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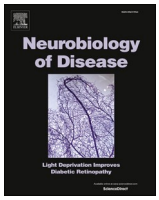

The contribution of Neanderthal introgression and natural selection to neurodegenerative diseases

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ABSTRACT

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

Abbreviations: SNPs, single nucleotide polymorphisms; ALS, amyotrophic lateral sclerosis; GWAS, genome-wide association studies; LDSC, linkage disequilibrium score regression; LD, linkage disequilibrium; FDR, False discovery rate.

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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.

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, amyotrophic lateral sclerosis and Parkinson's disease.

We found no evidence for enrichment of positively-selected SNPs in the heritability of Alzheimer's disease, amyotrophic lateral sclerosis and Parkinson's disease, suggesting that 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.

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.

1. 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.(Walker and Jucker, 2017; Diederich et al., 2019; Cookson, 2012) This is seen in Alzheimer's and Parkinson's disease, which seldom occur naturally on a pathological or phenotypic level in non-human species.(Walker and Jucker, 2017; Diederich et al., 2019) Likewise, unique motor dysfunction in amyotrophic lateral sclerosis (ALS) supports the selective vulnerability of the highly-developed cortico-motoneuronal system in humans.(Eisen et al., 1992; Chen et al., 2017; Henderson et al., 2019) Human-lineage-specific genomic sequences have been shown to be enriched for brain-specific elements and risk loci for neurodegenerative disorders.(Chen et al., 2021) Thus, while positive natural selection may have driven a proportion of human-specific adaptive evolution,(Voight et al., 2006; Mangan et al., 2022) 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. (Stewart and Stringer, 2012) As a result, Neanderthal DNA accounts for approximately 1–4% of the modern Eurasian genome.(Green et al., 2010; Prüfer et al., 2017; Skov et al., 2020) While most Neanderthal DNA experienced purifying selective pressures,(Sankararaman et al., 2014) positive selection of these archaic alleles may have contributed to modern human adaptation to the non-African environment(Racimo et al., 2015) through modulating dermatological,(Sankararaman et al., 2014) immunological(Abi-Rached et al., 2011; Yan et al., 2021) and metabolic function.(Khrameeva et al., 2014; Silvert et al., 2019) These introgressed Neanderthal alleles have also been implicated in contributing to the risk of some conditions, including actinic keratosis, depression and obesity.(Simonti et al., 2016)

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 in electronic health records of European patients, these nervous system traits were not representative of neurodegenerative diseases.(Simonti et al., 2016) More recently, two studies aimed to address the complex nature of medically-relevant traits and the genome-wide influence of Neanderthal admixture using UK Biobank data.(Dannemann et al., 2022; McArthur et al., 2021) The former study found that Neanderthal introgression did not significantly contribute to neurological and psychiatric traits and the latter found that introgressed variants were depleted for heritability of high-level cognitive traits.(McArthur et al., 2021) However, neither looked specifically at neurodegenerative diseases of interest.

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,(Jansen et al., 2019) ALS(van Rheenen et al., 2021) and Parkinson's disease(Nalls et al., 2019) from recent genome-wide association studies (GWAS) with SNP-based signatures of natural selection.(Pardinas et al., 2018) Using stratified-linkage disequilibrium score regression (LDSC), we found that there was no significant enrichment of Neanderthal introgression or positive selection in the SNP-heritability of Alzheimer's disease, ALS or Parkinson's disease. 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.

2. 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.(Visscher et al., 2008) 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.(Tenesa and Haley, 2013) Stratified-LDSC analysis estimates the SNP-based heritability (h^2_{SNP}) of complex traits stratified across different annotations using GWAS data.(Bulik-Sullivan et al., 2015; Finucane et al., 2015) 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.(Pardinas et al., 2018)

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).(Sankararaman et al., 2014; Pardinas et al., 2018) 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.(Pardinas et al., 2018) A detailed summary of the calculation of these metrics is shown in Supplementary Table 1 and code is available from https://github.com/RHReynolds/als-neanderthal-analysis. LA, CLR and CMS were directly retrieved from published references. For both iHS and XP-EHH, we used the metrics calculated previously(Pardinas et al., 2018) using the European superpopulation of the 1000 Genomes Project Panel 3

dataset, with the African superpopulation used as the second population for XP-EHH.(Pardinas et al., 2018; Consortium GP et al., 2015) 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. A summary of the workflow is found in Fig. 1. 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.(Voight et al., 2006) CMS identifies the regions under positive selection by combining long-range haplotypes, differentiated alleles and high frequency derived alleles.(Grossman et al., 2010) Both iHS and CMS detect more recent selective sweeps in the last 30,000 years.(Voight et al., 2006; Grossman et al., 2010) 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.(Sabeti et al., 2006a) Lastly, CLR detects incomplete selective sweeps, quantifying the relative influence of recombination and selection and corrects for background selection.(Vy and Kim, 2015) It can thus detect older signals from ~60,000 to 240,000 years ago.(Pardinas et al., 2018) We did not use any other metrics of purifying selection such as McVicker B-statistic (McVicker et al., 2009) as a metric of background selection is already incorporated into the baseline LDSC model (v.2.2.).

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 >5%. Binary annotations were generated from the natural selection metrics, with thresholds at the top 1%, 2%, 3%, 4% and 5% of the genome-wide values of each metric in the full set of baseline SNPs.(Pardinas et al., 2018) This centile approach was used in previous studies due to difficulties defining the thresholds for selection.(Pardinas et al., 2018) Annotations were then added individually to the baseline LDSC model of 97 annotations (v.2.2, GRCh37),(Hujoel et al., 2019) comprising genome-wide annotations reflecting genetic and LD architecture. HapMap Project Phase 3 (HapMap3)(Altshuler et al., 2010) SNPs and 1000 Genomes Project Phase 3(Abecasis et al., 2012) 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 25 annotations per GWAS). A stringent FDR-corrected p-value (FDR P) < 0.05 was taken to be significant. We assessed the annotation for h^2_{SNP} contribution in complex brain-related disorders of apparently sporadic Alzheimer's disease,(Jansen et al., 2019) Parkinson's disease (excluding 23&Me participants)(Nalls et al., 2019) and ALS (European cases only)(van Rheenen et al., 2021) using recent corresponding GWAS summary statistics (further description in Supplementary Table 2). 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. We assessed the SNP coverage for each of the annotations at the different centiles, defined as the proportion of SNPs accounted for by the annotation within the baseline set of SNPs, to ensure all annotations could be reliably interpreted. Annotations with low SNP coverage should be interpreted with caution as they are more likely subject to model misspecification.(Finucane et al., 2015) 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.

3. Results

To quantify the contribution of Neanderthal introgression and

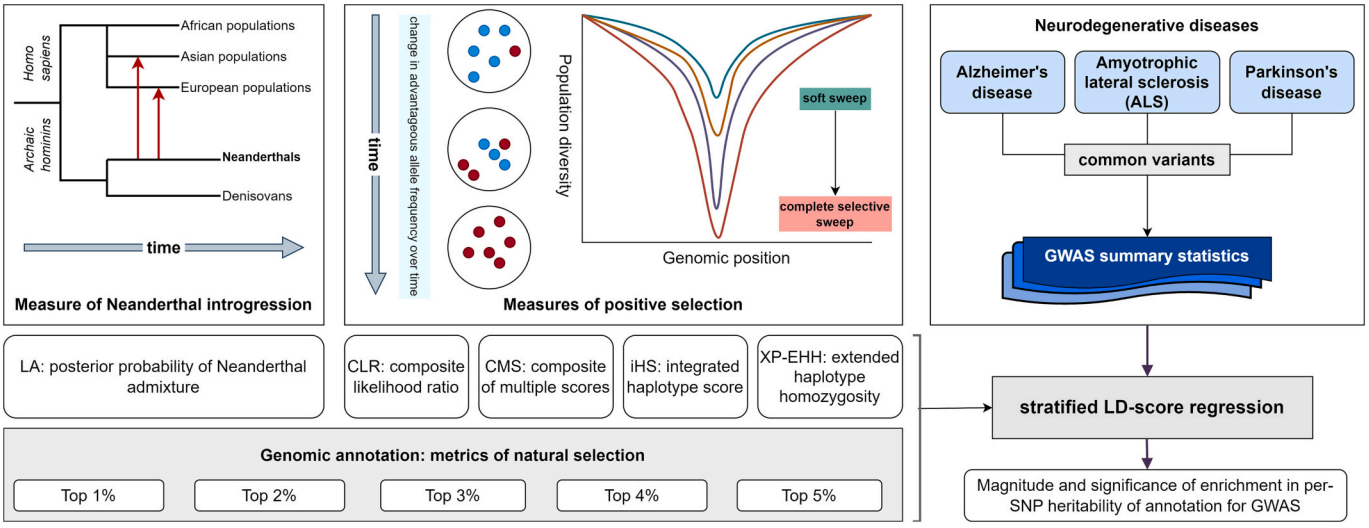

Fig. 1. Study workflow. Schematic figure showing key concepts of the study workflow. The red arrows signify admixture from Neanderthals to Eurasian populations; the posterior probability of Neanderthal admixture is measured by LA and partitioned into the top 1–5% metrics and inputted into the stratified-linkage disequilibrium (LD) score regression. Not all gene flow from archaic hominins to *Homo sapiens* is represented in the figure and phylogenetic branches are not to scale. For simplified measures of positive selection, the middle panel shows that with time, an advantageous allele rises in frequency in the population. At the same time, the population diversity decreases at that particular genomic position, and also in other SNPs in linkage disequilibrium that hitchhike with the beneficial allele. This resultant dip in diversity can be shallower in incomplete sweeps and deeper in more complete selective sweeps. Four metrics can measure this positive selection (CLR; CMS; iHS and XP-EHH). These four measures of positive selection were partitioned into the top 1–5% for use in the stratified-LD score regression. We used stratified-LD score regression analysis to test whether these natural selection metrics contribute significantly to heritability of neurodegenerative disease. We assessed the annotation for SNP-heritability contribution in the three most prevalent complex neurodegenerative disorders of Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis using recent corresponding GWAS summary statistics. Illustrative figures for natural selection are adapted from a review by Vitti et al. (Vitti et al., 2013) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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 an FDR-corrected 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, Fig. 2, full results in Supplementary Table 3).

We used the top five percentiles for each annotation at one percentile increments in the analyses. However, the proportion of SNPs accounted for by the annotation within the baseline set of SNPs was very low at the smaller percentiles of top 1–2% metric values (range: 0.0080 to 0.0226) (Supplementary Table 3). This lower SNP-coverage corresponded to larger standard errors at the top 1% and 2% annotations that are difficult to interpret (Supplementary Fig. 1). Thus, the low coverage annotations at top 1% and 2% metrics did not appear to be informative and we present the results for the top 3–5% annotations for further interpretation.

After correction for multiple testing, we found no evidence for enrichment in Alzheimer's disease, ALS or Parkinson's disease h^2_{SNP} in alleles most subjected to Neanderthal introgression, as annotated by LA across the top third to fifth centiles (Fig. 2). This was the case when using the τ_c taking into other annotations in the baseline model.

A significant depletion of Parkinson's disease h^2_{SNP} was also observed in SNPs under positive selection, as defined by the top 3 and 4% XP-EHH metric (τ_c: -6.770×10^{-9}, -5.890×10^{-9}; FDR $P = 0.043$, 0.043 respectively) (Table 1, Fig. 2). 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 more likely depleted for association with Parkinson's disease compared to other annotations in the baseline model (Supplementary Table 4). However, it should be noted that the τ_c values are relatively small. Furthermore, given the larger standard errors towards the top centiles reflecting their lower SNP coverage (Supplementary Fig. 1, Supplementary Table 3), the interpretation of a negative τ_c here should be interpreted with caution. 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 centiles used, we found that the background selection metric used in the baseline-LD model was not enriched (τ_c FDR $P < 0.05$) 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 4, Fig. 2). Therefore, these findings suggest that there is unlikely to be an enrichment of positively-selected SNPs in the genetic architecture of Parkinson's disease.

A significant depletion of Alzheimer's disease h^2_{SNP} was found using the top third and fourth centile CLR statistic ($\tau_c - 2.20 \times 10^{-9}$, -2.24×10^{-9}; FDR $P = 0.023$, 0.023 respectively). Again, this finding is not conclusive in suggesting that SNPs under positive selection are depleted for association with Alzheimer's disease (Fig. 2). Given that there was no evidence for other metrics of natural selection to be enriched for Alzheimer's disease h^2_{SNP}, it is also unlikely that positive selection contributed to the evolution of common variants contributing towards the risk of this disease.

After correction for multiple testing, no significant enrichment or depletion of ALS h^2_{SNP} were observed in metrics of positive selection, suggesting that positive selection did not play a role in the common genetic risk of ALS.

4. Discussion

Humans are particularly vulnerable to neurodegeneration.(Walker and Jucker, 2017; Diederich et al., 2019) 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.(Eisen et al., 2014) 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.(Sankararaman et al., 2014) 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.(Sabeti et al.,

Table 1
Heritability analysis of natural selection metrics. Stratified-LDSC results for SNPs defined by top 3–5% genome-wide percentiles of all SNPs annotated for each natural selection metric. 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 FDR-corrected *p*-value (FDR P) is the coefficient p-value following correction for multiple testing. Coefficient FDR $P < 0.05$ and corresponding τ_c values are highlighted in bold. SE represents the standard error of τ_c. 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),(Jansen et al., 2019) ALS2021.EUR (European cases only from amyotrophic lateral sclerosis GWAS, van Rheenen et al. 2021)(van Rheenen et al., 2021) and PD2019.met5.ex23&Me (Nalls et al. 2019, excluding 23&Me participants).(Nalls et al., 2019) Full results are shown in Supplementary Table 3.

		Top 3% scores			Top 4% scores			Top 5% scores		
GWAS	Metric	τc	FDR P	SE	τc	FDR P	SE	τc	FDR P	SE
Alzheimer's disease (AD2019)	**CLR**	−2.20E-09	**0.023**	7.20E-10	−2.24E-09	**0.023**	7.47E−10	−1.91E-09	0.054	7.25E−10
	CMS	−1.29E-09	0.639	1.93E-09	-1.28E-09	0.639	1.73E-09	-1.38E-09	0.635	1.66E-09
	iHS	−2.16E-09	0.635	2.56E-09	−8.97E-10	0.753	2.05E-09	−3.72E-10	0.908	1.79E-09
	LA	2.01E-10	0.908	1.24E-09	1.06E-09	0.639	1.61E-09	9.16E-10	0.639	1.36E-09
	XP-EHH	−3.26E-09	0.406	2.15E-09	−2.90E-09	0.406	1.85E-09	−2.21E-09	0.518	1.67E-09
ALS (ALS2021.EUR)	**CLR**	−1.01E-08	0.160	4.07E-09	−3.76E-09	0.852	6.62E-09	−3.75E-09	0.852	5.58E-09
	CMS	−3.38E-09	0.852	1.12E-08	−1.12E-09	0.953	1.05E-08	3.00E-10	0.976	9.94E-09
	iHS	1.51E-08	0.473	1.20E-08	1.03E-08	0.667	1.04E-08	6.50E-09	0.852	9.22E-09
	LA	2.68E-09	0.852	5.76E-09	2.63E-09	0.852	5.11E-09	1.65E-09	0.852	4.64E-09
	XP-EHH	1.88E-08	0.295	1.20E-08	1.89E-08	0.219	1.07E-08	1.88E-08	0.215	9.78E-09
Parkinson's disease (PD2019.meta5.ex23&Me)	**CLR**	−7.29E-11	0.955	8.96E-10	−5.65E-10	0.691	7.81E-10	−7.13E−10	0.563	7.79E−10
	CMS	−1.21E-10	0.955	2.18E-09	-1.22E-10	0.955	1.92E-09	-1.28E-10	0.955	1.79E-09
	iHS	−4.64E-09	0.285	2.93E-09	−4.61E-09	0.183	2.44E-09	−4.31E-09	0.163	2.16E-09
	LA	−1.10E-09	0.426	9.35E−10	−1.23E-09	0.340	8.55E-10	-1.06E-09	0.422	8.34E-10
	XP-EHH	−6.77E-09	**0.043**	2.43E-09	−5.89E-09	**0.043**	2.18E-09	−4.86E-09	0.062	1.94E-09

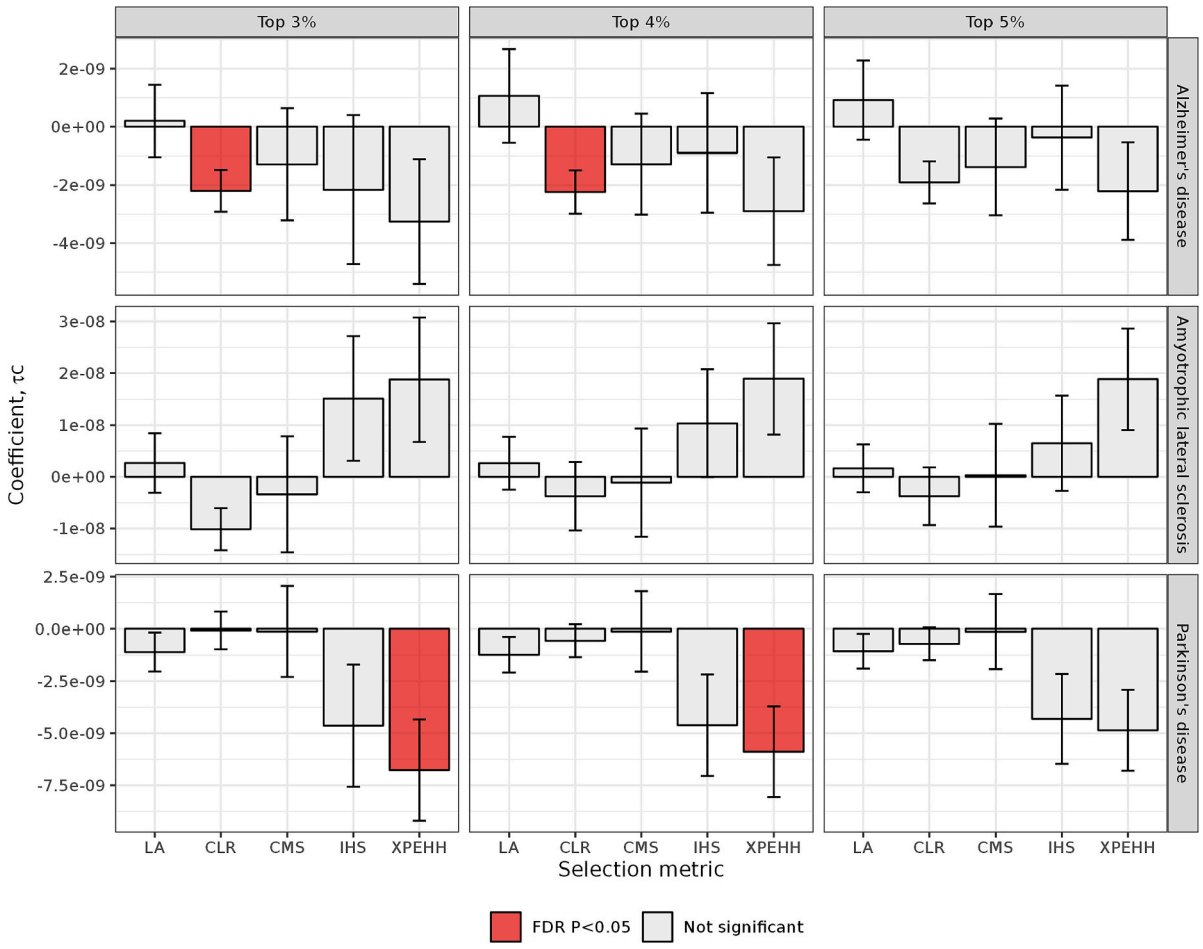

Fig. 2. Stratified-linkage disequilibrium score regression analysis across three neurodegenerative disorders comparing SNP-based signatures of Neanderthal introgression and natural selection, stratified across top genome-wide percentiles (3–5%) of annotated SNPs. The regression coefficient (τ_c) represents 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 compared to other annotations within the baseline model. Bars filled with red shading represent significant FDR-corrected two-sided *p*-values of the regression coefficient (FDR 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),(Jansen et al., 2019) ALS2021.EUR (European cases only from amyotrophic lateral sclerosis GWAS, van Rheenen et al. 2021)(van Rheenen et al., 2021) and PD2019.met5.ex23&Me (Nalls et al. 2019, excluding 23&Me participants).(Nalls et al., 2019) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2006b; Magusali et al., 2021; Zeberg and Pääbo, 2020) Alternatively, deleterious variants in LD with an advantageous allele may have hitchhiked during positive selection, rising in frequency in the population.(Chun and Fay, 2011) This would be consistent with the proposed Northern founders of the p.91D > A *SOD1* variant in ALS(Saeed et al., 2009) and the pathogenic *C9orf72* hexanucleotide repeat expansion associated with ALS and frontotemporal dementia.(Smith et al., 2013; Pliner et al., 2014) 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.(Gluckman et al., 2011) 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.(Dilliott et al., 2021) With the increased availability of high-depth next generation sequencing, many rare variants have now been found to be associated with ALS,(van Rheenen et al., 2021; Smith et al., 2014; Cirulli et al., 2015) Parkinson's disease(Nalls et al., 2019; Robak et al., 2017) and Alzheimer's disease,(Prokopenko et al., 2021; Sims et al., 2017) 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.

We found no significant enrichment of Alzheimer's disease, ALS or Parkinson's disease h^2_{SNP} associated with Neanderthal admixture. This observation is consistent with recent studies using UK Biobank data that showed introgressed variants were depleted for contribution to the heritability of most complex traits or at least not enriched.(Dannemann et al., 2022; McArthur et al., 2021) These studies did not specifically focus on neurodegenerative diseases. Our findings suggest that Neanderthal admixture is unlikely to have maintained the common genetic variant architecture of these neurodegenerative diseases in modern humans.

Positive selection is seen as an evolutionary mechanism for adaptation to a new environment.(Vitti et al., 2013) 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.(Vitti et al., 2013) SNPs under positive selection were found to be

depleted for association with Parkinson's disease h^2_{SNP} compared to other annotations in the baseline model (τ_c) but the absolute values were small and the simultaneous presence of a negative enrichment estimate with low SNP-coverage across the annotation suggests that there is at least no evidence of enrichment for positive selection in the heritability of these diseases. This suggests that positive selection does not maintain common risk alleles in Parkinson's disease. Heritability needs to be considered using this approach to estimate the contribution of natural selection to disease risk. The negative τ_c estimates may also, in part, stem from the relatively low heritability of Parkinson's disease compared to other neurodegenerative and psychiatric diseases (0.22 according to estimates from genome-wide meta-analysis),(Nalls et al., 2019) making it more difficult to definitely interpret the depletion in τ_c as a true depletion in Parkinson's disease h^2_{SNP}. Therefore, given the relatively low heritability of Parkinson's disease, 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. The lack of enrichment 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.(Uher, 2009)

In Alzheimer's disease, this depletion of positively selected SNPs was even less clear, indicating that positive selection is unlikely to be associated with persistence of these common disease-associated variants.

For ALS, we saw no evidence for the enrichment of positive selection in contributing to its trait heritability. 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. This is consistent with a previous study that uses UK Biobank data that found positive selection, as tagged by CMS, is not enriched for heritability of neurological traits.(Song et al., 2021) 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 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, where the extent of introgression may have differed and thus affects the sensitivity of the analysis. Secondly, the h^2_{SNP} estimates using stratified-LDSC analysis are limited by the quality of LD information underpinning the heritability calculations(Finucane et al., 2015) 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.(Abi-Rached et al., 2011) We are also excluding rarer Neanderthal introgressed and positively-selected variants by using a MAF cut-off and thus are not able to conclude on the heritability contribution of these variants with lower population frequency. Thirdly, each metric of natural selection and Neanderthal admixture has its own strengths and shortcomings and our analysis is limited by these measures.(Vitti et al., 2013) However, we attempted to overcome this issue by using a range of SNP-based signatures.(Pardinas et al., 2018) We also note that the negative enrichment estimates are difficult to interpret in this context, possibly due to the SNP coverage of the annotations, which we have tried to compensate for by using higher percentiles of each selection metric. 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.(Sulovari et al., 2019)

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 showed no evidence for the contribution in Alzheimer's disease, ALS and Parkinson's disease SNP-heritability. This suggests that positive selection does not maintain common risk variants for these disorders in the population even after controlling for background selection. These findings provide further insight into the evolution of the genetic architecture of these disorders.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2023.106082.

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.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.

Patient consent for publication

Not applicable.

Ethics approval

This study does not involve human participants.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information. Code is available from: https://github.com/RHReynolds/als-neanderthal-analysis.

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