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More evidence for association of a rare *TREM2* mutation (R47H) with Alzheimer's disease risk

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Abstract

Over twenty risk loci have been identified for late onset Alzheimer's disease (LOAD), most of which display relatively small effect sizes. Recently, a rare missense (R47H) variant, rs75932628 in *TREM2,* has been shown to mediate LOAD risk substantially in Icelandic and Caucasian populations. Here we present more evidence for the association of the R47H with LOAD risk in a Caucasian population comprising 4,567 LOAD cases and controls. Our results show that carriers of the R47H variant have a significantly increased risk for LOAD (OR=7.40, *P*=3.66E-06). In addition to AD risk, we also examined the association of R47H with AD-related phenotypes, including age-at-onset, psychosis, and amyloid deposition, but found no significant association. Our results corroborate those of other studies implicating *TREM2* as a LOAD risk locus and indicate the need to determine its biological role in the context of neurodegeneration.

Keywords

TREM2; rare variants; LOAD

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Disclosure

The authors report no conflict of interests.

Introduction

Late-onset Alzheimer's disease (LOAD) is a fatal neurodegenerative disorder affecting more than 5 million Americans (http://www.alz.org/alzheimers_disease_facts_and_figures.asp#quickFacts, [accessed 12 Jan 2015]). Alzheimer's patients exhibit progressive deficits in cognitive function thought to be caused by the combination of abnormal aggregation of beta-amyloid (Aβ) and hyperphosphorylation of the microtubule-stabilizing tau protein in the brain. The full molecular mechanism of disease has yet to be determined. Previously, 21 risk loci—*APOE*, *CR1*, *BIN1*, *INPP5D*, *MEF2C*, *CD2AP*, *HLA-DRB1/HLA-DRB5*, *EPHA1*, *NME8*, *ZCWPW1*, *CLU*, *PTK2B*, *PICALM*, *SORL1*, *CELF1*, *MS4A4/MS4A6E*, *SLC24A4/RIN3*, *FERMT2*, *CD33*, *ABCA7*, and *CASS4* —have been identified for LOAD in large genome-wide association studies (GWAS) (Harold et al., 2009, Hollingworth et al., 2011, Lambert et al., 2013, Naj et al., 2011, and Seshardi et al., 2010). These loci are varied in genomic location, biological function, and cellular localization and expression. Rare mutations affecting LOAD risk also have been identified with sequencing methods in the *APP* and *PLD3* genes (Bamne et al., 2014, Cruchaga et al., 2014, Jonsson et al., 2012, and Kero et al., 2013).

Triggering receptor expressed on myeloid cells 2 (*TREM2*) is differentially expressed by microglia among different brain regions (Schmid et al., 2002). Two independent groups found a rare missense variant, rs75932628, in exon 2 of *TREM2* (Guerreiro et al., 2013a and Jonsson et al., 2013). This substitution of histidine for arginine at residue 47 (R47H) increases LOAD risk at a magnitude similar to that of *APOE*4.* Other groups have found similar associations in Caucasian populations from both Europe and North America (Benitez et al., 2013, Giraldo et al., 2013, Gonzalez et al., 2013, and Roussos et al., 2014). This variant has also been associated with early-onset Alzheimer's disease (EOAD) in a case/control study of Caucasian individuals of French descent (Pottier et al., 2013). An association between R47H carriers with both history of parental LOAD and earlier maternal age- at -onset in a cohort of middle-aged unaffected individuals has been described as well (Engelman et al., 2014).

In addition to its association with LOAD, variants in *TREM2* have been shown to cause autosomal recessive Nasu-Hakola disease (polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, PLOSL), a disease which counts among its features early onset neurodegeneration (Paloneva et al., 2002 and Sorgana et al., 2003). Risk for other neurodegenerative diseases, including frontotemporal dementia (FTD) (Cuyvers et al., 2013, Guerreiro 2013b, 2013c, and Rayaprolu 2013), Parkinson's disease (PD) (Rayaprolu et al., 2013), and sporadic amyotrophic lateral sclerosis (ALS) (Cady et al., 2014), also appears to be mediated by *TREM2* variation. Network analysis revealed connections of other known AD genes to *TREM2*, as well as genes with known functions in other neurological diseases, suggesting a microglial link among these diseases (Forbosco et al., 2013).

Neuroinflammation is thought to play a key role in LOAD pathogenesis (reviewed by Latta et al., 2014). *TREM2* is expressed primarily by microglial cells of the brain, is involved in neuroinflammatory responses, and complexes with DAP12 (aka TYROBP) for intracellular signaling (reviewed by Ma et al., 2014). Ligands for TREM2 have yet to be identified,

although one study shows an increase of these unknown ligands on apoptotic cells, including neurons (Hsieh et al., 2009). An examination of TREM2 in senescence-accelerated mice showed TREM2 levels increase with age. The same study demonstrated decreased levels of TREM2 are responsible for increased expression of pro-inflammatory cytokines, tumor necrosis factor (TNF) –α and interleukin (IL)-6 and decreased expression of anti-inflammatory cytokine, IL-10 (Jiang et al., 2014). The aim of this study is to replicate the association of the *TREM2* R47H variant in a large AD case/control sample. Additionally, the associations of this variant with psychosis (a common LOAD endophenotype), fibrillar amyloid-beta (Aβ) deposition determined by Pittsburgh Compound-B (PiB) positron emission tomography (PET), and age-at-onset (AAO) are examined.

Methods

Study Population

The study population and informed consent procedures have been described previously (DeKosky et al., 2008 and Kamboh et al., 2012). Briefly, 4,885 individuals from two cohorts, the University of Pittsburgh Alzheimer's Disease Research Center (ADRC) and Gingko Evaluation of Memory (GEM) study, were used in this study. The ADRC cohort was comprised of 1,283 cases (mean AAO 72.8±6.5, 63% female, 25% autopsy confirmed) and 996 controls (mean age 75.6 ± 6.4, 64% female). The GEM cohort consisted of 338 cases (48% female) and 1,950 controls (mean age 78.3 ± 3.1, 44% female). Diagnosis of LOAD in cases for both cohorts was determined based upon DSM-IV criteria. Following quality control procedures and removal of non-Caucasian samples, 4,567 samples remained for analysis. These samples were comprised of 1,621 cases (59.8% female) and 2,946 controls (51% female).

Genotyping

Genotyping was performed with a custom designed TaqMan® assay for *TREM2*/rs75932628 according to the manufacturer's protocol. (Life Technologies, Grand Island, NY, USA). For each cohort 10% replicates were included for quality control. Two control samples that are heterozygous for the R47H variant (courtesy of Dr. Carlos Cruchaga, Washington University) also were included on each plate. Assayed plates were read using a 7900 HT Fast Real Time PCR (Applied Biosystems). Genotyping calls were made using Applied Biosystems TaqMan® Genotyper Software (v1.0.1, Life Technologies, Inc., 2010). Automated calls were manually reviewed for discrepancies in replicate samples. There were no discrepancies for the ADRC cohort and a discrepancy of rate of 0.0042 for the GEM cohort. We removed those discrepant samples prior to analysis. Twenty-seven samples failed genotyping, bringing the effective sample size for association analysis to 4,540.

Determination of Psychosis in AD Patients

We evaluated the association of psychosis in 1,204 ADRC participants with AD who had been genotyped for the *TREM2* 'T' allele, 1,069 of whom were characterized during life for cognition and for psychotic symptoms by the Clinical Core of the ADRC, as previously used successfully to examine antemortem (DeMichele-Sweet et al., 2011 and Hollingworth et al., 2011) and post-mortem correlates of AD+P (Murray et al., 2012). The presence or absence

of delusions and hallucinations are indicated as part of the semi-structured examinations, and ratings scored on the CERAD Behavioral Rating Scale (Tariot et al., 1995). Delusions are defined as a false belief, not attributable to membership in a social or cultural group, based on incorrect inference about external reality. Delusions are differentiated from confabulations due to cognitive impairment by their persistence and their resistance to persuasion or contrary evidence. Hallucinations are defined as sensory perceptions for which there is no reality basis. Hallucinations occurring when the subject is not fully awake (i.e. hypnagogic or hypnapompic) are not considered hallucinations for the purpose of diagnosis or ratings of psychopathology.

The CERAD Behavioral Rating Scale was administered at initial and annual visits and in some subjects between annual visits by telephone (DeMichele-Sweet et al., 2011). AD+P was considered present when any of the CBRS items #33 - #45 were rated as occurring ≥3 times in the past month at any visit. Individuals with scores of 0 on the same CBRS items at all visits were classified as AD-P. Inter-rater reliability of the psychosis assessments used, including telephone assessments, has been previously described (Sweet et al., 2010 and Wilkosz et al., 2007). Psychotic symptoms typically emerge in the moderate stages of AD (Hollingworth et al. 2006, and Sweet et al., 2010), therefore those categorized as AD-P who were in the mild stages of disease at their last assessment (mini-mental state examination score (Folstein et al., 1975) >20) were considered to be at substantial risk of going on to develop delusional or hallucinatory behaviour. These individuals were therefore excluded from the analysis, leaving 547 AD+P and 356 AD-P subjects available for analysis.

Measurement of Amyloid Deposition in the Brain

Deposition of amyloid-beta in the brain was measured by positron emission tomography (PET) scanning with ^{11}C-labeled Pittsburgh Compound- B (PiB) (Klunk et al., 2004). PiB data was available in 321 subjects that were also genotyped for R47H. PiB retention values from anterior cingulate cortex, frontal cortex, lateral temporal cortex, parietal cortex, and precuneus (areas typically highest in AD) were averaged in each subject to calculate a mean global score (GBL5) as the quantitative phenotype.

Statistical Analyses

The association between AD disease status and the R47H variant was tested using an additive logistic regression model that included age, gender, and *APOE*4* status as covariates. Association of this variant with AAO was analyzed using an additive linear regression model adjusted for sex and *APOE*4* status. Association of this variant with the average PiB uptake derived from five brain regions was analyzed using an additive linear regression model adjusted for sex, age, and AD status as covariates. Psychosis in AD was analyzed using a Pearson Chi-Square test with sex and AAO as covariates. All analyses were implemented in PLINK or R.

Results

Table 1 presents the distribution of R47H variant in cases and controls. A total of 37 individuals of the 4,567 successfully genotyped samples were carriers of the R47H variant

(29 cases, 8 controls). Consistent with previous findings, the minor allele frequency (MAF) for *TREM2*/rs75932628 in the total sample was less than 0.01 (MAF=0.008), which explains why no homozygous individuals were observed in this population. The MAF was over six times higher in cases as compared to controls (0.0180 versus 0.0027, respectively). The odds ratio (OR) for association of the *TREM2* variant with LOAD risk adjusted for age, sex, and *APOE*4* status was 7.40 (95% CI: 3.171-17.26, *P*=3.66E-06). These results are consistent with previous findings that the minor 'T' allele of *TREM2*/rs75932628 significantly and substantially increases risk for LOAD. Table 2 presents the association results of R47H variant with AAO and psychosis in AD and with PiB deposition in the brain. There was no significant association with any of these AD-related phenotypes.

Discussion

A rare *TREM2* (R47H) variant that considerably increases LOAD risk has been identified in populations of European descent (Benitez et al., 2013, Giraldo et al., 2013, Guerreiro et al., 2013, Jonsson et al., 2013, Gonzalez et al., 2013). In this study, the association between this rare variant, rs75932628, and LOAD risk has been replicated in an independent population. While these results show the same direction of effect for this single nucleotide polymorphism (SNP), our odds ratio is dramatically higher than most other studies have reported. (Table 3) It is possible that this population was enriched for affected carriers, likely by chance rather than by a true difference in this population compared to others. Of note, the MAF of R47H seems to be even lower in the northern Han Chinese population (Yu et al., 2014) compared to European populations, and was not associated with LOAD risk in a Japanese population (Miyashita et al., 2014), suggesting this variant's effect may be limited to European populations. More recently, a meta-analysis of family-based and case-control data supported the association of the R47H variant with increased LOAD risk, however the effect was much smaller (OR=1.67, 95% CI= 0.95-2.92) than that seen in other studies, including our own (Hooli et al., 2014). Slattery et al (2014) also confirmed this association while reporting a smaller odds ratio (OR=2.19, 95% CI= 1.04-4.51), while Finelli et al. (2015) observed an odds ratio even higher than ours (OR=7.87, 95% CI=1.75-35.34). The association of *TREM2* with LOAD risk appears to be real and should be vetted with the same intensity as other risk loci, especially with respect to its effect size. Future studies should aim to characterize better this variant's effects in other populations and to determine TREM2's function in neurodegeneration, including how it interacts with other established LOAD risk loci.

Slattery et al. (2014) suggested the association of R47H variant with earlier disease onset. However, in our sample, we found no association between the R47H variant and AAO. In addition to association of *TREM2* with LOAD risk and AAO, we also examined the association of this variant with deposition of amyloid, a hallmark of the disease, and psychosis, which can emerge during the progression of LOAD (reviewed by Murray et al., 2014). We found no evidence for either association, possibly due to small sample size and subsequently, lack of power to detect association.

A GWAS of Alzheimer's endophenotypes revealed associations with the *TREM* region on chromosome 6 and cerebrospinal fluid (CSF) tau and ptau levels, two biomarkers of LOAD.

Included among these associations was that of the R47H variant with CSF ptau levels (Cruchaga et al., 2014). Our results showed no association between amyloid deposition and the R47H variant, further suggesting TREM2's role in LOAD risk is a function of its interaction with or effect on tau. However, Aβ1-42 clearance is significantly diminished in primary microglia from *TREM2* knockout mice, and *TREM2* causative mutations for other neurodegenerative diseases have been shown to alter general phagocytic ability, albeit to a greater degree than the R47H variant (Kleinberger et al., 2014). Furthermore, *TREM2* has been shown to be a "hub" gene in the hippocampus, and its expression has been linked to the molecular signature of microglia, the cells responsible for clearing Aβ in the brain (Forbasco et al., 2013). Thus, the exact mechanism by which TREM2 affects LOAD risk remains to be determined.

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Highlights

- We replicated the association of the rare *TREM2* R47H variant with LOAD in Caucasians.
- No association of this variant with age-at-onset was observed.
- This variant did not affect amyloid deposition or psychosis in AD in our sample.
- We provide further evidence that the R47H variant confers significant LOAD risk.

Table 1

Association of R47H variant with LOAD risk

	Genotype			MAF	OR (95% CI)	*P*
	CC	CT	TT			
Controls	2919	8	0	0.0027	----	----
Cases	1584	29	0	0.018	7.40 (3.171-17.26)	3.66E-06
Total	4503	37	0	0.008		

Table 2

Association of R47H variant with AAO **(A),** Amyloid deposition **(B),** and Psychosis in AD **(C)**

A. Age-at-Onset*		
Genotype	**N**	**Mean AAO (SD)**
CC	1253	72.8 (6.51)
CT	25	73.0 (6.29)
Total	1278	*P=0.94*

B. Amyloid Deposition		
Genotype	**N**	**Mean PIB value (SD)**
CC	314	1.89 (0.58)
CT	7	2.10 (0.99)
Total	321	*P*=0.287

C. Psychosis in AD		
Genotype	**AD + P**	**AD - P**
CC	533	352
CT	14	4
Total	547	356
		P=0.13

*Age at onset only available for ADRC samples

Table 3

Published of odds ratios for association of R47H variant with LOAD

Cases	Controls	Odds Ratio (95% CI)	*P*	Publication
474	608	7.87 (1.75-35.34)	0.007	Finelli *et al*, 2015
265	225	4.76 (1.37-16.54)	0.014	Roussos *et al*, 2014
3220	3112	1.67 (0.95-2.92)	0.034	Hooli *et al*, 2014[a]
917	199	4.97 (1.18-20.80)	0.004	Hooli *et al*, 2014, NIMH[b]
860	1036	3.03 (0.5-18.0)	0.39	Hooli *et al*, 2014, NIA-LOAD[b]
1002	534	2.19 (1.04-4.51)	0.03	Slattery *et al*, 2014
2082	1648	2.63 (1.44-4.81)	0.000917	Jin *et al*, 2014
2190	2498	0.57 (0.05-6.30)	1.00	Miyashita *et al*, 2014
2037	9727	2.83 (1.45-4.50)	0.002	Jonsson *et al*, 2013
1091	1105	4.5 (1.7-11.90)	<0.001	Guerreiro *et al*, 2013
1541	1132	3.30 (1.3-9.80)	0.0044	Giraldo *et al*, 2013[a]
504[c]	550	not reported	0.009	Benitez *et al*, 2013
427	2540	3.5 (1.30-8.80)	0.0076	Gonzalez *et al*, 2013
1216	1094	3.01 (0.83-10.94)	0.08	Cuyvers *et al*, 2013
1613	2927	7.40 (3.171-17.26)	0.00000366	This study

[a] meta-analysis

[b] family-based sample

[c] LOAD and EOAD combined