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RESEARCH ARTICLE

Genome-wide association study of rate of cognitive decline in Alzheimer's disease patients identifies novel genes and pathways

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Abstract

Introduction: Variability exists in the disease trajectories of Alzheimer's disease (AD) patients. We performed a genome-wide association study to examine rate of cognitive decline (ROD) in patients with AD.

Methods: We tested for interactions between genetic variants and time since diagnosis to predict the ROD of a composite cognitive score in 3946 AD cases and performed pathway analysis on the top genes.

Results: Suggestive associations ($P < 1.0 \times 10^{-6}$) were observed on chromosome 15 in DNA polymerase-γ (rs3176205, $P = 1.11 \times 10^{-7}$), chromosome 7 (rs60465337, $P = 4.06 \times 10^{-7}$) in contactin-associated protein-2, in RP11-384F7.1 on chromosome 3 (rs28853947, $P = 5.93 \times 10^{-7}$), family with sequence similarity 214 member-A on chromosome 15 (rs2899492, $P = 5.94 \times 10^{-7}$), and intergenic regions on chromosomes 16 (rs4949142, $P = 4.02 \times 10^{-7}$) and 4 (rs1304013, $P = 7.73 \times 10^{-7}$). Significant pathways involving neuronal development and function, apoptosis, memory, and inflammation were identified.

Discussion: Pathways related to AD, intelligence, and neurological function determine AD progression, while previously identified AD risk variants, including the apolipoprotein (*APOE*) $\varepsilon 4$ and $\varepsilon 2$ variants, do not have a major impact.

KEYWORDS
cognitive decline, disease progression, genetic association, pathway analysis

1 | INTRODUCTION

Alzheimer's disease (AD) is characterized by progressive cognitive deterioration, and substantial variability exists in the cognitive trajectories of affected individuals. Several studies have examined factors associated with cognitive decline in non-demented adults,[1-9] conversion from mild cognitive impairment (MCI) to AD,[10-18] and rate of cognitive decline (ROD) after AD diagnosis.[19-26] Several non-genetic determinants of decline, including lifestyle factors, biomarkers and biometric variables, and co-morbid diagnoses have also been reported.[26-38]

Several genetic and epigenetic factors that may contribute to ROD in AD cases have also been identified. Expression levels of leucine rich repeat and fibronectin type III domain containing 2 (*LRFN2*),[39] beta-nerve growth factor and its receptors,[40] myocyte-enhancer factor 2C,[41] and inositol polyphosphate-5-phosphatase[42] have been associated with ROD in the brains of people with AD. Epigenetic protein dysregulation has also been implicated in AD progression.[43,44] A recent study identified 519 proteins, the abundance of which was associated with cognitive trajectory in adults without dementia at baseline. These proteins were enriched in pathways related to the neuronal mitochondrial activities synaptic abundance, inflammation, and apoptosis.[45] Two studies have examined the role of AD risk genes in cognitive decline and found that specific single-nucleotide polymorphisms (SNPs) and polygenic risk scores predict ROD in older, non-demented individuals.[46,47] A different study also found that the AD risk variants or polygenic risk scores do not affect ROD in AD individuals.[26] Genetic association studies identified two SNPs in astrocytic water channel aquaporin-4 that predict ROD,[48] and a genome-wide association study (GWAS) identified variants in six genes that interacted with AD diagnosis (vs MCI) to predict longitudinal cognitive change.[49] We previously conducted a GWAS for ROD using AD cases from the Alzheimer's Disease Neuroimaging Initiative (ADNI, N = 303) and cases from the Religious Orders Study and Rush Memory and Aging Project (ROS/MAP,

N = 323) as replication, and identified significant associations with variants in several genes, including F-spondin (*SPON1*), whose product binds the central domain of the amyloid precursor protein (APP).[50] We present here the results from a GWAS of ROD in an expanded sample of 3946 AD cases of European ancestry and discuss methodological challenges related to analysis of cognitive data and interaction tests (SNP genotype x time with AD) using longitudinal data.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using PubMed sources. Although the genetics of cognitive decline has not been widely studied (except by our group), non-genetic factors influencing AD progression have been identified. The relevant citations are appropriately cited.
2. Interpretation: Our findings point to novel variants and pathways affecting cognitive decline, and show a limited role for known AD risk variants. These results may inform the design and analysis of future clinical trials of AD drugs.
3. Future directions: This article outlines a framework for the generation and analysis of longitudinal cognitive scores that will be applied to larger samples and specific domains of cognitive function in order to confirm and expand these findings. Functional studies are necessary to determine whether the genes/pathways identified are suitable for drug targets.

2 | METHODS

2.1 | Composition of the data

Eleven cohorts with longitudinal cognitive data and genome-wide SNP data were available for study: ADNI[51] (PMID: 23932184), ROS/MAP[52,53] the Three City Study (3C),[54] AddNeuroMed,[55-57] Myriad Flurizan phase III clinical trial,[58] National Alzheimer's Coordinating Centers,[59] Pfizer,[60] Lilly Semagacestat phase III clinical trial,[61] Washington University in St. Louis,[26] the Adult Changes in Thought study (ACT),[62] and the Washington Heights Inwood Community Aging Project (WHICAP).[63] Details about the design, recruitment, and genotyping methods for each cohort are provided in supplemental materials.

2.2 | Imputation and quality control

Following genotype chip quality control (removal of low call rate SNPs and individuals, individuals with excess heterozygosity, or ambiguous sex), each data set was phased and imputed to the 1000 Genomes Project (phase 1 integrated release 3, March 2012)[64] using SHAPEIT/IMPUTE2[65,66] or MaCH/Minimac[67,68] software. All reference population haplotypes were used for the imputation. Rare variants with minor allele frequency (MAF) less than 2% and those with an r^2 <0.70 were excluded from further analyses. In the mega-analysis, variants were excluded if they were missing or poorly imputed in >30% of all samples. King Robust[69] was used to generate a kinship coefficient for each pair of individuals using a set of genotyped SNPs common to each cohort (N = 41,625 after linkage disequilibrium pruning) using a merged data set from all 11 cohorts. The member of each related or duplicate pair (kinship coefficient ≥0.1) with the shortest amount of follow-up time was removed. Individuals were assigned ancestry using K-means clustering implemented in R, where K = 3 based on the three reference populations (Eur, Afr, Asn) in the 1000 Genomes populations. Individuals were assigned to the cluster. The member of each related pair (kinship coefficient ≥0.1) with the shortest amount of follow-up time was removed. Individuals were assigned ancestry using K-means (K = 3) clustering with the 1000 Genomes populations (Eur, Afr, Asn) whose centroid was nearest across the first 10 principal components. Those samples that did not cluster with Eur reference population were removed from downstream analysis. Subsequent PC analysis was conducted within the cohort and also in the combined sample.

2.3 | Composite cognitive score

Methods for combining cognitive tests in each cohort and harmonizing them across cohorts to produce a composite indicator of general cognitive performance (GCP) are published elsewhere.[70] Each study administered at least 2 and as many as 21 cognitive tests.Briefly, we used item response theory (IRT) methods to derive a measure of GCP. We first identified common tests across studies (ie, anchor tests) and tests that were not common. Anchor tests serve to anchor the cognitive metric across studies so that a unit difference in the underlying factor score has the same meaning across the study.[71] Next, we estimated a confirmatory factor analysis, consistent with a graded-response IRT model,[72,73] of all tests across all studies and time. This approach allows items to be weighted differently, by accommodating different factor loadings. Items also provide measurement at different locations or points along the general cognitive trait depending on how well respondents do on the tests.

2.4 | Association tests

Association tests were performed using two regression-based repeated measures methods. In one approach, linear regression models were solved with generalized estimating equations (GEEs) assuming an autoregressive correlation structure with GCP as the outcome. To assess *rate* of decline rather than levels of cognitive performance, models included a term for the interaction between SNP allele dosage and time since AD diagnosis as the predictor of interest. This construct tests whether SNP genotype modifies the effect of duration of illness on cognitive performance. All models

TABLE 1 Demographic information by study cohort

Cohort	Age at first visit, μ (SD)	N males/N females	Follow-up years, μ (SD)	Change in GCP[a], μ (SD)	Change in MMSE[a] μ (SD)	λ[b] GEE[c]	λ LME[d]
3C	77.9 (5.6)	139/216	6.5 (2.5)	2.8 (4.5)	2.1 (3.6)	1.06	1.36
ACT	78.2 (6.1)	68/106	7.7 (2.8)	4.1 (5.4)	1.40 (.9)	1.45	1.16
AddNeuroMed	77.3 (6.8)	110/179	1.2 (1.0)	1.5 (4.9)	1.9 (3.9)	1.15	3.25
ADNI	75.7 (6.4)	157/115	2.7 (1.4)	4.8 (5.1)	2.4 (4.6)	1.11	3.18
Flurizan	74.6 (8.2)	548/533	1.2 (0.6)	2.2 (7.1)	3.6 (5.0)	1.05	2.26
NACC	78.3 (7.9)	271/268	2.2 (1.7)	6.2 (6.2)	1.8 (3.8)	1.10	2.14
Pfizer	75.7 (5.0)	69/92	1.5 (2.5)	2.5 (4.3)	2.0 (3.6)	1.06	2.31
ROS/MAP1	82.4 (6.5)	120/262	7.9 (4.5)	4.5 (7.0)	1.1 (3.5)	1.08	3.23
ROS/MAP2	82.6 (7.7)	24/55	1.4 (.5)	3.5 (5.8)	0.9 (3.3)	1.28	2.94
Semagacestat	74.1 (7.7)	152/155	1.3 (.5)	1.5 (4.9)	2.6 (4.4)	1.08	10.37
WashU	74.2 (7.5)	110/129	5.7 (4.9)	2.9 (4.9)	1.5 (3.3)	1.14	5.37
WHICAP	82.3 (7.9)	20/48	5.0 (3.5)	1.1 (6.1)	1.7 (3.8)	3.42	1.63

[a]During the first two years of follow up post Alzheimer's Disease diagnosis.
[b]Genomic inflation factor.
[c]Generalized Estimating Equations.
[d]Linear Mixed Effects.

were adjusted for age, sex, ancestry principal components (computed within cohorts for cohort specific analyses and in the total sample for the mega-analyses), the main effects of SNP and time since diagnosis, and squared and cubic terms for time since AD diagnosis, which account for any non-linear effects of time since diagnosis on GCP. Analyses were conducted within cohort and in the total sample through fixed-effects inverse variance meta-analysis. In another approach, we analyzed the total sample using linear mixed-effects models including the same interaction term and covariates with random intercepts for individual and cohort. All association tests were performed using Universal Genome Analyst (Koesterer, Ryan. Universal Genome Analyst (uga). https://github.com/rmkoesterer/uga. https://doi.org/10.5281/zenodo.578712.), which parallelizes tests within the R packages GEEpack (https://CRAN.R-project.org/package = geepack) and LME4 (https://github.com/lme4/lme4/). We limited analyses to cognitive tests performed during the first 2 years of post-diagnosis follow-up. The top variants were further tested for association with GCP after adjusting for years of education.

2.5 | Functional annotation of variants

We assessed regulatory potential for genic and intergenic SNPs using the online databases Genotype-Tissue Expression project (GTEx, http://www.gtexportal.org/home/) and BRAINEAC (www.braineac.org) to identify any expression quantitative trait loci (eQTLs) among the top SNPs. All SNPs were annotated using SNPeff, which uses data from ENCODE and other sources to assign SNPs to promoter regions, CpG islands, and DNAase hypersensitivity sites, and quantifies cross-species conservation and the impact of coding mutations.[74]

2.6 | Pathway analysis

Genes containing variants with P-values $< 1 \times 10^{-4}$ (N = 334) in at least two models tested were included in an Ingenuity pathway analysis (QIAGEN Inc., https://www.qiagenbioinformatics.com/products/ingenuitypathway-analysis). Only SNPs within introns, exons, and 3′ and 5′ UTRs (according to SNPeff annotation) were considered.

3 | RESULTS

After quality control, 3946 AD cases were available for analysis. Table 1 shows characteristics of each cohort, including the mean age at baseline, length of follow-up, and change in GCP during the study period, which we limited to the first 2 years of follow-up. The interaction terms between time with AD and age ($P = 0.0001$), sex ($P = 0.02$), and education status ($P = 3.5 \times 10^{-5}$) were significantly associated with GCP.

3.1 | Inflation

Significant inflation (λ) of the genome-wide interaction term test statistics was observed in several cohorts using both LME and GEE. The λ was moderately correlated with sample size. We attempted several approaches to reduce λ, including computing P-values using F and t distributions, setting the degrees of freedom (df) equal to the sample size minus the number of variables in the model, using the Boss R package,[75] including terms for time with AD squared and cubed, and limiting the follow-up time to 2 years post diagnosis. Ultimately, none of these steps eliminated inflation, and in three cohorts λ remained

above 1.2 (ACT, ROS/MAP2, WHICAP), although inflation was reduced in models including non-linear time with AD terms and limiting to 2 years of follow-up. Consequently, we corrected all test statistics for the cohort-specific λ and conducted the meta-analyses with and without cohorts with $\lambda > 1.2$. Figures S1-3 show the λ-corrected quintile-quintile plots for both the GEE (meta-analysis with (Figure S1) and without (Figure S2) ACT, ROS/MAP2, WHICAP, and LME (mega-analysis including all cohorts; Figure S3).

3.2 | Association results

Although multiple SNPs and structural variants in several independent regions were significantly associated with ROD in the GEE or LME models including all cohorts, none of these showed evidence in both GEE and LME models and they were not robust to the exclusion of the three cohorts with $\lambda > 1.2$. Using these stringent criteria, no SNPs showed genome-wide significance for associations with ROD. Table 2 shows variants (trimmed for LD) with *P*-values $< 1 \times 10^{-4}$ in all three models, as well as any gene(s) whose expression was predicted to be significantly altered by the SNP according to the GTEx database (https://gtexportal.org/home/).[76] Suggestive associations ($P < 1.0 \times 10^{-6}$) were observed in a large region on chromosome 15 spanning several genes including DNA polymerase-γ (*POLG*) (rs3176205, $p_{LME} = 1.11 \times 10^{-7}$, Figure 1), on chromosome 7 (rs60465337, $p_{GEE} = 4.06 \times 10^{-7}$, Figure 2) in an intron of contactin-associated protein 2 (*CNTNAP2*), in the lincRNA RP11-384F7.1 gene region on chromosome 3 (rs28853947, $p_{GEE} = 5.93 \times 10^{-7}$), and family with sequence similarity 214 member A (*FAM214A*) on chromosome 15 (rs2899492, $p_{GEE} = 5.94 \times 10^{-7}$); and in intergenic regions on chromosomes 16 (rs4949142, $p_{GEE} = 4.02 \times 10^{-7}$) and 4 (rs1304013, $p_{GEE} = 7.73 \times 10^{-7}$). A variant in *SPON1* was associated with ROD at rs200230690 ($p_{GEE} = 2.36 \times 10^{-5}$). Fourteen of the SNPs in Table 2 are significant eQTLs, including several predicted to affect *POLG* expression.

We also examined the top SNPs in 32 known AD risk genes,[77-79] and also the SNPs tagging the *APOE* ε2 and ε4 alleles, for association with ROD. After correcting for the number of SNPs tested, only rs1476679 in zinc finger CW-type and PWWP domain containing 1 (*ZCWPW1*, $p_{LME} = 3.07 \times 10^{-6}$, $p_{GEE} = 3.9 \times 10^{-4}$), was significantly associated with ROD. Notably, the minor allele (C) is protective for AD and associated with slower ROD.[77] Although the associations were observed with different variants, *CNTNAP2*[79] and phospholipase C gamma 2 (*PLCG2*)[80] have also recently been implicated as AD risk genes.

3.3 | Pathway analysis

Among the genes that met criteria for inclusion in pathway analysis (Table S1), several have direct links to AD pathology, including amyloid beta (Aβ) precursor protein binding family A member 1 (*APBA1*), beta-secretase 1 (*BACE1*), and paired immunoglobin like type 2 receptor alpha (*PILRA*). Others are in the same gene families as established AD risk genes such as ATP-binding cassette subfamily A member 1 (*ABCA1*) and EPH receptor B1 (*EPHB1*). Three genes are related to other neurodegenerative diseases. Synuclein alpha (*SNCA*), and parkin RBR E3 ubiquitin protein ligase (*PRKN*) are associated with Parkinson disease risk, and HECT, C2, and WW domain containing E3 ubiquitin protein ligase 1 (*HECW1*) is associated with familial amyotrophic lateral sclerosis. Table S2 shows the individual SNP results for these genes. Subsets of these genes were significantly overrepresented in 56 canonical pathways (many of which are closely related and contain a largely overlapping set of genes) at Benjamini-Hochberg[81] *P*-value < 0.05 (Table S3). Many of these pathways are related to neuronal development and function (Gαq signaling, ephrin signaling, synaptic long-term depression, axonal guidance signaling), neuronal apoptosis (G beta gamma signaling, Huntington disease signaling, phospholipase C signaling), memory (CREB signaling in neurons, protein kinase A signaling), and inflammation and immunity (CXCR4 signaling, thrombin signaling). Similarly, a portion of these genes were significantly (false discovery rate corrected *P*-value ≤ 0.05) overrepresented in 53 physiological systems (Table S4) related to nervous system function, including development of neurons ($P = 7.03 \times 10^{-9}$), neuritogenesis ($P = 9.02 \times 10^{-8}$), morphology of the nervous system ($P = 9.08 \times 10^{-8}$), neurite branching ($P = 1.64 \times 10^{-7}$), neurotransmission ($P = 3.03 \times 10^{-7}$), and synaptic transmission ($P = 3.61 \times 10^{-7}$).

4 | DISCUSSION

We report results from a GWAS for ROD in the largest cohort of AD cases with longitudinal cognitive data assembled to date. We identified several suggestive associations in genes with no previous links to AD risk, as well as one study-wide significant association with *ZCWPW1* in tests focused on previously established AD risk genes, and identified novel variants in *CNTNAP2* and *PLCG2*. These newly implicated genes have roles in a diverse set of physiological pathways that have functions related to known AD processes and more generalized neural biology and development. Several of these pathways showed statistically significant enrichment of the top-ranked genes in the GWAS.

POLG is involved in proofreading during mitochondrial DNA (mtDNA) replication.[82] Mutations in the gene have been associated with multiple mitochondrial disorders including Alpers type mtDNA depletion syndrome[83] and progressive external ophthalmoplegia.[84] Several animal studies have induced accelerated aging phenotypes by altering the function of *POLG*.[85,86] and the effects appear to be driven by increased neuronal apoptosis.[85] Given the well-established role of mitochondrial dysfunction in AD (reviewed in[87-89]) and the links between variants in this gene and aging phenotypes, this gene is a biologically compelling candidate for a ROD mediator. The top variant in the gene is a significant eQTL for POLG, suggesting that its effects on ROD might be through increased expression.

CNTNAP2 encodes a neuronal member of the neurexin superfamily and is involved in neural-glia interactions and clustering of potassium channels in axons. It is expressed at high levels in the prefrontal and anterior temporal cortex, and the dorsal thalamus,

TABLE 2 Results with $P < 1 \times 10^{-4}$ in all models tested

Chr	SNP	A1[a]	A2[b]	Freq[c]	Gene	eQTLs[d]	Beta[e]	P_{GEE}	$P_{GEE\lambda}$[f]	P_{LME}	Direction[g]
1	rs61776523	A	G	0.86	Y_RNA	-	−0.51	5.99E-05	5.97E-05	6.28E-05	+---x---++
2	rs62146087	A	G	0.62	CD8B	CD8B, PLGLB1	0.40	1.96E-05	2.47E-05	7.49E-05	+++++++-+x-+
2	rs10930401	T	C	0.88	intergenic	METTL5	−0.49	7.00E-05	6.85E-05	7.81E-05	-----+-x-
2	rs11683533	G	A	0.63	intergenic	-	−0.45	2.09E-06	6.50E-06	9.10E-05	------+-
3	rs1447793	G	A	0.95	ROBO2	-	0.89	5.73E-05	1.19E-05	2.22E-05	+x+++++x-+xx
3	rs79279449	T	C	0.84	LSAMP	-	−0.48	2.54E-05	8.21E-05	1.77E-05	-+-+----x
3	rs28853947	C	T	0.70	RP11-384F7.1	-	−0.45	2.29E-06	5.93E-07	8.59E-05	-----+++x
3	rs4857800	T	A	0.65	intergenic	-	−0.40	7.90E-06	1.03E-06	8.39E-05	---+---++
4	rs12501599	G	C	0.78	CLNK	ZNF518B	0.46	1.34E-05	7.35E-05	2.42E-05	++++-+++++++
4	rs2168075	A	G	0.45	CCSER1	CCSER1	−0.37	4.62E-05	8.89E-05	9.38E-05	-----+-+-
4	rs1304013	C	T	0.73	intergenic	-	0.50	4.73E-07	8.82E-06	2.48E-05	-++++++x-+++
6	rs9393409	A	G	0.36	intergenic	-	−0.39	2.70E-05	1.81E-05	9.17E-05	---x++--+
6	rs9380681	T	C	0.70	intergenic	-	0.46	1.40E-06	1.80E-06	3.09E-05	++++-++x-+-+
6	rs45604140	C	G	0.90	PTK7	DNPH1, KLHDC3	−0.54	6.07E-05	1.98E-05	7.15E-06	-+---+--++
6	rs4897203	T	C	0.09	TRDN	-	0.74	1.34E-06	2.14E-06	9.56E-07	+++++++-+-++
7	rs7806833	T	G	0.22	SCIN	-	−0.46	4.99E-05	5.64E-05	4.44E-05	-------+-
7	rs39437	G	C	0.16	OSBPL3-CYCS	-	0.51	4.68E-06	2.15E-06	9.70E-05	++++++++-++-
7	rs17150563	T	C	0.72	intergenic	HIBADH, TAX1BP1	0.40	6.08E-05	2.13E-05	3.61E-05	++-++++x-+-+
7	rs7792776	G	A	0.87	intergenic	-	−0.55	1.08E-05	1.68E-05	2.07E-05	-------+-
7	rs6959165	A	G	0.45	HECW1	-	0.36	2.96E-05	1.82E-05	1.64E-05	+++++++x-++
7	rs60465337	C	T	0.97	CNTNAP2	-	1.03	8.59E-07	4.06E-07	2.86E-05	++++++++++x-
8	rs16877878	A	G	0.96	RP11-566H8.3	-	1.18	1.13E-05	9.35E-05	1.33E-05	x+++++x++++x
10	rs182768834	G	A	0.95	intergenic	-	−0.87	1.60E-06	9.96E-06	6.31E-05	-------x-
11	rs61897000	G	A	0.66	CHRDL2	XRRA1	−0.36	7.25E-05	1.69E-05	6.44E-05	-+---+-++
12	rs7301894	A	G	0.44	ANO2	-	−0.34	8.59E-05	6.21E-05	7.54E-05	-----x+-+
12	rs10785192	T	A	0.07	RP11-585P4.5	RP11-585P4.5, GLIPR1L2	−0.69	2.23E-05	5.99E-05	1.69E-06	-+-----x
12	rs660322	G	A	0.24	TMEM132D	-	0.53	1.07E-05	9.44E-06	1.14E-05	x+-+++++-xx+
15	rs2899492	C	T	0.16	FAM214A	ARPP19	0.62	5.94E-07	9.70E-07	1.37E-05	++-++++x+xx+
15	rs8041705	T	C	0.56	HMGB1P8	-	−0.41	1.76E-05	2.66E-05	2.22E-05	---x--x+-
15	rs12324317	T	C	0.61	RLBP1	RLBP1, POLG	−0.40	1.80E-05	2.11E-05	1.91E-05	---+-+x+-+-
15	rs9788714	G	A	0.62	RLBP1-FANCI	POLG	−0.42	2.50E-06	1.70E-06	1.70E-06	---++-+-+x
15	rs2238301	A	G	0.61	FANCI	POLG	−0.46	3.30E-07	1.59E-07	3.15E-07	----+-+-+x
15	rs3176205	T	C	0.61	POLG	POLG	−0.46	2.75E-07	1.49E-07	1.11E-07	---++-+-+x
16	rs4949142	A	G	0.85	intergenic	-	−0.60	5.83E-07	4.02E-07	7.82E-06	-----x-x+
16	rs12448088	G	C	0.40	PLCG2	-	−0.41	2.91E-05	2.36E-05	1.10E-05	+--x---x-+
17	rs2071194	C	A	0.36	EVPL	TEN1	0.41	1.44E-05	3.84E-05	6.67E-05	+++++++x-+++

[a]Effect allele.
[b]Other allele.
[c]Frequency of effect allele.
[d]Expression Quantitative Trait Locus: genes differentially expressed by SNP genotype according to GTEx database.
[e]Beta from GEE model including all cohorts.
[f]*P*-value from GEE model excluding cohorts with $\lambda > 1.2$.
[g]Effect direction in individual cohorts from the GEE model including all cohorts. The order of the symbols is Pfizer, 3C, ADNI, Flurizan, NACC, ROS/MAP1, Semagacestat, ADNeuroMed, ACT, WashU, WHICAP, ROS/MAP2.

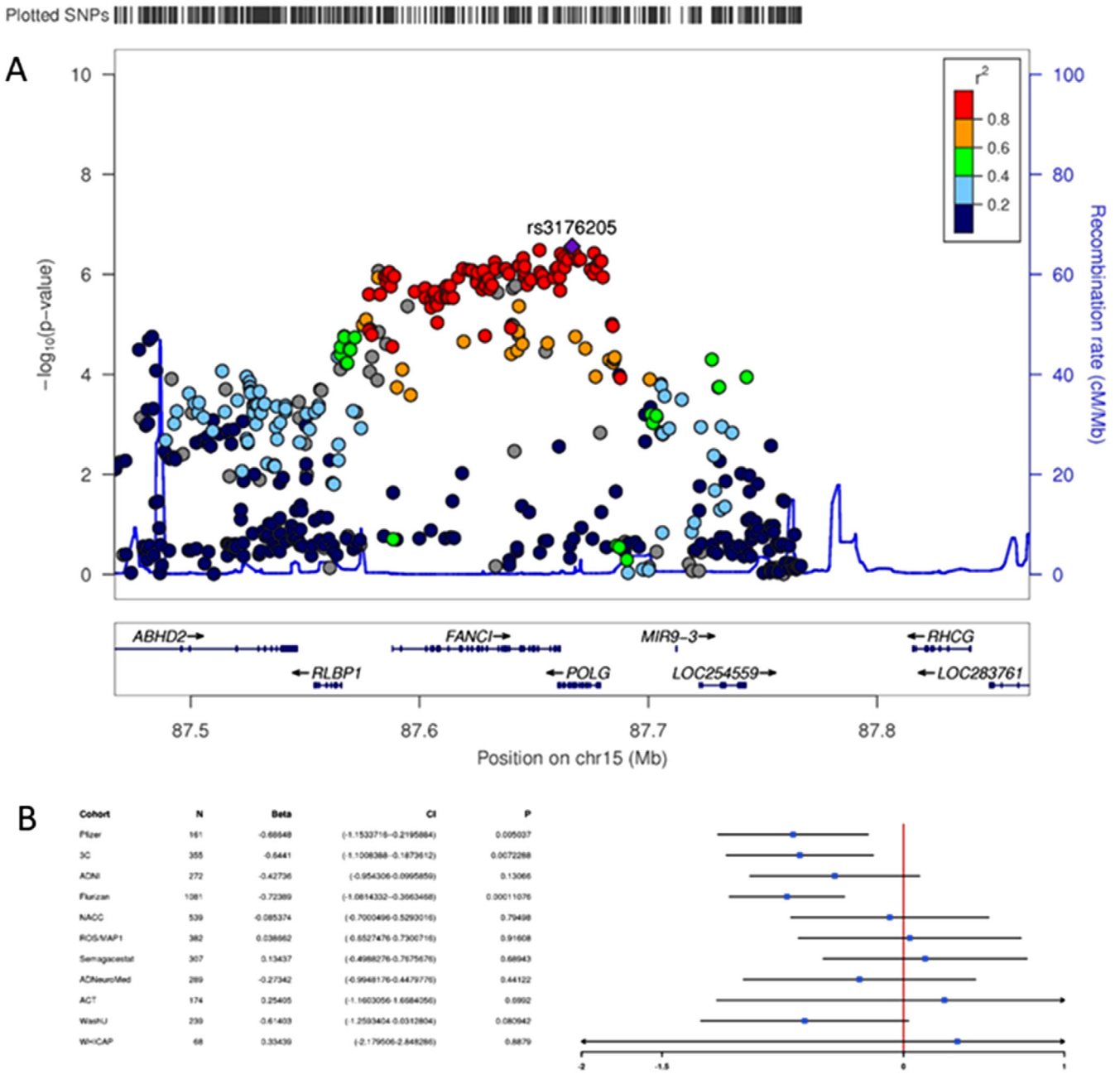

FIGURE 1 Association results for the region containing DNA polymerase-γ on chromosome 15. Regional Manhattan plot (A) and forest plot (B) showing the full generalized estimating equation model results for the region containing DNA polymerase-γ on chromosome 15. Single-nucleotide polymorphisms (SNPs) are color coded according to their linkage disequilibrium with the lead SNP in the region. The forest plot shows the β and associated 95% confidence interval in each cohort.

caudate, putamen, and amygdala, with enriched expression in circuits involved in higher cortical functions including language.[90] Variants have been associated with neurodevelopmental disorders including autism,[91-93] Attention-Deficit/Hyperactivity Disorder (ADHD),[94] and intellectual disabilities[95] through multiple protein function and regulatory mechanisms. It is downregulated in the hippocampus of AD patients, possibly through increased expression of the transcription factor Storkhead box 1A.[96] The variant we identified is intronic with no known regulatory effects.

There is evidence that several of the top-ranked genes have roles in the immune system and neuroinflammation, including (cytokine dependent hematopoietic cell linker) (*CLNK*),[97] CD8b molecule (*CD8B*),[98] and *PLCG2*.[99] Hect, c2, and ww domain-containing e3 ubiquitin-protein ligase 1 (*HECW1*) binds to mutated superoxide dismutase 1 to produce Lewy body–like hyaline inclusions in ventral horn motor neurons in familial amyotrophic lateral sclerosis patients.[100]

The pathway analysis results highlight additional mechanisms affecting ROD, broadly implicating neuronal development, apoptosis,

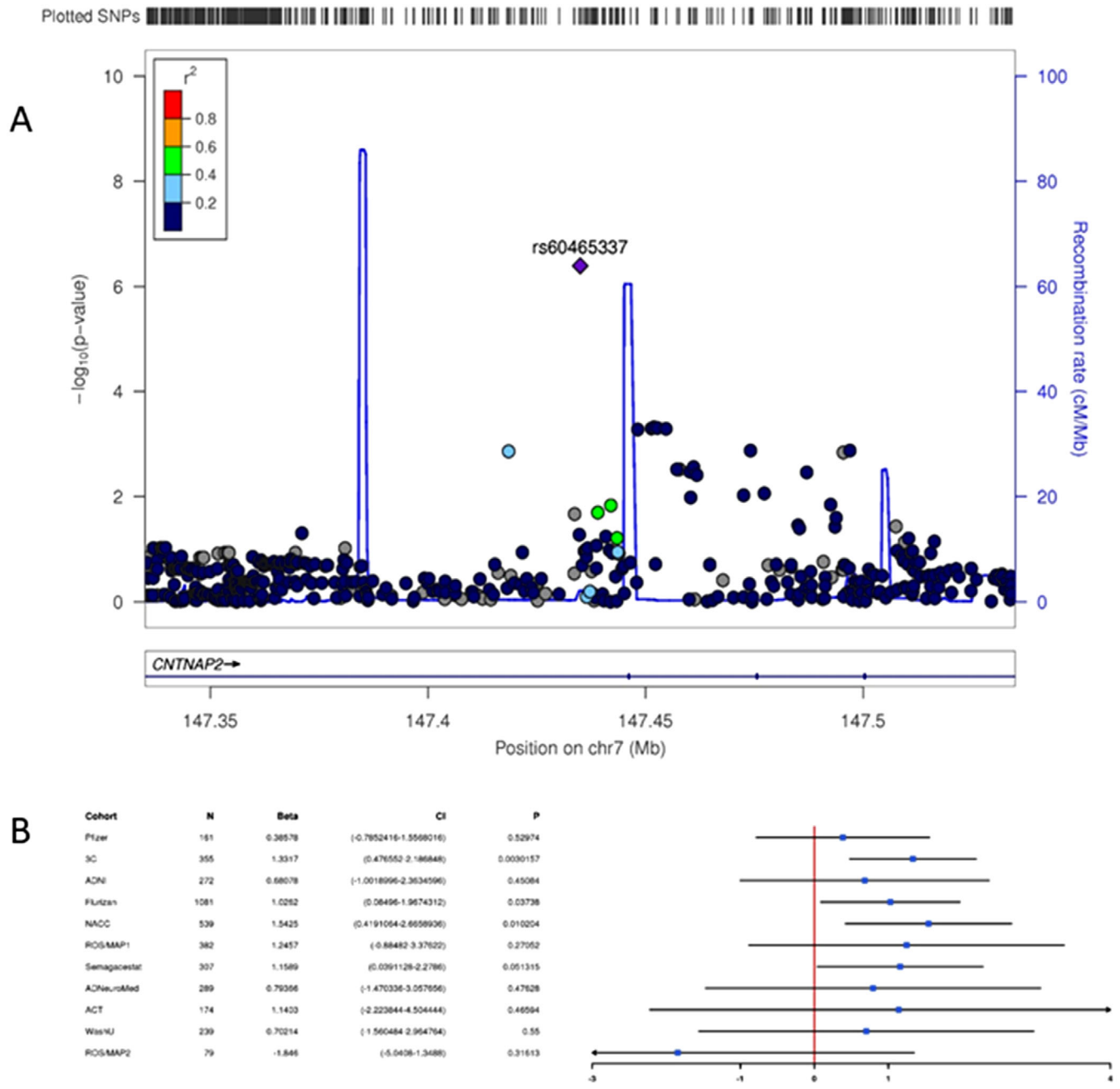

FIGURE 2 Association results for contactin-associated protein 2 on chromosome 7. Regional Manhattan plot (A) and forest plot (B) showing the full generalized estimating equation model results for the region containing contactin-associated protein 2 on chromosome 7. Single-nucleotide polymorphisms (SNPs) are color coded according to their linkage disequilibrium with the lead SNP in the region. The forest plot shows the β and associated 95% confidence interval in each cohort.

and synapse formation. The vast majority of the significant canonical pathways are linked by the involvement of genes encoding G protein–coupled receptor (GPCR) subunits. GPCRs regulate many neurotransmitters in the brain and also directly influence the amyloid cascade by modulating α-, β-, and γ-secretase, proteolysis of the APP, and regulation of Aβ degradation.[101] The top pathway, Gαq signaling, is involved in axon growth and has been a drug target for multiple disorders, including a negative phase 2 clinical trial for AD.[102] The second ranked pathway, G beta gamma signaling, has also been studied in the context of AD and affects apoptosis.[103] The significant diseases and biological functions largely involve a set of genes different from those overrepresented in the canonical pathways and suggest roles for neural development and neurotransmission in ROD. *CNTNAP2*, *APBA1*, and *BACE1* are all involved in the top functions, although it is unclear from these data whether these findings represent pre- or post-disease alterations.

Our findings also highlight genetic links between intelligence and AD-related pathways. A recent study identified 187 independent loci

associated with intelligence from a meta-analysis of 248,482 non-demented subjects.[104] Of these loci, 10 (*APBA1* $p_{min} = 1.63 \times 10^{-6}$, *BANK1* $p_{min} = 4.30 \times 10^{-5}$, *KCNH5* $p_{min} = 5.42 \times 10^{-5}$, *NEGR1* $p_{min} = 3.09 \times 10^{-7}$, *PDE4D* $p_{min} = 1.01 \times 10^{-6}$, *PTPRN2* $p_{min} = 1.59 \times 10^{-5}$, *RBFOX1* $p_{min} = 2.23 \times 10^{-5}$, *SGCZ* $p_{min} = 3.91 \times 10^{-6}$, *SLC17A3* $p_{min} = 4.27 \times 10^{-5}$, and *ZCCHC4* $p_{min} = 2.34 \times 10^{-5}$) were among our top-ranked genes for ROD measured in individuals after onset of AD symptoms. Each of these associations remained or increased in significance after adjusting for years of education, suggesting that the effects of these genes are not limited to general, pre-disease cognitive ability and may actively alter disease pathology. Of these genes, only *APBA1* is known to be involved in AD pathology.[105,106] None of the top SNPs in these 10 genes that were associated with ROD were tagged by the lead SNP associated with intelligence in,[104] making it impossible to determine whether the effect directions matched, but also suggesting the possibility that different causal variants within those genes may affect ROD and general intelligence. These results, combined with the significant ROD pathways we identified and the observation that ROD is associated with rs1476679 in *ZCWPW1* only among known AD risk variants (although different variants in *CNTNAP2* and *PLCG2* were associated with ROD), suggest that post-diagnosis cognitive functioning may be determined more by genetic variation influencing general neural function and connectivity than by genes involved in the cascade of events leading to AD-related pathology.

In aggregate, these results suggest that like AD itself, cognitive decline is highly polygenic and controlled by a diverse set of pathways. The individual variant results suggest roles for mitochondrial dysfunction, neuron function, and immunity, whereas the pathway results implicate, GPRC-mediated Aβ and/or neurotransmitter processing neuronal development, pruning, and survival.

4.1 | Strengths and limitations

Several limitations to this work should be noted. The data comprise multiple, relatively small cohorts with different ascertainment schemes. This, combined with the inherently heterogeneous nature of AD presentation, symptom profile, and pathology, suggests that participants in this study may be at different stages of the disease and/or may represent multiple biologically distinct AD subtypes. The different sets of cognitive tests performed across cohorts may have limited our ability to detect true genetic associations with ROD, although our previous work demonstrated that the metric of the GCP composite factor is consistent across studies.[70] Finally, the longitudinal interaction tests we used were associated with inflation in the test statistics for both LME and GEE models and, consequently, our results may be less robust after a heavy correction for genomic control. However, we minimized this concern by excluding data sets showing high levels of inflation.

Despite these issues, several indicators suggest that our findings are robust. First, the significance of the top results are commensurate with the sample size, and the effect sizes and directions are generally consistent across cohorts, with no single sample exerting an excessive effect on the overall association. The variants reported are also associated with ROD using two distinct regression-based approaches to modeling correlated data, and are robust even when the cohorts showing the greatest inflation are excluded. The top-ranked findings were observed generally with relatively common variants that were well imputed ($r^2 \geq 0.8$). In addition, evidence suggesting that we identified genes in AD-relevant pathways, significant pathways related to neuronal function, and genes that are also significantly associated with cognitive performance more broadly suggest our analysis uncovered true determinants of ROD. Future directions include further expanding of the sample and repeating the analyses using pre-diagnosis cognitive scores. Finally, our phenotype is a measure of global cognitive function and it is possible that additional genes contribute to specific domains of cognition (ie, memory or executive function).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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