The contribution of Neanderthal introgression and natural selection to neurodegenerative diseases

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Abstract

Background: Humans are thought to be more susceptible to neurodegeneration than equivalently-aged primates. It is not known whether this vulnerability is specific to anatomically-modern humans or shared with other hominids. The contribution of introgressed Neanderthal DNA to neurodegenerative disorders remains uncertain. It is also unclear how common variants associated with neurodegenerative disease risk are maintained by natural selection in the population despite their deleterious effects. In this study, we aimed to quantify the genome-wide contribution of Neanderthal introgression and positive selection to the heritability of complex neurodegenerative disorders to address these questions.

Methods: We used stratified-linkage disequilibrium score regression to investigate the relationship between five SNP-based signatures of natural selection, reflecting different timepoints of evolution, and genome-wide associated variants of the three most prevalent neurodegenerative disorders: Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.

Results: We found a significant depletion of positively-selected SNPs in the heritability of Parkinson's disease, raising the possibility that these variants may modulate disease risk, in addition to conferring an evolutionary advantage. For Alzheimer's disease and amyotrophic lateral sclerosis, common deleterious disease variants are unlikely to be maintained by positive selection. There was no enrichment of Neanderthal introgression in the SNP-heritability of these disorders, suggesting that Neanderthal admixture is unlikely to have contributed to disease risk.

Conclusions: These findings provide insight into the origins of neurodegenerative disorders within the evolution of *Homo sapiens* and addresses a long-standing debate, showing that Neanderthal admixture is unlikely to have contributed to common genetic risk of neurodegeneration in anatomically-modern humans.

Introduction

Encephalisation and the evolution of complex human-specific traits are thought to have increased the susceptibility of *Homo sapiens* to disorders of the brain compared to their aged non-human primate counterparts.[1-3] This is seen in Alzheimer's and Parkinson's disease, which have not been observed naturally on a pathological or phenotypic level in non-human species.[1 2] Likewise, unique motor dysfunction in amyotrophic lateral sclerosis (ALS) supports the selective vulnerability of the highly-developed corticomotoneuronal system in humans.[4-6] Human-lineage-specific genomic sequences have been shown to be enriched for brain-specific elements and risk loci for neurodegenerative disorders.[7] Thus, while positive natural selection has driven human adaptive evolution,[8] it may be possible that the same selected variants also influence the risk of neurodegenerative disease.

It is not known whether this neuro-vulnerability arose after divergence from other species or whether it represents a more recent phenomenon, characteristic of modern-day humans over other hominids. As anatomically-modern humans migrated out of Africa 50 to 100 thousand years ago, they interbred with archaic hominins including Neanderthals.[9] As a result, Neanderthal DNA accounts for approximately 1–4% of the modern Eurasian genome.[10-12] While most Neanderthal DNA experienced purifying selective pressures,[13] positive selection of these archaic alleles may have contributed to modern human adaptation to the non-African environment[14] through modulating dermatological[13], immunological[15 16] and metabolic function.[17 18] These introgressed Neanderthal alleles have also been implicated in contributing to the risk of some conditions, including actinic keratosis, depression and obesity.[19]

It remains unclear how much Neanderthal admixture has affected our risk of neurodegenerative disorders. While Neanderthal single nucleotide polymorphisms (SNPs) may be associated with "neurological" phenotypes through electronic health records of European patients, these nervous system traits were not representative of neurodegenerative diseases.[19] More recently, one study aimed to address the complex nature of medically-relevant traits and the genome-wide influence of Neanderthal admixture using UK Biobank data.[20] This found that introgressed variants were depleted for heritability of high-level cognitive traits.[20]

Thus, to quantify the contribution of Neanderthal admixture to the heritability of neurodegenerative diseases and to examine whether natural selection maintains common genetic risk of these disorders, we tested the relationship between alleles associated with Alzheimer's disease[21], ALS[22] and Parkinson's disease[23] from recent genome-wide association studies (GWAS) with SNP-based signatures of natural selection.[24] Using stratified-linkage disequilibrium score regression (LDSC), we found that there was a significant depletion of SNP-heritability for Parkinson's disease in alleles most subjected to Neanderthal introgression and positive selection. There was no significant enrichment of Neanderthal introgression or positive selection in the SNP-heritability of Alzheimer's disease. Variants from more recent selective sweeps were nominally enriched for association with ALS heritability, while SNPs from older selective sweeps showed a trend for depletion of ALS heritability. Thus, positive selection is unlikely to have played a significant role in the maintenance of common deleterious variants in the genetic architecture of these neurodegenerative diseases.

Methods

Heritability is defined as the fraction of a trait that is explained by inherited genetic variants in a given environment, and is important for understanding the biology of disease.[25] More specific to stratified-LDSC, narrow-sense heritability is defined as the proportion of phenotypic variance that can be attributed to variation in the additive effects of genes.[26] Stratified-LDSC analysis estimates the SNP-based heritability (h^2_{SNP}) of complex traits stratified across different annotations using GWAS data.[27] [28] Thus, we were able to use stratified-LDSC to assess the enrichment and depletion of common-h^2_{SNP} of complex neurodegenerative diseases for metrics of Neanderthal introgression and positive selection.[24]

For the metric of Neanderthal introgression, we used the average posterior probability of each human haplotype being the result of Neanderthal admixture estimated by comparing human and Neanderthal genomes (LA).[13] [24] We used four metrics of positive selection: integrated haplotype score (iHS), composite of multiple signals (CMS), cross-population extended haplotype homozygosity (XP-EHH), and composite likelihood ratio (CLR). These metrics were chosen to reflect the different timeframes of the selective processes used and described in previous analyses.[24] iHS measures the amount of extended haplotype homozygosity at a given SNP in the ancestral allele relative to the derived allele and estimates positive selective sweep.[8] CMS identifies the regions under positive selection by combining long-range haplotypes, differentiated alleles and high frequency derived alleles.[29] Both iHS and CMS detect more recent selective sweeps in the last 30,000 years.[8] [29] XP-EHH compares two populations to detect an allele that has reached fixation in one population but remains polymorphic in another, identifying alleles that have undergone different selective pressures since population divergence.[30] Lastly, CLR detects incomplete selective sweeps, quantifying

the relative influence of recombination and selection and corrects for background selection.[31] It can thus detect older signals from ~60,000 to 240,000 years ago.[24] We did not use any other metrics of purifying selection such as McVicker B-statistic[32] as a metric of background selection is already incorporated into the baseline LDSC model (v.2.2.). LA, CLR and CMS were directly retrieved from published references. For both iHS and XP-EHH, we used the metrics calculated previously[24] using the European superpopulation of the 1,000 Genomes Project Panel 3 dataset, with the African superpopulation used as the second population for XP-EHH.[24 33] Further, we transformed the absolute iHS and $-\log_{10}$ XP-EHH metrics to ensure that all metrics were on a common scale, in which larger values indicate stronger effect of selection or increased probability of introgression.

We used stratified-LDSC v.1.0.1 (https://github.com/bulik/ldsc/wiki) to test whether these natural selection metrics contribute significantly to heritability of neurodegenerative disease. All natural selection metrics were annotated to the ~9,997,000 SNPs present in the baseline LDSC model (v.2.2), which only includes SNPs with a minor allele frequency of more than 5%. Binary annotations were generated from the natural selection metrics, with thresholds at the top 2%, 1% and 0.5% of the genome-wide values of each metric in the full set of baseline SNPs.[24] This centile approach was used in previous studies due to difficulties defining the thresholds for selection.[24] Annotations were then added individually to the baseline LDSC model of 97 annotations (v.2.2, GRCh37),[34] comprising genome-wide annotations reflecting genetic and LD architecture. HapMap Project Phase 3 (HapMap3)[35] SNPs and 1000 Genomes Project Phase 3[36] European population SNPs were used for the regression and LD reference panels, respectively. The major histocompatibility complex region was excluded from all analyses owing to the region's complicated and long-range LD patterns. This analysis generated a regression coefficient (τ_c), from which we calculated a two-tailed p-value, testing

whether the regression coefficient of the annotation category contributes (either through enrichment or depletion) to the trait heritability conditional upon other annotations in the baseline-LD model. False discovery rate (FDR) multiple testing correction was applied across each GWAS, accounting for the number of annotations run (totalling 15 annotations per GWAS). A stringent FDR-corrected $p < 0.05$ was taken to be significant and nominal significance was defined as p-values <0.05 without FDR correction. We assessed the annotation for h^2_{SNP} contribution in complex brain-related disorders of apparently sporadic Alzheimer's disease[21], Parkinson's disease (excluding 23&Me participants)[23] and ALS (European cases only)[22] using recent corresponding GWAS summary statistics (further description in **Supplementary Table 1**). We chose these three neurodegenerative diseases given that they are the most prevalent of such disorders, have varying mean ages of onset which might affect selection pressures, and have correspondingly well-powered GWAS. All analyses were carried out in R version 4.0.5 (https://www.R-project.org/) and code is available from: https://github.com/RHReynolds/als-neanderthal-analysis.

Results

To quantify the contribution of Neanderthal introgression and positive natural selection to the heritability of three neurodegenerative disorders, we used stratified-LDSC to assess enrichment or depletion of the h^2_{SNP} of Alzheimer's disease, ALS and Parkinson's disease for each SNP-based signature of natural selection. For all analyses, we reported a two-tailed coefficient p-value that tested whether the regression coefficient (τ_c) of an annotation category contributes to trait heritability, conditional upon other annotations that account for the underlying genetic architecture (**Table 1**, **Figure 1**, full results in **Supplementary Table 2**).

After correction for multiple testing, we found a significant depletion of Parkinson's disease h^2_{SNP} in SNPs most subjected to Neanderthal introgression (top 0.5% LA, τ_c = -4.543×10^{-9}, FDR-corrected p = 0.044) (**Figure 1**). Furthermore, there was a nominal depletion (τ_c p < 0.05) of Parkinson's disease h^2_{SNP} using the top 1% LA (p = 0.027) (**Table 1**). A significant depletion of Parkinson's disease h^2_{SNP} was also observed in SNPs under positive selection, as defined by the top 0.5%, 1% and 2% XP-EHH metric (τ_c: -1.097×10^{-8}, -1.120×10^{-8}, -7.780×10^{-9}, FDR-corrected p = 0.044, 0.021, 0.044, respectively). Importantly, the baseline-LD model controls for metrics of background selection, suggesting that SNPs under positive selection, but under weak or no background selection, are depleted for association with Parkinson's disease. We then interrogated the contribution of the baseline-LD annotation for background selection for h^2_{SNP} in models including each of our natural selection metrics. For each of the five natural selection metrics across all three centiles used, we found that the background selection metric used in the baseline-LD model was nominally enriched (τ_c p <

0.05) only for Parkinson's disease h^2_{SNP} over and above the enrichment of any of the natural selection metrics and the other 96 baseline-LD annotations (**Supplementary Table 3**).

A significant depletion of Alzheimer's disease h^2_{SNP} was found using the top 2% CLR statistic (τ_c -2.210×10^{-9}, FDR-corrected p-value 0.041). However, there was no nominal depletion across either the top 0.5% or 1% of this positive selection metric. Given this inconsistency, this finding suggests that SNPs under positive selection are unlikely to be depleted for association with Alzheimer's disease.

After correction for multiple testing, no significant enrichment or depletion of ALS h^2_{SNP} were observed in metrics of Neanderthal introgression or positive selection. However, several nominal results were observed (τ_c p-value<0.05) (**Table 1**). We found a nominal enrichment of ALS h^2_{SNP} in the top 0.5% and 1% of the iHS metric (τ_c: 1.179×10^{-7}, 6.209×10^{-8}, p = 0.009, 0.021, respectively), and the top 2% of the XP-EHH metric (τ_c 2.888×10^{-8}, p = 0.042). Notably, both metrics are variations on extended haplotype homozygosity and are thought to be complementary in terms of their scope as they reflect measures of LD across the haplotype that contains the selected allele. On the other hand, we also found a nominal depletion of ALS h^2_{SNP} using the top 0.5%, 1% and 2% of the CLR metric (τ_c: -1.743×10^{-8}, -1.115×10^{-8}, -1.011×10^{-8}, p = 0.004, 0.017, 0.026 respectively). This may suggest that SNPs from more recent selective sweeps (~30,000 years ago), as indexed by iHS[24], are enriched for association with ALS, while SNPs from older selective sweeps (60,000 to 240,000 years ago)[24], as indexed by CLR, are depleted for disease association.

		Top 0.5% of scores			Top 1% of score			Top 2% of score		
GWAS	Metric	Enrichment	2-sided p-value	FDR-corrected p	Enrichment	2-sided p-value	FDR-corrected p	Enrichment	2-sided p-value	FDR-corrected p
AD2019 (Alzheimer's disease)	**LA**	0.645	0.454	0.661	0.583	0.398	0.661	0.551	0.261	0.560
	CLR	-0.138	0.484	0.661	-0.288	0.103	0.560	**-0.465**	**0.003**	**0.041**
	CMS	0.651	0.796	0.853	0.985	0.911	0.911	0.681	0.591	0.681
	iHS	-1.309	0.537	0.671	-1.872	0.217	0.560	-0.730	0.229	0.560
	XP-EHH	-1.119	0.299	0.560	-0.764	0.293	0.560	-0.751	0.122	0.560
ALS2021.EUR (Amyotrophic lateral sclerosis)	**LA**	1.265	0.784	0.784	1.144	0.784	0.784	0.796	0.779	0.784
	CLR	**-1.344**	**0.004**	0.067	**-0.795**	**0.017**	0.077	**-0.581**	**0.026**	0.077
	CMS	0.435	0.545	0.784	0.848	0.708	0.784	0.934	0.713	0.784
	iHS	**11.908**	**0.009**	0.068	**6.772**	**0.021**	0.077	3.611	0.079	0.141
	XP-EHH	5.064	0.085	0.141	4.102	0.060	0.129	**3.004**	**0.042**	0.104
PD2019.meta5.ex23&Me (Parkinson's disease)	**LA**	**-0.627**	**0.012**	**0.044**	**-0.042**	**0.027**	0.080	0.366	0.095	0.237
	CLR	0.078	0.673	0.841	0.279	0.773	0.892	0.575	0.845	0.906
	CMS	0.243	0.561	0.765	0.535	0.550	0.765	1.115	0.932	0.932
	iHS	-2.791	0.324	0.558	-1.020	0.335	0.558	-0.519	0.227	0.487
	XP-EHH	**-2.544**	**0.009**	**0.044**	**-2.502**	**0.001**	**0.021**	**-1.236**	**0.007**	**0.044**

Table 1. Heritability analysis of natural selection metrics. Stratified-LDSC results for SNPs defined by top genome-wide percentiles (0.5%, 1% or 2%) of all SNPs annotated for each natural selection metric. Enrichment values below 1 indicate a depletion of SNP-heritability (h^2_{SNP}) in an annotation category (i.e. showing a lower contribution than expected for a given number of SNPs). The two-sided p-values given are for the regression coefficient, which determines the contribution of an annotation to h^2_{SNP} conditional on all annotations in the LDSC baseline model (v.2.2). The FDR-corrected p is the coefficient p-value following correction for multiple testing. Coefficient p-values<0.05 and corresponding enrichment values are highlighted in bold. Neanderthal introgression metric (LA) indicates posterior probability of Neanderthal admixture. Positive selection metrics are composite likelihood ratio statistic (CLR), composite of multiple scores (CMS), integrated haplotype score (iHS), cross-population extended haplotype homozygosity (XP-EHH). Genome-wide association studies (GWAS) include AD2019 (Alzheimer's disease, Jansen *et al.* 2019)[21], ALS2021.EUR (European cases only from amyotrophic lateral sclerosis GWAS, van Rheenen *et al.* 2021)[22] and PD2019.met5.ex23&Me (Nalls et al. 2019, excluding 23&Me participants).[23] Full results are shown in Supplementary Table 2.

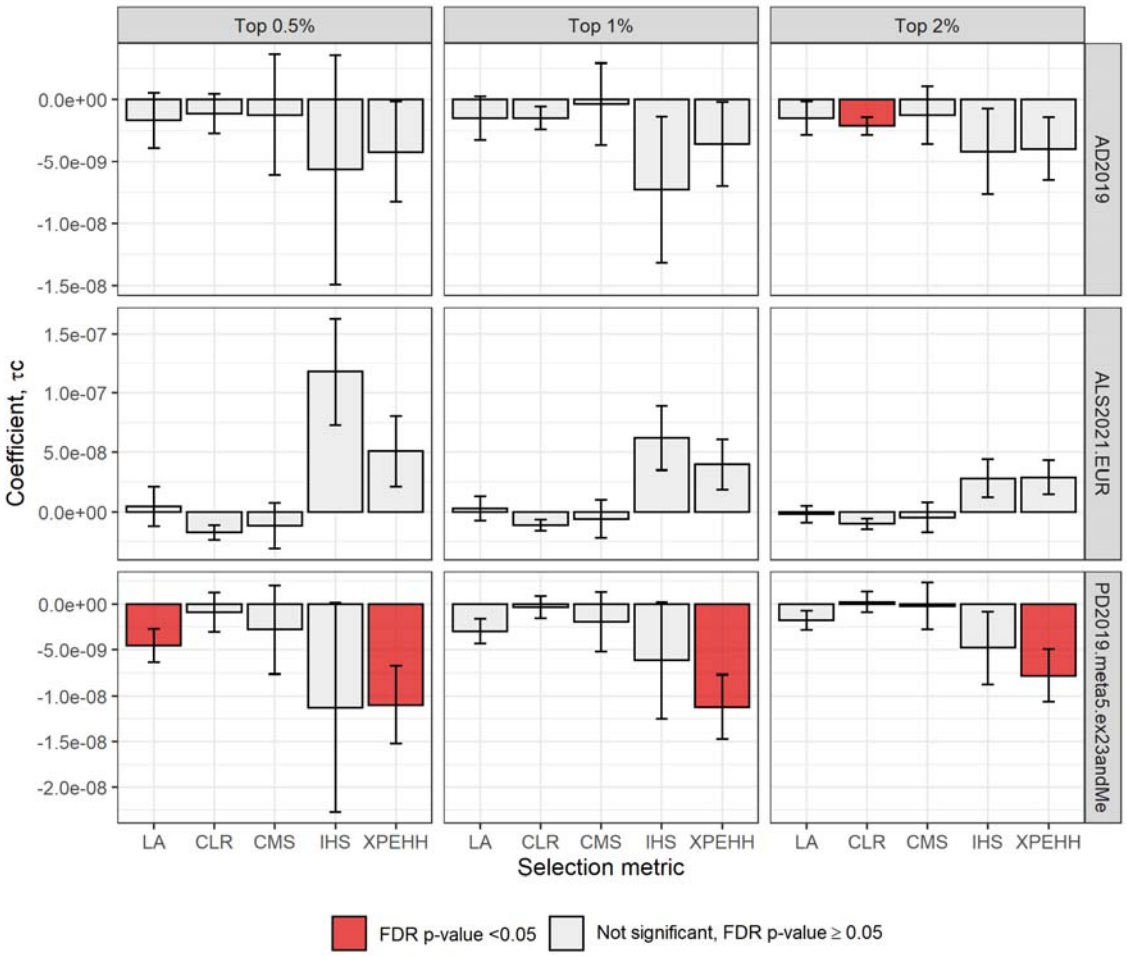

Figure 1. Stratified-linkage disequilibrium score regression analysis across three neurodegenerative disorders comparing SNP-based signatures of Neanderthal introgression and natural selection, stratified across top genome-wide percentiles (0.5%, 1% or 2%) of annotated SNPs. The regression coefficient (τ_c) represents the contribution of the annotation to trait SNP-heritability (h^2_{SNP}), controlling for all other annotations within the baseline model. The error bars represent 95% confidence intervals. Positive values represent enrichment of trait h^2_{SNP} within that annotation. Negative values represent depletion of trait h^2_{SNP} within that annotation. Bars filled with red shading represent significant FDR-corrected two-sided p-values of the regression coefficient (FDR-corrected $p < 0.05$). Neanderthal introgression metric (LA) indicates posterior probability of Neanderthal admixture. Positive selection metrics are composite likelihood ratio statistic (CLR), composite of multiple scores (CMS), integrated haplotype score (iHS), cross-population extended haplotype homozygosity (XP-EHH). Genome-wide association studies (GWAS) include AD2019 (Alzheimer's disease, Jansen *et al.* 2019)[21], ALS2021.EUR (European cases only from amyotrophic lateral sclerosis GWAS, van Rheenen *et al.* 2021)[22] and PD2019.met5.ex23&Me (Nalls et al. 2019, excluding 23&Me participants).[23]

Discussion

Humans are particularly vulnerable to neurodegeneration.[1 2] For example, in ALS, the most frequent neurodegenerative disease of mid-life, motor neurone degeneration results in disruption of multiple motor functions that are key to survival, and therefore of importance for evolutionary adaptation.[37] Any genetic variation predisposing to motor neurone degeneration might therefore be expected to be under major negative selection pressures. Thus, several possible evolutionary explanations may exist for common alleles contributing to neurodegenerative disease risk to persist in the population despite their deleterious effects.

First, any genetic variation predisposing to disease could have a corresponding benefit and therefore be positively selected. This is a mechanism by which the persistence of Neanderthal-derived sequences in the modern Eurasian human genome has been explained.[13] For example, a Neanderthal haplotype associated with protection against severe forms of SARS-CoV-2 infection (and other RNA viruses) is also linked to Alzheimer's disease risk.[38 39 40] Alternatively, deleterious variants in LD with an advantageous allele may have hitchhiked during positive selection, rising in frequency in the population.[41] This would be consistent with the proposed Northern founders of the p.91D>A *SOD1* variant in ALS[42] and the pathogenic *C9orf72* hexanucleotide repeat expansion associated with ALS and frontotemporal dementia.[43 44] Secondly, because neurodegenerative disorders are diseases of ageing, any genetic susceptibility might act after child-rearing years, and therefore outside the age window in which negative selection pressure could have an impact on allele frequency.[45] In this scenario, the negative effect of the genetic variant is mitigated by the timing of neurodegeneration. Thirdly, neurodegenerative diseases might result from multiple rare variants, each unique in the affected person, and therefore be too rare for selection to have a significant impact.[46] With the increased availability of high-depth next generation sequencing,

many rare variants have now been found to be associated with ALS[22 47 48], Parkinson's disease[23 49] and Alzheimer's disease[50 51], but common variants also contribute to risk. To address these hypotheses of how natural selection may have led to the persistence of common genetic risk variants of neurodegenerative disorders, we used stratified-LDSC to test the relationship between neurodegeneration-related SNPs and SNP-based signatures of natural selection.

Parkinson's disease h^2_{SNP} was depleted of introgressed Neanderthal SNPs. This observation is consistent with a recent study using UK Biobank data that showed introgressed variants were depleted for contribution to the heritability of most complex traits.[20] We also found no significant enrichment of Alzheimer's disease or ALS h^2_{SNP} in SNPs associated with Neanderthal admixture. Together, these findings suggest that negative selection likely purged some introgressed alleles that influence Parkinson's disease risk, while it may be possible that introgressed variants conferred no overall effect for Alzheimer's disease or ALS. Thus, Neanderthal admixture is unlikely to have maintained the common genetic variant architecture of these neurodegenerative diseases in modern humans.

Positive selection is seen as the main evolutionary mechanism for adaptation to a new environment.[52] In this situation, the beneficial allele sweeps to high frequencies and towards fixation (defined as 100% frequency) together with other variants on the same haplotype, reducing the population genetic diversity in a selective sweep.[52] SNPs under positive selection were found to be depleted for association with Parkinson's disease h^2_{SNP}. This suggests that positive selection does not maintain common risk alleles in Parkinson's disease. In fact, a depletion of these positively selected SNPs was seen after controlling for background selection. This raises the question of whether natural selection may modulate PD disease risk,

in addition to conferring an evolutionary advantage. There was a nominal enrichment of the LDSC baseline model background selection metric, leading to speculation that SNPs contributing to PD h^2_{SNP} are maintained by background selection, or at least, in part, are constrained within the genome as a result of background selection. In Alzheimer's disease, this depletion of positively selected SNPs was not as clear, indicating that positive selection is unlikely to be associated with persistence of these common disease-associated variants.

Heritability needs to be considered using this approach to estimate the contribution of natural selection to disease risk. Given the heritability of Parkinson's disease is low compared to other neurodegenerative and psychiatric diseases (0.22 according to estimates from the latest genome-wide meta-analysis)[23], a strong environmental component is implicated in the contribution to disease. This would mean that natural selection would have a limited role in Parkinson's disease risk. However, the depletion of alleles that have been positively selected through Neanderthal admixture or other selective sweeps implicate a strong gene-environment interaction. Indeed, gene-environment interaction frameworks have previously been proposed for the persistence of deleterious common variants in the population gene pool.[53]

For ALS, we saw nominally significant results suggesting SNPs from more recent selective sweeps (~30,000 years ago) are enriched for association with ALS, while SNPs from older selective sweeps (60,000 to 240,000 years ago) are depleted for disease association. Examples of recent adaptive events include persistence of lactose tolerance into adulthood in Europeans following the domestication of cattle.[54] This suggests that some ALS h^2_{SNP} can, in part, be accounted for by positive selection. In this case, the deleterious variants have only recently emerged so may not have yet had time to be subjected to purifying pressures to lead to their purging.[55] Given the potential contribution of positive selection to ALS h^2_{SNP} is more recent,

it could be hypothesised that the disease we see today is a unique disorder of anatomically-modern humans. This means that the development of traits unique to modern humans, such as manual dexterity and complex tool use may also be accompanied by a vulnerability to motor neurone degeneration or by their functional complex failure.[37] It is also worth noting that a degenerative myelopathy has been described in other species such as dogs[56] but there are distinct pathologic and phenotypic differences from human ALS. For example, white matter lesions of the spinal cord are the defining feature in canine degenerative myelopathy and the disease is comparatively more slowly progressive.[56] This relationship with positive selection is intriguing, providing support for an increased common allele frequency despite the selective removal of alleles that are deleterious, perhaps in combination with mitigation from the timing of disease onset. In addition, these findings showing the lack of enrichment from positive selection imply that the genetic architecture of Parkinson's and Alzheimer's diseases, and partially for ALS, may stem from multiple, rare, pleiotropic variants rather than polygenic variants with small effects.

This study has several limitations. Firstly, our analyses only studied individuals of European ancestry while Neanderthal introgression also occurred in non-European populations. Secondly, the h^2_{SNP} estimates using stratified-LDSC analysis are limited by the quality of LD information underpinning the heritability calculations[28] and the sample size of the GWAS, although we attempted to use only well-powered studies. LDSC also does not take into account the major histocompatibility complex region while Neanderthal alleles have been shown to play a role in modern immune function, thus missing those variants with pleiotropic effects in the nervous system.[15] Thirdly, each metric of natural selection and Neanderthal admixture has its own strengths and shortcomings and our analysis is limited by these measures.[52] However, we attempted to overcome this issue by using a range of SNP-based

signatures.[24] Lastly, this analysis did not take into account structural variants, short tandem repeats or other repetitive genomic elements that may have been acquired through positive selection. A recent study showed a number of repeat elements have risen *ab initio* in *Homo sapiens* which may have implications for positive selection in disease given that these are the most mutable regions of the genome.[57]

In this analysis, we quantified the contribution of positive selection and Neanderthal introgression to the heritability of Alzheimer's disease, ALS and Parkinson's disease using stratified-LDSC. We found no significant enrichment of Neanderthal introgression in the SNP-heritability of these neurodegenerative diseases. We also found that genomic regions with positive selection were depleted in heritability of Parkinson's disease with no evidence for the contribution of positive selection in Alzheimer's disease heritability. This suggests that positive selection does not maintain common risk variants for these disorders in the population even after controlling for background selection. Variants from more recent selective sweeps were nominally enriched for association with ALS heritability, while SNPs from older selective sweeps showed a trend for depletion of disease association. This provides further insights into the evolution of the genetic architecture of these disorders.

Contributorship statement

ZC, MRT, MR and AAC conceived and designed the study. ZC, RHR and SAGT critically analysed and interpreted the data. RHR set up and ran the stratified-LDSC analysis pipeline. AFP provided metrics for natural selection. WvR provided summary statistics from the ALS GWAS used. ZC wrote the first draft of the manuscript. JAH, HH, MJO, MRT, MR and AAC supervised the study. KL, AS, EKG, IF and ARJ contributed to the analyses. WR, PC, AC, PJS, KEM, JHV, LHvdV, CES, JFP, and VS contributed to GWAS data used in this study. All authors approved the manuscript and contributed to generation of the submitted draft.

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Competing interests

AAC reports consultancies or advisory boards for Amylyx, Apellis, Biogen, Brainstorm, Cytokinetics, GenieUs, GSK, Lilly, Mitsubishi Tanabe Pharma, Novartis, OrionPharma, Quralis, and Wave Pharmaceuticals.

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