ABSTRACT

Human leukocyte antigen (HLA), which is critically involved in immune response to foreign antigens and in autoimmunity, has been implicated in dementia and Parkinson’s disease. Here we report on the correlations between the population frequencies of 127 HLA Class I and II alleles and the population prevalence of dementia and Parkinson’s disease in 14 Continental Western European countries, extending previous work. We used these correlations to construct and compare HLA profiles for each disease. We found that (a) the HLA profiles of the two diseases were significantly correlated across both HLA Class I and Class II alleles, (b) negative (“protective”) HLA-disease correlations did not differ significantly for either HLA class, but (c) positive (“susceptibility”) HLA-disease correlations were significantly higher in dementia than in Parkinson’s disease for both HLA classes of alleles. These findings indicate that (a) dementia and Parkinson’s disease share immunogenetic HLA-related mechanisms, (b) HLA-related protective mechanisms (presumably against pathogens) do not differ between the two diseases, but (c) HLA-related susceptibility mechanisms (presumably underlying autoimmunity) are significantly stronger in dementia than in Parkinson’s disease.

Introduction

Nearly 50 million people worldwide are living with dementia or Parkinson’s disease, the two most common neurodegenerative diseases, resulting in a considerable toll on affected individuals, caregivers, and society. Despite decades of extensive investigation, the etiology of both conditions remains unknown, hampering intervention and prevention efforts; however, growing research points to the involvement of pathogens as potential causes and autoimmunity as pathogenic mechanisms that are triggered by, and subsequently contribute to, chronic neuroinflammation in both conditions. In light of overlapping pathogen associations and autoimmune-related neuroinflammation in dementia and Parkinson’s disease, and the known involvement of the Human Leukocyte Antigen (HLA) in pathogen elimination and autoimmunity, we sought in the present study to evaluate the correspondence between the HLA disease profiles in these two diseases as an indicator of immunogenetic overlap.

The HLA system is involved in both pathogen elimination (as a preventive/protective factor) and autoimmunity (as a susceptibility factor). Two main classes of HLA genes code for cell-surface glycoproteins that are critically involved in facilitating cellular and...
humoral immune system responses to foreign antigens derived from various pathogens. With respect to pathogen elimination, HLA Class I molecules (of the A, B, C genes) are expressed on nucleated cells and present intracellular antigen peptides to CD8+ cytotoxic T cells to signal cell destruction, thus eliminating infected cells. On the other hand, HLA Class II molecules (of the DR-, DQ- and DP-genes) are expressed on professional antigen-presenting cells (e.g., macrophages, dendritic cells) and present endocytosed extracellular antigen peptides to CD4+ T cells to promote B-cell mediated antibody production against the offending pathogens and adaptive immunity for the future. HLA molecules are coded in the Major Histocompatibility Complex (MHC) in chromosome 6. MHC is the most highly polymorphic region in the human genome resulting in considerable individual and population variation in HLA composition, reflecting the long evolutionary history of exposure to and dealing with elimination of, and ultimate protection from, various pathogens14,15. With respect to autoimmunity, both HLA Class I and Class II molecules are intimately involved in autoimmune disorders16.

Burgeoning evidence has demonstrated HLA associations with dementia and Parkinson's disease1,3,9,17-21. Using an across-countries population immunogenetic epidemiological approach22, we initially investigated associations between the population frequency of HLA Class II DRB1 alleles and dementia across 14 countries in Continental Western Europe11-12. This approach permits identification of an HLA profile wherein HLA alleles may presumably be characterized as protective alleles (negatively correlated with population prevalence of a disease) or susceptibility alleles (positively correlated with the population prevalence of a disease). With respect to HLA Class II DRB1 alleles, we recently found that the HLA profiles of dementia and Parkinson's disease for a small number of HLA alleles are very similar, suggesting that similar immunogenetic mechanisms may underlie the pathogenesis of these conditions3. Here we extend that line of research to evaluate the correspondence in HLA profiles for Parkinson's disease and dementia were natural-log transformed1-3 (see Table 1). Briefly, the prevalences derived as described previously3. The association between the HLA profiles of Parkinson's disease and dementia was computed for each of the following 14 Continental Western European countries as determined by the Global Burden of Disease study4,5: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Portugal, Norway, Spain, Sweden, and Switzerland. Specifically, the total number of people with dementia or Parkinson's disease in each of the 14 Continental Western European countries was divided by the total population of each country in 2016 (Population Reference Bureau)23 and expressed as a percentage. We have previously shown that life expectancy for these countries are virtually identical1; therefore, life expectancy was not included in the current analyses.

Materials and Methods

Prevalence of dementia and Parkinson’s disease

The population prevalence of dementia and Parkinson’s disease was computed for each of the following 14 countries in Continental Western Europe: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Portugal, Norway, Spain, Sweden, and Switzerland. Specifically, the total number of people with dementia or Parkinson’s disease in each of the 14 Continental Western European countries was divided by the total population of each country in 2016 (Population Reference Bureau)23 and expressed as a percentage. We have previously shown that life expectancy for these countries are virtually identical1; therefore, life expectancy was not included in the current analyses.

HLA

The frequencies of all reported HLA alleles of classical genes of Class I (A, B, C) and Class II (DQB1, DQB1, DRB1) for each of the 14 Continental Western European countries were retrieved from the website allelefrequencies.net (Estimation of Global Allele Frequencies24,25) on October 20, 2020. There was a total of 2746 entries of alleles from the 14 Continental Western European countries, comprising 844 distinct alleles. Of those, 127 alleles occurred in 9 or more countries and were used in further analyses. The distribution of those alleles to the HLA classes and their genes is given in Table 1.

Data analysis

HLA profiles for Parkinson’s disease and dementia were derived as described previously1. Briefly, the prevalences (fractions of total country population) of Parkinson’s disease and dementia were natural-log transformed1-3 (see below) and the Pearson correlation coefficient, r, between disease prevalence and the population frequency of each one of the 127 HLA alleles above calculated and Fisher z-transformed26 to normalize their distribution:

$$r' = \text{atanh}(r)$$

The HLA disease profile consisted of 127 values of r'. The association between the HLA profiles of Parkinson’s disease and dementia was computed as the Pearson correlation between their HLA profiles. Since negative and positive correlations have the same magnitude, but opposite signs, we used Fisher z-transforms to ensure that they are on a common scale. Fisher z-transforms are used to normalize correlation coefficients so that they follow a standard normal distribution, which allows for easier interpretation and comparison of correlation coefficients across different datasets. The transformed correlation coefficients, z, can be calculated using the following formula:

$$z = \frac{1}{2} \ln \left( \frac{1 + r}{1 - r} \right)$$

The transformed correlation coefficients range from -1.96 to 1.96, representing 95% confidence intervals. Therefore, a correlation coefficient of 0.5 corresponds to a z-score of 0.84 and a significance level of 0.20.

Table 1: Distribution of 127 HLA alleles analyzed to Class and Genes.

| Gene   | Class I (N = 69) | Class II (N = 58) |
|--------|-----------------|-------------------|
| Count  |                 |                   |
| A      | 20              | 20                |
| B      | 36              | 36                |
| C      | 13              | 14                |
| DPB1   | 15              | 14                |
| DQB1   |                 |                   |
| DRB1   | 29              |                   |
positive correlations ($-r, +r$) between allele frequency and disease prevalence can be interpreted as indicating a protective or susceptibility effect of the allele on the disease, respectively, additional analyses were carried out on the counts of signed (negative, positive) correlations using two-way tables and associated statistics (chi-square test, Fisher’s exact test, phi coefficient). Finally, the quantitative differences between Parkinson’s disease and dementia with respect to protective (negative $r$) and susceptibility (positive $r$) alleles were assessed by a paired t-test in two groups, namely one on alleles protective to both diseases, and the other on susceptibility alleles for both diseases. Statistical analyses were performed using the IBM-SPSS package (IBM SPSS Statistics for Windows, Version 26.0, 64-bit edition. Armonk, NY: IBM Corp; 2019) and Intel FORTRAN (Microsoft Visual Studio Community Version 16.8.3; Intel FORTRAN Compiler 2021).

**Results**

HLA-disease profiles consist of correlations between allele frequency and disease prevalence, suitably Fisher z-transformed (Equation 1) to normalize their distribution for further analyses. We showed previously$^1$ that dementia prevalence varies in an exponential fashion with allele frequency, such that the logarithm of disease prevalence is a linear function of allele frequency. Therefore, the correlation entered in a HLA-disease profile is that computed using the natural log-transformed disease prevalence and allele frequency. Two examples are illustrated in Figures 1 and 2, one for a presumed dementia protective allele (DRB1*04:01; Figure 1) and another for a presumed dementia susceptibility allele (DPB1*02:01; Figure 2).

**HLA profiles of Parkinson’s disease and dementia**

The frequency distributions of alleles in HLA profiles for Parkinson’s disease and dementia (Table 2) are shown in Figures 3 and 4, respectively. It can be seen that they are similar, with a broad overlap. The HLA profiles of the two diseases were positively and highly significantly correlated (Figure 5) ($r = 0.904, P = 6.4 \times 10^{-48}, N = 127$). This positive association extended across the two HLA classes (color

![Figure 1](example.png)

**Figure 1. Example from a presumed protective HLA allele.** Dementia prevalence for 13 CWE countries (for which DRB1*04:01 frequency was available) is plotted against the corresponding DRB1*04:01 allele frequency in the original (percentage) dementia prevalence scale (A) and its natural log transformed values (B). The fitted line is an exponential function (A) that becomes a linear function in the log-transformed prevalence scale (B). The statistics for the linear case are: Pearson correlation $r = -0.877, P < 0.001$; $r' = \text{atanh}(r) = -1.363$

![Figure 2](example.png)

**Figure 2. Example from a presumed susceptibility HLA allele.** Dementia prevalence for 11 CWE countries (for which DPB1*02:01 frequency was available) is plotted against the corresponding DPB1*02:01 allele frequency in the original (percentage) dementia prevalence scale (A) and its natural log transformed values (B). The fitted line is an exponential function (A) that becomes a linear function in the log-transformed prevalence scale (B). The statistics for the linear case are: Pearson correlation $r = -0.905, P = 0.003$; $r' = \text{atanh}(r) = 1.112$
Figure 3. Frequency distribution of HLA profiles for Parkinson’s disease. N = 68 alleles for Class I and 59 alleles for Class II.

Figure 4. Frequency distribution of HLA profiles for dementia. N = 68 alleles for Class I and 59 alleles for Class II.

Figure 5. The HLA profile (r²) of Parkinson’s disease is plotted against the HLA profile of dementia. The two HLA disease profiles were highly correlated. N = 127.

coded in Figure 5). More specifically, the correlation between the two disease HLA profiles was r = 0.868 (P = 4.8 x 10⁻²², N = 69) for Class I (Figure 6) and r = 0.939 (P = 1.3 x 10⁻²⁷, N = 58) for Class II (Figure 7). In addition, this positive correlation extended across the 3 genes of Class I and the 3 genes of Class II (color coded in Figures 6 and 7, respectively). More specifically, the correlations between disease profiles were as follows: r = 0.854 (Class I, gene A,
Table 2: The signed z-transformed correlation coefficient ($r'$) between 127 HLA alleles and disease prevalence.

| Allele   | Class | N | $r'(PD)$ | $r'(GEN)$ |
|----------|-------|---|----------|-----------|
| A*01:01  | 1     | 11 | -0.263   | -0.237    |
| A*02:01  | 1     | 11 | -0.583   | -0.593    |
| A*02:05  | 1     | 9  | 0.486    | 0.853     |
| A*03:01  | 1     | 11 | -0.313   | -0.412    |
| A*11:01  | 1     | 11 | 0.233    | 0.347     |
| A*23:01  | 1     | 11 | 0.018    | 0.317     |
| A*24:02  | 1     | 11 | 0.272    | 0.051     |
| A*25:01  | 1     | 12 | -0.078   | -0.031    |
| A*26:01  | 1     | 11 | 0.421    | 0.478     |
| A*29:01  | 1     | 11 | -0.067   | 0.147     |
| A*29:02  | 1     | 11 | -0.115   | 0.131     |
| A*30:01  | 1     | 11 | 0.508    | 0.357     |
| A*30:02  | 1     | 12 | 0.390    | 0.580     |
| A*31:01  | 1     | 9  | -0.051   | -0.361    |
| A*32:01  | 1     | 12 | 0.277    | 0.392     |
| A*33:01  | 1     | 10 | 0.308    | 0.672     |
| A*33:03  | 1     | 9  | -0.059   | 0.320     |
| A*36:01  | 1     | 10 | 0.126    | 0.551     |
| A*68:01  | 1     | 11 | -0.391   | -0.220    |
| A*68:02  | 1     | 10 | -0.323   | -0.137    |
| B*07:02  | 1     | 10 | -0.416   | -0.941    |
| B*08:01  | 1     | 12 | -0.545   | -0.797    |
| B*13:02  | 1     | 11 | -0.047   | -0.240    |
| B*14:01  | 1     | 11 | 0.100    | 0.409     |
| B*14:02  | 1     | 10 | 0.457    | 0.719     |
| B*15:01  | 1     | 10 | -0.216   | -0.611    |
| B*15:17  | 1     | 9  | 0.728    | 0.903     |
| B*15:18  | 1     | 9  | 0.302    | 0.479     |
| B*18:01  | 1     | 12 | 0.381    | 0.597     |
| B*27:02  | 1     | 10 | -0.095   | 0.060     |
| B*27:05  | 1     | 12 | -0.090   | -0.195    |
| B*35:01  | 1     | 11 | 0.186    | 0.306     |
| B*35:02  | 1     | 9  | 0.200    | 0.651     |
| B*35:03  | 1     | 9  | 0.268    | 0.672     |
| B*35:08  | 1     | 9  | 0.733    | 0.971     |
| B*37:01  | 1     | 10 | 0.110    | -0.412    |
| B*38:01  | 1     | 9  | 0.398    | 1.026     |
| B*39:01  | 1     | 11 | 0.375    | 0.284     |
| B*39:06  | 1     | 9  | -0.332   | -0.080    |
| B*40:01  | 1     | 12 | -0.230   | -0.509    |
| B*40:02  | 1     | 12 | 0.050    | -0.010    |
| B*41:01  | 1     | 11 | 0.144    | 0.391     |
| B*41:02  | 1     | 10 | -0.014   | 0.436     |
| B*44:02  | 1     | 12 | -0.799   | -0.841    |
| B*44:03  | 1     | 12 | -0.077   | 0.086     |
| B*44:05  | 1     | 9  | 0.167    | 0.327     |
| B*45:01  | 1     | 10 | -0.248   | -0.028    |
| B*47:01  | 1     | 11 | -0.391   | 0.113     |
| B*49:01  | 1     | 11 | 0.431    | 0.847     |
| B*50:01  | 1     | 10 | 0.019    | 0.509     |
| B*51:01  | 1     | 10 | 0.402    | 0.535     |
P = 2.0 x 10^{-4}, N = 20), 0.867 (Class I, gene B, P = 7.8 x 10^{-12}, N = 30), 0.903 (Class I, gene C, P = 2.3 x 10^{-5}, N = 13), 0.974 (Class II, gene DPB1, P = 9.5 x 10^{-10}, N = 15), 0.957 (Class II, gene DQB1, P = 8.8 x 10^{-8}, N = 14), 0.914 (Class II, gene DRB1, P = 4.1 x 10^{-12}, N = 29).

Analysis of counts of signed correlations

The two-way distribution of the counts of signed correlations between allele frequency and disease prevalence is given in Table 3. There was a highly significant positive association (chi-square = 73.89, P (2-sided) = 8.2 x 10^{-16}; Fisher’s exact test (2-sided) P = 4.4 x 10^{-19}; phi = 0.763).

This positive association was present in both HLA Class I (Table 4) and Class II (Table 5). For Class I: chi-square = 31.68, P (2-sided) = 1.8 x 10^{-8}; Fisher’s exact test (2-sided)

P = 1.4 x 10^{-6}; phi = 0.678). For Class II, this association was stronger: chi-square = 43.18, P (2-sided) = 5.0 x 10^{-11}; Fisher’s exact test (2-sided) P = 5.2 x 10^{-12}; phi = 0.863).

Similar results were obtained for each one of the six alleles (Table 6).

Comparison of Parkinson’s disease and dementia with respect to protective and susceptibility alleles

Protective alleles. There were 48 alleles protective for both diseases. The magnitude of r’ did not differ significantly between the two diseases (P = 0.221, paired t-test); for Parkinson’s disease, r’ (mean ± SEM) was -0.403 ± 0.043, and for dementia -0.440 ± 0.050. Very similar results were obtained when the data were analyzed separately by a paired t-test for Class I and Class II alleles: for Class I, P = 0.156, N = 24, and for Class II, P = 0.824, N = 24).

Susceptibility alleles. There were 64 susceptibility alleles for both diseases. The magnitude of r’ was significantly higher for dementia than for Parkinson’s disease (P = 7.9 x 10^{-9}, paired t-test); for Parkinson’s disease, r’ (mean ± SEM) was 0.338 ± 0.032, and for dementia 0.552 ± 0.033.
Table 7: Correlation coefficients between $r^*(PD)$ and $r^*(DEM)$ at various levels of numbers of alleles available in the 14 CWE countries.

| Number of countries with N alleles | Number of distinct alleles | Correlation between $r^*(PD)$ and $r^*(DEM)$ | P-value |
|-----------------------------------|---------------------------|-----------------------------------------------|---------|
| ≥ 3                               | 266                       | 0.748                                         | < 0.0001|
| ≥ 4                               | 217                       | 0.798                                         | < 0.0001|
| ≥ 5                               | 186                       | 0.852                                         | < 0.0001|
| ≥ 6                               | 171                       | 0.877                                         | < 0.0001|
| ≥ 7                               | 162                       | 0.878                                         | < 0.0001|
| ≥ 8                               | 151                       | 0.884                                         | < 0.0001|
| ≥ 9                               | 127                       | 0.904                                         | < 0.0001|
| ≥ 10                              | 95                        | 0.903                                         | < 0.0001|
| ≥ 11                              | 73                        | 0.920                                         | < 0.0001|
| ≥ 12                              | 40                        | 0.941                                         | < 0.0001|
| ≥ 13                              | 19                        | 0.964                                         | < 0.0001|
| 14                                | 7                         | 0.946                                         | 0.0012  |

Very similar results were obtained when the data were analyzed separately by a paired t-test for Class I and Class II alleles: for Class I, $P = 4.1 \times 10^{-7}$, $N = 34$, and for Class II, $P = 0.003$, $N = 30$.

### Analyses with different sample sizes

For the analyses above, we used a minimum sample size of 9 countries as a reasonable choice of sample size. However, we also computed HLA profiles for all available samples sizes ≥ 3 and calculated correlations between these PD and dementia HLA profiles to check for consistency of their correlation. The results are shown in Table 7. It can be seen that a highly significant positive correlation between the 2 disease profiles was obtained for all cases of $N \geq 3$.

### Discussion

Here we used an across-countries immunogenetic epidemiological approach to identify HLA profiles for dementia and Parkinson’s disease and evaluate their correspondence using data obtained from 14 countries in Continental Western Europe. The results demonstrated that the HLA profiles of the two diseases are remarkably similar when examined in aggregate and separately for each of the Class I and Class II alleles. However, when considered with respect to HLA protection or susceptibility, the correlation of susceptibility HLA alleles with dementia was significantly stronger than their correlation with Parkinson’s disease, whereas there was no significant difference regarding the correlation of protective/preventive alleles with dementia or Parkinson’s disease. These findings extend previous research demonstrating highly similar HLA DRB1 profiles in dementia and Parkinson’s disease to a large number of other Class I and Class II HLA alleles and point to increased immunogenetic susceptibility to dementia relative to Parkinson’s disease. Our view of how HLA could be involved in prevention/protection from, and susceptibility to, these and other diseases is discussed below and exemplified in the schematic diagram of Figure 8.

It is well-established that the HLA system evolved for, and is explicitly involved in, pathogen elimination. Thus, with respect to protective effects identified here, we assume that protective HLA alleles exert their effects via elimination of pathogens, thereby preventing deleterious downstream health effects. Our finding that protective HLA profiles (i.e., alleles with negative $r^*$) did not differ significantly between the two diseases is consistent with evidence implicating similar families of pathogens in both Parkinson’s disease and dementia.

In the absence of HLA protection against pathogens, disease may result from directly damaging effects of a pathogen on cells or as a result of susceptibility HLA alleles (i.e., alleles with positive $r^*$) that promote autoimmunity (i.e., production of autoantibodies) due to chronic inflammation. This is in accord with evidence documenting inflammatory and autoimmune processes in both dementia and Parkinson’s disease as well as evidence of autoantibodies in both conditions. Here, susceptibility (i.e., positively associated) alleles occurred more frequently than protective (i.e., negatively associated) alleles, indicating a preponderance of HLA alleles that may increase susceptibility to autoimmunity.

At the individual level, HLA composition plays a critical role in influencing health vs immune-mediated disease outcomes due to the protective role of HLA in eliminating foreign antigens and to its predisposing role in autoimmunity. As previously noted, HLA is the most highly polymorphic region of the human genome. This is notable in that subtle alterations in HLA have been shown to affect the binding groove, resulting in differential binding affinity of antigens. We have hypothesized that protection against diseases including dementia and Parkinson’s disease conferred by specific HLA alleles is related to their superior ability to bind, and therefore eliminate, harmful antigens. On the other hand, inability to
bind antigens and mount an immune response is posited to result in persistent antigens that may directly damage cells and/or may potentially stimulate chronic inflammatory responses and/or autoimmunity\textsuperscript{46-49} and ultimately clinical disease\textsuperscript{45}. Dementia commonly occurs in individuals with Parkinson’s disease\textsuperscript{46}. The extent to which the co-occurrence may be a result of pathogen-driven cell death or autoimmunity is unclear.

It is worth noting that the persistent antigen hypothesis is complementary rather than inconsistent with prevailing theories implicating aggregated self-proteins in dementia and Parkinson’s disease. Indeed, both amyloid-β and alpha-synuclein, proteins associated with dementia and Parkinson’s disease, respectively, have been shown to exhibit anti-microbial properties\textsuperscript{29,49,50}. That is, growing research suggests that aggregated proteins that have long been characterized as the hallmark pathological characteristics of neurodegenerative disorders may initially reflect a protective immune response to infections\textsuperscript{29,49,50}. If, however, foreign antigens persist due to lack of HLA-antigen congruence as suggested by the persistent antigen hypothesis\textsuperscript{45}, the amyloid-β and/or alpha-synuclein protein aggregation may continue, resulting in unchecked protein deposition. In turn, aggregated self-proteins may be recognized as foreign antigens, stimulating further immune system reactivity\textsuperscript{47}.

Here we found no differences between dementia and Parkinson’s disease prevalence with respect to protective HLA alleles for both conditions; however, the association of susceptibility HLA alleles was stronger with dementia than the association of those same alleles with Parkinson’s disease. These findings suggest that similar immunogenetic mechanisms along the lines of those discussed above (i.e., elimination of pathogens) are involved in protection against these conditions but that additional factors are involved in moderating HLA-mediated autoimmunity in dementia and Parkinson’s disease, including variations in apoE\textsuperscript{51,52}, modifiable risk factors including diet, exercise, and smoking, among others\textsuperscript{45,53}, and other environmental exposures that have been differentially associated with dementia and Parkinson’s disease\textsuperscript{45}. These issues represent important areas for future investigation.

A broad link between HLA and neurodegenerative diseases such as dementia and Parkinson’s disease has been increasingly recognized\textsuperscript{1-3,9,17-21}; however, the influence of specific genes on these diseases has not been clearly established and findings have often been inconsistent. For example, we have identified population-level protective effects of DRB1*15:01 on dementia and Parkinson’s disease here, and have previously shown that DRB1*15:01 binds with viruses linked to dementia and Parkinson’s disease with very high affinity\textsuperscript{54}. In contrast, another recent study identified DRB1*15:01 as a risk factor for Alzheimer’s dementia\textsuperscript{55}; however, in that study HLA was imputed rather than directly sequenced, and the findings regarding DRB1*15:01 were limited to men lacking the ApoE4 risk gene. Thus, additional research using direct sequencing of HLA is warranted to further evaluate the association of HLA alleles, including DRB1*15:01, to dementia and to evaluate the effects of gender and other moderating factors. Similarly, although the findings regarding associations between HLA (including DRB1*15:01) and Parkinson’s disease are more compelling\textsuperscript{55-57}, additional research is warranted to more conclusively establish HLA associations with Parkinson’s disease and to evaluate variations in HLA-disease associations across different populations given global variations in HLA. Determining specific HLA influences on diseases move beyond the common influence of inflammation in dementia and Parkinson’s disease to facilitate in silico analyses that permit identification of pathogen families that may contribute to inflammation and disease (e.g., ref\textsuperscript{55}).

Limitations and qualifications

There are several limitations/qualifications of this study, as follows. First, these results are based on correlations between disease prevalences and HLA allele frequencies in large populations of 14 CWE countries and, as such, they need to be validated in studies using assessments of disease and allele presence in specific individuals. Second, it is known that HLA-disease associations may vary from place to place\textsuperscript{58,59}, and across countries\textsuperscript{22,59} and, therefore, the results of this study are properly applicable to the 14 CWE countries used here but could be extended to other countries/regions with further analyses, as done for malaria\textsuperscript{22}. Finally, it should be noted that the dementia population(s) in the GBD study used here\textsuperscript{4} include dementia cases from Parkinson’s disease. However, the estimated percentage of dementia attributable to Parkinson’s disease in the population is only 3-4% globally\textsuperscript{60}, and reducing the GBD dementia population counts accordingly would yield the same correlations between the adjusted dementia prevalence and HLA allele frequency, since the percentage above is generally consistent from country to country.

Summary and Conclusions

The present study documents highly overlapping HLA profiles for dementia and Parkinson’s disease at the population level in Continental Western Europe, suggesting that similar population-level immunogenetic mechanisms contribute to prevention and/or susceptibility to both conditions. With respect to prevention, HLA plays a major role in the elimination of foreign antigens and, hence, its protective role found here can be attributed to the elimination of potential pathogens implicated as putative causative agents for these diseases (e.g., human herpes viruses\textsuperscript{31}). HLA also
plays a major role in autoimmunity which may occur in the absence of protection and in the presence of ensuing chronic inflammation. In both protection (pathogen elimination) and susceptibility (autoimmunity) cases, the HLA overlap between dementia and Parkinson’s disease indicates a similarity/overlap in the family of putative pathogens and autoantigens, respectively. The identification of such pathogens and autoantigens could be further investigated (e.g., in silico) using information from the specific alleles involved in protection and susceptibility. Finally, the present findings and future prospects regarding identification of disease-associated pathogens and autoantigens based on a disease’s HLA-profile extend beyond common neurodegenerative diseases to include a wide range of conditions for which pathogens and/or autoimmunity have been implicated, both in specific regions and globally.

Abbreviations

HLA: Human Leukocyte Antigen

Author contributions

APG contributed to data analysis; LMJ and APG contributed to writing the manuscript.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval

The research was approved by the Minneapolis VA Health Care System Research and Development Committee (Reference Number 006265).

Consent to Participate

Not applicable.

Consent to Publication

Not applicable.

Availability of Data and Materials

The datasets analyzed for this study are publicly available. The data can be found in the Allele Frequency Net Database (allelefrequencies.net) and in publications4,5,23.

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