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R47H TREM2 variant increases risk of typical early-onset Alzheimer's disease but not of prion or frontotemporal dementia

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Abstract

Background—Rare *TREM2* variants are significant risk factors for Alzheimer's disease.

Methods—We used next generation sequencing of the whole gene (n=700), exon 2 Sanger sequencing (n=2634), p.R47H genotyping (n=3518) and genome wide association study imputation (n=13048) to determine whether *TREM2* variants are risk factors or phenotypic modifiers in patients with Alzheimer's disease (n=1002), frontotemporal dementia (n=358), sporadic (n=2500) and variant (n=115) Creutzfeldt-Jakob disease.

Results—We confirm only p.R47H as a risk factor for Alzheimer's disease (OR=2.19; 95%CI=1.04-4.51; P=0.03). p.R47H does not significantly alter risk for frontotemporal dementia (OR=0.81), variant or sporadic Creutzfeldt-Jakob disease (OR=1.06 95%CI=0.66-1.69) in our

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Supplementary Material
Please see supplementary methods and information tables S1-S3.

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cohorts. Individuals with p.R47H associated Alzheimer's (n=12) had significantly earlier symptom onset than individuals with no *TREM2* variants (n=551) (55.2years vs. 61.7years, P=0.02). We note that heterozygous p.R47H Alzheimer's disease is memory led and otherwise indistinguishable from "typical" sporadic Alzheimer's.

Conclusion—We find p.R47H is a risk factor for Alzheimer's disease, but not frontotemporal dementia or prion disease.

Keywords

TREM2; Alzheimer's; frontotemporal dementia; prion; phenotype

1. Introduction

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), is a recessively inherited early onset frontal dementia with bone cysts and basal ganglia calcification [1, 2] due to variants in either *TREM2* (triggering receptor expressed on myeloid cells 2, chr6:41,126,244-41,130,924, hg19) or *TYROBP* (TYRO protein tyrosine kinase binding protein) [3-5]. This phenotype has since been expanded, with PLOSL associated homozygote *TREM2* variants (p.Q33X, p.T66M and p.Y38C) described in 3 individuals with typical cognitive impairment, white matter change and frontal atrophy, but without bone cysts [6]. Association study has also identified p.R47H (rs75932628), a rare variant in *TREM2*, that confers risk for late onset Alzheimer's disease (LOAD) in populations of European descent [7, 8]. p.R47H associations have subsequently been reported with frontotemporal dementia (FTD) [9] and Parkinson's disease [9, 10]. Enrichment of rare *TREM2* variants has been observed in both AD and FTD patients compared to controls [11, 12]. Furthermore, microglial proliferation and *CSF1R (*colony stimulating factor 1 receptor) activation, implicated in the same inflammatory pathway as the *TREM2*/*TYROBP* complex, are thought to be a major component of prion related neurodegeneration [13] and a partial loss of function variant in *CSF1R* causes hereditary diffuse leukoencephalopathy with spheroids [14].

Given that microglial mediated inflammation is implicated in several dementias, this raises the question as to whether p.R47H *TREM2* effects are selective for AD or generic to neurodegeneration, and it remains unclear whether *TREM2* variants in AD have a distinctive phenotype, of importance clinically. This study sought to provide detailed clinical phenotyping of *TREM2* associated neurodegeneration across multiple dementias; AD, FTD and Creutzfeldt-Jakob disease (CJD).

2. Methods

2.1 Cohorts

DNA samples from individuals with clinical diagnoses of AD (n=1002), FTD (n=358), variant CJD (vCJD, n=115) and sporadic CJD (sCJD, n=2500) were identified from the Medical Research Council Prion Unit research sample database (1990 onwards). For further details see supplementary methods.

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Ethical approval was obtained from the National Hospital for Neurology and Neurosurgery Research Ethics Committee. Informed consent for genetic studies was obtained from all participants.

2.2 Genetics

Exon 2 of the *TREM2* gene was Sanger sequenced for individuals with AD (n=971), FTD (n=358), vCJD (n=115), sCJD (UK n=721, German n=49) and UK controls (n=534).

2381 UK controls from the 1958 birth cohort (University of Leicester) and 2437 sCJD samples (UK n=722, German n=824 and US n=891) were directly genotyped for p.R47H using a Taqman minor groove binding probe.

CJD study cases (UK sCJD n=731, German sCJD n=818, US sCJD n=951) and controls (UK n=5020, German n=2691 and US n=2837) were genotyped on several different Illumina Genome Wide Bead Chip arrays (550 Bead Chip arrays or larger platforms), see supplementary methods.

Exon capture and next generation sequencing was undertaken on genomic DNA from patients with AD (exome sequencing n=33, dementia gene sequencing n=504), FTD (n=29), variant CJD (n=86), and UK sCJD (n=48), see supplementary methods.

APOE status p.R47H variant associated AD (n=13) was ascertained by Minor Groove Binding probe and fluorescent PCR.

2.3 Clinical phenotyping

We established age at symptom onset (AAO), where available, and reviewed medical records for p.R47H Alzheimer's cases (n=14) and a group of nil *TREM2* variant cases (n=33), matched for sex and age at symptom onset (table S1) to determine sex, annualised rates of decline on the mini-mental state examination (MMSE) based on the longest available interval, presenting clinical features (visual, language, behavioural/dysexecutive, memory), neurological and psychiatric signs and symptoms.

We extracted the following neuropsychometric data, where available: general intellectual function - Wechsler Adult Intelligence Scale-Revised or the Wechsler Abbreviated Scale of Intelligence [15, 16]; verbal and visual memory - Recognition Memory Test for words and faces respectively [17]; and visuospatial and visuoperceptual skills - Visual Object and Spatial Perception battery [18]. Raw scores were converted into percentiles for reporting.

Post mortem data reports for individuals with p.R47H variants held in the Queen Square brain bank (University College London) and Institute of Psychiatry brain bank (Kings College London) were also reviewed where available

2.4 Brain magnetic resonance imaging (MRI)

T1 weighted volumetric brain MRI scans were reviewed retrospectively and volumetric region of interest comparisons performed for p.R47H variant individuals (3T n=3 and 1.5T

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n=1) and 22 AAO and disease duration matched (table S1) AD individuals with no *TREM2* variants (3T n=17, 1.5T n=5). All analyses were performed blind to genetic status.

2.5 Statistics

The association between *TREM2* variants and each neurodegenerative condition was examined using odds ratios and Fisher exact test based on allelic frequencies.

The characteristics of the p.R47H variant and nil *TREM2* variant AD cases were compared using two tailed t-tests or Wilcoxon-Mann-Whitney test where appropriate. Brain and total hippocampal volumes (expressed as ratio of TIV to correct for head size) between p.R47H positive and *TREM2* negative AD subjects were compared using the Wilcoxon-Mann-Whitney test.

All statistical tests were two-tailed, with significance set at $p<0.05$ without any correction for multiple hypothesis testing. Statistical analyses were performed using Stata (version 12).

3. Results

3.1 p.R47H TREM2 variants in AD, FTD and CJD

Minor allele frequencies (MAF) for p.R47H in AD (n=1002), FTD (n=358), vCJD (n=115) and sCJD (genotyped n=2437, combined GWAS analysis n=2500) cases are shown in table 1. Fifteen non reference alleles causing p.R47H variants (13 heterozygote individuals and 1 homozygote) were found in the AD population, giving an odds ratio of increased risk verses UK controls based on allelic frequencies of 2.19 (95%CI=1.04-4.51, *P*=0.03), confirming the significant association demonstrated in previous studies [7, 8, 19-21]. We found no significant association between p.R47H variants and FTD or sCJD. Outside exon 2 p.S162R and p.L211p may be associated with AD, but this must be considered very provisional given the small sample numbers and the fact that both variants are thought to be non-damaging; further studies will be required. (see table S2 for other variants in exon 2, and table S3 for variants in exons 1 and 3-5).

3.2 TREM2 variants are associated with earlier disease onset in AD

Patients with p.R47H *TREM2* variants had significantly younger ages at onset than individuals with no *TREM2* variants (AAO=55.2±8.5yrs, n=12 vs. AAO=61.7±13.1yrs, n=551, P=0.024). 10/12 (83%) of these p.R47H variant individuals met criteria for young onset AD (YOAD, defined as symptom onset less than 65 years), with 4/12 (33%) of individuals having an age at onset <50 years, indicating very early onset disease.

3.3 R47H variants in AD: clinical features and neuropsychological profiles

Disease duration (age from first reported symptom to death) was known for 6/14 individuals, for whom the mean was 11.3 years (range 7-15 years). 6/12 (50%) of the individuals with detailed clinical information had at least one first or second degree relative with a diagnosis of AD. Case 1 (p.R47H homozygote) had a mother who developed AD in her 70s who died in her 80s, and a brother with disease onset at 52 years, who died in his 60s. Their *TREM2* statuses are unknown.

The majority of p.R47H individuals (10/12, 83%) for whom clinical information was available had an amnestic presentation. This was supported by neuropsychology data, available on seven individuals (table 2). The disease duration at time of testing varied from one to seven years. All cases had impairment (<5th percentile) on at least one recognition memory test at the time of testing. Three also had some evidence of visuospatial and/or visuoperceptual disturbance, but in no cases was this disproportionate to the degree of amnesia.

Anecdotally, none of the AD p.R47H patients were reported to have had bone cysts or pathological fractures, but this was not examined or investigated for systematically.

There was no significant difference in the annual rate of MMSE decline between the p.R47H variant (n=5) and nil *TREM2* variants (n=21) groups, albeit with small numbers (4.3 points/yr +/− 3.8 vs. 3.2 points/yr +/− 2.6 respectively, P=0.43). Whilst most individuals in both *TREM2* positive and nil *TREM2* variants groups had an amnestic presentation, there was a trend for cognitive deficits referable to parietal lobe dysfunction as the presenting feature to be less common than in the p.R47H variant cases; *P*=0.09 (table 3). There were no significant differences in the frequency of neurological signs between the p.R47H variant positive (n=12) and nil *TREM2* variant (n=33) cases (table 3).

3.4 Neuroimaging in p.R47H variants

MRI in the p.R47H cases (n=4) was typical for AD, revealing generalised cerebral and symmetrical hippocampal atrophy (figure 1). Other than case 10, who had participated in the AN1792 vaccination trial [22], none of the other individuals with neuroimaging had any white matter disease greater than would have been expected for age. No basal ganglia calcification was evident on any of the T1 sequences. Quantitative analysis of cross-sectional brain volumes revealed no difference in brain volume/TIV (median, IQR=0.69, 0.66-0.70 vs. 0.70, 0.66-0.73, P=0.40), or total hippocampal volume*1000/TIV (median, IQR=3.5, 3.2-3.6 vs. 3.3, 2.9-3.6, P=0.43), between p.R47H positive (n=4) and nil *TREM2* variant (n=22) AD cases.

3.6 Pathology in p.R47H cases

AD pathology was confirmed in all 4 p.R47H AD individuals who had post mortem examination, and two had at least moderate cerebral amyloid angiopathy. Pathological slides for case 10, previously published elsewhere [7], showed mature diffuse amyloid plaques. Case 1 (p.R47H homozygote, behavioural/dysexecutive presentation) showed marked frontal atrophy macroscopically, as is typical in PLOSL cases [23], however the associated typical white matter lesions were absent. There was extensive formation of senile plaques, neurofibrillary tangles and neuropil threads throughout the grey matter, but relative preservation of the hippocampus histologically. In the sCJD cohort, all five p.R47H patients having had autopsy demonstrated the classical neuropathology of CJD, however there was evidence of concurrent Abeta or tau pathology in three individuals.

4. Discussion

We report a sequencing and genotyping survey of *TREM2* variants in three major neurodegenerative dementias. We confirm the significant association between p.R47H and AD and describe the related clinical phenotype. We find possession of a p.R47H *TREM2* variant in AD is associated with a significantly younger age at symptom onset than nil *TREM2* variant cases, and p.R47H associated AD is otherwise usually indistinguishable from typical, amnestic AD on clinical, imaging, and neuropsychometric grounds.

It remains unclear whether p.R47H is a risk factor for neurodegeneration in general, or is specific to AD. We did not find any association between p.R47H and CJD, and no other groups have yet published data on *TREM2* variants in prion disease. We did not find any evidence that p.R47H variants are associated with FTD. Whilst there were no p.R47H variants identified in either French (n=175) [24], or Spanish (n=628) [25] FTD populations, a North American cohort (n=609) found a significant association (OR=5.06, P=0.001) [9]. Our UK data were not consistent with an association as large as an OR=5 but do not rule out a more modest association between p.R47H and frontotemporal dementia (95% CI=0.09-3.36). Whether these differences reflect the underlying pathological heterogeneity of patients presenting with behavioural problems or population differences in risk remains to be determined and further studies are warranted, ideally with post mortem confirmation of the underlying pathology, or using other biomarkers (e.g. CSF tau and beta, amyloid imaging) to improve the diagnostic certainty in life.

The majority of individuals with p.R47H had YOAD, with 4/12 of our cases identified having exceptionally young AAO (<50yrs) in the absence of other known genetic variants, consistent with results from a French YOAD population [21]. p.R47H has previously been found to correspond with earlier age of onset in both Icelandic (3.18 years, P=0.20) and Dutch populations (3.65 years, P=0.13) [8]. In our UK YOAD enriched AD population we find the mean AAO for p.R47H variant AD patients were *significantly* earlier than nil *TREM2* variant cases (6.5 years, P=0.024).

In the majority of cases, heterozygous p.R47H variants were associated with typical ‘amnestic’ AD presentations. Atypical presentations are more commonly seen in YOAD than LOAD, accounting for between 30-40% of cases [26, 27]. Our data suggest that, if anything, individuals with *TREM2* variants were less likely to have a non-memory presentation compared with other YOAD individuals. Our p.R47H cohort had a mean disease duration fairly typical for sporadic AD, rates of MMSE decline were within the published range [28, 29] and there were no specific neurological features that could reliably be useful in identifying p.R47H *TREM2* variants. Our brain volume analysis revealed no differences between p.R47H carriers and non carriers, which may reflect the small numbers in this study. Interestingly, data from ADNI has shown individuals with TREM2 variants lose 1.4 to 3.3% more brain tissue per year than non carriers, and p.R47H is significantly associated with smaller hippocampal volumes [30].

All p.R47H AD individuals with post mortem data available had Alzheimer’s pathology confirmed, although the topography of atrophy seen in case 1, (p.R47H homozygote) was

similar to the ‘generalised cerebral gyral atrophy with frontal accentuation’ pathologically observed in a case series of eight patients with PLOSL [23].

Due to the relative rarity of *TREM2* variants the numbers of individuals identified were small, and not all had post-mortem diagnostic confirmation. The retrospective nature meant clinical information was limited and collected in a non-standardised manner, hence limiting direct comparisons and inferences with respect to the whole cohort. Whilst very large multicentre prospective studies will be needed to establish the true spectrum of clinical features, neuroimaging and pathological signatures of *TREM2* variants in AD, our findings suggest *p.R47H* confers specific risk for typical, amnestic and often very young onset AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AAO	age at symptom onset
APOE	ε4apolipoprotein ε4 allele
CI	confidence interval
CSF	Cerebrospinal fluid
CSF1R	colony stimulating factor 1 receptor
LOAD	late onset Alzheimer’s disease
MAF	minor allele frequency
MMSE	mini-mental state examination
OR	odds ratio
PCA	posterior cortical atrophy
PCR	polymerase-chain-reaction

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PGM	Personnel Genome Machine
PIQ	performance intelligence quotient
PLOSL	polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy
PS1	Presenillin 1
RMT-F	Recognition Memory Test for faces
RMT-W	Recognition Memory Test for words
sCJD	sporadic Creutzfeldt-Jakob disease
SD	standard deviation.
TIV	Total intracranial volumes
TREM2	triggering receptor expressed on myeloid cells 2
TYROBP	TYRO protein tyrosine kinase binding protein
vCJD	variant Creutzfeldt-Jakob disease
VIQ	verbal intelligence quotient
VOSP	Visual Object and Spatial Perception battery
YOAD	Young onset Alzheimer's disease

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Systematic review

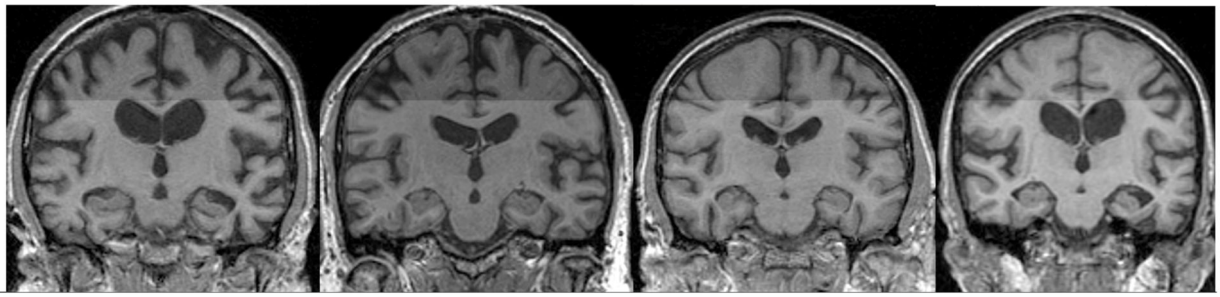
We searched PubMed up to December 2013 with the terms “Alzheimer’s disease”, “young onset Alzheimer’s disease”, “frontotemporal dementia”, “prion”, “Creutzfeldt-Jakob disease”, and “TREM2”. p.R47H is a risk factor for Alzheimer’s disease (AD) and can be associated with young onset. Associations have also been reported with frontotemporal dementia. The clinical phenotype of p.R47H associated AD and p.R47H association with prion disease is unknown.

Interpretation

We show that individuals with p.R47H associated AD are significantly younger at symptom onset than individuals with no TREM2 variants. Heterozygous p.R47H AD is memory led with disease duration, neuroimaging and pathological features otherwise indistinguishable from “typical” sporadic AD. p.R47H does not significantly alter risk for frontotemporal dementia or Creutzfeldt-Jakob disease in our cohorts.

Future directions

The mechanism by which p.R47H leads to earlier age at Alzheimer’s symptom onset remains to be elucidated, but may lead to the identification of novel therapeutic targets.



Case	4	5	6	10
Age at scan (yrs)	55 yrs	58 yrs	60 yrs	60 yrs
Disease duration	6 yrs	4 yrs	1 yr	9 yrs

Figure 1.

Coronal MRI images in 4 individuals with Alzheimer's disease and p.R47H variant. Disease duration denotes time from first symptom to time of scan.

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Table 1

p.R47H *TREM2* variants in Alzheimer's disease, frontotemporal dementia, and CJD cohorts

	n	non reference alleles	MAF cases	MAF controls	OR	95% CI	P
AD	1002	15†	0.0075†	0.0034†	2.19	1.04-4.51	0.03¶
FTD	358	2†	0.0028†	0.0034†	0.81	0.09-3.36	1.00¶
UK vCJD	115	0†	0†	0.0034†	NA	NA	1.00¶
UK sCJD	722	7†	0.0049†	0.0034†	1.41	0.50-3.49	0.47¶
UK sCJD			0.0057‡	0.0041‡	1.39	0.66-2.93	
German sCJD	824	2†	0.0020‡	0.0026‡	0.80	0.24-2.63	
US sCJD	891	7†	0.0055‡	0.0058‡	0.94	0.46-1.89	
Combined sCJD	2500	22.1‡	0.0044‡	0.0042‡	1.06	0.66-1.69	0.60‡
Total:	**3975**						

MAF; minor allele frequency, OR; odds ratio, CI; confidence interval.

†Directly genotyped by Sanger sequencing or MGB R47H probe. Both genotyped and imputed data are shown for UK sCJD and controls.

‡Allele counts, frequencies and P values calculated using IMPUTEv2 and SNPTEST from genome wide array data (including 731 UK sCJD, 818 German sCJD and 951 US sCJD compared against 5020 UK, 2691 German and 2837 US controls).

¶P values were calculated using 2 sided Fisher's exact test.

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Table 2

Clinical features of Alzheimer's disease individuals with p.R47H variant

Case	*M/F*	*TREM2 R47H*	*Other gene variants*	*APOE ε genotype*	*Age of onset (yrs)*	*Disease duration (yrs)*	*Family history*	*Leading symptoms*	*Neuropsychology*						
									years since onset	*VIQ*	*PIQ*	*RMT-W*	*RMT-F*	*Visuo-Perceptual (VOSP)*	*Visuo-spatial (VOSP)*
1	F	**homozygote**	nil	3 4	64	14	yes	frontal	-	-	-	-	-	-	-
2	F	heterozgote	nil	3 3	44	-	no	memory	3	86	77	<5	<5	-	-
3	M	heterozgote	nil	3 4	49	15	yes	memory	3	67	64	<5	<5	10-25	-
4	M	heterozgote	nil	3 3	49	-	no	memory	3	80	65	-	-	25-75	25-75
5	M	heterozgote	nil	3 3	54	-	yes	memory	4	55	63	<5	<5	<5	<5
6	M	heterozgote	nil	3 3	60	-	yes	memory	1	87	72	<5	10-25	<5	25-75
7	F	heterozgote	nil	3 4	71	8	yes	memory	-	-	-	-	-	-	-
8	F	heterozgote	nil	3 3	46	-	no	memory	-	-	-	-	-	-	-
9	M	heterozgote	nil	4 4	50	-	no	language	-	-	-	-	-	-	-
10	F	heterozgote	nil	4 4	51	15	no	memory	7	78	83	<5	<5	25-75	25-75
11	F	heterozgote	nil	3 3	59	7	yes	memory	4	-	-	<5	-	25-75	10-25
12	F	heterozgote	E318G PS1	3 4	65	9	no	memory	5	73	62	<5	25-75	25-75	25-75
13	F	heterozgote	nil	-	unknown	-	unknown	unknown	-	-	-	-	-	-	-
14	F	heterozgote	nil	3 3	unknown	-	unknown	unknown	-	-	-	-	-	-	-

AD, Alzheimer's disease; F, female; M, male; positive family history denotes those with at least one secondary case of AD diagnosed in a first or second degree relative; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; RMT-W, Recognition Memory Test for words; RMT-F, Recognition Memory Test for faces; VOSP, Visual object and spatial perception battery. RMT and VOSP scores given as percentiles. '-' indicates no data available.

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Table 3

Leading symptoms and neurological features in AD patients by p.R47H genotype

		AD p.R47H variant (n=12)		AD nil *TREM2* variant (n=33)		P value†
		n	%	n	%	
Leading symptom	memory	10	83.3	21	63.6	0.29
	language	1	8.3	1	3.0	0.47
	frontal	1	8.3	2	6.1	1.00
	parietal	0	0.0	9	27.3	0.09
Neurological features	myoclonus	3	25.0	10	30.3	1.00
	seizures	2	16.7	2	6.1	0.29
	cerebellar signs	2	16.7	0	0.0	0.07
	extrapyramidal motor features	2	16.7	3	9.1	0.60
	pyramidal motor features	1	8.3	3	9.1	1.00
	dystonia	1	8.3	0	0.0	0.27
	hallucinations	1	8.3	3	9.1	1.00
	other psychiatric symptoms	1	8.3	12	36.4	0.13
	sleep disturbance	1	8.3	2	6.1	1.00
	dyspraxia	2	16.7	5	15.2	1.00

AD, Alzheimer's disease.

†P values calculated using Fisher's exact test.