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The effect of rare variants in *TREM2* and *PLD3* on longitudinal cognitive function in the Wisconsin Registry for Alzheimer's Prevention

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ABSTRACT

Recent studies have found an association between functional variants in *TREM2* and *PLD3* and Alzheimer's disease (AD), but their effect on cognitive function is unknown. We examined the effect of these variants on cognitive function in 1449 participants from the Wisconsin Registry for Alzheimer's Prevention, a longitudinal study of initially asymptomatic adults, aged 36–73 years at baseline, enriched for a parental history of AD. A comprehensive cognitive test battery was performed at up to 5 visits. A factor analysis resulted in 6 cognitive factors that were standardized into *z* scores ($\sim$N [0, 1]); the mean of these *z* scores was also calculated. In linear mixed models adjusted for age, gender, practice effects, and self-reported race/ethnicity, *PLD3* V232M carriers had significantly lower mean *z* scores ($p = 0.02$) and lower z scores for story recall ($p = 0.04$), visual learning and memory ($p = 0.049$), and speed and flexibility ($p = 0.02$) than noncarriers. *TREM2* R47H carriers had marginally lower *z* scores for speed and flexibility ($p = 0.06$). In conclusion, a functional variant in *PLD3* was associated with significantly lower cognitive function in individuals carrying the variant than in noncarriers.

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for 60%–80% of dementia cases. Over 5 million Americans have AD, and that number is expected to increase to nearly 14 million by 2050 due to the projected increase in the number of older Americans (Alzheimer's Association, 2016). AD is the sixth leading cause of death in the United States and the only of the top 10 causes of death with no way to prevent, cure, or impede its progression (Alzheimer's Association, 2013). There are currently few known risk factors that are highly predictive of AD. Individuals with a family history of AD are known to be at increased risk for developing the disease, and the ε4 allele of the apolipoprotein E gene (*APOE*) is also a well-established risk factor. Carrying 1 copy of the *APOE* ε4 allele results in a 3-fold higher risk of developing AD than those with 2 copies of the more common ε3 allele, and those with 2 copies of the ε4 allele have an 8- to 12-fold higher risk (Holtzman et al., 2012; Loy et al., 2014).

Recent genome-wide association studies (GWAS) have identified 19 additional genetic regions that are associated with AD (Lambert et al., 2013; Naj et al., 2011). While potentially important for risk prediction, the genetic variants in these regions are of unknown function and have modest odds ratios (ORs) ranging from 1.1 to 1.2 per risk allele. Moreover, these variants together explain a relatively small portion of the full genetic contribution to AD (Ridge et al., 2013). GWAS have typically focused on common genetic variants, with minor allele frequencies $\geq$5%, as these were historically the types of variants included on genome-wide chips. However, recent sequencing studies have identified 3 functional low-frequency (minor allele frequency 0.5%–5%) variants with a more substantial effect (OR of approximately 2–5) on risk for AD: (1) R47H in the triggering receptor expressed on myeloid cells 2 gene (*TREM2*) (Guerreiro et al., 2012; Jonsson et al., 2012) and (2) V232M and

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A442A (splice site variant) in the phospholipase D family member 3 gene (*PLD3*) (Cruchaga et al., 2014). We sought to examine the effect of these variants on cognitive performance in a longitudinal study of middle-aged adults who were cognitively healthy at enrollment and enriched for a parental history of AD.

2. Methods

2.1. Study population

Study participants were from the Wisconsin Registry for Alzheimer's Prevention (WRAP), a longitudinal study of initially asymptomatic adults, aged 36–73 years at baseline, that allows for the enrollment of siblings and is enriched for a parental history of AD (i.e., a biological parent with either autopsy-confirmed AD, probable AD as defined by NINCDS-ADRDA research criteria (McKhann et al., 1984), or dementia due to AD based on the Dementia Questionnaire (Ellis et al., 1998)). Details of the study design and methods have been previously described (Engelman et al., 2014; La Rue et al., 2008; Sager et al., 2005). Baseline recruitment began in 2001 with initial follow-up after 4 years and subsequent ongoing follow-up every 2 years or until a participant receives a clinical diagnosis of AD, at which point they are no longer followed. Data from up to 5 study visits were available for the current analyses. A total of 1449 WRAP participants had genotypic data for the low-frequency variants analyzed in the present study. This study was conducted with the approval of the University of Wisconsin Institutional Review Board, and all subjects provided signed informed consent before participation.

2.2. Neuropsychological assessment

The WRAP cognitive test battery assesses many domains and has been previously described (Darst et al., 2015; Sager et al., 2005). For these analyses, we used 1 composite variable estimating cognitive functioning at the age of 54 years (the mean age at baseline) and 6 factor scores representing longitudinal functioning across memory and executive function domains.

2.2.1. Composite progression score

A composite index, named progression score (PS), was computed using a set of 8 cognitive measures, including Trails A and B (Reitan and Wolfson, 1985), Digit Span Forward and Digit Span Backward (Wechsler, 1997), Rey Auditory Verbal Learning Test summed score across 5 learning trials (Lezak et al., 2004), Auditory Verbal Learning Test delayed recall (Lezak et al., 2004), Boston Naming Test (Kaplan et al., 1983), and the Mini–Mental State Examination (Folstein et al., 1975). Visits with fewer than 4 of these measurements were excluded. We applied the PS model (Bilgel et al., 2015; Jedynak et al., 2012) to align individuals along a linear cognitive trajectory based on their longitudinal cognitive measure profiles, adjusting for interindividual differences in rates of change, with a higher PS indicating greater overall cognitive decline across the 8 measures. We accounted for correlations among cognitive measures and constrained the PSs to increase linearly with age within each individual. To remove confounding effects of age at entry into WRAP, the PS was estimated at the age of 54 years, the mean age at baseline.

2.2.2. Longitudinal factor scores

A factor analysis of the neuropsychological test scores was performed as described previously (Dowling et al., 2010; Jonaitis et al., 2015; Koscik et al., 2014). The resulting factor scores were standardized into z scores ($\sim$N [0, 1]), using means and standard deviations obtained from the whole sample at baseline (visit 1) or visit 2 for a subset of tests that were first administered at this visit. There were 4 cognitive factor z scores for memory (immediate memory, verbal learning and memory, story recall, and visual learning and memory) and 2 for executive function (working memory, as well as speed and flexibility). Tests comprising each of these factors have been previously described (Darst et al., 2015). Owing to the small number of individuals carrying the functional variants, these 6 factor scores were also averaged to create a summary cognitive measure of the factor scores for each individual. Consequently, we did not adjust for multiple comparisons when examining the mean z score and used the individual cognitive factor scores to inform which domains were driving the association with the mean z score.

2.3. DNA collection, genotyping, and quality control

DNA was extracted from whole blood samples as described previously (Engelman et al., 2013). Genotyping of the *TREM2* variant R47H (rs75932628) and *PLD3* variants V232M (rs145999145) and A442A (rs4819; splice site variant) was performed using competitive allele-specific polymerase chain reaction–based KASP genotyping assays (LGC Genomics, Beverly, MA). The quality control process has been described previously (Darst et al., 2017). The *PLD3* splice site variant, A442A, was monomorphic in our sample. Consequently, no genetic association analysis could be performed on this variant. The other *PLD3* variant and the *TREM2* variant were in Hardy-Weinberg equilibrium.

2.4. Statistical analysis

Differences in allele frequencies between those with a parental history of AD and those without were tested using a Fisher's exact test. *TREM2* and *PLD3* associations with each of the cognitive factor scores and the PS at the age of 54 years were tested using linear mixed models (SAS PROC MIXED) by comparing carriers of one of the rare variants to noncarriers of either. For each cognitive factor score, models included fixed effects for age, gender, practice effects, and self-reported race/ethnicity and random effects for family (siblings) and participants (repeated measures). For the PS, the model included fixed effects for gender and race/ethnicity (age was not adjusted for as it was used to calculate the PS) and a random effect for family. To visually display the cognitive factor z scores,

Table 1
WRAP participant characteristics at baseline, mean (*SD*) or *n* (%)

Characteristic	*TREM2* (R47H) carrier[a] ($n = 16$)	*PLD3* (V232M) carrier[a] ($n = 13$)	Noncarrier ($n = 1413$)
Age (years)	52.4 (5.6)	51.8 (8.9)	53.8 (6.6)
Gender (female)	13 (81.3)	10 (76.9)	898 (70.0)
Race/ethnicity			
Caucasian	15 (93.8)	13 (100.0)	1253 (88.8)
African American	0	0	113 (8.0)
Hispanic	1 (6.3)	0	33 (2.3)
Other	0	0	12 (0.9)
Years of education	15.3 (2.8)	15.7 (3.1)	16.2 (2.3)
APOE genotype			
ε2/ε2	0	0	5 (0.4)
ε2/ε3	1 (6.3)	3 (23.1)	113 (8.0)
ε2/ε4	1 (6.3)	0	46 (3.3)
ε3/ε3	6 (37.5)	4 (30.8)	742 (52.5)
ε3/ε4	7 (43.8)	6 (46.2)	447 (31.6)
ε4/ε4	1 (6.3)	0	60 (4.2)

Key: *APOE*, apolipoprotein E gene; *PLD3*, phospholipase D family member 3 gene; SD, standard deviation; *TREM2*, triggering receptor expressed on myeloid cells 2 gene; WRAP, Wisconsin Registry for Alzheimer's Prevention.

[a] No participants carried both the *TREM2* and *PLD3* variants; 7 participants had a missing genotype for either *TREM2* or *PLD3* and are not included in this table. Minor/risk allele for *TREM2* R47H was T; minor/risk allele for *PLD3* V232M was A.

Table 2
Carrier frequency (n) by parental history of AD

Gene (variant)	No parent with AD ($n = 409$)	Parent with AD ($n = 1040$)	p value[a]
TREM2 (R47H)	0.00 (0)	0.015 (16)	0.009
PLD3 (V232 M)	0.005 (2)	0.011 (11)	0.54

Key: AD, Alzheimer's disease; *PLD3*, phospholipase D family member 3 gene; *TREM2*, triggering receptor expressed on myeloid cells 2 gene.
[a] Fisher's exact test of the difference in allele frequency in individuals without versus with a parent with AD.

adjusted mean z scores (a weighted average of the predicted z scores across all classes of gender and race/ethnicity and for the average age) were calculated and plotted for *TREM2* R47H and *PLD3* V232M carriers, as well as for *APOE* ε4 homozygotes, ε4 heterozygotes, and noncarriers of any of these 3 risk variants, using the LSMEANS statement in PROC MIXED with the OM option to weight the average of the predictions to be proportionate to the input data set. This was especially important for race/ethnicity, which was not evenly distributed in the WRAP cohort. All analyses were performed in SAS v9.4 and used a p value threshold of <0.05 to determine significance.

3. Results

Characteristics of the 1449 participants, according to *TREM2* and *PLD3* carrier status, are shown in Table 1. No participants carried both the *TREM2* R47H (T allele) and *PLD3* V232M (A allele) low-frequency variants. There were no significant ($p < 0.05$) differences in the characteristics between carriers of either variant or noncarriers. Of the 16 participants who carried the *TREM2* variant, 15 were non-Hispanic Caucasian, 1 was Hispanic, and none were African American or another race/ethnicity. All 13 *PLD3* carriers were non-Hispanic Caucasian.

Presence of the *TREM2* R47H variant was associated with AD parental history status; all 16 participants with R47H were in the parental history group (Table 2). Patterns appeared similar for the relationship between *PLD3* V232M and AD parental history.

In linear mixed models, *PLD3* carriers had significantly lower mean z scores and lower z scores for story recall, visual learning and memory, and speed and flexibility than noncarriers (Table 3; results for *APOE* ε4 count are shown for comparison). *TREM2* carriers had marginally lower z scores for speed and flexibility ($p = 0.06$). Although the PS at the age of 54 years was higher for both *TREM2* and *PLD3* carriers, indicating greater disease progression, these differences were not statistically significant. Adjusted mean z scores for the 6 cognitive factors for *TREM2* carriers, *PLD3* carriers, as well as for *APOE* ε4 homozygotes, ε4 heterozygotes, and noncarriers of any of these 3 risk variants are shown in Fig. 1.

4. Discussion

Functional low-frequency variants in *TREM2* are established risk factors for AD and an additional variant in *PLD3* has been reported (Cruchaga et al., 2014), but their effect on cognitive function in the years before the typical onset of AD is unknown. We examined the effect of these variants on cognitive performance in a longitudinal study of middle-aged adults who were cognitively healthy at enrollment, the majority of whom had a parental history of AD. The *TREM2* R47H variant was found in 15 non-Hispanic Caucasians and 1 Hispanic, all with a parent who had AD. The *PLD3* V232M variant was only found in non-Hispanic Caucasians and was twice as common in individuals with a parental history of AD than in those without a parental history. Although both variants were generally associated with lower cognitive function in carriers of either variant than in noncarriers, only carriers of the *PLD3* variant had significantly lower cognitive function than noncarriers.

Our study population was intentionally enriched for individuals with a parental history of AD (72% of participants). Whereas the carrier percentages in the parental history group were 1.5% for *TREM2* R47H (T allele) and 1.1% for *PLD3* V232M (A allele), the percentages in the participants with no parental history of AD were 0% and 0.5%, respectively. The *TREM2* R47H carrier percentage is 0.4% in the Exome Aggregation Consortium database (ExAC; $N = 60{,}145$; accessed 11/15/16) (Lek et al., 2016) and 0.5% in the Genome Aggregation Database (gnomAD; $N = 140{,}485$; beta mode available at http://gnomad.broadinstitute.org; accessed 11/15/16; includes samples from the Alzheimer's Disease Sequencing Project and from ExAC). The *PLD3* V232M carrier percentage was 0.6% in ExAC ($N = 57{,}683$) and 0.7% in gnomAD ($N = 141{,}023$). Taken together, for both variants, the percentage of individuals carrying the low-frequency risk variant was higher in WRAP participants with a parental history of AD than in WRAP participants without a family history or in publicly available reference databases, illustrating the statistical power to be gained from a study design focusing on individuals with a family history of AD, in which low-frequency risk variants are likely to be more prevalent.

Our cohort is 89% non-Hispanic Caucasian, with only 113 African Americans and 34 Hispanics; however, despite these small sample sizes, we did observe 1 Hispanic carrier of the *TREM2* R47H variant. In gnomAD, the largest compilation of large-scale sequencing projects, the *TREM2* R47H (T allele) was carried by 0.7% of Latinos ($n = 18{,}221$), 0.5% of Europeans (non-Finnish; $n = 62{,}674$), and 0.1% of Africans ($n = 12{,}921$). This higher carrier frequency in Latinos and

Table 3
Association between risk variant and cognitive function

Cognitive function	β ± *SE* (p value)		
	TREM2 (R47H) ($n = 1446$)	*PLD3* (V232M) ($n = 1445$)	*APOE* ε4 count
Composite progression score			
Progression score at age 54[a]	0.19 ± 0.29 (0.52)	0.46 ± 0.33 (0.16)	0.11 ± 0.05 (0.04)
Longitudinal factor scores			
Mean of 6 factor scores	−0.14 ± 0.16 (0.38)	−0.41 ± 0.18 (0.02)	−0.10 ± 0.03 (0.002)
Immediate memory	−0.12 ± 0.20 (0.56)	−0.23 ± 0.23 (0.32)	−0.07 ± 0.04 (0.06)
Verbal learning and memory	−0.002 ± 0.22 (0.99)	−0.22 ± 0.25 (0.37)	−0.09 ± 0.04 (0.03)
Story recall	−0.16 ± 0.24 (0.49)	−0.55 ± 0.26 (0.04)	−0.14 ± 0.05 (0.002)
Visual learning and memory	−0.06 ± 0.22 (0.78)	−0.49 ± 0.25 (0.049)	−0.08 ± 0.04 (0.05)
Working memory	−0.15 ± 0.23 (0.51)	−0.26 ± 0.27 (0.34)	−0.11 ± 0.04 (0.01)
Speed and flexibility	−0.39 ± 0.20 (0.06)	−0.54 ± 0.24 (0.02)	−0.06 ± 0.04 (0.11)

Linear mixed model, adjusting for age, gender, practice effects, and race/ethnicity, and accounting for within-family (sibling) correlations and within-individual correlations from up to 10 y of follow-up.
Key: *APOE*, apolipoprotein E gene; *PLD3*, phospholipase D family member 3 gene; SE, standard error of the mean; *TREM2*, triggering receptor expressed on myeloid cells 2 gene.
[a] Linear mixed model, adjusting for gender and race/ethnicity, and accounting for within-family (sibling) correlations.

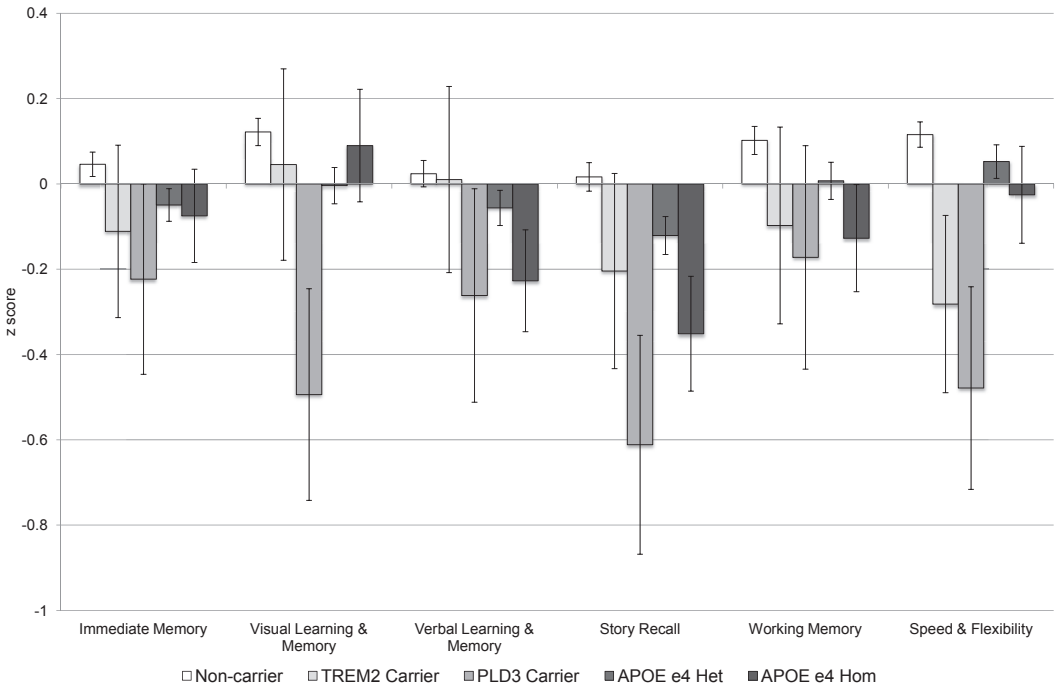

Fig. 1. Mean adjusted cognitive function by risk allele carrier status. Adjusted (for age, gender, practice effects, and race/ethnicity) mean *z* scores for the 6 cognitive factors for *TREM2* R47H (T allele) carriers (light gray), *PLD3* V232M (A allele) carriers (medium gray), *APOE* ε4 heterozygotes (dark gray), *APOE* ε4 homozygotes (very dark gray), and noncarriers of any of these 3 risk variants (white). *Z* scores were standardized (~ N [0, 1]), using means and standard deviations obtained from the whole sample at baseline. Error bars indicate standard error of the mean. Abbreviations: *APOE*, apolipoprotein E gene; *PLD3*, phospholipase D family member 3 gene; *TREM2*, triggering receptor expressed on myeloid cells 2 gene.

lower carrier frequency in Africans are consistent with our observation. Moreover, our lack of *PLD3* V232M (A allele) carriers in any group other than non-Hispanic Caucasian is not surprising given that the carrier percentage in gnomAD for this variant is 2.5–5 times higher for Europeans (non-Finnish; 1%) than for Latinos (0.4%) or Africans (0.2%).

PLD3 V232M carriers (6 of whom were *APOE* ε4 heterozygotes [Table 1]) had least square mean (predicted) cognitive *z* scores that were lower than both *APOE* ε4 heterozygotes and homozygotes across all 6 cognitive factors (Fig. 1). This suggests that the effect of the *PLD3* V232M variant on cognition may be even stronger than carrying 2 copies of the *APOE* ε4 allele. However, this requires replication in other longitudinal studies of cognitive function.

Although our findings show consistency across multiple cognitive factors, many of our findings were not statistically significant and those that were significant would not survive a correction for multiple testing. This is likely due to the rarity of the variants assessed but could also be because our relatively young (early 50s at baseline) population may not yet have experienced enough cognitive decline. It will be crucial to validate these findings with an external population, particularly one that has a larger number of carriers for these rare variants. Furthermore, to determine how these variants influence the pathology of AD, it will also be essential to evaluate their influence on β-amyloid and tau, as the accumulation of both occurs long before an AD diagnosis.

In conclusion, our results support previous findings that show an increased AD risk in carriers of low-frequency functional variants in *TREM2* and *PLD3* by suggesting that these variants may also be associated with lower cognitive function, likely due to an AD trajectory. This is particularly notable for the rare *PLD3* variant, which is a less-established AD risk factor. Although these functional variants are found at low frequencies in the population, their effect on risk for AD is much larger than common variants found through GWAS. In fact, their effect on cognition may be similar to, if not greater than, that of the *APOE* ε4 allele. Further research is necessary to assess the influence of these rare variants on other crucial neurological changes such as the accumulation of β-amyloid and tau that are biomarkers of AD pathology.

Disclosure statement

The authors have no actual or potential conflicts of interest to disclose.

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