Myelin oligodendrocyte basic protein and prognosis in behavioral-variant frontotemporal dementia

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ABSTRACT

Objective: To determine the prognostic utility of tauopathy-associated single nucleotide polymorphisms (SNPs) in sporadic behavioral-variant frontotemporal dementia (bvFTD).

Methods: Eighty-one patients with sporadic bvFTD were genotyped for tauopathy-associated SNPs at rs8070723 (microtubule-associated protein tau [*MAPT*]) and rs1768208 (myelin-associated oligodendrocyte basic protein [*MOBP*]). We performed a retrospective case-control study comparing age at onset and disease duration between carriers of ≥1 polymorphism allele and noncarriers for these SNPs. Subanalyses were performed for autopsied subgroups with tauopathy (n = 20) and TDP-43 proteinopathy (n = 12). To identify a potential biological basis for disease duration, neuroimaging measures of white matter integrity were evaluated (n = 37).

Results: Carriers of risk allele (T) in rs1768208 (i.e., *MOBP* RA+) had a shorter median disease duration (TC/TT = 5.5 years, CC = 9.5 years; $p = 0.02$). This was also found in the subset of cases with autopsy-confirmed tauopathies ($p = 0.04$) but not with TDP-43 proteinopathies ($p > 0.1$). By comparison, polymorphisms at rs8070723 (*MAPT*) had no effect on disease duration ($p > 0.1$), although carriers of protective allele (G) in rs8070723 had a younger median age at onset (AG/GG = 54.5 years, AA = 58 years; $p < 0.01$). *MOBP* RA+ patients had increased radial diffusivity in the superior corona radiata and midbrain, and reduced fractional anisotropy in the superior corona radiata as well as superior and inferior longitudinal fasciculi compared with noncarriers ($p < 0.01$).

Conclusions: The rs1768208 risk polymorphism in *MOBP* may have prognostic value in bvFTD. *MOBP* RA+ patients have more severe white matter degeneration in bvFTD that may contribute to shorter disease duration. Future studies are needed to help confirm these findings. ***Neurology*®** **2014;83:1–8**

GLOSSARY

AD = Alzheimer disease; **ALS** = amyotrophic lateral sclerosis; **bvFTD** = behavioral-variant frontotemporal dementia; **FA** = fractional anisotropy; **FTD** = frontotemporal dementia; **FTLD** = frontotemporal lobar degeneration; **GM** = gray matter; **GMD** = gray matter density; **ILF** = inferior longitudinal fasciculus; ***MAPT*** = microtubule-associated protein tau; ***MOBP*** = myelin-associated oligodendrocyte basic protein; **PA** = protective allele; **PSP** = progressive supranuclear palsy; **RA** = risk allele; **RD** = radial diffusion; **SCR** = superior corona radiata; **SLF** = superior longitudinal fasciculus; **SNP** = single nucleotide polymorphism; **STG** = superior temporal gyrus; **TDP-43** = TAR DNA-binding protein 43; **WM** = white matter.

Significant heterogeneity exists in the natural history of behavioral-variant frontotemporal dementia (bvFTD), the most common clinical phenotype in frontotemporal lobar degeneration (FTLD) spectrum pathology. Approximately equal numbers of cases appear to be attributable to the 2 main broad categories of proteinopathies[1,2]: those containing pathologic aggregations of the microtubule-associated protein, tau (i.e., FTLD-tau),[3] and those with inclusions composed of the RNA-binding protein, TDP-43 (i.e., FTLD-TDP).[3] Prognostic markers are critical for clinical care and for disease-modifying clinical trials targeting these abnormal proteinaceous aggregates.[4] Studies of survival between FTLD-tau and FTLD-TDP have been inconsistent.[5–9] While the signs of clinical amyotrophic lateral sclerosis (FTD-ALS) are a reasonably reliable

Supplemental data at Neurology.org

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marker for underlying TDP-43 pathology and shorter survival in bvFTD,[2,9] prognostic information related to the presence of tau pathology in bvFTD is unknown.

A recent case-control, genome-wide association study of autopsy-proven cases identified risk alleles in rs1768208 (myelin-associated oligodendrocyte basic protein [*MOBP*], OMIM600948) and rs8070723 (microtubule-associated protein tau [*MAPT*], OMIM157140) associated with progressive supranuclear palsy (PSP), a form of FTLD-tau.[10] We previously found that these SNPs are associated with FTLD-tau compared with FTLD-TDP, and correlated with neuroanatomical gray matter (GM) and white matter (WM) degeneration on MRI.[11] This study did not constrain analyses by FTLD clinical phenotype and did not examine disease duration. Here, we examined the prognostic correlates for *MOBP* rs1768208 and *MAPT* rs8070723 genotype in the most common FTLD phenotype, sporadic bvFTD. Our findings suggest that rs1768208 risk allele in *MOBP* is associated with a shorter disease course, and that this may be related to worse WM disease.

METHODS

Subjects. Patients included for study were seen at the Penn Frontotemporal Degeneration Center or Alzheimer's Disease Center. The target population for study was sporadic patients with a clinical diagnosis of bvFTD and underlying FTLD neuropathology (i.e., FTLD-tau or FTLD-TDP) without ALS. To confirm that all cases met current clinical criteria,[1] charts were retrospectively reviewed by separate investigators (D.J.I., C.T.M., K.R., J.B.T.) and discussed at consensus meetings. All cases who met "probable" bvFTD criteria had CSF samples obtained during routine diagnostic lumbar puncture and were screened for levels of Alzheimer disease (AD)-associated analytes (i.e., β-amyloid, total tau, and phosphorylated tau), as previously described.[12] All of the probable bvFTD cases in this cohort have a total tau/β-amyloid ratio that is not suggestive of an autopsy-confirmed AD profile (i.e., <0.34),[12] minimizing the possible inclusion of atypical AD cases that can influence clinically derived FTLD cohorts.[13,14] In a subset of patients followed to autopsy (i.e., "definite" bvFTD), neuropathologic examination was performed as previously described[15] using well-established monoclonal antibodies and current neuropathologic criteria (table 1).[3] The final cohort included 81 patients who met probable or definite bvFTD criteria.[1]

We further constrained our bvFTD sample to presumed sporadic cases because SNPs may potentially have specific associations in hereditary cases,[16] and hereditary cases may also have different rates of survival.[8] A validated pedigree analysis[17] was performed to assess family history and found 33 cases (40.7%) classified as "low" risk or "apparent sporadic" and only 6 (7.4%) as "medium" risk and 3 (3.7%) with a "high" risk score for hereditary disease. The remaining 39 cases (48.1%) had insufficient clinical data for comprehensive pedigree analysis. As such, we performed full genotyping for the 3 major molecular etiologies

Table 1 Patient clinical, demographic, and pathologic characteristics

	Total bvFTD cohort	FTLD-tau subgroup	FTLD-TDP subgroup
No. (M/F)	81 (53/28)	20 (12/8)	12 (7/5)
Pathologic diagnosis		AGD = 1, CBD = 5, PiD = 9, PSP = 2, MST = 3	A = 3, B = 2, C = 6
Age at onset, y	57 (51.5–64)	59 (51–73)	58.5 (51.25–68.75)
Race, % Caucasian	91.4	95	100
Age at death, y	65 (59–78.5); n = 36	69 (59–83.5); n = 20	67.5 (57–76.5); n = 12
Disease duration, y	7 (4–11.75)	8 (4–12)	8 (3.25–11.75)
Education, y	16 (12–18)	12 (12–16)	14 (12–20)
MMSE score at first visit	25 (19.5–28); n = 65	24 (13.75–26.25); n = 14	21 (11.5–28.5); n = 9
rs8070723 genotype, n			
AA	55	17	8
AG	16	2	2
GG	10	1	2
rs1768208 genotype, n			
CC	38	7	8
TC	33	10	3
TT	10	3	1

Abbreviations: A, B, C = FTLD-TDP subtypes; AGD = argyrophilic grain disease; bvFTD = behavioral-variant frontotemporal dementia; CBD = corticobasal degeneration; FTLD-TDP = frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions; MMSE = Mini-Mental State Examination; MST = multisystem tauopathy; PiD = Pick disease; PSP = progressive supranuclear palsy.
Data are median (interquartile range) unless otherwise indicated.

of hereditary FTLD in all living cases (i.e., *GRN*: OMIM138945; *MAPT*: OMIM157140; *C9orf72*: OMIM614260) as described,[18–20] which account for the vast majority of hereditary FTLD,[17] and excluded all cases with known pathogenic mutations in these genes. Retrospective genotyping in autopsy-confirmed cases targeted only genes associated with the neuropathologic diagnosis (i.e., *GRN* and *C9orf72* for FTLD-TDP and *MAPT* for FTLD-tau).[3] Further, 6 of the "medium" and "high" score cases were additionally genotyped and were negative for mutations in 43 genes with known associations to neurodegenerative disease. Thus, participants in this cohort have a high likelihood of sporadic disease.

Standard protocol approvals, registrations, and patient consents. All procedures, including DNA and CSF collection and autopsy, required informed consent and were performed in accordance with the rules of the institutional review board at Penn.

SNP genotyping. DNA was extracted from peripheral blood samples or brain tissue using the manufacturer's protocol (FlexiGene; Qiagen, Valencia, CA) or Quick-Gene DNA whole blood kit (AutoGen, Holliston, MA). Genotyping for rs1768208 and rs8070723 was performed using a matrix-assisted laser desorption/ionization time-of-flight spectroscopy SNP genotyping technology (MassArray; Sequenom, San Diego, CA) as previously described.[11]

MRI analysis. A subset of the cohort (n = 37) and 31 healthy elderly controls (table e-1 on the *Neurology*® Web site at Neurology.org) underwent structural T1-weighted MRI and diffusion-weighted imaging. Twenty-eight patients with bvFTD were included as a subset of a previously reported cohort that contained clinically heterogeneous samples and different statistical measures.[11] We measured GM density (GMD), fractional anisotropy (FA), and radial diffusion (RD). Neuroimaging analyses were performed as previously reported,[21] using nonparametric permutation analysis with 10,000 permutations. GMD was restricted to voxels containing GM using an explicit mask generated from the average GM probability map of all subjects. FA and RD were restricted using an explicit mask (FA $\geq$0.25) to constrain comparisons to regions of high probability WM. Clusters were accepted that survived an extent threshold of 50 voxels (GMD) or 200 voxels (FA/RD). We used a height threshold of $p < 0.05$ with family-wise error correction for multiple comparisons in patient vs control analyses and a height threshold of $p < 0.01$ for direct comparisons between bvFTD rs1768208 risk allele carriers and noncarriers. For further details, see appendix e-1.

Statistical analysis. Clinical data, including dates and ages at onset and death, were obtained from the Penn Integrated Neurodegenerative Disease Database,[15] and disease duration was calculated from these values and reported in years. Clinical variables were evaluated for normality using a Kolmogorov-Smirnov test and because of a nonnormal distribution analyzed with Mann-Whitney *U* tests. SNP genotypes were coded for the presence of one or more polymorphism alleles (i.e., *MOBP* RA+, *MAPT* PA+) and zero polymorphism alleles (i.e., *MOBP* RA−, *MAPT* PA−) and analyzed in a dominant model. Risk allele carrier frequencies and other categorical variables were compared using a 2 × 2 contingency table with χ^2 analysis. Clinical data are reported as median with interquartile range. All analyses were 2-sided with $\alpha = 0.05$, and we did not correct for multiple comparisons because of our a priori hypotheses. Statistical analyses were performed with SPSS version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Risk alleles in patient groups. The presence of one or more copies of *MOBP* rs1768208 risk allele (T) (i.e., *MOBP* RA+) is marginally associated with an increased risk of FTLD-tau,[10,11] and there was an increased frequency of *MOBP* RA+ patients (CT/TT) in FTLD-tau (13/20) compared with the FTLD-TDP subgroup (4/12; $\chi^2 = 3.0$, $p = 0.08$) that failed to reach significance. The rs8070723 risk allele (G) marks the H2 haplotype of *MAPT* and confers a decreased risk for FTLD-tau,[10,11] and rs8070723 protective allele carriers (AG/GG) (i.e., *MAPT* PA+) were similarly low in frequency for FTLD-tau (3/20) compared with the FTLD-TDP subgroup (4/12; $\chi^2 = 1.3$, $p > 0.1$). There was no association of *MAPT* and *MOBP* allele genotype ($\chi^2 = 0.06$, $p > 0.1$).

Age at onset and disease duration. *MOBP* RA+ patients had a shorter median disease duration ($U = 2.3$, $p = 0.02$) than patients without this risk allele genotype (i.e., *MOBP* RA−; CC; table 2, figure 1A) and nominally significant earlier age at death ($U = 2.0$, $p = 0.04$); however, age at onset did not differ between *MOBP* RA+ and *MOBP* RA− patients ($U = 0.3$, $p > 0.1$; table 2). To illustrate the independent effect of *MOBP* RA+ genotype on disease duration and age at death, we performed univariate analyses comparing *MOBP* RA+ and *MOBP* RA− groups and found no difference in sex, *MAPT* rs8070723 genotype, or Mini-Mental State Examination score at first visit (all $p > 0.1$). The cohort was largely Caucasian (90%) and after excluding non-Caucasians from our analysis (n = 7), the effect of shorter disease duration ($U = 2.2$, $p = 0.03$) in *MOBP* RA+ cases persisted.

Analyses of autopsy subgroups found a nominally significant modification of disease duration in FTLD-tau ($U = 2.1$, $p = 0.04$) while the association was not significant in the FTLD-TDP subgroup ($U = 1.2$, $p > 0.1$) (table 2; figure 1, B and C). In contrast, direct comparison of FTLD-tau and FTLD-TDP, irrespective of rs1768208 genotype, found similar median disease duration (FTLD-tau = 8 years [interquartile range = 4–12], FTLD-TDP = 8 years [interquartile range = 3.25–11.75]; $U = 0.7$, $p > 0.1$) (figure 1D).

We assessed the specificity of the disease-duration effect associated with the *MOBP* rs1768208 risk allele by assessing the *MAPT* rs8070723 protective allele. We found that *MAPT* PA+ (GG/GA) patients had an earlier age at onset compared with those without this genotype (i.e., *MAPT* PA−; AA: $U = 3.0$, $p < 0.01$; table 2). However, there was no effect on age at death ($U = 1.0$, $p > 0.1$) or disease duration associated with *MAPT* PA+ ($U = 0.9$, $p > 0.1$). Univariate analyses found no difference between *MAPT* PA+ and *MAPT* PA− patient groups for sex,

Table 2 Median (interquartile range) disease duration stratified by rs8070723 and rs1768208 risk allele carrier status

	Group	No. (deceased)	Age at onset, y	Age at death, y	Disease duration, y
rs8070723					
AA	Total cohort	55 (26)	58 (55–66)	69 (59.75–79.75)	7 (4–11.25)
AG/GG		26 (10)	54.5 (47–58.25)	63 (54.75–74)	8 (5.5–13.25)
			$U = 3.0$, $p = 0.002$	$U = 1.0$, $p = 0.3$	$U = 0.9$, $p = 0.4$
rs1768208					
CC	Total cohort	38 (16)	57 (53.75–64.25)	72 (63–78.5)	9.5 (6.25–12.75)
CT/TT		43 (20)	57 (50–63)	60.5 (55.25–78.25)	5.5 (4.0–9.5)
			$U = 0.3$, $p = 0.8$	$U = 2.0$, $p = 0.04$	$U = 2.3$, $p = 0.02$
CC	FTLD-tau	(7)	64 (58–70)	72 (67–84)	12 (8–13)
CT/TT		(13)	57 (50–77)	61 (57.5–83)	5 (4–10.5)
			$U = 0.5$, $p = 0.6$	$U = 1.1$, $p = 0.3$	$U = 2.1$, $p = 0.04$
CC	FTLD-TDP	(8)	61.5 (55–70.5)	72.5 (63–76.5)	9 (4.25–12.75)
CT/TT		(4)	50 (47.25, 64.0)	54.5 (51.75–73)	5 (3–10)
			$U = 1.7$, $p = 0.09$	$U = 1.5$, $p = 0.1$	$U = 1.2$, $p = 0.2$

Abbreviation: FTLD-TDP = frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions.

rs1768208 genotype, or Mini-Mental State Examination score at first visit (all $p > 0.1$), suggesting an independent association of *MAPT* PA+ with age at onset. Neuropathologic subgroup analyses for rs8070723 were limited by the small number of risk allele carriers in FTLD-tau and FTLD-TDP (table 1).

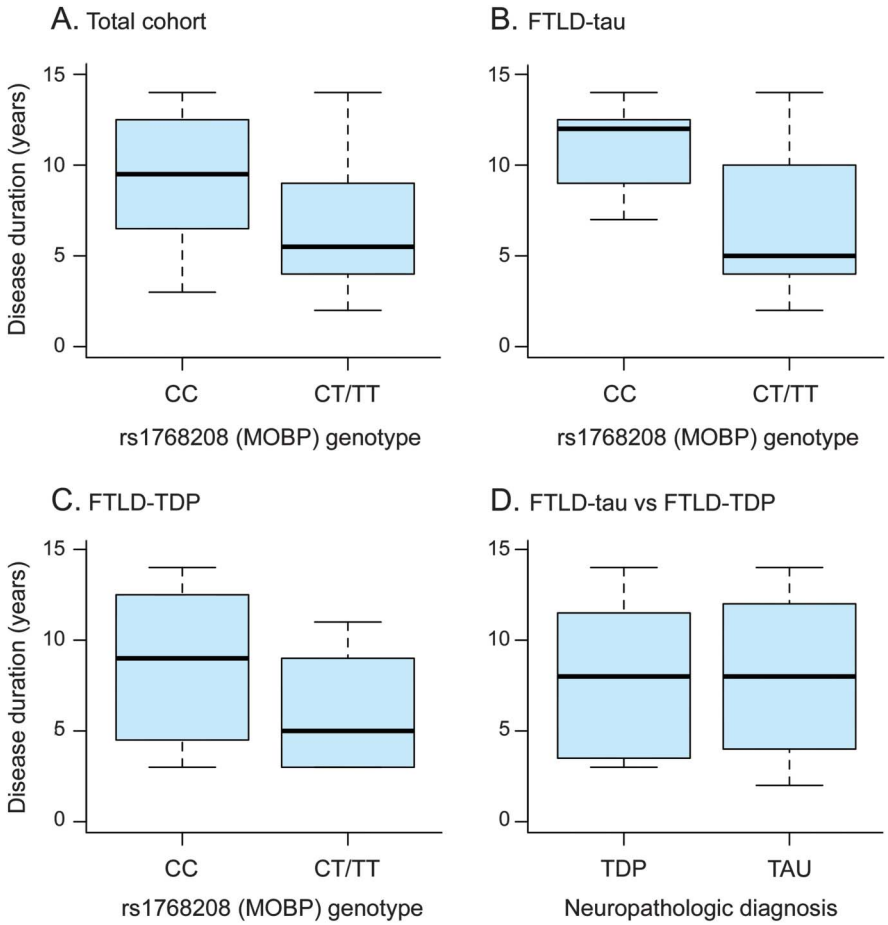
Neuroimaging analyses. We examined the relationship of rs1768208 genotype with MRI measures of GMD and WM integrity (RD and FA) in a subset of patients with available neuroimaging data (n = 37). Patient groups and controls had similar demographics ($p > 0.1$; table e-1). GMD was significantly reduced across multiple frontal and temporal cortical regions in both *MOBP* RA+ and *MOBP* RA− patients compared with healthy elderly controls, consistent with bvFTD[22] (table e-2, figure e-1). RD was increased and FA was reduced in both *MOBP* RA+ and *MOBP* RA− patients compared with controls in several frontal and temporal subcortical association and commissural tracts (table e-2, figure e-1).

Direct comparison of *MOBP* RA+ patients with *MOBP* RA− patients found reduced FA in left superior corona radiata (SCR), right superior longitudinal fasciculus (SLF), and left inferior longitudinal fasciculus (ILF) (figure 2A, table 3), and increased RD in the left midbrain and left SCR (figure 2B, table 3). There were 2 small clusters (i.e., 50–70 voxels) of significantly increased FA in the midbrain that approached significance ($p < 0.05$; data not shown). Direct comparison of *MOBP* RA+ and *MOBP* RA− patient groups found reduced GMD in the right superior temporal gyrus (STG) and precuneus (figure 2C, table 3).

DISCUSSION Herein, we describe the prognostic value of tauopathy-associated SNPs in a well-characterized cohort of patients with sporadic bvFTD. Specifically, we found shorter disease duration and age at death in *MOBP* RA+ (CT/TT) patients in the total cohort. This effect was confirmed in the subgroup of autopsied patients with FTLD-tau pathology. Furthermore, we found WM neurodegeneration in the midbrain, SCR, SLF, and ILF as well as significant GM atrophy in the STG and precuneus associated with rs1768208 *MOBP* risk allele carriers in direct comparison with *MOBP* RA− cases, suggesting that this risk allele is associated with more severe neurodegeneration. In contrast, we found decreased age at onset in *MAPT* PA+ (GG/GA) patients but no effect for disease duration, emphasizing the specificity of the disease-duration effect associated with the rs1768208 *MOBP* risk allele in bvFTD patients with FTLD-tau.

Overall median disease duration for our cohort (table 1) was similar to previous autopsy-confirmed reports for bvFTD[1,6–9] of approximately 6 to 9 years from onset of symptoms, suggesting that our cohort is representative of bvFTD. While previous studies have suggested differences in disease duration depending on FTLD-tau or FTLD-TDP pathology, it is unlikely that this is contributing to our observation of a shorter disease course in association with the T risk allele of rs1768208 in *MOBP*. Some authors have reported similar disease durations in bvFTD with underlying FTLD-tau and FTLD-TDP pathology,[5,7] while others have found a longer disease duration in FTLD-tau,[9] and our group previously demonstrated a worse

Figure 1 Box plots of disease duration for the behavioral-variant frontotemporal dementia cohort

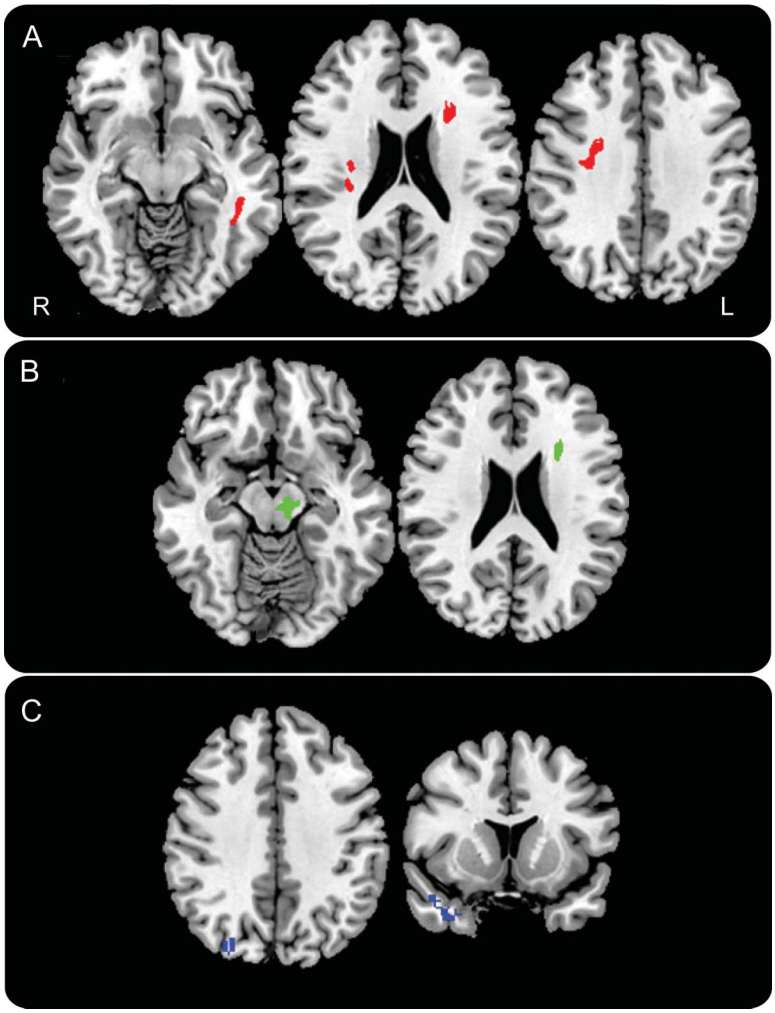


rs1768208 *MOBP* RA+ carriers of risk allele T (CT/TT) have a shorter median disease duration than noncarriers (CC) in (A) total cohort ($p = 0.02$) and (B) FTLD-tau subgroup ($p = 0.04$) but not (C) FTLD-TDP subgroup ($p > 0.1$). (D) FTLD-TDP and FTLD-tau have a similar disease duration ($p > 0.1$). FTLD-TDP = frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions; *MOBP* = myelin-associated oligodendrocyte basic protein; RA = risk allele.

prognosis in FTLD-tau.[23] These discrepancies may be explained in part by inclusion of hereditary cases. There were also differences in clinical criteria used across studies, with known effects of clinical phenotypes included in some studies. For example, ALS associated with FTLD-TDP pathology has shorter survival,[9,24] and FTLD motor phenotypes such as PSP and corticobasal syndrome may have shorter survival than other forms of FTLD-tau.[6,8] In the present study, the bvFTD phenotype was not associated with a motor disorder that could have biased survival, and FTLD-tau and FTLD-TDP autopsy subgroups did not differ in disease duration (figure 1D). Thus, reduced disease duration in patients with *MOBP* RA+ bvFTD does not appear to be biased by a motor phenotype or the association of the *MOBP* risk allele with FTLD-tau pathology in our cohort.

Several observations are consistent with the possibility that the *MOBP* risk allele is associated with more aggressive underlying neuropathology, and in particular, significant WM disease. In addition to finding that poor prognosis in clinically diagnosed bvFTD is associated with the T risk allele of rs1768208 in *MOBP*, examination of autopsy subgroups demonstrated shorter disease duration in T allele carriers with FTLD-tau pathology (figure 1B). We did not find a similar effect for *MOBP* RA+ in the FTLD-TDP subgroup (figure 1C). The association of rs1768208 SNP in *MOBP* with autopsy-proven PSP was identified in a case-control, genome-wide association study,[10] and we previously demonstrated that this risk allele is associated with an increased likelihood of all forms of FTLD-tau in direct comparison with FTLD-TDP.[11] MOBP is a major component of myelin associated exclusively with oligodendrocytes, and may serve to stabilize myelin in times of oxidative stress or myelin turnover.[25] The *MOBP* gene involves alternative splicing to form several different protein isoforms, and the rs1768208 locus is situated in an intronic region between exons 1 and 2 (NC_000003.11: g.39523003T>C, NM_182935.2:c.−5+1389T>C). From this perspective, it is tempting to hypothesize that

Figure 2 Increased white and gray matter degeneration in direct comparison of patients with behavioral-variant frontotemporal dementia who are rs1768208 risk allele positive (CT/TT) to risk allele negative (CC)



(A) Regions of reduced fractional anisotropy (red). (B) Increased radial diffusivity (green). (C) Reduced gray matter density (blue).

the risk polymorphism could alter gene splicing/function to exacerbate myelin-associated degeneration in the setting of WM pathology found in FTLD-tau,[26,27] although the exact locus conferring disease risk for tauopathies marked by this SNP is currently unclear. Indeed, PSP and other forms of FTLD-tau have significant WM oligodendritic pathology[28,29] that is more prominent than in FTLD-TDP.[30–32]

While animal- and cell-model experiments are needed to clarify the normal function of *MOBP* and the association of the rs1768208 polymorphism with neurodegeneration in FTLD, our neuroimaging findings are consistent with the possibility that degeneration particularly involving WM myelin may be contributing to poorer prognosis in *MOBP* RA+ patients. Specifically, we found increased RD in the WM of the midbrain and SCR, and additional decrease in FA in the SLF and ILF (figure 2, A and B) in *MOBP* RA+ patients. These are areas of known WM degeneration in tauopathies such as PSP.[28] Moreover, increased RD is associated with reduced myelin integrity.[33] Thus, it is possible that the observed reduced disease duration reflects an association of *MOBP* RA+ with a more malignant subtype of FTLD-tau, which compromises WM myelin. We previously demonstrated that WM disease in these regions is a robust marker of FTLD-tau pathology,[32] and others found that brainstem hypometabolism conferred worse prognosis in nonautopsy-confirmed bvFTD.[34] *MOBP* rs1768208 risk allele carriers also had more severe GM atrophy in STG and parietal lobe (precuneus). These areas are implicated in both FTLD-tau and FTLD-TDP.[22,32,35,36] We previously found that lower copy numbers of rs1768208 *MOBP* risk allele are associated with reduced FA in SLF in a clinically mixed cohort; however, this was in a more posterior and superior region than in the current study of sporadic bvFTD.[11] Additional work is needed to further investigate these imaging findings. These results suggest that the rs1768208 polymorphism appears to affect WM degeneration in FTLD-tau more than FTLD-TDP. The small number of carriers in the FTLD-TDP subgroup in this study precluded quantitative analyses of this finding.

We found that the protective allele marking the H2 haplotype in rs8070723 had no effect on disease duration. Therefore, these results suggest that the association of reduced disease duration with rs1768208 in *MOBP* for bvFTD is specific for this risk allele. Carriers of the G protective allele in rs8070723 nevertheless had an earlier age at onset by a median of 3.5 years (table 1). Others have found similar results of earlier age at onset for H2 carriers by 5 years in a clinically mixed FTLD cohort without autopsy confirmation.[37] The H1 and H2 haplotypes comprise inverted sequences of polymorphisms in linkage disequilibrium in the region on chromosome 17 coding *MAPT*, and the H1 haplotype is overrepresented in forms of FTLD-tau.[38,39] Cases with FTLD-tau have been reported to have an older age at onset.[9] Thus, the observed association of an older age at onset in *MAPT* PA− patients could reflect differences in the natural history of patients with bvFTD who have underlying FTLD-tau compared with FTLD-TDP. The low frequency of the protective allele in both neuropathologic subgroups limited clarification of this association in the current study, and additional work is needed in a larger sample with autopsy-proven disease.

Several caveats should be kept in mind when interpreting the results. First, this was a small, highly educated, and largely Caucasian cohort from a tertiary academic center, which has inherent referral bias, and a population-based approach is required for

Table 3 Direct comparison of MRI findings of neurodegeneration between rs1768208 risk allele carriers (CT/TT) and noncarriers (CC)

Anatomical locus (Brodmann area)	MNI coordinates X	Y	Z	Cluster size (voxels)
Areas of significant WM degeneration (reduced FA) in rs1768208 carriers compared with noncarriers				
R superior longitudinal fasciculus	31	−15	34	797
L superior corona radiata	−26	17	23	568
L inferior longitudinal fasciculus	−47	−35	−11	430
Areas of significant WM degeneration (increased RD) in rs1768208 carriers compared with noncarriers				
L midbrain	−8	−21	−13	304
L superior corona radiata	−26	13	23	212
Areas of significant cortical atrophy (reduced GMD) in rs1768208 carriers compared with noncarriers				
R superior temporal gyrus (38)	44	10	−26	66
R precuneus (19)	26	−80	38	65

Abbreviations: FA = fractional anisotropy; GMD = gray matter density; MNI = Montreal Neurological Institute; RD = radial diffusion; WM = white matter.

generalizability and further elucidation of genotype frequencies across racial groups, but publically available samples for such analyses do not yet exist. Our neuroimaging cohort consisted largely of living cases (table e-1), therefore we cannot confirm prognostic associations of neuroimaging findings in sporadic bvFTD with direct assessment of pathology. Finally, although direct comparisons within the patient groups were robust and supported our survival observations with rs1768208, we did not assess genotype in the control group for neuroimaging analyses, so we cannot exclude the possibility that genetic makeup of controls influenced our imaging results.

With these caveats in mind, the risk polymorphism at rs1768208 in *MOBP* may confer a worse prognosis in patients with bvFTD, and this may be related to more severe neurodegeneration particularly in subcortical WM. Tauopathy-associated SNPs thus may provide a promising candidate for prognostic biomarkers in bvFTD. Prospective studies utilizing emerging biomarkers for FTLD-tau[40] will be helpful to confirm these observations in a larger bvFTD cohort with known pathology.

AUTHOR CONTRIBUTIONS

David J. Irwin, MD: study concept and design, acquisition of data, statistical analyses, interpretation of data, drafting of the manuscript, critical revision of the manuscript. Corey T. McMillan, PhD: study concept and design, acquisition of data, statistical analyses, interpretation of data, critical revision of the manuscript. EunRan Suh, PhD: acquisition of data, interpretation of data, critical revision of the manuscript. John Powers, BA: acquisition of data, statistical analyses, interpretation of data, critical revision of the manuscript. Katya Rascovsky, PhD, Elisabeth M. Wood, MSc, Jon B. Toledo, MD, and Steven E. Arnold, MD: acquisition of data, interpretation of data. Virginia M.-Y. Lee, PhD, MBA: study concept and design, interpretation of data, obtained funding, administrative support. Vivianna M. Van Deerlin, MD, PhD: study concept and design, interpretation of data, administrative support. John Q. Trojanowski, MD, PhD: study concept and design, interpretation of data, obtained funding, administrative support. Murray Grossman, MD: study concept and design, acquisition of data, interpretation of data, critical revision of the manuscript, obtained funding, administrative support, study supervision.

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DISCLOSURE

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