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TMEM106B RISK VARIANT IS IMPLICATED IN THE PATHOLOGIC PRESENTATION OF ALZHEIMER DISEASE

TDP-43 protein is the major component of the ubiquitin-positive inclusions in neurons and glia of patients with amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD-TDP).[1] TDP-43 pathology has also been detected in as many as 56% of patients with Alzheimer disease (AD) and in 70% of patients with AD and concomitant hippocampal sclerosis (HpScl).[2] Importantly, clinical, neuropsychological, and imaging studies suggested that the presence of TDP-43 pathology in AD may be associated with a modified phenotype.[3] A better understanding of what factors predispose to TDP-43 pathology in AD is therefore critical and could have important clinical implications.

Last year, a genome-wide association study identified the uncharacterized transmembrane protein 106B (TMEM106B) as a novel risk factor for FTLD-TDP.[4] Follow-up studies confirmed the importance of *TMEM106B* in FTLD and suggested that TMEM106B may influence risk for FTLD-TDP by modulating the levels of the secreted growth factor progranulin (GRN).[5] Here, we study the role of TMEM106B in the pathologic presentation of AD using *TMEM106B* SNP rs1990622, previously associated with reduced levels of GRN in human plasma.[5]

Methods. We studied a cohort of 907 white AD cases (57% female) from the Mayo Clinic Brain Bank. The neuropathologic diagnosis of AD was made according to NIA–Reagan criteria and mean age at death was 80.3 ± 9.4 years. The presence of HpScl was diagnosed if there were neuronal loss and gliosis in the subiculum and CA1 regions of the hippocampus that were disproportionate to the degree of neurofibrillary degeneration. TDP-43 immunoreactivity was assessed in a standardized section of medial temporal lobe using TDP-43 immunohistochemistry (rabbit polyclonal antibody; ProteinTech Group, Chicago, IL; n = 167)[2] or an affinity-purified C-terminal specific polyclonal antibody to TDP-43[6] (n = 740). Genotyping of *TMEM106B* rs1990622 was performed using an inventoried Taqman SNP genotyping assay (Applied Biosystems).

PLINK software (http://pngu.mgh.harvard.edu/purcell/plink/) was used to perform logistic regression analysis of *TMEM106B* rs1990622 under an additive, dominant, and recessive model adjusting for age, sex, and presence of the *APOE* ϵ4 allele.

Results. Out of a total of 907 pathologically confirmed AD cases, 301 cases (33.2%) showed abnormal TDP-43 immunoreactivity. HpScl was present in 88 AD cases (9.7%). Association analyses of *TMEM106B* rs1990622 in this pathologically confirmed cohort showed a highly significant decrease in the frequency of the rs1990622 C-allele in AD cases with TDP-43 pathology compared to AD cases without TDP-43 pathology (C-allele frequency of 37.8% vs 46.5%; $p = 5.0 \times 10^{-4}$) (table 1). More specifically, there were fewer homozygous carriers of this minor C-allele in the subgroup of AD cases with TDP-43 pathology (CC genotype frequency of 13.0% vs 20.7%; $p = 5.0 \times 10^{-3}$ in a recessive model). Association analyses further showed a highly significant association of rs1990622 with the presence of HpScl ($p = 1.95 \times 10^{-6}$) (table 1). AD cases carrying at least 1 copy of the rs1990622 C-allele were significantly less likely to develop HpScl (odds ratio [OR] = 0.39; 95% confidence interval [CI] = 0.27–0.57; $p = 8.36 \times 10^{-7}$ in an additive model). The association of rs1990622 with HpScl persisted when all patients with TDP-43 immunoreactivity were excluded from the analyses (OR = 0.42; 95% CI = 0.18–0.97; $p = 0.04$ in an additive model) (table e-1 on the *Neurology*® Web site at www.neurology.org). Similarly, when all patients with HpScl were excluded from the analyses, rs1990622 continued to show a significant association with TDP-43 pathology ($p = 0.04$ in a recessive model; table e-2), suggesting the associations of rs1900622 with TDP-43 pathology and HpScl are, at least in part, independent.

Discussion. We evaluated the contribution of the *TMEM106B* rs1990622 risk variant to the development of TDP-43 pathology and HpScl. In AD cases with TDP-43 pathology we showed significantly reduced frequencies of homozygote carriers of the minor C-allele of rs1990622 compared to AD cases without TDP-43 pathology. Since the minor C-allele of rs1990622 was previously associated with increased GRN levels,[5] we speculate that reduced levels of GRN may increase the risk to develop TDP-43 pathology in AD. The mechanisms by which low levels of GRN lead to TDP-43 pathology are not completely understood; however, activation of programmed cell death pathways may be involved.[7]

HpScl is common in elderly subjects with dementia. Interestingly, HpScl can be detected in more than 75% of FTLD-TDP cases and up to 83% of *GRN* mutation carriers, suggesting a link between HpScl, TDP-43 pathology, and GRN levels. In our AD series, we observed a highly significant association of rs1990622 with HpScl. We showed that AD cases carrying at least 1 minor C-allele were significantly protected from the development of HpScl. These data suggest that increased levels of this neu-

Supplemental data at www.neurology.org

Supplemental Data

Table 1 Association analyses of *TMEM106B* in pathologically confirmed AD series

	TDP-43− (n = 605)		TDP-43+ (n = 301)		Allelic association, *p* value	Genotypic association		
	No.	%	No.	%		Model	OR (95% CI)	*p* Value
rs1990622								
TT	167	27.6	112	37.2	4.7×10^{-4}	ADD	0.66 (0.53–0.83)	2.3×10^{-4}
CT	313	51.7	150	49.8		DOM	0.61 (0.45–0.83)	1.8×10^{-3}
CC	125	20.7	39	13.0		REC	0.55 (0.37–0.83)	4.6×10^{-3}
	HpScl− (n = 819)		**HpScl+ (n = 88)**		**Allelic association**	**Genotypic association**		
rs1990622								
TT	233	28.4	47	53.4	1.95×10^{-6}	ADD	0.39 (0.27–0.57)	8.36×10^{-7}
CT	428	52.3	35	39.8		DOM	0.31 (0.20–0.50)	1.0×10^{-6}
CC	158	19.3	6	6.8		REC	0.29 (0.12–0.69)	4.9×10^{-3}

Abbreviations: AD = Alzheimer disease; ADD = additive; CI = confidence interval; DOM = dominant; HpScl = hippocampal sclerosis; OR = odds ratio; REC = recessive.

rotrophic factor in the hippocampus may protect against neurotoxic insults which would otherwise lead to hippocampal damage.

Together, these data implicate *TMEM106B* in the pathologic presentation of AD.

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Author contributions: Nicola Rutherford, Dr. Carrasquillo: drafting/revising the manuscript for content, analysis or interpretation of data, acquisition of data. Ma Li, Gina Bisceglio, and Joshua Menke: analysis or interpretation of data, acquisition of data. Drs. Josephs, Parisi, Petersen, Graff-Radford, Younkin, and Dickson: drafting/revising the manuscript for content, including medical writing for content, contribution of vital reagents/tools/patents, obtaining funding. Drs. Rademakers: drafting/revising the manuscript for content, including medical writing for content, study concept and design, analysis or interpretation of data, study supervision, obtaining funding.

Acknowledgment: The authors thank Dr. Petrucelli for the use of the custom-made affinity-purified C-terminal specific polyclonal antibody to TDP-43.

Study funding: Supported by the National Institute of Health grant P50 AG16574 (to R.C.P., D.W.D., N.R.G.-R., and R.R.), R01 NS065782 (to R.R.), R01 AG26251 (to R.R.), R01 AG 037491 (to K.J.), and the Consortium for frontotemporal dementia (to R.R.).

Disclosure: N. Rutherford, M. Carrasquillo, M. Li, G. Bisceglio, and J. Menke report no disclosures. K. Josephs receives research support from the NIH and The Dana Foundation. J. Parisi serves as a Section Editor for Neurology® *and receives research support from the NIH. R. Petersen serves on scientific advisory boards for Elan Pharmaceuticals, Wyeth, Pharmaceuticals, and GE Healthcare, and receives research support from the NIH. N. Graff-Radford serves on a scientific advisory board for Codman and receives research support from Pfizer, Elan Corporation, Forest Laboratories, Inc., Mediva-tion, Inc. Janssen, Allon, and the NIH. S. Younkin receives research support from NIH and the Robert and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program. D. Dickson receives research support from the NIH, CurePSP and the State of Florida Department of Elder Affairs Alzheimer Disease Initiative. R. Rademakers receives research support from the NIH, the ALS Association, the ALS Therapy Alliance, CurePSP, and the Consortium for Frontotemporal Degeneration Research.* ***Go to Neurology.org for full disclosures.***

Received December 7, 2011. Accepted in final form March 19, 2012.

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