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RESEARCH ARTICLE

Alzheimer's genetic risk is reduced in primary age-related tauopathy: a potential model of resistance?

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Abstract

Objective: Nearly all adults >50 years of age have evidence for neurofibrillary tau tangles (NFTs) and a significant proportion of individuals additionally develop amyloid plaques (Aβ) consistent with Alzheimer's disease (AD). In an effort to identify the independent genetic risk factors for NFTs and Aβ, we investigated genotypic frequencies of AD susceptibility loci between autopsy-confirmed AD and primary age-related tauopathy (PART), a neuropathological condition defined by characteristic neurofibrillary tau tangles (NFTs) with minimal or absent Aβ. **Methods**: General linear models assessed the odds of AD (N = 1190) relative to PART (N = 376) neuropathologically confirmed cases from two independent series: the Penn Brain Bank (PENN; AD N = 312; PART N = 65) and National Alzheimer's Coordinating Center (NACC; AD N = 878; PART N = 311). We also evaluated the odds of Braak stage NFT burden. **Results**: Three genotypes significantly associated with reduced AD risk relative to PART in the PENN (N = 377) and NACC (N = 1189) cohorts including *APOE* ε4, *APOE* ε2, and rs6656401 in the *CR1* gene. The genotypes rs6733839 in the *BIN1* gene and rs28834970 in the *PTK2B* gene approached significance in the PENN cohort and were significantly associated with reduced AD risk in the NACC cohort. In a combined cohort analysis (N = 1566), *APOE* ε4 dosage was highly associated with higher Braak stage of NFT burden in Probable PART and AD, but not Definite PART. **Interpretation**: The presence of genotypic differences between PART and AD suggest that PART can provide a genetic model of NFT risk and potential Aβ resistance to inform disease-modifying therapies.

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Introduction

Neuropathological studies suggest that nearly all adults over the age of 50 have evidence for neurofibrillary tangle (NFT) inclusions[1,2] and aging adults lacking evidence for any molecular pathology are extremely rare at an estimated rate of <1% of the population.[3,4] Moreover, a substantial proportion of older adults develop amyloid plaques (Aβ) in addition to NFTs consistent with Alzheimer's disease (AD) neuropathology. The recently defined neuropathological condition, primary age-related tauopathy (PART), is characterized by the accumulation of NFTs in the absence of, or minimal, Aβ,[5] and provides a potential model to investigate the relative risk factors for NFT and Aβ pathology in aging individuals. For example, it remains unclear why some individuals develop AD and most of remaining aging individuals develop PART.

Beyond age-related risk factors, we hypothesize that genetic risk factors are likely to play a role in the relative risk of NFT or Aβ neuropathology in PART and AD. While *APOE*ε4 provides the strongest known genetic risk factor for Aβ neuropathology,[6] it does not appear to be associated with PART.[5] From this perspective PART individuals may have a reduced genotypic frequency for known AD susceptibility loci and thus potentially have "resistance" to Aβ pathology. Beyond *APOE*ε4, it has also been suggested that *MAPT* H1 haplotype is associated with tangle-predominant dementia,[7] which likely constitutes a subset of PART. From this perspective, PART individuals may have a genetic background that increases their risk for NFT accumulation independently from their genetic risk for AD.

In this study we evaluate whether differences in the genetic profiles of autopsy-confirmed PART cases compared to AD cases (cases with NFT and Aβ pathology) contribute to the relative risks of NFT and/or Aβ pathological accumulation. Critically, single nucleotide polymorphisms (SNPs) for clinical AD risk were previously identified in large-scale genome wide association studies (GWAS)[8,9] where the majority of cases and controls were clinically defined, and while these studies provided strong statistical power, they lack data on the underlying molecular pathology and thus are unable to look at pathologically-differentiated subtypes of AD. Furthermore, approximately 17% of clinical AD cases do not have evidence for AD molecular pathology at autopsy[10] and 40% of individuals with autopsy-confirmed PART are asymptomatic of cognitive impairment[11] and therefore are not "controls" lacking molecular pathology. Therefore, we implemented a "case-case" design to define genetic differences between PART and AD in an effort to isolate genetic contributions that are specific to tau and/or Aβ neuropathology. We hypothesize that while "noise" associated with clinically defined cases and controls allows for the successful identification of significant genetic risk factors, an alternative case-case study design precludes estimation of subtype-specific exposure-outcome associations, provides a cost-effective approach for preliminary assessments of heterogeneity between subtypes, and helps to reduce the "search space" and Type I error burden for second stage

analyses looking at genotype-subtype case-control associations.[12] We hypothesize that by evaluating the genotypic frequencies of AD-related genetic risk factors among autopsy-confirmed samples with varying levels of NFTs (i.e., PART) and NFT + Aβ (i.e., AD) molecular pathology, we will be able to better elucidate the differences in genetic contributors between PART and AD that can facilitate the discovery of disease-modifying drugs.

Methods

Participants

We identified two cohorts of participants with neuropathologically defined AD or PART based on published international consensus criteria.[5,13] Briefly, in both cohorts individuals were defined as AD if they had a minimum Braak stage NFTs ≥ III (out of VI) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[14] amyloid plaque score of ≥2 on a scoring basis of 0–3.[13] PART cases were defined with NFTs consistent with Braak Stage I–IV and further classified as having "Definite" (CERAD score = 0) or "Possible" (CERAD score = 1) PART using published criteria.[5] To minimize potential confounding effects of race/ethnicity on genetic associations, we constrained our cohort to self-reported white non-Latino individuals. The PENN cohort (N = 377) included individuals from the Integrated Neurodegenerative Disease Database[15,16] and all cases were re-reviewed by a board-certified neuropathologist (EBL). The National Alzheimer's Coordinating Center (NACC) cohort (N = 1189) included cases from 31 past and present Alzheimer's Disease Centers (ADCs) that submitted data acquired between January 2005 and December 2013.

Genotyping methods

To focus our hypothesis-driven analyses we preidentified 11 SNPs that (1) have previously been identified as risk factors for AD in two large-scale case-control GWAS[8,9] (see Table 2) and (2) have a minor allele frequency (MAF) greater than 20% to maximize statistical power. Given the strong prior associations of *APOE*ε4 and *APOE*ε2 on AD risk and prior association of *MAPT* H1 haplotype with tangle-predominant senile dementia risk, we also evaluated *APOE*ε4, *APOE*ε2, and *MAPT* H1 genotypes. A summary of all genotyping procedures for the PENN and NACC Cohorts are described in Data S1.

Statistical analyses

Demographic variables were assessed using nonparametric Wilcoxon rank-sum tests and Chi-Square statistics. To evaluate relative odds of categorical AD compared to PART, we generated binomial general linear models (GLMs) using R software for independent analyses in the PENN and NACC cohorts. We additionally report combined cohort analyses in Table S1 that was accomplished by adding together the cases from the PENN and NACC cohorts to form one large, more highly powered cohort. Since age is an established risk factor for AD we covaried for age at death in all GLMs. We also covaried for sex to minimize sex-related confounds in genetic analyses. To test genetic associations with NFT severity we performed linear regression analyses in the larger, combined cohort comprised of PENN and NACC cases to assess an additive genotype model with Braak stage using a three-point ordinal scale (I–II, III–IV, V–VI) while adjusting for age and sex. For our hypothesis-driven analyses we use a statistical threshold of $\alpha = 0.05$ and further denote results that survive Bonferroni correction for multiple comparisons ($\alpha < 0.0036$) to account for the 14 genetic factors assessed across each experiment.

Results

Demographic characteristics

Demographic analyses within each cohort are summarized in Table 1 and revealed that the PART cases are significantly older than AD cases in the NACC cohort (W = 82074, $P < 0.001$), but matched in the PENN cohort (W = 9352, P = 0.324). The NACC cohort also had a larger proportion of females with PART relative to AD (X^2 = 4.345, P = 0.037), but sex was matched in the PENN (X^2 = 0.022, P = 0.883) cohort. Given these differences, and potential associations between age with AD or PART risk along with potential sex-related genetic differences, we included covariate adjustment for all associations modeled for age and sex in all statistical analyses. Finally, a comparison across cohorts revealed a higher proportion of Definite PART cases in the PENN cohort relative to the NACC cohort (X^2 = 20.882, $P < 0.001$).

Categorical associations

All categorical genotype associations in the PENN and NACC cohorts are summarized in Table 2 and a combined cohort analysis is reported in Table S1. In our PENN cohort we observed two genotype signals that differed significantly between PART and AD with PART patients having a reduced genotype frequency of these AD risk factors. *APOE*ε4 frequency was reduced for PART (9%) in comparison to AD (39%), whereas *APOE*ε2 was increased for PART (22%) in comparison to AD (4%). Also, rs6656401 in the *CR1* gene had a lower frequency in

Table 1. Demographic characteristics of the University of Pennsylvania (PENN) and National Alzheimer's Coordinating Center (NACC) Cohorts.

	PENN		NACC	
	PART	AD	PART	AD
Cases (*N*)	65	312	311	878
Sex, % female	53.85	55.77	50.80	43.73
Age at death, mean years (SD)	78.23 (10.11)	76.49 (10.86)	88.18 (8.14)	81.51 (9.83)
PART, % definite	78.46	–	56.59	–

Table 2. Genotype results for AD-PART categorical associations in the PENN and NACC cohorts.

Genetic marker		1000 Genome	PENN cohort				NACC cohort			
Marker[1]	Gene	MAF REF[3]	MAF AD	MAF PART	Odds ratio (CI)	*P*-value	MAF AD	MAF PART	Odds ratio (CI)	*P*-value
rs3752246	*ABCA7*	0.19	0.20	0.15	0.65 (0.37–1.08)	0.111	0.20	0.15	**0.7 (0.54–0.9)**	**0.007***
rs28834970	*PTK2B*	0.34	0.39	0.31	**0.71 (0.47–1.05)**	**0.092^**	0.38	0.32	**0.77 (0.63–0.94)**	**0.013****
rs11136000[2]	*CLU*	0.39	0.36	0.33	0.89 (0.6–1.31)	0.572	0.39	0.41	1.16 (0.95–1.42)	0.141
rs10948363	*CD2AP*	0.25	0.29	0.24	0.72 (0.45–1.12)	0.156	0.28	0.28	1.09 (0.87–1.35)	0.451
rs983392	*MS4A6A*	0.42	0.42	0.40	0.93 (0.63–1.34)	0.684	0.37	0.35	0.88 (0.71–1.08)	0.219
rs4938933	*MS4A4A*	0.40	0.42	0.36	0.8 (0.54–1.17)	0.257	0.39	0.37	0.87 (0.72–1.07)	0.185
rs561655	*PICALM*	0.35	0.31	0.44	1.88 (1.26–2.8)	**0.002****	0.34	0.33	0.94 (0.77–1.16)	0.579
rs3851179	*PICALM*	0.37	0.33	0.52	**2.11 (1.44–3.13)**	**<0.001****	0.35	0.36	1.03 (0.85–1.26)	0.741
rs7561528	*BIN1*	0.32	0.35	0.35	0.82 (0.55–1.21)	0.322	0.39	0.30	**0.69 (0.56–0.85)**	**0.001****
rs6733839	*BIN1*	0.38	0.44	0.34	**0.71 (0.48–1.03)**	**0.072^**	0.35	0.25	**0.61 (0.48–0.77)**	**<0.001****
rs6656401	*CR1*	0.17	0.22	0.13	**0.54 (0.31–0.91)**	**0.028***	0.19	0.16	**0.74 (0.56–0.96)**	**0.027***
H1	*MAPT*	0.24	0.22	0.21	0.98 (0.22–3.16)	0.973	0.22	0.24	1.33 (0.73–2.35)	0.339
ε2	*APOE*	0.06	0.04	0.22	**5.82 (2.59–13.1)**	**<0.001****	0.03	0.10	**2.93 (1.94–4.44)**	**<0.001****
ε4	*APOE*	0.16	0.39	0.09	**0.16 (0.08–0.3)**	**<0.001****	0.33	0.11	**0.29 (0.22–0.39)**	**<0.001****

Bold text indicates observed statistically significant associations: *$P < 0.05$ (uncorrected); **$P < 0.0036$ (Bonferroni correction); ^marginally significant at $P < 0.1$.

[1]An additive model was used to evaluate all SNPs (0, 1, or 2 risk alleles) and *APOEε4* and *APOEε2* (0, 1, or 2 APOEε alleles) were coded using an additive model.

[2]proxy SNP with high linkage disequilibrium ($d' > 0.970$) for rs9331896 and rs153278.

[3]Reference minor allele frequencies (MAF) retrieved from 1000 genomes Phase 3 data reported on niagads.org.

PART (MAF = 0.13) compared to AD (MAF = 0.22; OR = 0.54, $P = 0.028$). All three associations were also significant in the NACC cohort analyses (*APOEε4*: OR = 0.16, $P < 0.001$; *APOEε2*: OR = 5.82, $P < 0.001$; rs6656401: OR = 0.74, $P = 0.027$) and combined cohort analyses (see Table S1).

We additionally observed two genotypic associations of marginal significance in the PENN cohort also reflecting lower AD risk in PART patients. These included rs6733839 in the *BIN1* gene (OR = 0.71, $P = 0.072$) that had a reduced frequency for PART (MAF = 0.34) compared to AD (MAF = 0.44) and rs28834970 in the *PTK2B* gene (OR = 0.71; $P = 0.092$) that also had a reduced frequency for PART (MAF = 0.31) compared to AD (MAF = 0.39). Moreover, in the larger NACC cohort both of these genotypes were significantly less frequent for PART compared to AD (rs6733839: OR = 0.61, $P < 0.001$ and rs28834970: OR = 0.77, $P < 0.013$; see Table 2 for MAFs). These were also significant in the combined cohort analyses (see Table S1). One genotype, rs3752246 in the *ABCA7* gene did not differ between PART (MAF = 0.31) and AD (MAF = 0.39) in the PENN cohort (OR = 0.65, $P = 0.111$), but was significantly less frequent for PART compared to AD in the NACC (OR = 0.70, $P = 0.007$; see Table 2 for MAFs) as well as the combined cohort analyses (see Table S1).

Only two genotypes, both in the *PICALM* gene, were associated with an increased frequency of PART compared to AD in the PENN cohort. These included rs561655 (PART MAF = 0.44; AD MAF = 0.31; OR = 1.88; $P = 0.002$) and rs3851179 (PART MAF = 0.52; AD MAF = 0.33; OR = 2.11; $P < 0.001$) but neither of these survived significance in the NACC or the combined cohort analyses.

Table 3. Genetic associations with Braak stage severity of neurofibrillary tau pathology.

		Definite PART		Probable PART		Alzheimer's disease	
Marker	Gene	*B*	*P*-value	*B*	*P*-value	*B*	*P*-value
rs3752246	*ABCA7*	−0.013	0.850	−0.042	0.564	0.021	0.259
rs28834970	*PTK2B*	0.021	0.663	0.024	0.696	−0.001	0.951
rs11136000	*CLU*	−0.006	0.904	0.037	0.498	0.004	0.792
rs10948363	*CD2AP*	0.000	0.993	0.015	0.815	−0.019	0.267
rs983392	*MS4A6A*	−0.038	0.403	−0.086	0.127	−0.019	0.250
rs4938933	*MS4A4A*	**−0.090**	**0.043***	−0.084	0.115	−0.019	0.236
rs561655	*PICALM*	−0.013	0.763	−0.059	0.342	−0.009	0.603
rs3851179	*PICALM*	−0.023	0.602	−0.070	0.225	−0.003	0.860
rs7561528	*BIN1*	0.028	0.591	0.058	0.324	−0.002	0.879
rs6733839	*BIN1*	0.030	0.586	**0.187**	**0.003****	0.008	0.624
rs6656401	*CR1*	0.002	0.977	−0.019	0.804	0.028	0.164
H1	*MAPT*	−0.196	0.151	−0.122	0.430	−0.026	0.611
ε2	*APOE*	0.114	0.115	−0.108	0.286	−0.088	0.064
ε4	*APOE*	−0.001	0.995	**0.209**	**0.008***	**0.056**	**0.001****

Bold text indicates observed statistically significant associations: $*P < 0.05$ (uncorrected); $**P < 0.0036$ (Bonferroni correction of $P < 0.05$); Beta-weights refer to incremental increase in Braak stage tau pathology with each additional genotype risk allele.

Associations with tau pathological stage

An assessment of NFT Braak stage in the combined cohort revealed that *APOEε4* was highly associated with more severe tau in Probable PART ($\beta = 0.209$, $P = 0.008$) and AD ($\beta = 0.056$, $P = 0.001$), but not Definite PART ($\beta = 0.001$, $P = 0.995$) (Table 3). We also observed that rs6733839 in the *BIN1* gene was associated with tau severity in the probable PART group ($\beta = 0.187$, $P = 0.003$), but not in the definite PART ($\beta = 0.30$, $P = 0.586$) or AD ($\beta = 0.008$, $P = 0.624$) groups. There was also a weak, inverse association of rs4938933 in *MS4A4A* of the *MS4A* gene cluster for the Definite PART group ($\beta = -0.090$, $P = 0.043$) but not Probable PART ($\beta = -0.084$, $P = 0.115$) or AD ($\beta = -0.019$, $P = 0.236$).

Discussion

We evaluated differences in patterns of genotypic associations among AD susceptibility loci between two independent samples of autopsy-confirmed PART and AD cases. We identified five genetic risk factors with a different frequency for PART compared to AD, including *APOEε4*, *APOEε2*, rs6656401 in the *CR1* (Complement Receptor-1) gene, rs6733839 in the *BIN1* (Bridging Integrator-1) gene, and rs28834970 in the *PTK2B* (Protein-tyrosine kinase 2-beta) gene. Moreover, *APOEε4* and rs6733839 (*BIN1*) were associated with NFT severity in individuals with Probable PART or AD, which range from mild to severe Aβ burden, but were not associated with tau in Definite PART defined by no Aβ burden. Together, these findings suggest that PART does not share the same genetic variants observed in AD and support the hypothesis that PART can provide a genetic model for both potential Aβ resistance and NFT accumulation. These findings of different genetic profiles in PART and AD additionally support the idea that there are different mechanisms of tau pathophysiology across these conditions.

APOEε4 is the strongest known genetic risk factor for AD and quantitative trait analyses have also established that APOE alleles are associated with increased Aβ plaque and NFT burden.[17] In previous work, it was suggested that *APOEε4* allele frequency is reduced in PART,[5] but this study was criticized for having no direct comparison of PART to AD or across Braak stages[18] and *APOEε2* was not assessed. In this study, we confirm that *APOEε4* frequency is indeed reduced in PART across levels of NFT severity in Definite PART cases, whereas *APOEε2* frequency is higher in PART relative to AD. These findings are consistent with prior observations that *APOEε4* is only significantly associated with NFT severity in individuals with Aβ pathology and not individuals without Aβ pathology.[19] Moreover, our observation that *APOEε4* was associated with NFT severity in Probable PART was likely because these cases by definition have some, albeit minimal, Aβ pathology. This suggests that in future work Probable and Definite PART may be better considered different neuropathological groups with Probable PART reflecting a potential early form of AD, whereas definite PART is independent from the AD continuum. These findings are also consistent with prior claims that *APOEε2* may provide a neuroprotective benefit against the risk of Aβ pathology.[20] While we did not observe a significant association between *APOEε2* and NFT severity in individuals with Aβ pathology (i.e., AD and probable PART) as previously reported,[19] this association approached

significance in a consistent pattern. Importantly, all of our other reported genotype associations were confirmed when controlling for *APOEε4* effects, suggesting that there are additional genetic differences between PART and AD that extend beyond APOEε4.

Prior association studies relating AD genotypes to Aβ pathology have suggested a dose effect for minor alleles in rs6656401 in *CR1* yielding more abundant Aβ plaque accumulation.[6,21] *CR1* expression has been reported to be reduced in homozygous allele carriers and expression has been linked to clearance rate of immune complexes.[22] Our observation of reduced allele frequency for rs6656401 in PART cases who by definition have less abundant Aβ relative to AD, is potentially consistent with the concept that PART may have relative resistance to developing Aβ plaques. In two recent studies, including focused analyses of prior AD-associated variants[23] and a neuropathological GWAS,[17] rs28834970 in the *PTK2B* was not directly associated with AD neuropathology. Thus it is not clear why this risk locus is under-represented in PART relative to AD. The *PTK2B* gene has previously been associated with blocking inflammation and calcium-signaling which are both mechanistic processes that have been evaluated in AD as well.[24] Together, our observation that genotypes in *CR1* and *PTK2B* are under-represented in PART relative to AD is suggestive that PART may reflect enhanced innate immunity relative to AD that leads to potential resistance to both Aβ accumulation and general pathophysiologic processes driving development of AD.

Beyond group-level genotypic differences between PART and AD we observed that rs6733839 in the *BIN1* gene is associated with NFT Braak stage pathology only in the Probable PART group. This SNP, along with other *BIN1* variants, have been associated with NFT pathology in AD,[25,26] but this association was not replicated in two recent studies[17,23] and we failed to observe an association between rs6733839 and NFTs in AD. Nonetheless, our observation suggests that polymorphisms in this gene may only confer increased risk of NFTs in the presence of at least some degree of Aβ, as in the case of Probable PART, or with more significant burden in AD, as suggested by some of this prior work. It follows from this observation that beyond potential Aβ resistance distinguishing PART from AD, the underlying biological factors associated with tau accumulation may also be distinct between these neuropathological conditions. Indeed, we observed an inverse association with NFT pathology that was only present for Definite PART suggesting that there are different mechanisms that support NFT accumulation in the absence (e.g., Definite PART) and presence (e.g., AD, Probable PART) of Aβ neuropathology.

Notably, the minor allele frequencies observed in PART relative to AD are reduced relative to reference control populations (see Table 2), whereas APOEε2 previously hypothesized to be protective[20] has a higher frequency in PART relative to a control reference population. For example, we observed a MAF of 15% for rs6656401 (*CR1*) in the PART cohort, which is not only reduced relative to AD (20%) but also relative to a 17% MAF in the 1000 genome reference cohort. Likewise, *APOEε4* has an allele frequency of approximately 14% in reference cohorts, but only a 10% allele frequency in the combined PART cohort, compared to 34% frequency in the combined AD cohort. This suggests that not only does PART have lower risk of pathological burden relative to AD but also relative to clinical controls, which likely include some at-risk or preclinical AD cases. This raises an important methodological issue related to traditional case-control GWAS in which "controls" are often poorly defined and may include individuals who have genetic risk for AD that obscure potentially large effect sizes. Indeed, in an aging cohort of cognitively normal "controls" more than 40% of individuals had neuropathological evidence of Aβ molecular pathology.[27] While our cohorts are relatively small by GWAS standards, we suspect that we were able to identify distinct genetic characteristics between PART and AD by focusing on well-characterized neuropathological samples. This is consistent with evidence suggesting that risk loci in *APOE, CLU, CR1,* and *PICALM* genes have a enhanced odds ratio when evaluating neuropathologically confirmed AD cases rather than clinical AD cases.[28] Likewise, polygenic risk scores for AD have substantially higher prediction accuracy in neuropathologically confirmed case-control samples (84%) relative to clinically defined samples (79%).[29] Therefore, these convergent observations of enhanced genetic associations using neuropathologically confirmed samples suggest that future studies in AD genetics should more carefully consider selection of control and AD populations.

The conceptualization of PART as a neuropathologically distinct entity from AD[5] has recently been challenged in the literature.[18] Specifically, some neuropathologists have suggested that PART simply reflects a continuum of the AD spectrum and that "no clinical or genetic characteristics permit the differentiation of PART from preclinical/early AD (page 754)[18]". In contrast, our observations of genetic differences between PART and AD across two neuropathological cohorts as well as differences between PART and reference "control" allele frequencies provides direct evidence for several genetic differences between PART and AD and therefore supports the importance for using distinct PART and AD neuropathological criteria.

There are several limitations of this study. We only focused on a hypothesis-driven subset of SNPs

previously associated with AD risk and it will be important to evaluate other novel candidate genotypes that may differ between PART and AD. Broader studies could also explore the degree to which genetic factors influence the degree of NFT burden among PART cases. While we observe several genetic differences between PART and AD, there were also several AD susceptibility loci that did not differ between groups and it is possible that larger scale studies may increase the statistical power to identify additional differences in genetic risk across these two neuropathological groups. To maximize statistical power, we also did not directly assess genotype frequencies across Definite and Probable PART and it will be valuable for larger cohort studies to perform these comparisons. However, if Probable PART with minimal Aβ reflects the AD phenotypic spectrum then our collapsing across PART groups would only make it more difficult to detect group genotypic differences. It is conceivable that probable PART reflects an early form of AD that shares similar genetic characteristics and should not be considered in future evaluations of definite PART neuropathology and genetics. While we also did not evaluate the genotypic frequency of "controls" lacking molecular pathology, this occurs in less than 1% of the aging population[3,4] and therefore future mega-analyses are necessary to evaluate PART and AD genetic risk factors relative to these rare cases. Another potential limitation is variability in neuropathological diagnoses by ADCs in the NACC cohort since not all centers use the same neuropathology methods. Importantly, a recent multicenter validation study of NIA-AA criteria for AD neuropathological criteria demonstrated good-to-excellent agreement among neuropathological ratings across ADCs.[30] Relatedly, future investigations are warranted to assess whether additional mechanisms beyond AD susceptibility loci like Lewy body pathology and vascular comorbidities reported in aging individuals[27] also contribute to biological differences between PART and AD. Lastly, while the observed associations in this study are suggestive of Aβ resistance in PART, as with any other genetic association study, we can only speculate about the functional role of these associations and follow-up cellular and animal studies will be necessary to test PART models.

In conclusion, we posit that genotypic characteristics differ across AD and PART, reflecting a distinct pathological process in which individuals with PART appear to have reduced genetic risk for Aβ and thus resistance to AD. More detailed genetic evaluations, especially focused on definite PART, are necessary to confirm whether NFT risk factors, Aβ resistance, and innate immunity potentially contribute to the neuropathological differences between PART and AD.

Conflict of Interest

McMillan, Jefferson-George, Naj, Van Deerlin, and Trojanowski have nothing to disclose. Lee has received personal fees from GLG Consulting. Wolk has received personal fees and/or grant support from industry partners including Avid Radiopharmaceuticals, Merck, Janssen, and Biogen; all of which are unrelated to this work.

Author Contributions

CTM and DAW involved in conception and design of the study. CTM, EBL, KJ-G, AN, VMVD, JQT, and DAW involved in acquisition and analysis of data.CTM, EBL, KJ-G, AN, VMVD, JQT, and DAW involved in drafting the manuscript or figures.

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Supporting Information

Additional Supporting Information may be found online in the supporting information section at the end of the article:

Data S1. Supplementary genotyping methods of the NACC and PENN cohorts.
Table S1. Categorical associations between PART and AD in the Combined Cohort of NACC and PENN cases.

