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Frequency of the *TREM2* R47H variant in various neurodegenerative disorders

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Abstract

Objective: A rare variant in *TREM2* (p.R47H, rs75932628) has been consistently reported to increase the risk for Alzheimer's disease, while mixed evidence has been reported for association of the variant with other neurodegenerative diseases. Here, we investigated the frequency of the R47H variant in a diverse and well-characterized multicenter neurodegenerative disease cohort.

Methods: We examined the frequency of the R47H variant in a diverse neurodegenerative disease cohort, including a total of 3,058 patients clinically diagnosed with Alzheimer's disease, frontotemporal dementia spectrum syndromes, mild cognitive impairment, progressive supranuclear palsy syndrome, corticobasal syndrome, or amyotrophic lateral sclerosis and 5,089 control subjects.

Results: We observed a significant association between the R47H variant and Alzheimer's disease, while no association was observed with any other neurodegenerative disease included in this study.

Conclusions: Our results support the consensus that the R47H variant is significantly associated with Alzheimer's disease. However, we did not find evidence for association of the R47H variant with other neurodegenerative diseases.

Introduction

TREM2 encodes the triggering receptor expressed on myeloid cells 2, a receptor involved in immune response that is expressed in the brain by microglia.[1] The p.R47H (rs75932628)[2,3] and other *TREM2* rare variants[4] have been shown to be associated with Alzheimer's disease (AD), but their role in other neurodegenerative diseases is still unclear. The R47H variant has been investigated as a possible risk variant for frontotemporal dementia (FTD), progressive supranuclear palsy syndrome (PSP-S), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD) with inconsistent results. While Rayaprolu et al. reported association of the R47H variant with FTD (n = 609) and PD (n = 1493) but no association with ALS (n = 765) or PSP-S (n = 772)[5], Cady et al. observed an association with ALS (n = 923)[6], and a subsequent meta-analysis by Lill et al. did not find consistent association with FTD (n = 2673), PD (n = 8311), or ALS (n = 5544).[7]

This study aimed to assess whether the *TREM2* p.R47H variant is associated with disease in a large series including 3,058 patients with neurodegenerative disease and 5,089 healthy control subjects.

Methods

Participants.

We included 3,058 patients with neurodegenerative disease and 5,089 controls recruited across collaborating centers worldwide (Supplementary Table 1):

(i) University of California Los Angeles (UCLA), (ii) University of California San Francisco Memory and Aging Center (UCSF-MAC series), (iii) Emory University (Emory), (iv) University of California San Francisco PSP series (UCSF-PSP), (v) University of California Davis (UCD), (vi) University of California Irvine (UCI), (vii) University of Southern California (USC), (viii) University of Brescia and San Raffaele Scientific Institute (ITA), (ix) Rush Alzheimer's Disease Center (Religious Orders Study and Rush Memory and Aging Project), (x) University of Athens (GRE), (xi) School of Medicine, Yale University (Turkish series), and (xii) National Institute of Mental Health (NIMH control series).

Patients consisted of individuals of 79.1% European ancestry, 9.9% African ancestry, 7.3% Asian ancestry, 1.8% Latin American ancestry, and 1.8% mixed or other ancestry. Controls consisted of individuals aged 65 or older, of 68.5% European ancestry, 28.5% African ancestry, 1.8% Asian ancestry, 0.9% Latin American ancestry, and 0.4% mixed or other ancestry. Patients were diagnosed with AD, ALS, FTD spectrum syndromes including behavioral variant FTD, semantic and nonfluent variants of primary progressive aphasia, PSP-S, corticobasal syndrome (CBS), and mild cognitive impairment (MCI) (Table 1).

A multidisciplinary team including neurology, nursing, and project coordinators reviewed cases. Diagnosis protocol used the McKhann et al. (2011) criteria for AD and Albert et al. (2011) for the diagnosis of MCI due to AD, and the incorporation of AD biomarkers whenever they were available.[8,9] The International bvFTD Criteria Consortium for bvFTD (Rascovsky et al., 2011), Gorno-Tempini et al. for primary progressive aphasia and its variants (2011), Armstrong et al. (2013) for CBS, and the Movement Disorder Society criteria for PSP-S (2017) were also used.[10,11,12,13] A large aged control group was obtained from the NIMH Human Genetics Initiative. Inclusion criteria for the rest of our normal control cohort included availability of a reliable study partner with frequent contact, CDR score of zero, no subject or informant report of significant cognitive decline during the previous year, no evidence from the screening visit suggesting a neurodegenerative disorder (per the team's clinical judgment), and MMSE score >25. Participants or their surrogates provided informed consent upon study enrollment.

Genetic Analysis.

Genotypes were obtained using TaqMan® SNP assays from ThermoFisher on a LightCycler® 480 System. A commercially available assay (C_100657057_10) for *TREM2 R47H* rs75932628 was used. Statistical analysis was performed in R (version 3.1.3, www.r-project.org). Association *P*-values were calculated using Fisher's exact test.

Results

We identified 35 p.R47H heterozygous carriers and 1 homozygous carrier (Table 1) among 3,058 patients with neurodegenerative disease, and 22 heterozygous carriers among control subjects. The allele frequency observed in the control group (0.23%) is similar to the 0.25% frequency reported by the Genome Aggregation Database (gnomAD, gnomad.broadinstitute.org/variant/6–41129252-C-T).

Combined analysis on the 3,058 patients resulted in an estimated OR of 2.74 (CI = 1.57–4.91, Fisher's exact test, P = 1.82E-04) across neurodegenerative diseases versus controls (Figure 1). Analyses on the individual disease series produced odds ratios ranging from 0.59 (CI = 0.01–3.67, in the PSP-S series) to 9.20 (CI = 0.21–61.8, in the ALS series). However, the association was only significant for the AD series (OR = 4.46, CI = 2.35–8.48, Fisher's exact test, P = 2.07E-06).

Due to the unequal ethnicity distribution between case and control populations, we repeated the analysis on the subset of the series restricted to subjects of European descent (Supplementary Figure 1, Supplementary Table 2). Among the 2,203 patients and 2,969 controls of European descent, combined analysis across neurodegenerative diseases versus controls resulted in an OR of 2.29 (CI = 1.19–4.56, Fisher's exact test, P = 0.00824). Analyses on the individual disease series resulted in odds ratios ranged from 0.55 (CI = 0.01–3.55, in the PSP-S series) to 9.69 (CI = 0.22–69.1, in the ALS series). As in the complete cohort, the association was only significant for the AD series (OR = 4.62, CI = 2.21—9.73, Fisher's exact test, P = 1.70E-05).

Similar results were also obtained after excluding carriers of known causal variants (Supplementary Figure 2).

Discussion

In this study, we focused on the rare *TREM2* R47H missense variant, which is located on the protein surface and affects ligand binding.[1] The R47H variant has been repeatedly reported to confer an increased risk for AD.[14,15,16,17,18] However, studies examining potential association of the R47H variant with other neurodegenerative diseases have generated mixed evidence.

To further examine the potential association of *TREM2* with various neurodegenerative diseases, we assessed the risk effect of the R47H variant using a large multicenter neurodegenerative disease cohort comprised of AD, FTD, MCI, CBS, PSP-S, and ALS patients. We found the strongest risk association in the AD series (OR = 4.46, CI = 2.35–8.48, P = 2.07E-06), corroborating previous studies. Rayaprolu et al. (2013) reported association of the R47H variant with FTD diagnosis (n = 609).[5] However, a subsequent meta-analysis (n = 2,673) incorporating results from Rayaprolu et al. (2013), produced only modest support for association with FTD, not reaching the suggested genome-wide significance threshold.[7] No significant association was found in the FTD series (OR = 2.17, CI = 0.78–5.27, P = 0.088) in this study. We also observed no association within the MCI, PSP-S, CBS, or ALS series. However, it should be noted that statistical power was weak for

our CBS (n = 123) and ALS (n = 26) series due to small sample size. Because of this, analyses on the CBS and ALS series produced odds ratios with large confidence intervals (CBS: OR = 1.89, CI = 0.05–11.9, $P = 0.423$) (ALS: OR = 9.20, CI = 0.21–61.7, $P = 0.111$).

In summary, our study confirms previous findings of association between the rare *TREM2* R47H variant and an increased risk of AD. We also found no evidence of a risk association within FTD, MCI, PSP-S, and CBS series. Further genetic studies are needed to conclusively evaluate potential association of the R47H variant with other neurodegenerative disorders such as ALS and PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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NIMH series. Control subjects from the National Institute of Mental Health Schizophrenia Genetics Initiative (NIMH-GI), data and biomaterials are being collected by the ‘Molecular Genetics of Schizophrenia II’ (MGS-2) collaboration. The investigators and co-investigators are: Alan R. Sanders, MD; Emory University School of Medicine, Atlanta, GA, MH59587, Farooq Amin, MD (PI); Louisiana State University Health Sciences Center, New Orleans, LA, MH067257, Nancy Buccola APRN, BC, MSN (PI); University of California-Irvine, Irvine, CA, MH60870, William Byerley, MD (PI); Washington University, St Louis, MO, U01, MH060879, C. Robert Cloninger, MD (PI); University of Iowa, Iowa, IA, MH59566, Raymond Crowe, MD (PI), Donald Black, MD; University of Colorado, Denver, CO, MH059565, Robert Freedman, MD (PI); University of Pennsylvania, Philadelphia, PA, MH061675, Douglas Levinson, MD (PI); University of Queensland, Queensland, Australia, MH059588, Bryan Mowry, MD (PI); Mt Sinai School of Medicine, New York, NY, MH59586, Jeremy Silverman, PhD (PI).

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Cohort	#Individuals	#Carriers	%Carriers	Odds Ratio	P–value
AD	1157	22	1.90	4.46	2.07E–06
FTD	751	7	0.93	2.17	0.08808
MCI	610	4	0.66	1.52	0.35335
PSP–S	391	1	0.26	0.59	1
CBS	123	1	0.81	1.89	0.42332
ALS	26	1	3.85	9.20	0.11083
Control	5089	22	0.43		
Overall	**3058**	**36**	**1.18**	**2.74**	**1.82E–04**

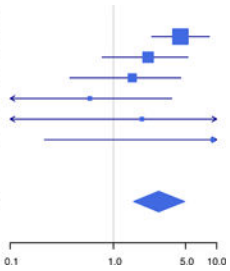

Figure 1: *TREM2*p.R47H carrier frequencies and associated odds ratios for the different disease series

Total number of individuals and *TREM2* p.R47H carriers for each disease series and control group is shown in the table (*left*), with odds ratios and *P*-values represented in the forest plot (*right*). AD: Alzheimer's disease, FTD: frontotemporal dementia, MCI: mild cognitive impairment, PSP-S: progressive supranuclear palsy syndrome, CBS: corticobasal syndrome, ALS: amyotrophic lateral sclerosis. Overall refers to the combined neurodegenerative disease patient samples. In the forest plot, squares are drawn proportional to the number of samples in each series, and lines represent 95% confidence intervals.

Table 1:

Demographic characteristics by disease series in a series of 3,058 patients and 5,089 controls

Series	Total Individuals	R47H carriers	% Female	% European	Average Age at Onset
AD	1157	22 (1.90%)	56.4	67.9	63.9 ±10.7
FTD	751	7 (0.93%)	45.5	92.4	58.9 ±**9.4**
MCI	610	4 (0.66%)	55.5	75.1	63.0 ±**10.7**
PSP-S	391	1 (0.26%)	46.9	93.1	64.3 ±**7.5**
CBS	123	1 (0.81%)	48.8	91.2	61.0 ±**7.4**
ALS	26	1 (3.85%)	34.6	83.3	55.9 ±**10.4**
Overall	3058	36 (1.18%)	51.9	79.1	62.0 ±**10.2**
Control	5089	22 (0.43%)	57.4	68.5	N/A

AD: Alzheimer's disease, FTD: frontotemporal dementia, MCI: mild cognitive impairment, PSP-S: progressive supranuclear palsy syndrome, CBS: corticobasal syndrome, ALS: amyotrophic lateral sclerosis. Overall refers to the combined neurodegenerative patient samples.

Age of onset was available in: AD (674/1157), FTD (524/751), MCI (245/610), PSP-S (121/391), CBS (112/123), ALS (19/26).

Gender was available in: AD (1085/1157), FTD (672/751), MCI (609/610), PSP-S (382/391), CBS (123/123), ALS (26/26), Controls (4550/5089).

Ancestry was available in: AD (1085/1157), FTD (605/751), MCI (594/610), PSP-S (363/391), CBS (113/123), ALS (24/26), Controls (4333/5089).