HLA in isolated REM sleep behavior disorder and Lewy body dementia.

Running head: HLA in iRBD and LBD

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What is the current knowledge on the topic?

Variants in HLA-DRB1 have been associated with Parkinson's disease. However, it is unknown whether specific HLA types or variants are associated with isolated REM sleep behavior disorder (iRBD) and dementia with Lewy body dementia (LBD).

What question did this study address?

Whether specific HLA types or variants are associated with isolated REM sleep behavior disorder (iRBD) and Lewy body dementia (LBD).

What does this study add to our knowledge?

This study suggests an association between three HLA haplotypes and iRBD.

How might this potentially impact on the practice of neurology?

Understanding the genetic risk underlying iRBD may help with stratification in clinical studies and trials and provide directions for studying the mechanisms underlying this disorder.

Abstract

Isolated/idiopathic REM sleep behavior disorder (iRBD) and Lewy body dementia (LBD) are synucleinopathies that have partial genetic overlap with Parkinson's disease (PD). In this study, we examined if the human leukocyte antigen (*HLA*) locus plays a similar role in iRBD, LBD and PD. The DQA1*01:02~DQB1*06:02~DRB1*15:01 haplotype is associated with reduced risk for iRBD (OR=0.72, 95%CI=0.50-0.93, $p=2.07*10^{-3}$), while the haplotypes DQA1*02:01~DQB1*03:03~DRB1*07:01 (OR=1.57; 95%CI=[1.28-1.86]; $p=2.45*10^{-3}$) and DQA1*05:05~DQB1*03:01~DRB1*11:01 (OR=1.39; 95%CI=[1.17-1.60]; $p=3.01*10^{-3}$) are associated with increased risk for iRBD. This effect was not replicated in LBD. Our results suggest that the *HLA* locus may have different roles across synucleinopathies.

Introduction

Isolated/idiopathic rapid-eye-movement (REM) sleep behavior disorder (iRBD) is a prodromal synucleinopathy characterized by enactment of dreams, vocalization and absence of muscle atonia during REM sleep.[1] iRBD is one of the strongest predictors for certain neurodegenerative disorders, as approximately 80% of patients will convert to Parkinson's disease (PD), Lewy body dementia (LBD) or multiple system atrophy (MSA) after 10-15 years on average following iRBD diagnosis.[2]

Previous evidence has shown that iRBD and other synucleinopathies share a partial genetic overlap.[3] While certain loci (*SNCA*, *GBA*, *TMEM175*) were found to be shared between these traits, distinct loci were also identified, such as *LRRK2* and *MAPT* for PD and *APOE* for LBD.[3] Furthermore, while the *SNCA* locus is important in PD, LBD and iRBD, the association with *SNCA* is driven by different variants for the different traits.[3] Similar phenomenon occurs in the *SCARB2* locus, where different variants are associated with PD or RBD.[3] Understanding the shared genes and pathways, as well as the genetic differences, will lead to better characterization of these disorders. For instance, microglial activation, a form of neuroinflammation, was found in all these disorders,[4-6] yet the role of the immune system in their pathophysiology is not well understood.

Recently, a fine-mapping study of the human leukocyte antigen (*HLA*) locus in PD demonstrated a strong association of HLA-DRB1 amino acids 11V, 13H and 33H with reduced PD risk.[7] Located on chromosome 6, the *HLA* locus is a highly polymorphic region known to have complicated linkage pattern. *HLA* plays an essential role in the adaptive immune system by presenting antigens to T-cells.

Since the role of the *HLA* locus is unknown in iRBD and LBD, the aim of this study is to examine whether *HLA* variants may affect the risk for these disorders. We analyzed the association of different *HLA* alleles, haplotypes and amino acids in two cohorts of iRBD and LBD patients.

Methods

Study population

iRBD and LBD cohorts from two previous genome-wide association studies (GWAS) were included in this analysis (Table 1).[3, 8] iRBD patients were diagnosed according to the International Classification of Sleep Disorders (2nd or 3rd Edition) with video polysomnography. LBD was diagnosed according to consensus criteria, as described elsewhere.[8-10] The iRBD cohort is composed of 1,072 patients and 9,505 controls with genotyping data from the OmniExpress GWAS chip (Illumina inc.). The control group includes five publicly available cohorts: controls from the International Parkinson's Disease Genomics Consortium (IPDGC) NeuroX dataset (dbGap phs000918.v1.p1), National Institute of Neurological Disorders and Stroke (NINDS) Genome-Wide genotyping in Parkinson's Disease (dbGap phs000089.v4.p2), NeuroGenetics Research Consortium (NGRC) (dbGap phs000196.v3.p1), Parkinson's Progression Markers Initiative (PPMI).

The LBD cohort consisted of 2,604 LBD patients and 4,032 controls with whole-genome sequencing data as described elsewhere.[8] Study participants signed informed consent forms and the study protocol was approved by the Institutional Review Board at McGill University.

Quality control

Standard GWAS quality control steps were performed for both cohorts. SNPs that were heterozygosity outliers (|F| > 0.15), sample call rate outliers (<0.95) and samples failing sex check were also excluded. Ancestry was determined by merging samples with HapMap3 and clustering with principal components analysis (PCA). Relatedness check was performed with GCTA to remove third-degree relatives or closer. Then, we removed SNP call rate outliers (<0.95), SNPs with significantly different missingness between cases and controls ($p<0.0001$), SNPs that failed –test-mishap ($p<0.0001$) and SNPs in controls that deviated from Hardy-Weinberg equilibrium ($p<0.0001$). iRBD samples passing quality control were imputed on the Michigan Imputation Server with the HRC (Version r1.1 2016) reference panel using Minimac3.

Statistical analysis

To examine the association of *HLA* alleles, haplotypes and amino acids, we also performed *HLA* imputation using HLA genotype Imputation with Attribute BAGging (HIBAG). HIBAG is a robust random forest algorithm that has been widely used in previous studies.[7, 11, 12] *HLA* haplotypes were calculated using haplo.stats R package which employs an Expectation–maximization (EM) algorithm. Logistic regression with a dominant model was tested on each *HLA* allele, haplotype and amino acid. All rare associations (carrier frequency < 1%) were excluded. A 5% false-discovery rate (FDR) for multiple testing was applied.

Code availability

All scripts used in this study can be found at https://github.com/gan-orlab/HLA_HIBAG.

Results

We performed *HLA* imputation on both cohorts and examined the association of *HLA* alleles, haplotypes and amino acids. Three independent haplotypes were associated with iRBD: the DR15 haplotype, DQA1*01:02~DQB1*06:02~DRB1*15:01 (OR=0.72,95%CI=0.50-0.93, $p=2.07*10^{-3}$, pFDR=0.0251, Table 2), is associated with reduced risk for iRBD while the DR7, DQA1*02:01~DQB1*03:03~DRB1*07:01 (OR=1.57, 95%CI=1.28-1.86, $p=2.45*10^{-3}$, p FDR=0.0251, Table 2), and DR11 haplotypes, DQA1*05:05~DQB1*03:01~DRB1*11:01 (OR=1.39, 95%CI=1.17-1.60, $p=3.01*10^{-3}$, pFDR= 0.0251, Table 2), are associated with increased risk for iRBD. Specific *HLA* alleles did not pass multiple testing corrections in iRBD (Table 3). When combining carriers of different DR15, DR11 and DR7 alleles respectively, the association of DR15 increased while DR11 decreased (Table 3). DR7 did not have additional alleles. For LBD, no association was statistically significant after correction for multiple comparisons. We also examined the association of HLA-DRB1 33H, which was reported to be associated with PD (Supplementary Table #3).[7] Although DRB1 33H was not associated with in iRBD (pFDR=0.51), the carrier frequencies in cases and controls were 0.22 vs 0.27 respectively, similar to the frequencies previously reported in PD and controls (0.29 vs 0.33).[7] Meanwhile, the DRB1 33H allele frequency in both LBD cases and its controls was 0.27. Our results suggest that DRB1 33H could be associated with iRBD, but our study may lack the power to detect it.

Discussion

This study shows an association between three haplotypes: HLA-DR15 with a protective effect toward iRBD and DR7 and DR11 with risk for iRBD. DR15 was previously associated with numerous neurological disorders such as multiple sclerosis and Alzheimer's disease (AD).[13] DR15 is also strongly associated with narcolepsy Type I, a disorder where 30-60% of patients

presents mild secondary RBD with no other marker of neurodegeneration.[14] The protective effect of this allele in iRBD brings a new evidence that the mechanism of RBD is different between iRBD and narcolepsy. DR15 was also nominated to be associated with PD, but it was not replicated in larger studies.[7, 15, 16] Our results also suggest that the DR15 association driven by DRB1*15 alleles as the combination of DRB1*15:01 and 15:02 increased the association with iRBD. Meanwhile, a similar analysis with DR11 showed a decreased association. In addition, DRB1 33H, a variant also associated with PD, was not significantly associated with iRBD or LBD. However, the difference in carrier frequency between iRBD cases and controls for DRB1 33H, which was similar to that seen in PD, suggests that our study may lack the power to detect this association in iRBD. A recent study has suggested shared mechanism between PD, AD, amyotrophic lateral sclerosis and HLA-DRB1*04, harboring the 33H amino acid change.[17] This subtype was associated with decreased neurofibrillary tangles in postmortem brains and binds to a K311 acetylated Tau PHF6 sequence.[17] Our study also suggests a shared mechanism of DR15 with AD and iRBD. These results exemplify the possibility of different HLA types with specific genetic variants that may affect binding of substrates relevant for neurodegenerative disorders and activating inflammatory response.

We were not able to replicate the association of a previous study of HLA antigens with 25 iRBD cases that showed significant association for DQB1*05 and DQB1*06.[18] The most likely explanation for the discrepancy is that the previous study had reduced power to detect a true effect. Another study has suggested that HLA-DR expression was associated with iRBD.[19] Fine-mapping and colocalization studies for these findings will be required once larger datasets of iRBD become available. Whether the mechanism underlying the associations with PD and

iRBD is through functional effects of specific amino acid changes or due to different expression of *HLA* genes in various brain tissues is still to be determined.

Although the involvement of the immune system across synucleinopathies is still elusive, the varying effects of HLA between prodromal and clinical stages could be associated with HLA presenting different antigens in different brain regions. Another possibility is that the varying effects originate in the gastrointestinal tract.[20] For example, constipation, which is a common symptom in the early stages of PD, can aggravate or be caused by gut inflammation. In iRBD patients, one study showed a prevalence of constipation between 18-41%.[20]

Our study has several limitations. First, since we do not have a replication cohort, future replication studies with larger cohorts would be needed to increase statistical power. Note that we used the largest available cohorts for iRBD and LBD.[3, 8] Due to the polygenicity of the Major histocompatibility complex, various populations have large differences in HLA allele frequencies. This study was done only on samples with European ancestry, and multi-ancestry analysis could provide more refined evidence on the role of HLA in synucleinopathies. The cohorts used in the study were also not matched for age and sex. However, we adjusted for these variables in the analysis.

To conclude, we found an alternative *HLA* association of iRBD compared to PD and LBD. More experimental evidence is necessary to characterize the genetic landscape of synucleinopathies and the role of the immune system.

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Author Contributions

E.Y., Z.G.O. contributed to conception and design of the study; E.Y, L.K., J.A.R., F.A., D.S., Z.S., R.C., I.A., M.T.M.H., J.Y.M., J-F.G., A.D., Y.D., G.L.G., M.V., F.J., A.B., B.H., A.S., A.I., A.H., K.S., P.D., D.K., W.O., A.J., G.P., E.A., M.F., M.P., B.M., C.T., F.S.D., V.C.D.C, C.C.M.., L.F.S., F.D., M.V., B.A., B.F.B, G.A.R., R.B.P., ILBDGC, S.W.S contributed to the acquisition and analysis of data; E.Y. and Z.G.O. contributed to drafting of the manuscript. A full list of ILBDGC members is listed in Supplementary Table #7.

Potential Conflict of Interest

S.W.S. serves on the Scientific Advisory Council of the Lewy Body Dementia Association and the Multiple System Atrophy Coalition. S.W.S. receives research support from Cerevel Therapeutics.

Table 1: Study population after quality control.

Variable	Isolated REM sleep behavior disorder		Lewy body dementia	
	Patients (n = 1,072)	Controls (n = 9,505)	Patients (n = 2,604)	Controls (n = 4,032)
Age (years), (SD)	60.54 (11.06)	63.49 (16.59)	74.36 (11.76)	72.63 (16.99)
Male, number (%)	860 (80.22)	4824 (50.75)	1656 (63.59)	1967 (48.78)

SD, standard deviation; n, number

Table 2: HLA haplotypes in isolated REM sleep behavior disorder

Haplotypes	Carrier Frequency in cases	Carrier Frequency in controls	Effect size	Standard Error	P-value	P-value (FDR)
DQA1*01:02~DQB1*06:02~DRB1*15:01	0.218	0.268	-0.335	0.109	0.00207	0.0251
DQA1*02:01~DQB1*03:03~DRB1*07:01	0.086	0.0682	0.452	0.149	0.00245	0.0251
DQA1*05:05~DQB1*03:01~DRB1*11:01	0.201	0.146	0.327	0.110	0.00301	0.0251

FDR, false discovery rate

Table 3: HLA alleles in isolated REM sleep behavior disorder.

Alleles	Carrier Frequency in cases	Carrier Frequency in controls	Effect size	Standard Error	P-value	P-value (FDR)
DRB1*11:01	0.207	0.151	0.333	0.105	0.00153	0.208
DR15	0.239	0.287	-0.301	0.0999	0.00262	0.208
DRB1*15:01	0.227	0.271	-0.269	0.102	0.00851	0.329
DR11	0.249	0.198	0.229	0.0995	0.0216	0.347
DRB1*07:01	0.298	0.261	0.209	0.0919	0.0227	0.347

FDR, false discovery rate; DR15 includes DRB1*15:01 and DRB1*15:02 carriers; DR11 includes DRB1*11:01, DRB1*11:02, DRB1*11:03, DRB1*11:04 carriers.

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