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Multiancestry analysis of the HLA locus in Alzheimer's and Parkinson's diseases uncovers a shared adaptive immune response mediated by *HLA-DRB1*04* subtypes

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Across multiancestry groups, we analyzed Human Leukocyte Antigen (HLA) associations in over 176,000 individuals with Parkinson's disease (PD) and Alzheimer's disease (AD) versus controls. We demonstrate that the two diseases share the same protective association at the HLA locus. HLA-specific fine-mapping showed that hierarchical protective effects of *HLA-DRB104 subtypes best accounted for the association, strongest with *HLA-DRB1**04:04 and *HLA-DRB1**04:07, and intermediary with *HLA-DRB1**04:01 and *HLA-DRB1**04:03. The same signal was associated with decreased neurofibrillary tangles in postmortem brains and was associated with reduced tau levels in cerebrospinal fluid and to a lower extent with increased Aβ42. Protective *HLA-DRB1**04 subtypes strongly bound the aggregation-prone tau PHF6 sequence, however only when acetylated at a lysine (K311), a common posttranslational modification central to tau aggregation. An *HLA-DRB1**04-mediated adaptive immune response decreases PD and AD risks, potentially by acting against tau, offering the possibility of therapeutic avenues.**

HLA | Alzheimer's dementia | Parkinson's disease | neurodegeneration | autoimmunity

Alzheimer's disease (AD) and Parkinson's disease (PD) are responsible for considerable morbidity and mortality. Pathophysiology involves the accumulation of tau (neurofibrillary tangles) and Amyloid-β-rich aggregates (amyloid plaques) in AD, and α-synuclein-rich aggregates (Lewy bodies) in PD, although copresence of these aggregates may occur. Consensus is growing that tau may also play a key role in PD (1–3).

Innate immune responses and microglial involvement have long been implicated in neurodegenerative diseases (4–6). More recently, a role for adaptive immunity in PD and AD has also been outlined through genetic (7–10) and immunological studies (11–15). Notably, comparisons of healthy controls and individuals with neurodegenerative diseases have shown that a complex polyclonal T cell response develops against α-synuclein, and tau (11–13). Whether or not these responses are epiphenomenal, contribute to, or protect against neurodegeneration is unknown.

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A cornerstone of the adaptive immune response is the highly polymorphic HLA (Human Leukocyte Antigen) locus located on human chromosome 6. *HLA* genes encode a set of proteins that bind peptides derived from foreign or self-antigens, allowing recognition by T cells and subsequent coordination of immune responses. In this context, PD (8) and AD (10) have genome-wide associations in the HLA class II region, within a region containing HLA-DR and DQ, two tightly linked sets of genes. Depending on one's specific HLA, individuals present distinct repertoires of bound peptides to CD4+ T cells, thus HLA establishes how the immune system sees and reacts to foreign and self-antigens in different individuals.

In PD genome-wide association studies (GWAS), the HLA signal was initially attributed to *HLA-DRA, HLA-DRB1*15:01,* and *HLA-DRB5* (8), but recent studies indicate it marks *HLA-DRB1**04 (16–18). In AD, the HLA signal remains uncharacterized (7, 9, 19) or was assigned to *HLA-DRB1**15:01 (7). *SI Appendix*, Table S1 provides a list of previous studies reporting association results at the HLA locus in genetic association studies of AD and PD.

To better understand the involvement of HLA in these diseases, we first gathered genome-wide data available in PD and AD, refined the signal to the HLA subtype level through HIBAG imputation (20), and performed HLA haplotyping to disentangle causal alleles. HLA signals are best dissected across ancestry groups, due to the high variability of HLA alleles across ancestry, as first shown in narcolepsy (21). Therefore, we gathered a large and diverse set of participants including Europeans (10, 17), Asians (22–24), Latin Americans (25), and African Americans (26, 27) to perform fine-mapping of the HLA association in AD and PD. Second, we studied HLA association with pathological observations, finding the strongest protective associations with tau-associated biomarkers. Last, we tested the binding of HLA alleles associated with AD and PD, with epitopes from alpha-synuclein and tau, identifying potential epitopes mediating these effects.

Results

Multiancestry Local-GWAS of AD and PD and Colocalization at the HLA Locus. In our AD local-GWAS, 110,927 cases and proxy-cases, and 423,415 controls were included in the meta-analysis (*SI Appendix*, Table S2). Separate analyses were carried out per ancestry and per dataset and meta-analyzed at the HLA locus, with the full GWAS of European and Japanese cohorts now published separately with publicly available summary statistics (10, 24). The most significant association with AD was at rs35472547 (odds ratio [OR] = 0.91; 95% CI, [0.89; 0.93]; $P = 9.7 \times 10^{-23}$, *SI Appendix*, Fig. S1). In our PD local-GWAS, 41,205 cases and proxy-cases and 474,597 controls were included in the meta-analysis (*SI Appendix*, Table S2). Summary statistics from three published studies (8, 22, 25) were included in this meta-analysis at the HLA locus. The most significant association with PD was at rs504594 (OR = 0.84; 95% CI, [0.80; 0.88]; $P = 1.83 \times 10^{-13}$, *SI Appendix*, Fig. S1). Colocalization analysis emphasized that the same HLA association signal is shared across AD and PD (posterior probability of colocalization, PP4 = 99.5%, Fig. 1), with rs601945 common to the two GWAS and lead variant in their combination. *SI Appendix*, Figs. S3 and S4 provide locus zoom plots per ancestry of the AD and PD local-GWAS.

Same Protective HLA Association in Other Neurodegenerative Diseases. Amyotrophic lateral sclerosis (ALS) GWAS (9) recently reported a genome-wide significant protective association at the HLA locus. Our colocalization analysis shows that this association is shared with AD and PD (PP4 = 94.6%, and PP4 = 60.6%, respectively, Fig. 1 and *SI Appendix*, Fig. S1). The largest Lewy body dementia (LBD) GWAS (28) to date did not contain a genome-wide significant peak at the HLA locus. However, querying rs601945 in this GWAS summary statistics, we noted an association with decreased LBD risk close to nominal significance (OR = 0.91; [0.83; 1.01]; $P = 0.07$) and in the same range as observed in AD and PD, suggesting that a larger sample size may lead to a similarly shared protective association.

Fine-Mapping of the HLA Association—Allele-, Haplotype-, Amino Acid–Level Analyses—Highlights Association with *HLA-DRB104 Alleles.** Our HLA-fine-mapping analysis includes a slightly different set of individuals than the local-GWAS. In the AD analysis, 121,411 cases and proxy-cases and 409,096 controls were included (*SI Appendix*, Table S3). In the PD analysis, 55,554 cases and proxy-cases and 1,454,443 controls were included (*SI Appendix*, Table S3). Briefly, all associations were tested under a dominant model as HLA effects are mostly dominant; the presence or absence of an allele allows for recognition of epitopes. All HLA associations from allele-, haplotype-, and amino acid–level analyses

Significance

We report that specific *HLA-DRB1**04 alleles are protective against Alzheimer's dementia (AD), Parkinson's disease (PD), and other neurodegenerative disorders. Further, we found that these HLA (Human Leukocyte Antigen) subtypes selectively bind a piece of Tau crucial to aggregation but only when it is acetylated (a-PHF6). This a-PHF6 piece is significant as it is a common posttranslational modification of Tau found in Alzheimer's brains. Only when someone is *HLA-DRB1**04:04 or *HLA-DRB1**04:01 can PHF6 be presented as a T cell epitope to T cell receptors and mount a memory immune response against this pro-aggregation fragment. This immune response would protect against AD, PD, and neurodegeneration, explaining the HLA association. Vaccination with a-PHF6 in *HLA-DRB1**04 individuals could have preventive effects.

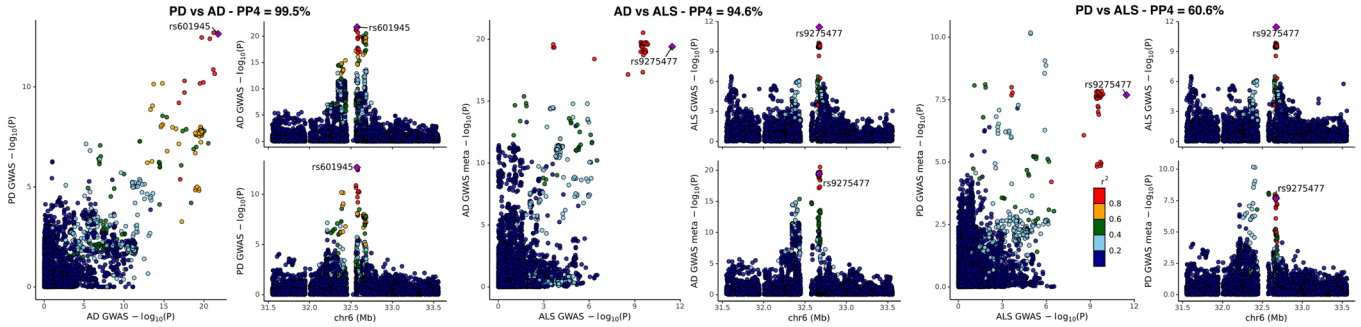

Fig. 1. Colocalization of the HLA locus signal in AD, PD, and ALS. PP4: posterior probability of colocalization.

are reported in *SI Appendix*, Tables S4 and S5, respectively, for AD and PD, with key findings highlighted in Table 1 and details per cohort in Datasets S1–S5.

In the HLA-allele-level analysis, the most significant association in AD was observed for *HLA-DQB1**03:02 (OR = 0.89[0.86; 0.91]; P = 1.2E-19), which was the second most significant allele in PD (OR = 0.91[0.88; 0.93]; P = 2.6E-14). In PD, the most significant association was observed for *HLA-DQA1**03:01 (OR = 0.89[0.87; 0.91]; P = 2.3E-20), which was the second most significant allele in AD (OR = 0.89[0.87; 0.91]; P = 1.7E-18). In both AD and PD, *HLA-DRB1**15:01 only had a marginal effect (Table 1). It is worth noting that *HLA-DQA1**03:01 and *DQB1**03:02 are in high linkage disequilibrium and typically found on haplotypes harboring *HLA-DRB1**04 subtypes. Because *HLA-DRB1**04 alleles are numerous and have more variations, each individually is less common than *HLA-DQA1**03:01 and *DQB1**03:02; thus, the strength of this association may reflect the sum of *HLA-DRB1**04 subtype association.

This is particularly clear in the HLA-haplotype-level analysis, where haplotypes harboring *HLA-DRB1**04 subtypes are most significant (Table 1 and *SI Appendix*, Tables S4 and S5). The two significant haplotypes in linkage with DQA1*03:03~DQB1*03:01 are the most interesting since they advocate against the causality of DQA1*03:01~DQB1*03:02 (Fig. 2). Finally, DQA1*03:01~DQB1*03:02~DRB1*08:02, relatively common in East-Asian populations, does not show any association (Fig. 2), which also argues against DQA1*03:01~DQB1*03:02 causality. Overall, the data suggest hierarchical protective effects of *HLA-DRB1*04* subtypes, with *04:04 and *04:07 having the strongest effects on disease protection than other subtypes (Table 1), followed by weaker effects of *04:01, *04:06, and *04:03, and no effect of *04:05.

Last, the HLA-amino acid–level analysis emphasized the pair of *HLA-DRB1* amino acids H13 and H33 as the most significant amino acid changes associated with AD and PD risks (H13 association with AD: OR = 0.91[0.89; 0.93]; P = 1.7E-18; and with PD: OR = 0.89[0.87; 0.91]; P = 9.3E-22). This pair of amino acid changes is in complete linkage disequilibrium across ancestries and present on all *HLA-DRB1**04 subtypes. It is worth emphasizing that the lead variant in the local-GWAS (rs601945) is also in high linkage disequilibrium with these amino acids (D′ close to 1 in Europeans and East-Asians, and R^2 above 0.9 in Europeans, *SI Appendix*, Fig. S4). Importantly, no significant heterogeneity in effect sizes between AD and PD was observed (Table 1), as formally tested using heterogeneity tests at each allele, haplotype, and amino acid.

Conditional Analyses Suggest a Shared Association Signal at HLA across AD and PD. A subset of the participants analyzed with HLA-fine-mapping was also available for conditional analyses using the lead variant (rs601945) and lead amino acid (*HLA-DRB1* H13). In the AD analysis, 120,403 cases and proxy-cases and 408,720 controls were included (*SI Appendix*, Table S6). In the PD analysis, 41,515 cases and proxy-cases and 518,923 controls were included (*SI Appendix*, Table S6). Four conditional analyses were implemented i) local-GWAS conditioned on rs601945, ii) local-GWAS conditioned on *HLA-DRB1* H13, iii) HLA-class II amino acid level conditioned on rs601945, and iv) HLA-class II amino acid level conditioned on H13 (*SI Appendix*, Tables S7 and S8). Overall, the main signal colocalized at the HLA locus across AD and PD disappeared after conditional analyses. Of note, however, whereas no other signals were observed in PD, two independent signals remained genome-wide significant in AD after conditional analysis (*SI Appendix*, Fig. S5). The first significant signal is between *BTLN2* and *HLA-DRA* at lead variant rs3129841 (OR = 0.94[0.92; 0.96]; P = 1.0E-08), while the second is between *HLA-DQB1* and *HLA-DQA2* at lead variant rs9275222 (OR = 1.05[1.03; 1.07]; P = 6.6E-09). In the HLA-class II amino acid–level conditional analyses, no significant associations were observed in PD (*SI Appendix*, Table S8), while in AD there were several significant associations when conditioning on H13 (*SI Appendix*, Table S7). The two most significant ones were *HLA-DRB1* amino acid changes, N37 (OR = 0.94[0.92; 0.96]; P = 6.0E-08) and H32 (OR = 0.94[0.92; 0.96]; P = 9.3E-08). However, given the location of the two AD peaks in the conditional analysis (*SI Appendix*, Fig. S5), it seems unlikely that these will be related to these amino acid changes, and other regulatory mechanisms should be explored. In conclusion, the HLA signal in AD is likely more complex than initially described. However, conditional analyses confirmed a shared signal across AD and PD, and this main common signal was the only one pursued in all additional analyses.

***HLA-DRB1* H13/H33 Is Associated with Decreased Tau Braak Staging.** How could an *HLA-DRB1**04 subtype-specific association be involved in AD? To investigate this question, we first used neuropathological information from 7,259 postmortem samples of European ancestry available through the Religious Orders Study and Memory and Aging Project (29) and the National Institute on Aging–AD Center cohorts 1 to 7 (30), looking at the effect of *HLA-DRB1* on tau Braak staging and neuritic plaque density in pathological samples. As shown in Table 2, a significant association of *HLA-DRB1* H13/H33, with decreased neurofibrillary tangles (β = −0.13, 95% CI, [−0.21; −0.05]; P = 0.001), but not neuritic plaque density (β = −0.04, 95% CI, [−0.10; 0.02]; P = 0.19), was observed, suggesting the involvement of tau. Due to linkage disequilibrium, the same associations were observed for rs601945, and by extension for *HLA-DRB1**04 alleles (*SI Appendix*, Tables S9 and S10). Last, in a subset of autopsied individuals with either Lewy Body pathology, AD pathology, or both pathologies, we tested the association of rs601945 with each pathology group versus pathology-free controls. In this comparison, rs601945 was

Table 1. *HLA-DRB1* alleles *HLA-DRB104:04 and *HLA-DRB1**04:01 are associated with a decreased risk of Parkinson's and ADs**

		PD				AD				PD + AD		
	HLA	FreqC	N	OR	*P*-val	FreqC	N	OR	*P*-val	OR	*P*-val	p-het
HLA Alleles	*HLA-DRB1**04:01	0.196	1,484,656	0.92[0.89; 0.95]	2.4E-08	0.191	486,478	0.93[0.9; 0.96]	6.4E-07	0.92[0.91; 0.94]	8.9E-14	0.56
	*HLA-DRB1**04:02	0.019	1,474,730	0.92[0.85; 0.99]	0.02	0.022	155,846	1.00[0.91; 1.10]	0.99	0.95[0.89; 1.01]	0.07	0.17
	*HLA-DRB1**04:03	0.012	980,868	0.89[0.81; 0.97]	0.01	0.072	7,587	1.09[0.91; 1.30]	0.34	0.93[0.85; 1.01]	0.07	0.04
	*HLA-DRB1**04:04	0.074	1,475,574	0.84[0.80; 0.88]	1.5E-11	0.073	476,236	0.86[0.82; 0.90]	8.9E-12	0.85[0.82; 0.88]	9.3E-22	0.60
	*HLA-DRB1**04:05	0.013	1,507,057	1.00[0.95; 1.05]	0.86	0.026	169,080	0.98[0.91; 1.06]	0.62	0.99[0.95; 1.03]	0.68	0.75
	*HLA-DRB1**04:06	0.046	32,327	0.95[0.82; 1.09]	0.46	0.058	7,587	0.95[0.78; 1.15]	0.60	0.95[0.85; 1.06]	0.37	0.99
	*HLA-DRB1**04:07	0.021	526,189	0.79[0.69; 0.91]	7.3E-04	0.019	474,840	0.88[0.81; 0.96]	4.5E-03	0.86[0.79; 0.92]	2.7E-05	0.18
	*HLA-DRB1**04:10	0.041	4,853	0.91[0.67; 1.25]	0.57	0.031	7,985	1.23[0.94; 1.59]	0.13	1.08[0.89; 1.32]	0.42	0.16
	*HLA-DRB1**01:01	0.181	1,485,033	1.05[1.01; 1.09]	7.0E-03	0.186	487,120	1.07[1.04; 1.10]	3.9E-07	1.06[1.04; 1.09]	1.3E-08	0.44
	*HLA-DQB1**03:02	0.191	1,501,065	0.91[0.88; 0.93]	2.6E-14	0.190	510,130	0.89[0.86; 0.91]	1.2E-19	0.90[0.88; 0.91]	4.7E-32	0.23
	*HLA-DQA1**03:01	0.177	1,507,147	0.89[0.87; 0.91]	2.5E-20	0.186	507,263	0.89[0.87; 0.91]	1.8E-19	0.89[0.88; 0.91]	3.E-37	0.79
	*HLA-DRB1**15:01	0.272	1,507,057	1.06[1.03; 1.10]	5.0E-04	0.263	485,383	1.02[0.99; 1.04]	0.13	1.03[1.01; 1.05]	1.1E-03	0.054
HLA Haplotypes	DRB1*04:01~DQA1*03:01~DQB1*03:02	0.088	1,473,386	0.95[0.92; 0.98]	3.6E-03	0.092	342,115	0.91[0.87; 0.95]	6.5E-06	0.93[0.91; 0.96]	3.2E-07	0.10
	DRB1*04:01~DQA1*03:03~DQB1*03:01	0.12	1,481,518	0.98[0.97; 0.99]	5.2E-04	0.133	346,157	0.98[0.94; 1.02]	0.36	0.98[0.97; 0.99]	3.4E-04	0.86
	DRB1*04:04~DQA1*03:01~DQB1*03:02	0.077	1,475,734	0.84[0.80; 0.89]	1.7E-10	0.086	344,760	0.85[0.81; 0.89]	5.4E-11	0.85[0.82; 0.88]	5.7E-20	0.78
	DRB1*04:07~DQA1*03:01~DQB1*03:02	0.198	1498	0.58[0.44; 0.76]	6.1E-05	0.063	1,865	0.75[0.47; 1.21]	0.23	0.62[0.49; 0.78]	4.6E-05	0.36
	DRB1*04:07~DQA1*03:03~DQB1*03:01	0.021	524,845	0.87[0.73; 1.04]	0.12	0.017	340,065	0.87[0.79; 0.97]	8.0E-03	0.87[0.80; 0.95]	2.1E-03	0.99
	DRB1*04:05~DQA1*03:03~DQB1*04:01	0.11	35,369	0.99[0.92; 1.06]	0.76	0.21	4,149	0.97[0.83; 1.13]	0.68	0.99[0.92; 1.05]	0.65	0.81
	DRB1*08:02~DQA1*03:01~DQB1*03:02	0.026	5,602	1.10[0.76; 1.60]	0.61	0.02	4,149	0.85[0.55; 1.31]	0.46	0.99[0.74; 1.31]	0.93	0.37
	DRB1*01:01~DQA1*01:01~DQB1*05:01	0.150	1,485,406	1.05[1.01; 1.09]	0.02	0.222	351,276	1.08[1.05; 1.11]	4.8E-07	1.07[1.04; 1.09]	6.8E-08	0.27
Amino acid:	*HLA-DRB1* 13H/33H	0.300	1,507,057	0.89[0.87; 0.91]	9.3E-22	0.315	527,173	0.91[0.89; 0.93]	1.7E-18	0.90[0.89; 0.92]	2.0E-38	0.36

Effect sizes are reported as odds ratio (OR), with 95% CI, and significance (*P*-value). FreqC: frequency of carriers, N: number of individuals analyzed for a given allele/haplotype/amino acid, p-het: heterogeneity test *P*-value.

associated with reduced AD only pathology (OR = 0.81[0.69; 0.96], $P = 0.01$) and concordant protective effects in the Lewy Body only pathology group (OR = 0.84[0.69; 1.03], $P = 0.09$) and in the dual pathology group (OR = 0.81[0.59; 1.09], $P = 0.16$), though the last two associations were not significant due to smaller sample sizes in these groups (*SI Appendix*, Table S10).

***HLA-DRB1* H13/H33 Is Associated with Decreased Tau in CSF and Increased Age-at-Onset.** The analysis of cerebrospinal fluid (CSF) Aβ42 and tau levels in 8,074 subjects of European ancestry independently confirmed this observation (Table 2 and *SI Appendix*, Table S10). In CSF, HLA-DRB1 H13/H33 was significantly associated with lower levels of phosphorylated- and total-tau (for total tau, β = −0.11, 95% CI, [−0.17; −0.05]; $P = 0.0006$), but the association with increased Aβ42 levels was less significant (β = −0.08, 95% CI, [−0.14; −0.02]; $P = 0.02$). Interestingly, HLA-DRB1 H13/H33 was also associated with older age-at-onset in AD (β = 0.39, 95% CI, [0.03; 0.76]; $P = 0.03$), as also previously reported in PD (31), further supporting a protective role.

In Vitro Test of *HLA-DRB1*04* Subtypes Binding to Tau and Alpha-Synuclein Peptides Emphasizes the Differential Binding of *HLA-DRB104 to Acetylated PHF6 Tau.** Based on these results, we hypothesized that an *HLA-DRB1**04-restricted adaptive immune response directed against tau may be protective in AD.

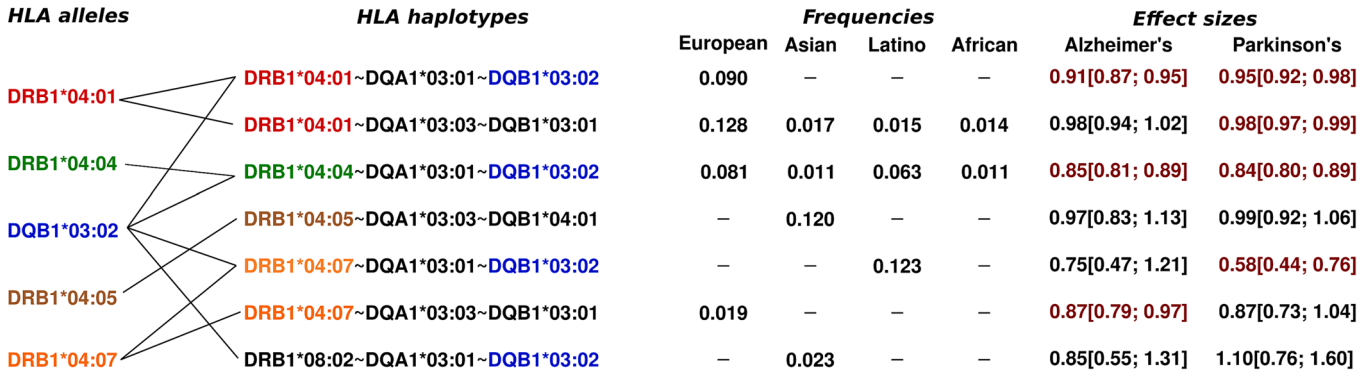

Fig. 2. Haplotypes harboring key *HLA-DRB1**04 subtypes and/or *HLA-DQB1**03:02. Effect sizes highlighted in red were nominally significant ($P < 0.05$).

Table 2. *HLA-DRB1* H13/H33 amino acid is associated with reduced tau and neurofibrillary tangles and to a lesser extent with reduced Amyloid-β or neuritic plaques, when testing their association with AD neuropathology and CSF biomarkers

		DRB1 H13			
	Phenotype	N	Freq	β [95% CI]	*P* val
All individuals	Tau Braak staging	7,456	0.293	−0.13[−0.21; −0.05]	1.4E-03
	Neuritic plaques density	5,876	0.292	−0.04[−0.10; 0.02]	0.19
	total-tau in CSF	5,289	0.232	−0.11[−0.17; −0.05]	5.5E-04
	p-tau in CSF	5,269	0.234	−0.08[−0.14; −0.02]	1.0E-02
	Aβ42 in CSF	5,368	0.232	0.08[0.01; 0.14]	0.02
Cases only	Tau Braak staging	5,126	0.283	−0.07[−0.12; −0.01]	0.02
	Neuritic plaques density	4,124	0.289	−0.01[−0.04; 0.02]	0.39
	total-tau in CSF	–	0.228	−0.14[−0.23; −0.06]	8.2E-04
	p-tau in CSF	–	0.228	−0.10[−0.19; −0.01]	0.02
	Aβ42 in CSF	–	0.227	0.09[0.02; 0.16]	1.0E-02
	Age-at-AD-onset	11,900	0.278	0.39[0.03; 0.76]	0.03

p-tau: phosphorylated tau, t-tau: total tau, N: number of individuals, MAF: minor allele frequency, OR: odds ratio, β: parameter estimate, CI: confidence interval. Braak: Tau Braak staging, Neur: Neuritic plaques density.

To test this hypothesis, we screened the entire tau protein for *HLA-RB1**04 subtype-specific binding, using the highly protective *HLA-DRB1**04:04 subtype, the moderately protective *HLA-DRB1**04:01 subtype, and the neutral *HLA-DRB1**04:05 subtype (Fig. 3). Because tau is extensively modified posttranslationally, all most frequent posttranslational modified (PTM) changes (32) were also included, totaling 448 peptides (*SI Appendix*, Table S11). As a control, alpha-synuclein, another extensively PTM protein involved in PD was also tested (*SI Appendix*, Fig. S6) for a total of 62 peptides (*SI Appendix*, Table S12).

Among tested peptides (*SI Appendix*, Tables S11 and S12), only a few peptides strongly bound *HLA-DRB1**04 subtypes, with PHF6 in tau (R3/wt; ^{306}VQIVY(acetylK)PVDLSKV^{318}) standing as the main candidate (Fig. 3). Most interestingly, PHF6 sequences only bind *HLA-DRB1**04 when K311 is acetylated (titration repeated 3 times, *SI Appendix*, Fig. S8). Two-way repeated measure ANOVA comparing HLA binding to unacetylated versus acetylated PHF6 was significant for *HLA-DRB1**04:01, and *HLA-DRB1**04:04 ($p_{DRB1*04:01} = 3.58 \times 10^{-8}$, $p_{DRB1*04:04} = 1.19 \times 10^{-4}$, *SI Appendix*, Table S13). Additionally, acetylated sequences have significantly less affinity for *HLA-DRB1**04:05 versus other subtypes (*HLA-DRB1**04:04= *HLA-DRB1**04:01> *HLA-DRB1** 04:03> *HLA-DRB1**04:06> *HLA-DRB1**04:05), the same hierarchy observed in the case/control association results, with cores predicted to bind most strongly *HLA-DRB1**04:04 (*SI Appendix*, Fig. S7) (33, 34). Additional PTMs in the area, such as acetylated K317, do not alter binding, although the presence of phosphoserine at S305, another frequent PTM, slightly reduces PHF6 binding (Fig. 3). Other peptides were found to bind *HLA-DRB1*04* in both tau (Fig. 3) and α-synuclein (*SI Appendix*, Fig. S6), but in no other case was a PTM necessary for epitope binding.

In Silico Predictions Confirm *HLA-DRB104 Subtypes as the Unique Common *HLA-DRB1* Alleles Binding to PHF6 Tau.** In-silico predictions confirm that *HLA-DRB1**04-associated subtypes are the *only* frequent HLA-DRB1 and DQ subtypes with predicted high affinity for the PHF6 (*SI Appendix*, Fig. S9), likely explaining why *HLA-DRB1**04, and no other subtypes, mediate this effect. In-silico predicted binding to the PHF6 motif was also observed with accessory gene *HLA-DRB4**01 (*SI Appendix*, Fig. S9). This PHF6/*HLA-DRB4**01 strong binding was confirmed in vitro (*SI Appendix*, Fig. S10), but the absence of AD or PD association with *HLA-DRB1**07:01 and *HLA-DRB1**09:01, whose haplotypes are in linkage with *HLA-DRB4**01, ruled out its involvement (*SI Appendix*, Table S14). Last, an absence of predicted binding to PHF6 for DQA1*01:01~DQB1*05:01 or DQA1*03:01~DQB1*03:02 was notable (*SI Appendix*, Fig. S9) and we confirmed this prediction by testing binding in vitro *SI Appendix*, Fig. S10.

Discussion

Here, we show that HLA *HLA-DRB1**04 protects against AD, PD, and probably ALS, three prototypical neurodegenerative diseases and that *HLA-DRB1*04* selectively binds the K311-acetylated epitope of the PHF6 sequence of the microtubule-associated protein tau (35), an important region in the mediation of tau aggregates. Presence of *HLA-DRB1**04 was also associated with lower CSF tau and fewer neurofibrillary tangles in AD subjects. Although tau aggregation is unlikely to be the sole contributor to neurodegeneration in all these diseases, it may exacerbate pathology in the presence of other aggregates, as has been proposed previously (36, 37).

Tau, like other proteins involved in neurodegeneration, is highly posttranslationally modified (PTM) through e.g. phosphorylation and acetylation, phenomena that likely predispose tau to aggregation (32). In autoimmune diseases, PTMs frequently form part of culprit autoantigens, contributing to reduced self-tolerance as they are not presented in the thymus for negative selection (38). This likely explains the strong polyclonal T cell response observed in controls and AD/PD patients against tau, β-amyloid, and α-synuclein (11, 13, 39). A similarly broad B cell response against tau and α-synuclein is also reported in controls and patients (14, 15). As mentioned above, prior work has outlined strong polyclonal $CD4^+$ T cell responses against α-synuclein, β-amyloid, and tau peptides when presented by various HLA subtypes in both cases and controls, thus it is unclear if these responses are effective in limiting disease or are a simple bystander effect (11).

A recent study in humans showed presence of $CD4^+$ and $CD8^+$ T cells in the CSF of PD and AD patients (40), suggesting $CD8^+$ T cell–mediated clearing of amyloid plaques, or a response contributing to neuronal damage. Similarly, Wang et al. recently showed that a microglia-mediated T cell infiltration drives neurodegeneration in a mouse model with tau aggregates; the nefarious adaptive immune response was not observed in mice with amyloid deposition (41). These data suggest that T and B cell responses against tau are common and robust. In our case, we

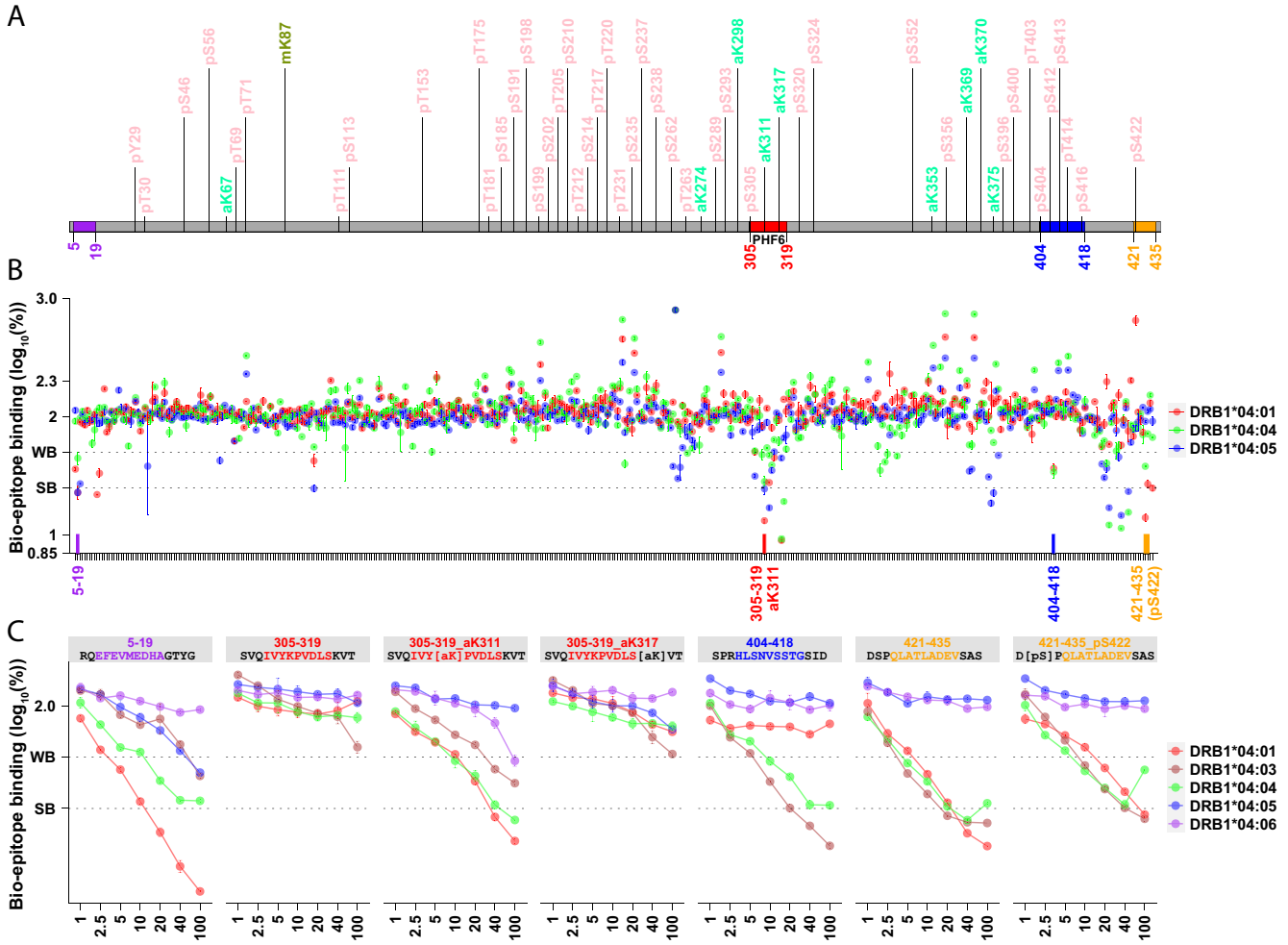

Fig. 3. The pro-aggregation PHF6 region of tau binds *HLA-DRB1**04 subtypes only when acetylated at K311. Fifteen-mer peptides (800 μM) encompassing the entirety of all tau isoforms (schematized in panel *A*), overlapping across 11 residues, were screened for HLA-DRB1*04:01, HLA-DRB1*04:04 and HLA-DRB1*04:05 binding (*Methods*), with and without common PTMs as reported by Wesseling et al. (32). Four regions (labeled in purple, red, blue, orange, panel *B*) containing strong HLA-DRB1*04 binders (log displacement <1 to 1.4, below 25% of baseline control) were further tested at various concentrations (panel *C*), showing three promising regions where binding was stronger with HLA-DRB1*04:04/ HLA-DRB1*04:01, intermediary with HLA-DRB1*04:03 and absent or weak with HLA-DRB1*04:05 and HLA-DRB1*04:06, a pattern similar to GWAS risk (Table 1). Among these candidate regions, PHF6 ^{306}VQIVY(acetylK)PVDLSK^{317} is the only one that strongly binds HLA-DRB1*04:01, HLA-DRB1*04:03, and HLA-DRB1*04:04 and only when posttranslationally modified at K311. This segment is well known to seed tau aggregation, and this process is increased in the presence of acetylK311. Outcompeting a biotinylated epitope (known binder) 75% and 50% is considered as strong binding (SB) and weak binding (WB), respectively. Predicted binding cores are highlighted correspondingly.

hypothesize that a specific *HLA-DRB1**04 restricted response, unlike other adaptive immune responses that may be pathological, targets a particular tau epitope important for the pathological conformation of tau and/or the spreading of aggregates, resulting in a protective effect (*SI Appendix*, Fig. S7). Interestingly, this may be critical to AD, PD, ALS, and other neurodegenerative diseases but not to 4R Tauopathies such as CBD and PSP, given that no large HLA signal has been reported in small sample GWAS of CBD and PSP (42). In line with this hypothesis, in CBD and PSP, acetyl-K311 may not be involved as polyclonal anti-acetyl-K311 antibodies do not recognize the associated tau aggregates (unlike in Pick's disease and AD, which are 3R or mixed 3/4R pathologies) (43). Further, CryoEM observations suggest that acetyl-K311 is critical to the formation of helical filaments of AD (mix of 3R/4R tau) (44), but not of tau fibrils of CBD (4R tau) (44).

The fact that *HLA-DRB1**04 only binds acetylated forms of PHF6 also supports the involvement of this epitope in the protective effect of *HLA-DRB1**04 in AD. With K317 located nearby, the K311 PTM of PHF6 is the most differentiating tau PTM found in AD versus control brains. Further, K311 acetylation has been shown by multiple investigators to promote aggregation of PHF6 in vivo (45), in vitro (46) and in silico (43), while K311 carbamylation is inhibitory (47). Crystallography studies have also shown that acetylated PHF6 dominates in the formation of long fibrils as in neurofibrillary tangles of AD (44, 48). PHF6 is also present in all other known forms of tau aggregates identified to date by cryoEM (49–51). It is also needed for all RT-Quick assays of tau (52). Finally, *HLA-DRB1**04-associated subtypes are the only frequent HLA-DRB1 and DQ subtypes with predicted high affinity for this epitope (*SI Appendix*, Fig. S9), likely explaining why *HLA-DRB1**04, and no other subtypes, mediate this effect. An absence of binding for DQA1*01:01~DQB1*05:01 or DQA1*03:01~DQB1*03:02 is for example notable and reported in *SI Appendix*, Fig. S10. Acetylation at the K311 tau residue may be mediated by SIRT1 and/or HDAC6, current therapeutic targets in AD (45, 53). Similarly, recent evidence suggests that reducing acetylated tau is neuroprotective in brain injury (54).

K311 is not only acetylated, but also methylated, ubiquitinated (32, 55), or succinylated (56), and the epitope is trafficked to the NLRP3 inflammasome of microglial cells (57), where HLA class II presentation of tau fragments by *HLA-DRB1**04 to T cells is also likely to occur (58). The involvement of microglial cells in

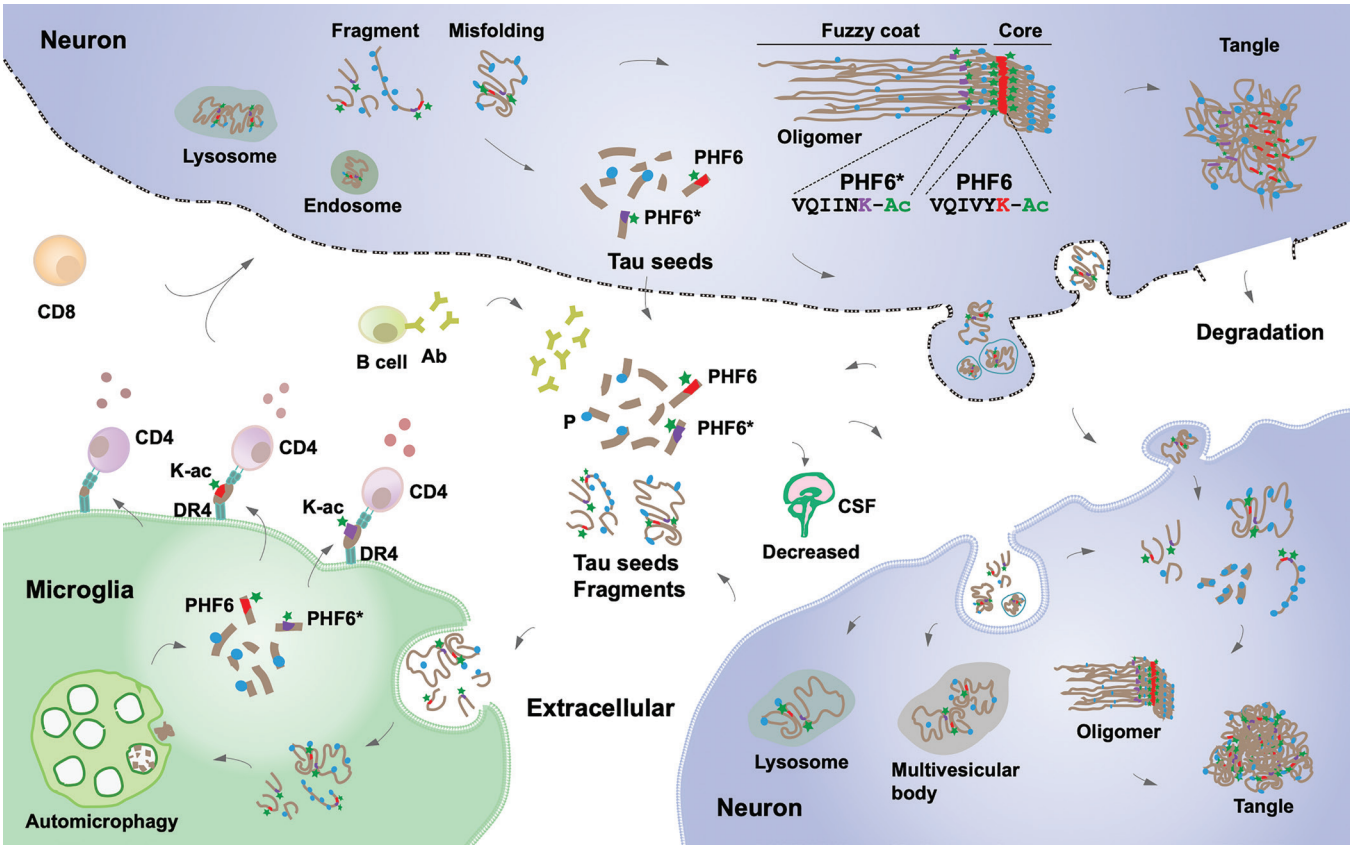

Fig. 4. Immune clearance of Acetylated PHF6 tau sequences may reduce neurodegeneration in AD and PD. Pathological tau seeds, soluble tau fragments, or misfolded tau present in the extracellular space are taken up and phagocytosed by activated microglia where it is processed. In addition to autophagy, resulting tau peptide fragments, notably acetylated lysine (K-ac) 311 PHF6 are bound to HLA-DRB1*04:01 or HLA-DRB1*04:04 and the resulting HLA-peptide complexes presented by microglial cells (or other antigen presenting cells) to $CD4^+$ T helper cells. $CD4^+$ T cells trigger beneficial downstream immune responses perhaps involving $CD8^+$ T and antibody producing B cells. These responses limit propagation of misfolded tau and reduce neuropathology, also explaining reduced CSF tau in *HLA-DRB1**04 individuals.

antigen processing and presentation is also suggested by various GWAS association signals observed in AD (4) and PD (5). Although the ubiquitinated K311 epitope is unlikely to bind *HLA-DRB1**04 due to steric hindrance at P4, ubiquitination at K317 at P10 could further modulate *HLA-DRB1**04 binding and the effect of K311 succinylation or methylation on DRB1*04 binding is unknown. Additional experiments exploring *HLA-DRB1**04 subtype binding of PTM segments of PHF6 in various combinations will be needed to further this line of investigation.

Overall, our results indicate that an *HLA-DRB1**04-subtype-specific adaptive immune response is protective against both AD and PD. The association with PD is more unexpected, but is in line with recent experiments implicating tau in human PD and in α-synuclein animal models of the disease (1–3, 59). For example, a large inversion that includes the *MAPT* gene encoding tau, is associated with PD (8, 60) and to a lesser extent with AD (10). These and associated polymorphisms are known to modulate tau levels (61), although other effects could be involved as the genetic inversion affects multiple genes and has pleiotropic effects (62, 63). Finally, tau has been involved in multiple other neurodegenerative diseases (37) and in chronic traumatic encephalopathy as well, suggesting it could be a cofactor in multiple brain diseases (64).

Although it is impossible to exclude the involvement of proteins other than tau in the *HLA-DRB1**04 observed effect, CD4+ T cell reactivity toward PHF6 fragments containing the acetylated K311 epitope of tau is a strong candidate for mediating most of the effect (Fig. 4). In vitro assays did not yield strong candidates for DRB1*04-mediated effects in alpha-synuclein (for example within the aggregation prone region), although we did identify a strong binding in the C terminus, whose truncation (65) or phosphorylation (66) could additionally modulate alpha-synuclein aggregation. Our results also open the possibility that targeting tau epitopes containing acetylated-K311 through chimeric antigen receptor T cells or antibodies could have therapeutic values. Further, vaccination with acetylated PHF6-like epitopes could reduce disease progression in *HLA-DRB1**04 individuals (~20 to 30% of the population across ancestries). It is noteworthy that antibodies, although not targeting acetylated-K311 per se, but adjacent regions within PHF6, were shown to reduce CSF tau and tau pathology in animal models (67) and are being tested as a means of preventing autosomal dominant forms of AD (68).

Methods

Samples. Participants or their caregivers provided written informed consent in the original studies. The current study protocol was granted an exemption by the Stanford University institutional review board because the analyses were carried out on deidentified, off-the-shelf data; therefore, additional informed consent was not required.

The AD samples included in the HLA fine-mapping analysis are part of the following datasets with phenotype, genotype ascertainment, and quality control described elsewhere (7, 10, 23, 24, 26, 69–71): the European AD BioBank (EADB), The Genome Research @ Fundació ACE project (GR@ACE), Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk

for AD Consortium (GERAD), the European AD Initiative (EADI), the Norwegian DemGene (DemGene), the Bonn study (Bonn), the Copenhagen City Heart Study (CCHS), the AD Genetics Consortium (ADGC), the Alzheimer Disease Sequencing Project (ADSP), the UK Biobank, the Gwangju Alzheimer's and Related Dementias (GARD) study, the Japanese Genetic Study Consortium for AD from Niigata University and National Center for Geriatrics and Gerontology (NCGG). The PD samples included in the HLA fine-mapping analysis are part of the following datasets for which the phenotyping, genotyping, and quality control have been described elsewhere (8, 16, 17, 22, 25, 72): International PD Genomics Consortium (IPDGC) NeuroX dataset, McGill University (McGill), National Institute of Neurological Disorders and Stroke (NINDS) Genome-Wide genotyping in PD, NeuroGenetics Research Consortium (NGRC), Oslo PD Study (Oslo), Parkinson's Progression Markers Initiative (PPMI), Autopsy-Confirmed Parkinson Disease GWAS Consortium (APDGC), the UK Biobank, East Asians samples from Japan, China, Singapore, Taiwan, and Hong-Kong (EastAsians-PD), 23andMe, and the Latin American Research Consortium on the Genetics of PD (LARGE-PD).

The samples assessed for AD and Lewy-body neuropathology included genetic data from the Rush Religious Orders Study and Memory and Aging Project (70) and from the AD Center cohorts 1 to 7 parts of the ADGC (7), and neuropathological assessment followed procedures described, respectively, in ref. 29 and in the National Alzheimer's Coordinating Center (NACC) postmortem evaluation protocol (30). The samples with CSF biomarkers included in the analysis for which phenotype, genotype ascertainment, and quality control is described elsewhere (10, 73), are mostly part of the EADB. The remaining of this dataset includes samples originating from the Gothenburg H70 Birth Cohort studies and clinical AD samples from Sweden.

Genome-Wide Association at the *HLA* Locus and Colocalization between AD and PD. Given the known signal at HLA in AD GWAS (7, 10) and PD GWAS (8), we aimed at refining the signal at the HLA locus using a multiancestry meta-analysis design. We considered a region, ± 1MB around *HLA-DRB1*, on chromosome 6 from base pair positions (hg38) 31578952 to 33589718. For the PD local-GWAS at the HLA locus, we meta-analyzed the summary statistics from the largest available GWAS to date in European ancestry (8) (distributed without 23andMe), with the Latino-Amerindian GWAS from Kunkle et al. (25) and the Asian GWAS from Kang et al. (22). For the AD local-GWAS at the HLA locus, we meta-analyzed the summary statistics the largest available GWAS to date in European ancestry (10) (which did not include their Stage 2), with the Korean/Japanese GWAS from (24), with in-house local-GWAS at the HLA locus on ADSP and ADGC data carried out by ancestry in European, Latino-Amerindian, African individuals, analyzed with a linear-mixed model as implemented in *GENESIS* (74) (see *Imputation and Statistical Analysis of HLA Alleles, Haplotypes, and Amino Acids* section) adjusted for 6 PCs and sex. All meta-analyses were implemented with a fixed-effect inverse variance weighted design implemented in *METAL* (75). Colocalization between the AD, PD, and ALS, HLA signals in these GWAS was assessed using the Bayesian model implemented in *coloc* (76) using default priors. We report the posterior probability of colocalization (PP4) between two GWAS associations in Fig. 2.

Imputation and Statistical Analysis of HLA Alleles, Haplotypes, and Amino Acids. Two-field resolution alleles of *HLA-A*, *HLA-B*, *HLA-C* class I genes, and *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1* class II genes were imputed using R package HIBAG v1.22 (20) for the following dataset: EADB, GR@ACE, GERAD, EADI, DemGene, Bonn, CCHS, UK Biobank, IPDGC, NINDS, NGRC, McGill, Oslo, PPMI, APDGC, LARGE-PD, ADSP, ADGC, GARD, NCGG. When available, training sets specific to ancestry (European, East Asian, Latino, African) and genotyping array were used, either available through HIBAG (20) or trained in-house as previously described (17).

In the allele-level analyses, alleles with an imputation posterior probability lower than 0.5 were considered as undetermined as recommended by HIBAG developers. Each allele was considered as a variant and analyzed under a dominant model; *SI Appendix, Supplementary Methods* provide details on the analysis per cohort.

In the haplotype-level analyses, only individuals with nonmissing allele genotypes were included in the haplotype-level analysis. Three-locus HLA class I or class II haplotypes were determined using the haplo.em function from the R haplo.stats package. Only haplotypes with posterior probability >0.5 and a carrier frequency of >1% were included in the analysis. Each haplotype was considered as a variant and analyzed under a dominant model; SI Appendix, Supplementary Methods provide details on the analysis per cohort.

In the amino acid–level analyses, HIBAG (20) was used to convert P-coded alleles to amino acid sequences for exon 2, 3 of HLA class I genes, and exon 2 of class II genes. Each amino acid was considered as a variant and analyzed under a dominant model; *SI Appendix, Supplementary Methods* provide details on the analysis per cohort.

For the East Asians-PD and 23andMe cohorts, the HLA alleles, haplotypes, and amino acids statistics were derived from GWAS summary statistics data using the DISH software (77) as described in ref. 16.

The allele-, haplotype-, amino acid–level analyses were, respectively, meta-analyzed separately between the two neurodegenerative diseases, and across diseases, using a fixed-effect inverse variance weighted design implemented in *METAL* (75).

Conditional Analyses. A posteriori conditional analyses were implemented to condition the AD and PD GWAS, on the lead variant common to the two GWAS (rs601945), and separately on the lead amino acid *HLA-DRB1* H13 (in complete linkage disequilibrium with H33). The set of conditional analyses were run the amino acid–level analysis, first conditioning on rs601945 and then conditioning on H13. As for the other analyses, these analyses were run across multiple centers and meta-analyzed with *METAL* (75).

Tau Peptide Binding. Competition binding studies were conducted as previously described (78). In brief, tau peptides at different concentrations were incubated with DRB1*04:01, DRB1*04:03, DRB1*04:04, DRB1*04:05, or DRB1*04:06 (from the Emory University NIH core tetramer facility http://tetramer.yerkes.emory.edu/support/faq) for 3 d at 37 °C together with biotinylated GAD or EBV (Bio-GAD, EBV). The reaction was quenched by adding neutralization buffer and then transferred into anti-DR antibody precoated on a 96-well plate. DELFIA® time-resolved fluorescence (TRF) intensity was detected using a Tecan SPARK after adding Europium (Eu)-labeled streptavidin. Nonspecific binding was removed through an extensive wash. Each peptide was duplicated. Competitor tau peptide with Eu TRF intensity that was lower than 25% and 25 to 50% of Bio-GAD or EBV epitope alone was considered a strong binder and a weak binder, respectively. Binding for tau peptides significant for an HLA-DRB1*04 allele (Fig. 2) was repeated three times. Two-way repeated measures ANOVA was used to assess the significance of the differential binding of acetylated vs. unacetylated PHF6 (305-SVQIVY[acetylK]PVDLSKVT-319) across molar ratios.

Data, Materials, and Software Availability. All HLA -alleles, -haplotypes, -amino-acid levels associations derived from this study are available per cohort in Datasets S1–S5, as well as the list of tau and alpha-synuclein peptides that were tested for binding.

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