adults free of dementia: identification of a novel locus for the attention domain

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ABSTRACT

To identify novel loci that affect cognitive decline in older adults free of dementia, we conducted genome-wide and gene-based meta-analyses on longitudinal slopes of 5 cognitive domains (memory, executive function, language, attention/processing speed, and visuospatial ability) derived from 2 population-based cohorts. For decline over time in each cognitive domain, we normalized intraindividual slopes within each cohort, accounting for baseline age, sex, and years of education. Normalized slope for each domain was used in cohort-specific genome-wide analyses after including top principal components as covariates followed by genome-wide and gene-based meta-analyses. Both analyses revealed a novel *WDFY2* locus at genome-wide ($p = 3.37E-08$) and gene-wide ($p = 7.10E-07$) significance levels for the attention/processing speed domain. In the GTEx eQTL analysis, genome-wide significant single-nucleotide polymorphism was associated with RNA expression levels of *WDFY2* in several brain regions: cerebellar hemisphere ($p = 1.07E-04$), cerebellum ($p = 6.92E-04$), hippocampus ($p = 2.18E-03$) and cortex ($p = 2.29E-02$), and in whole blood ($p = 4.41E-05$). Our results suggest that *WDFY2* genetic variation may affect individual differences in decline over time on tests of attention/processing speed.

1. Introduction

Cognitive function is an important predictor and determinant of quality of life, especially in old age. General or global cognitive function is derived from multiple theoretical but moderately correlated cognitive domains (memory, attention, executive function, language, visuospatial skill, processing speed etc.) Interindividual differences in cognitive abilities over the lifespan are likely to have a significant genetic component, as reflected by high heritability estimates (>50%) for both general cognitive ability and major cognitive domains (Harris and Deary, 2011; Plomin and Deary, 2015; Polderman et al., 2015).

To dissect the genetic component of cognitive function, early studies focused on *APOE*, an established risk factor for Alzheimer's disease (AD), and found association of *APOE*4* with poor performance on cognitive tests, especially in the memory domain in majority of the studies (Reitz and Mayeux, 2010; Wisdom et al., 2011), albeit not meeting the current standard of genome-wide significance threshold ($p < 5E-08$). Early genome-wide association studies (GWAS) that largely examined general cognitive function as the phenotype also failed to detect genome-wide significant associations despite using large sample sizes (Benyamin et al., 2014; Davies et al., 2011; Lencz et al., 2014). However, recent GWAS on even larger data sets have found multiple genome-wide significant loci for general cognitive function (Davies et al., 2015, 2016; Trampush et al., 2015) and for some specific cognitive

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domains (Debette et al., 2015; Ibrahim-Verbaas et al., 2016). A recent GWAS meta-analysis on more than 300,000 subjects identified 148 loci for general cognitive function that explained 4.3% of variance in general cognitive function (Davies et al., 2018). Although this number of loci seems high, an equally powered GWAS meta-analysis on more than 250,000 individuals identified 423 loci for human height that explained 16% of the variance in adult height (Wood et al., 2014). This highlights the complexity of cognitive function and challenges resulting from the use of substantially different cognitive tests to construct a general cognitive function phenotype in different studies.

The general or global cognition phenotype may be derived from multiple cognitive domains, where each domain is derived from different cognitive tests. A longitudinal study on the effect of aging on cognitive abilities found that cognitive aging is characterized at all 3 levels, where 39% of the effect of age was on general cognitive function, 33% at the domains level, and 28% at the tests level (Tucker-Drob, 2011). Thus, genetic studies focusing on only a general cognitive function phenotype may not fully characterize the genetic architecture of cognitive function. In the genetics of cognitive decline in aging, investigating specific domains as cognitive endophenotypes may be more informative than collapsing different domains under a unitary construct of global cognitive decline, as different age-associated diseases have various cognitive profiles of impairment and decline (Lezak et al., 2012; Salmon and Bondi, 2009).

In this study, we used longitudinal data on 5 cognitive domains (memory, executive function, language, attention/processing speed, and visuospatial ability) from 2 population-based cohorts and conducted GWAS meta-analyses to: a) examine the association of previously reported AD loci with cognitive decline over time and b) identify novel loci that affect decline in cognitive function across different cognitive domains.

2. Materials and methods

2.1. Sample description

All subjects provided written informed consent, and all study procedures were approved by the University of Pittsburgh Institutional Review Boards. Descriptive summary statistics of the 2 samples are provided in Table 1.

2.1.1. Monongahela-Youghiogheny Healthy Aging Team (MYHAT)

MYHAT is an ongoing population-based cohort study based in a region of southwestern Pennsylvania as described previously (Ganguli et al., 2009). From 2006 to 2008, an age-stratified random sample of participants aged 65 years or older was recruited from publicly available voter registration lists. Recruitment criteria included being age 65 or older, living within the selected area, and not living in a long-term care institution. Participants were excluded if they were too ill to participate, had severe hearing or vision impairment, or were decisionally incapacitated. Of 2036 original participants, 54 were excluded because of substantial baseline cognitive impairment (age-education–corrected MMSE of less than 21 out of 30), yielding a sample of 1982 participants who underwent the full baseline assessment. These participants subsequently underwent annual assessments and had been followed for a maximum of 6 years, or 7 total assessments, at the time of this report. Of the 1982 participants, 906 consented to genotyping, which was done from whole-blood samples. This group did not differ significantly in age, sex, or education from the 204 participants who did not provide DNA. Thirty-one genotyped participants of nonwhite race were excluded from these analyses to prevent confounding by race. A further 8 genotyped participants who had a baseline clinical dementia rating of 1.0 or higher, reflecting at least mild dementia, were excluded. Of the remaining participants, 100 were excluded because they lacked any follow-up beyond the baseline assessment, which would be required to quantify cognitive decline. Thus, the final sample size for MYHAT was 767. Mean length of cognitive follow-up for MYHAT was 4.68 years (SD = 1.79, range = 1–6 years).

Table 1
Sample characteristics of the Monongahela-Youghiogheny Health Aging Team (MYHAT) and Monongahela Valley Independent Elders Survey (MoVIES) cohorts

	MYHAT (n = 767)	MoVIES (n = 378)
Age (mean (SD))	77.1 (7.3)	70.1 (4.3)
Sex—Female (n (%))	464 (60.5)	254 (67.2)
Race—White (n (%))	767 (100.0)	378 (100.0)
Years education (mean (SD))	13.0 (2.5)	11.8 (2.3)
CDR at baseline		
0 (normal)	588 (76.7)	378 (100.0)
0.5 (mild cognitive impairment)	179 (23.3)	0 (0.0)

Key: CDR, clinical dementia rating.

2.1.2. Monongahela Valley Independent Elders Survey (MoVIES)

MoVIES was a population-based cohort study based in an adjoining area of southwestern Pennsylvania (Ganguli et al., 1993). From 1987 to 1989, an age-stratified random sample of participants aged 65 years or older was recruited from publicly available voter registration lists. Recruitment criteria included being age 65 or older, not living in a long-term care institution, fluency in English, not having severe vision or hearing impairment, and at least a sixth-grade education. A total of 1424 participants were randomly recruited, and an additional 259 volunteers meeting the same inclusion criteria yielded a total MoVIES sample size of 1683. Participants underwent assessments every 2 years, on average, and were followed for a maximum of 12 years or 7 total assessments. Of the original 1683 participants in 1987–89, we genotyped 887 white individuals who were still alive, participating, and not in nursing homes in 1994, when funding was received for *APOE* genotyping. Of the specimens, 88% were genotyped using whole blood venipuncture specimens, and 12% using dried blood specimens from finger stick. The 904 MoVIES participants from whom DNA was obtained for *APOE* genotyping were slightly but significantly younger (mean ± SD ages: 71.4 ± 4.9 vs. 74.8 ± 6.5 years), more likely to be female (63.8% vs. 50.7%), and more educated (mean ± SD: 11.3 ± 2.5 vs. 10.8 ± 2.8 years) than the 779 from whom DNA was not obtained (all $p < 0.001$). Of those who were genotyped for *APOE*, the 379 participants who provided sufficient DNA for genome-wide genotyping were also slightly but significantly younger (mean age ± SD: 70.1 ± 4.3 vs. 72.3 ± 5.1 years) and better educated (mean ± SD: 11.8 ± 2.3 vs. 10.9 ± 2.5 years) than the 525 whose DNA specimens were insufficient (all $p < 0.001$). For the present study, we had available these 379 MoVIES participants with clinical dementia rating = 0 throughout the course of the study, whom we had previously genotyped for an AD case-control GWAS (Kamboh et al., 2012). We excluded one genotyped individual because she did not provide neuropsychological data after her baseline assessment. Thus, the final sample size for MoVIES was 378. Mean length of cognitive follow-up for MoVIES was 9.91 years (SD = 2.07, range = 2–12 years).

2.2. Neuropsychological assessments

Neuropsychological assessment tests were grouped into 5 cognitive domains on a theoretical basis, including attention/processing speed, executive function, language, memory, and visuospatial ability, as shown in Table 2.

Table 2
Neuropsychological Tests done in Monongahela-Youghiogheny Health Aging Team (MYHAT) and Monongahela Valley Independent Elders Survey (MoVIES) cohorts

Cognitive domain	Neuropsychological tests	
	MYHAT	MoVIES
Attention/processing speed	Trailmaking test A Digit span forward	Trailmaking test A
Executive function	Trailmaking test B Initial letter fluency Clock drawing test	Trailmaking test B Initial letter fluency Clock drawing test
Language	Boston naming test Animal fluency Token test	Boston naming test Animal fluency
Memory	Story immediate recall Story delayed recall Visual reproduction immediate recall Visual reproduction delayed recall Fuld object memory evaluation	Story immediate recall Story delayed recall Word list learning Word list delayed recall
Visuospatial skill	Block design	Constructional praxis

2.3. Cognitive slopes normalization

2.3.1. Cognitive Domain Composites

In each cognitive domain, z-scores were created by first standardizing each test score according to the sample baseline mean and standard deviation and then averaging the standardized test scores within each domain for participants with at least one non-missing test score in that domain. Global z-scores were created by averaging all of the standardized test scores for participants who were not missing more than one test score.

2.3.2. Cognitive decline slopes

To create the cognitive decline phenotypes used in GWAS, we extracted age, sex, and education-adjusted person-specific slopes of cognitive domain z-scores, using a procedure similar to that reported in (De Jager et al., 2012). For MYHAT and MoVIES samples separately, a longitudinal linear mixed model was fit for each of the cognitive domains and for the global score. Age, sex, and years of education were included as covariates, both as main effects and in interactions with time. A random intercept and random slope were included in the model. Since the estimated person-specific slope distributions were left-skewed because of a few participants who showed more rapid cognitive decline, we rescaled the slopes so they conformed to a normal distribution (Peng et al., 2007). We first ranked the slope values, then scaled the ranks to the interval [0.1, 0.99], and finally transformed the scaled ranks to a standard normal distribution using the inverse standard normal cumulative distribution function (qnorm in R).

2.4. Genotyping, imputation, and quality control

Genome-wide genotyping was carried out using the Omni1-Quad chip in the MoVIES sample (Kamboh et al., 2012) and Illumina Omni2.5 chip in the MYHAT sample. *APOE* genotyping was performed as described previously (Kamboh et al., 2012). Imputation of nongenotyped single-nucleotide polymorphisms (SNPs) was performed with IMPUTE2 (Howie et al., 2009) using the 1000 Genomes Project Phase III (May 2013 release) data as the reference panel. As part of the quality control, SNPs with imputation info score <0.5, minor allele frequency <0.01, $P <$ 1E-06 in the Hardy Weinberg equilibrium test, and the missing rate >5% were removed along with insertions and deletions. After quality control measures, 5.6 million genotyped and imputed SNPs were included in the GWAS analysis. Genetic association analyses were conducted on normalized slope for each domain after including first 4 principal components calculated using smartPCA (Price et al., 2006).

2.5. Meta-analysis

METAL (Willer et al., 2010) software was used to perform meta-analysis on the 2 GWAS of normalized slopes for each domain. The summary effect size was calculated by averaging the study-specific effect sizes, with weights reflecting the standard errors from the study-specific effect sizes. The standard threshold of $p <$ 5E-08 statistical significance for genome-wide analyses was used.

2.6. Gene-based analysis

Gene-based analysis was conducted using MAGMA (de Leeuw et al., 2015) by inputting the SNP data from the meta-analysis. Input SNPs were mapped to 18,440 protein coding genes. A gene-wide significance threshold for gene-based association was used as $p =$ 2.71E-06 (0.05/18,440).

2.7. Functional annotations

We performed the following analyses to evaluate the biological significance of statistically significant signals.

2.7.1. Differentially expressed genes

We searched for differentially expressed genes using gene expression data from AlzBase (http://alz.big.ac.cn/alzBase/) that includes transcription data from the brain and blood from participants without dementia, and with mild cognitive impairment, early-stage AD, and late-stage AD subjects.

2.7.2. Human brain gene expression

We evaluated the expression level of top genes in human brain tissues from the Barres Human and Mouse Brain RNA-Seq Resource (http://www.brainrnaseq.org/).

2.7.3. Expression quantitative trait loci (eQTL) analysis

We first identified variants in linkage disequilibrium (LD) ($R^2 \geq$ 0.8) with the genome-wide significant SNPs listed in Table 3. The SNiPA website (https://snipa.helmholtz-muenchen.de/snipa3/) was used to search for variants in LD, using the 1000 Genomes, Phase 3v5 variant set for the European population. We then searched the list of variants for genes functionally linked via eQTLs to our expanded list of variants. Finally, we searched the genotype-tissue expression (GTEx) database (https://gtexportal.org/home/) for eQTL associations in various brain tissues and whole blood.

3. Results

3.1. Sample characteristics

The main characteristics of the 2 study populations are shown in Table 1, and neuropsychological assessment tests performed within each domain are listed in Table 2. Pearson correlation between the 5 cognitive domains was low to moderate (range r = 0.03–0.66) in both the MYHAT and MoVIES samples (Supplementary Fig. S1).

3.2. Association of APOE and other known AD loci

As *APOE*4* is an established risk factor for AD and is associated with poor performance on cognitive testing in older subjects, especially in the memory domain, we first examined its association (Supplementary Table S1) along with other known risk loci for AD

Table 3
Genome-wide significant SNPs ($p < 5E-08$) form the meta-analysis in the attention/processing speed domain

SNP	CHR	BP	A1	A2	Region	GENE	MAF MYHAT	MAF MoVIES	MAF Meta	LD[b]	BETA Meta	*p*-value Meta	BETA MYHAT	*p*-value MYHAT	BETA MoVIES	*p*-value MoVIES
rs17532412	13	52,308,103	A	C	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	3.37E-08	0.21	7.57E-04	0.49	1.47E-06
rs9535744	13	52,311,481	C	G	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	3.37E-08	0.21	7.57E-04	0.49	1.47E-06
rs9535749	13	52,328,844	A	T	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	3.37E-08	0.21	7.57E-04	0.49	1.47E-06
rs9535753[a]	13	52,335,201	C	T	UTR3	*WDFY2*	0.18	0.15	0.17	1.00	0.28	3.37E-08	0.21	7.57E-04	0.49	1.47E-06
rs17532524	13	52,316,599	A	G	intronic	*WDFY2*	0.18	0.15	0.17	0.99	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs17532936	13	52,332,745	G	A	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs2296029[a]	13	52,335,765	T	C	UTR3	*WDFY2*	0.18	0.15	0.17	0.99	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs73199746	13	52,323,602	A	T	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs9526793	13	52,327,020	A	G	intronic	*WDFY2*	0.18	0.15	0.17	0.99	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs9526794	13	52,330,268	C	T	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs9535743	13	52,309,076	T	C	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs9535745	13	52,312,297	G	A	intronic	*WDFY2*	0.18	0.15	0.17	0.99	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs9535747	13	52,322,184	G	C	intronic	*WDFY2*	0.18	0.15	0.17	0.99	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs9535750	13	52,330,240	C	G	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs9535751	13	52,333,057	T	C	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs9535752	13	52,333,283	A	C	intronic	*WDFY2*	0.18	0.15	0.17	1.00	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06
rs9535756	13	52,339,750	G	C	intergenic	*WDFY2*, *DHRS12*	0.18	0.15	0.17	1.00	0.28	4.78E-08	0.21	6.66E-04	0.47	3.21E-06

Key: MAF, minor allele frequency, which is denoted by A1.
[a] Bold font indicates genotyped SNPs.
[b] Linkage disequilibrium (LD) with rs9535753.

with each domain. As expected, *APOE*4* showed the most significant association in meta-analysis with memory decline ($p = 7.18E-06$; $\beta = -0.29$), followed by language ($p = 1.65E-04$; $\beta = -0.24$) and executive function ($p = 1.11E-03$; $\beta = -0.21$) decline. However, no association of *APOE*4* was observed with decline in visuospatial function or attention domains.

Because the causative genes in other AD loci are unknown, we examined regional association around the top International Genomic Alzheimer Project (IGAP) significant SNP within each region (Efthymiou and Goate, 2017), and the results are presented in Supplementary Tables S2.1–S2.6. The top SNP within each region in a given domain with nominal $p < 0.001$ is highlighted. Two loci showed associations with more than one domain, including *EPHA1* with visuospatial ($p = 1.24E-05$) and memory ($p = 5E-04$), and *ABCA7* with executive function ($p = 3E-04$), language ($p = 4E-04$), attention ($p = 5E-04$), and visuospatial ($p = 7E-04$).

3.3. Genome-wide analysis

Next we examined the entire GWAS data, along with *APOE* and other AD loci to identify novel signals for cognitive domains. Quantile-quantile (QQ) plots and lambda values for the meta-analysis for each domain showed that the combined results from meta-analysis were not inflated in their test statistics (Supplementary Fig. 2). Genome-wide *p*-values for each domain are shown in Manhattan plots in Supplementary Figs. S3.1–S3.6. Overall, meta *p*-values for the top SNPs in a specific domain were more significant than the corresponding meta *p*-values in the global cognitive domain (Supplementary Tables 3.1–3.5).

A genome-wide significant association was observed for decline in the attention domain on chromosome 13 in the *WDFY2* gene (Fig. 1A) where multiple SNPs showed identical *p*-values passing the genome-wide significant threshold of $p < 5E-08$ (Table 3; Fig. 2). Among the top 4 SNPs having identical $p = 3.37E-08$, one located in 3′UTR of *WDFY2* (rs9535753 T/C) was genotyped and the remaining were imputed. Of the next 13 SNPs with identical $p = 4.78E-08$, only one was genotyped, and it was also located in 3′UTR (Table 3). Although almost complete LD between these SNPs (Fig. 3) makes it difficult to ascertain which one is driving the association, for our discussion purposes here we have denoted rs9535753 as the sentinel SNP because it was genotyped, has a potential functional significance, given that it is located in 3′UTR, and it was among those with the lowest *p*-value.

The effect (minor) C allele of rs9535753 was associated with slower decline in attention over time ($\beta = 0.28$) as compared to the common T allele. In addition to its genome-wide significance with attention, rs9535753 (and those in complete LD with this) also showed association with decline in executive function ($p = 1.94E-05$; $\beta = 0.22$) but not with other domains. (Supplementary Table S4).

3.4. Gene-based analysis

Gene-based analysis on SNPs derived from meta-analysis was performed using MAGMA that uses a multiple regression approach to properly incorporate LD between markers and to detect multi-marker effects. A gene-wide significance signal was seen for the attention domain, also implicating the *WDFY2* gene ($p = 7.10E-07$) on chromosome 13 (Fig. 1B, Table 4). *WDFY2* was also the top gene for executive function ($p = 2.12E-05$; Table 4).

3.5. Functional bioinformatics analyses

In the GTEx expression data, *WDFY2* is expressed in multiple tissues, including in different human brain regions (Supplementary Fig. 4). Furthermore, RNA-Seq of cell types isolated from mouse and human brain show its expression in astrocytes, neurons, microglial, and oligodendrocytes (http://www.brainrnaseq.org/ Supplementary Fig. 5).

We evaluated the potential biological significance of *WDFY2* genome-wide significant SNPs in affecting gene expression in blood and brain tissues. In AlzBase database, *WDFY2* was shown to be downregulated in the listed 2 transcriptome studies of AD.

In the GTEx eQTL analysis (Supplementary Table S5), the effect C allele of the sentinel SNP (rs9535753 and those in LD with this) was associated with higher RNA expression levels of *WDFY2* in several brain regions: cerebellar hemisphere ($p = 1.07E-04$; $\beta = 0.34$), cerebellum ($p = 6.92E-04$; $\beta = 0.35$), hippocampus ($p = 2.16E-03$; $\beta = 0.30$), and cortex ($p = 2.29E-02$; $\beta = 0.20$) as well as in whole blood ($p = 3.34E-05$ $\beta = 0.20$). We also looked at the eQTL data for *WDFY2* in AlzBase that lists 2 SNPs to be cis eQTL for *WDFY2* in 2 brain regions: rs4555048 (an intronic WDFY2 variant located at position 52185855 bp) in visual cortex ($p = 6.74E-07$) and rs4943003 (located upstream of MIR 4703 at position 52090383 bp) in

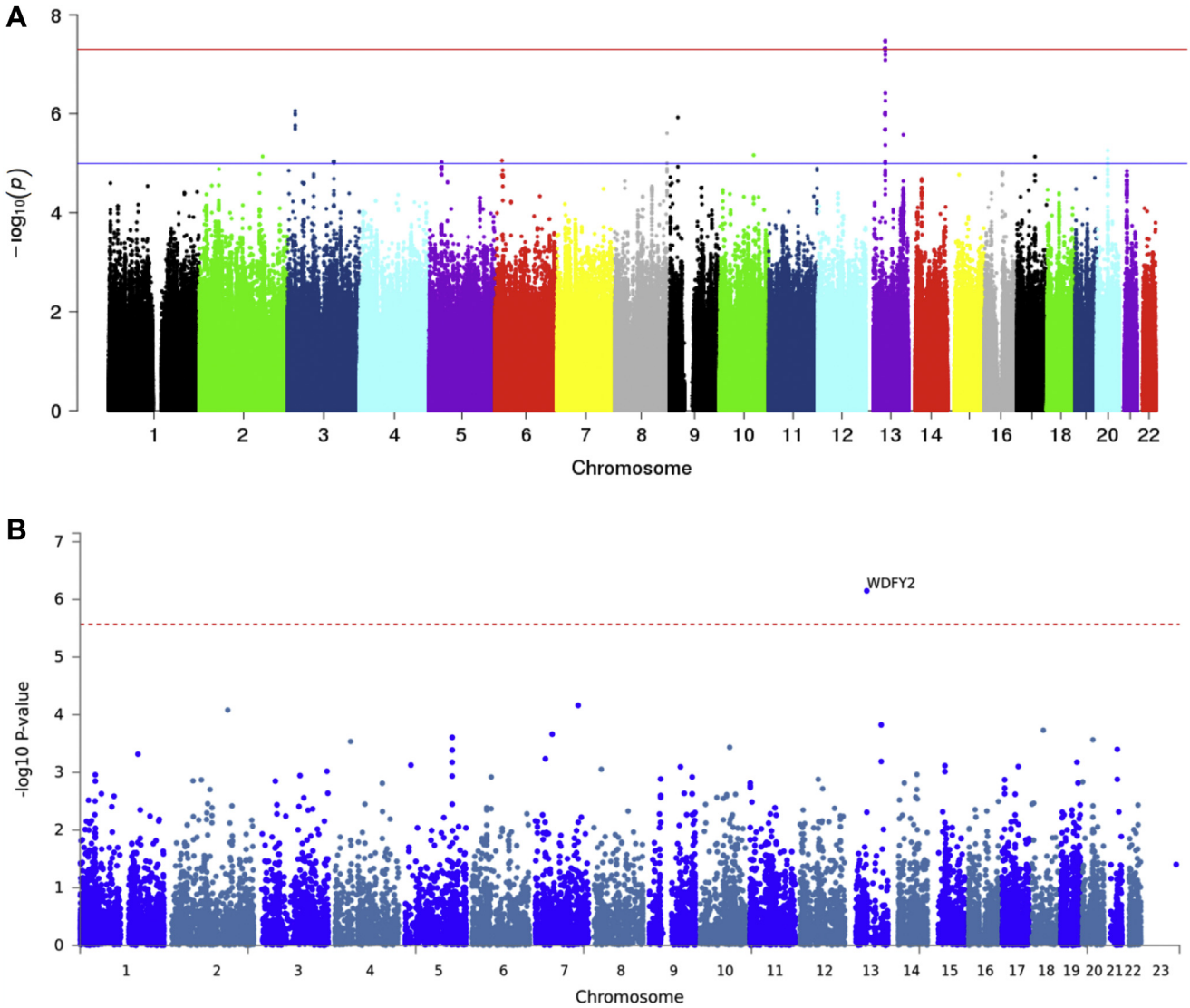

Fig. 1. (A) Manhattan plot showing the *p*-values of SNPs form genome-wide meta-analysis for the attention/processing speed domain. The red line represents the genome-wide significance threshold ($p = 5E-08$), and the blue line represents the suggestive significance threshold ($p = 1E-05$). (B) Manhattan plot showing the *p*-values of gene-based meta-analysis for the attention/processing speed domain. The red dotted line represents the gene-wide significance threshold ($p = 2.71E-06$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

prefrontal cortex ($p = 3.50E-07$). Although rs4555048 was in high LD with all genome-wide significant *WDFY2* SNPs ($r^2 = 0.92$; Fig. 3) and also showed significant association with attention/speed processing ($p = 2.07E-06$), rs4943003 is in moderate LD with genome-wide significant SNPs ($r^2 = 0.46$; Fig. 3) and with rs4555048 ($r^2 = 0.52$; Fig. 3) and showed a modest association with attention/speed processing ($p = 0.018$).

4. Discussion

The process and measurement of cognitive aging is multifaceted and is characterized by changes in different cognitive variables attributable to declines in general (global) cognitive function, domain-specific, and test-specific aspects of cognition (Harris and Deary, 2011; Tucker-Drob, 2011). Different cognitive domains reflect functioning of different brain regions and circuits which are differentially impaired in different disorders and thus may be considered as cognitive endophenotypes that are potentially informative for genetic studies. Full genetic contribution to age-related cognitive decline can ideally be captured by focusing on both general and domain-specific cognitive skills. However, previous GWAS have largely focused on a general cognitive function phenotype and may therefore have missed domain-specific genes/loci as well as loci that are specific to cognitive decline rather than baseline cognitive function. In this study, we followed 2 longitudinal cohorts free of dementia at baseline and calculated intra-individual slopes of linear decline over time in 5 cognitive domains (memory, executive function, language, attention/processing speed, and visuospatial ability). We performed genome-wide and gene-based meta-analyses to capture genetic variation associated with decline in each individual domain and compared results with global cognitive decline as constructed from the 5 domains.

Among the known AD loci, *APOE*4* showed the strongest association with memory change/decline, as predicted and providing validation to our cognitive assessment and statistical methods. Two other known AD loci showed associations with more than one domain at $p < 1E-03$, including *EPHA1* with visuospatial ability and memory and *ABCA7* with executive function, language, attention,

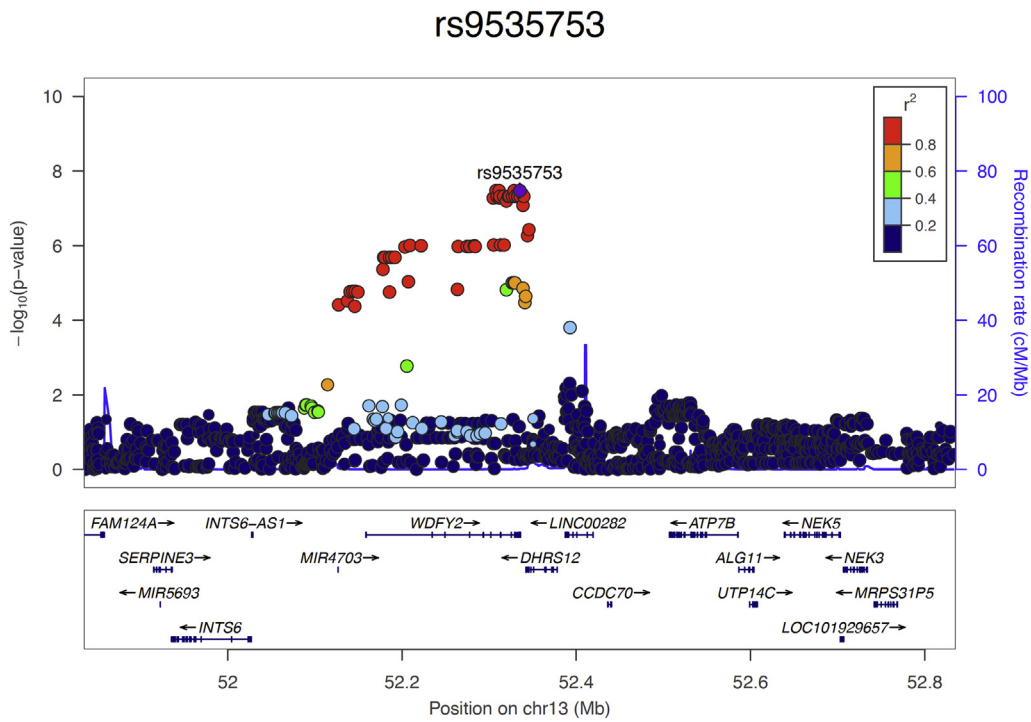

Fig. 2. Regional plot of the *WDFY2* region on chromosome 13 in the meta-analysis of the attention/processing speed domain. The relative location of genes and the direction of transcription are shown in the lower portion of the figure, and the chromosomal position is shown on the *x* -axis. The light blue line shows the recombination rate across the region (right *y* axis), and the left *y* axis shows the significance of the associations. The purple diamond shows the *p*-value for rs9535753 ($p = 3.37E-08$) that is among the most significant SNPs in the meta-analysis. The circles show the *p*-values for all other SNPs and are color coded according to the level of LD with rs9535753 in the 1000 Genome Project EUR population. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and visuospatial ability. However, none of these AD genes were the top genes in their respective domains.

Our GWAS meta-analysis identified a novel *WDFY2* locus ($p = 3.37E-08$) for the attention domain, which we would have missed had we used the global cognitive decline as a unitary phenotype. The attention domain comprised 2 tasks, reflecting verbal working memory storage capacity and psychomotor speed/visual search. Interestingly, these functions and tasks are not typical impaired in early AD-type neurodegeneration. More broadly, attention is a set of cognitive functions supporting all other higher

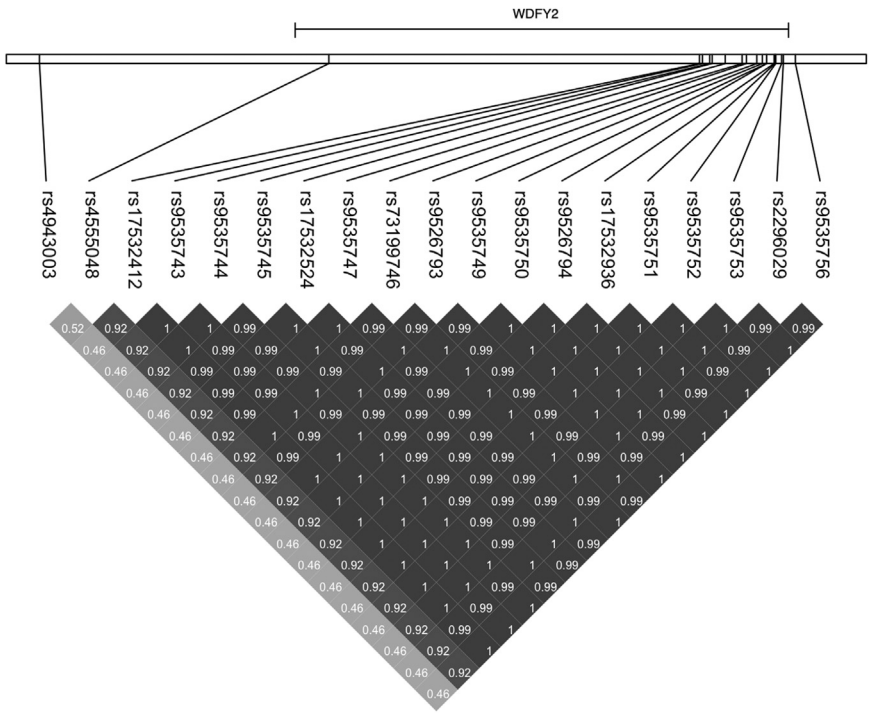

Fig. 3. Linkage disequilibrium (LD) pattern of *WDFY2* genome-wide significant SNPs ($p < 5E-08$) for attention/processing speed as shown in Table 3, along with 2 SNPs (rs4555048 and rs4943000 at far left) that are eQTLs for *WDFY2* in AlzBase database.

Table 4
Result of gene-based analysis showing the top genes ($p < 1E-04$) for each domain

Domain	ENSG #	Gene	CHR	START	END	# of SNPs	p-value[a]
Attention/processing speed							
	ENSG00000139668	*WDFY2*	13	52,158,644	52,336,171	151	7.10E-07
	ENSG00000106348	*IMPDH1*	7	128,032,331	128,050,306	38	6.79E-05
Executive function							
	ENSG00000139668	*WDFY2*	13	52,158,644	52,336,171	151	2.12E-05
	ENSG00000198837	*DENND4B*	1	153,901,977	153,919,172	15	2.23E-05
	ENSG00000143614	*GATAD2B*	1	153,777,201	153,895,451	142	3.37E-05
	ENSG00000160741	*CRTC2*	1	153,920,145	153,931,101	7	4.34E-05
	ENSG00000143570	*SLC39A1*	1	153,931,575	153,940,188	9	8.08E-05
	ENSG00000101166	*SLMO2*	20	57,608,200	57,617,964	9	9.49E-05
	ENSG00000143578	*CREB3L4*	1	153,940,010	153,946,839	9	9.68E-05
Language							
	ENSG00000196466	*ZNF799*	19	12,500,830	12,512,085	10	2.15E-05
	ENSG00000138758	*SEPT11*	4	77,870,856	77,961,537	150	4.32E-05
Memory							
	ENSG00000072415	*MPP5*	14	67,707,826	67,802,536	43	2.14E-05
	ENSG00000130203	*APOE*	19	45,409,011	45,412,650	5	4.29E-05
	ENSG00000162782	*TDRD5*	1	179,560,748	179,660,407	256	4.46E-05
	ENSG00000170054	*SERPINA9*	14	94,929,054	94,946,026	64	6.58E-05
	ENSG00000172717	*FAM71D*	14	67,656,110	67,695,267	35	7.34E-05
	ENSG00000072401	*UBE2D1*	10	60,094,735	60,130,513	24	7.42E-05
	ENSG00000100554	*ATP6V1D*	14	67,761,088	67,826,982	39	7.84E-05
	ENSG00000134001	*EIF2S1*	14	67,826,714	67,853,233	19	8.15E-05
Visuospatial function							
	ENSG00000183873	*SCN5A*	3	38,589,548	38,691,164	223	2.30E-05
	ENSG00000166825	*ANPEP*	15	90,328,120	90,358,633	98	2.82E-05
	ENSG00000118507	*AKAP7*	6	131,456,806	131,604,675	264	5.96E-05
	ENSG00000158717	*RNF166*	16	88,762,903	88,772,829	39	6.12E-05
	ENSG00000160613	*PCSK7*	11	117,075,053	117,103,241	73	7.76E-05
	ENSG00000148842	*CNNM2*	10	104,678,050	104,849,978	336	9.66E-05

[a] Input SNPs were mapped to 18,440 protein coding genes. Gene-wide significance was defined as $p = 2.71E-06$ (0.05/18,440).

cognitive functions, by allowing the appropriate selection of stimuli and maintenance of concentration (i.e., vigilance). As a multidimensional function with complex anatomic and neurochemical underpinnings, including subcortical networks, attention may be disturbed in a variety of medical conditions across the lifespan. There are shared processes and networks with executive functions, as well (Gitelman, 2003).

The credence to shared processes and networks between attention and executive functions is provided by our genetic data where genome-wide significant *WDFY2* SNPs also showed association with decline in executive function ($p = 1.94E-05$; $\beta = 0.22$) but not with other domains, and *WDFY2* was the top gene for both attention ($p = 7.10E-07$) and executive function ($p = 2.12E-05$) in the gene-based analysis.

Although the sample sizes in our 2 cohorts were relatively small, both showed consistent and directional association for the top GWAS attention signal that provides support for a genuine association. Additional support to the genome-wide analysis (based on single SNP test in a genome) is provided by the gene-based analysis (based on multiple SNPs test within a gene) that also identified the *WDFY2* gene as being gene-wide significant ($p = 7.10E-07$). The 2 *WDFY2*-genotyped SNPs that showed genome-wide significance (rs9535753; $p = 3.37E-08$ and rs2296029; $p = 4.78E-08$) are located in 3′UTR of *WDFY2*. 3′UTRs of mRNAs are known to be involved in the regulation of mRNA stability, translation, and mRNA localization. In addition, the formation of 3′UTR-mediated protein-protein interactions can also enable the transmit of genetic information stored in 3′UTRs to proteins (Mayr, 2018). In view of the wide range of functions associated with 3′UTRs, it is plausible that the identified SNPs in 3′UTR of *WDFY2* are functional. However, we cannot rule out the possibility that other SNPs with genome-wide significance, which were in tight LD with these 2 SNPs or yet to be discovered SNPs in this region, are involved in driving the association at this locus. Indeed, our all genome-wide significant SNPs were associated with *WDFY2* expression in different brain regions, at least at nominal significance.

WDFY2 [WD (tryptophan-aspartic acid dipeptide) repeat and FYVE domain containing 2] is a phosphatidylinositol 3-phosphate binding-protein that is localized to early endosomes necessary for endocytosis (Hayakawa et al., 2006). WDFY2-enriched endosomes also serve as a scaffold that enables specificity of insulin signaling through protein kinase Akt (Walz et al., 2010). *WDFY2* has also been identified as a tumor suppression gene via inactivation of the Akt pathway (Wang et al., 2017). *WDFY2* is widely expressed in multiple tissues, including the brain. A network analysis of bipolar disorder (BD) GWAS data has identified *WDFY2* as one of the 4 hub genes that might indirectly affect the risk of BD by interacting with genes directly related to BD (Xie et al., 2017). To our knowledge, *WDFY2* has not been previously implicated in GWAS of cognitive function or AD. However, *WDFY2* has been identified as a differentially coexpressed gene along with *TAX1BP3* or *SLC35E1*, where their coexpression was decreased in prefrontal cortex of AD cases relative to controls (Narayanan et al., 2014). Similarly, AlzBase database shows lower expression of *WDFY2* in AD, indicating its potential role in AD or AD-related dementia. In our study, the effect (minor) allele of the top *WDFY2* SNP (rs9535753 and other SNPs in LD; all located in *WDFY2*) was associated with slower decline in attention over time and was also associated with higher expression of *WDFY2* in different brain regions in the GTEx data. The underlying mechanism of this association is not clear at present. Another member of the WDFY family, WDFY4, which is predominantly expressed in immune tissues has been found to be genetically associated with lupus and rheumatoid arthritis (Yang et al., 2010; Zhang et al., 2014). It is likely that the observed association of *WFDY2* with a cognitive endophenotype and its differential expression in AD brains is also due to an immune-related mechanism, similar to that observed with some AD-associated genes (Pimenova et al., 2018) because *WFDY2* is also expressed in microglial/macrophage cells in the brain (Supplementary Fig. 5).

Strengths of this study include our focus on the genetics of cognitive decline in older adults from 2 well-characterized population-based cohorts. Participants were free of dementia at baseline and had measured trajectories of cognitive endophenotypes over time in multiple cognitive domains. Identical findings from genome-wide and gene-wide tests provide credence to our observed novel genetic association with the attention domain that is further supplemented by functional analyses, including gene expression data in relevant brain cells and regions. The main study limitation is the absence of replication cohorts. This was largely beyond our control as most of the published studies have used general cognition in GWAS as compared to our focus on domain-specific cognitive endophenotypes. This limitation is somewhat alleviated by the fact that the association and the direction of our top attention signal was similar in our both cohorts and that our genome-wide analysis finding was confirmed in the gene-based analysis. Although our finding of the association *WDFY2* with decline over time in attention appears to be novel, it will need to be replicated before its role is more thoroughly investigated.

In conclusion, we report a novel locus for decline in attention that also showed suggestive association with decline in executive function. Future larger studies focusing on domain-specific cognitive endophenotypes may help us to broaden our understanding about the complex genetic architect of cognitive change in aging.

Disclosure

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.02.024.

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