Overlapping genetic architecture between Parkinson disease and melanoma

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ORIGINAL PAPER

Overlapping genetic architecture between Parkinson disease and melanoma

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Abstract

Epidemiologic studies have reported inconsistent results regarding an association between Parkinson disease (PD) and cutaneous melanoma (melanoma). Identifying shared genetic architecture between these diseases can support epidemiologic findings and identify common risk genes and biological pathways. Here, we apply polygenic, linkage disequilibrium-informed methods to the largest available case–control, genome-wide association study summary statistic data for melanoma and PD. We identify positive and significant genetic correlation (correlation: 0.17, 95% CI 0.10–0.24; $P = 4.09 \times 10^{-06}$) between melanoma and PD. We further demonstrate melanoma and PD-inferred gene expression to overlap across tissues (correlation: 0.14, 95% CI 0.06 to 0.22; $P = 7.87 \times 10^{-04}$) and highlight seven genes including *PIEZO1*, *TRAPPC2L*, and *SOX6* as potential mediators of the genetic correlation between melanoma and PD. These findings demonstrate specific, shared genetic architecture between PD and melanoma that manifests at the level of gene expression.

Keywords Parkinson disease · Melanoma · Genetic correlation · Polygenic · TWAS · Shared genetic architecture

Introduction

An association between idiopathic Parkinson disease (PD), neuropathologically characterized by the degeneration of pigmented dopaminergic neurons, and cutaneous melanoma (melanoma), a cancer of pigment-producing melanocytes, was first reported in 1972 [80]. This association was hypothesized to result from the chronic systemic administration of levodopa (L-DOPA)—an intermediate in the dopamine synthesis pathway [23]—for the treatment of PD [4, 80] as L-DOPA is also a biosynthetic intermediate in the production of melanin [23]. Since that time, several epidemiologic studies have examined the association between PD and melanoma as well as other cancers [5, 17, 21, 27, 29, 36, 42, 53, 67, 68, 81, 87, 91]. The majority of studies have found that individuals with PD appear to have a lower incidence of most cancers, with the exception of melanoma [21, 27, 36, 67, 68, 81, 91]. Both prospective

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and retrospective studies have also found an increased risk of melanoma in PD that appears to be independent of L-DOPA treatment [5, 29, 42, 67, 91]. For example, 92 out of 2106 (4.4%) individuals with neurologist-confirmed PD had either a personal history or current dermatologist-diagnosed melanoma in a 2010 study [5]. The increased risk of melanoma in PD has been observed to extend to family members and be reciprocal in nature with individuals being at greater risk for PD if their relatives have a melanoma diagnosis and vice versa [29, 42]. For example, 40 of 1544 (2.6%) of individuals with pathologically confirmed melanoma had a neurologist-confirmed diagnosis of PD in a 2017 study [17]. However, not all studies have identified an association between melanoma and PD in affected individuals [19, 27] or their relatives [91]. An epidemiologic association between lighter hair color and PD, a potentially shared risk factor with melanoma [6], has also been inconsistently reported [19, 30]. Epidemiologic association studies are not without biases. PD is known to have an extended prodromal period and a melanoma diagnosis necessitates longitudinal follow-up, both of which increase medical surveillance and thus the chance for spurious epidemiologic associations [27, 33]. In contrast, studies of genetic variants associated with disease or cross-disease risk are not expected to be influenced by the usage of medical care, though they may be subject to similar misclassification [75] and ascertainment biases.

The first investigations of a genetic relationship between melanoma and PD focused on variants in *MC1R*, a gene strongly associated with pigmentation and melanoma risk [45]. While early reports identified an association between PD and *MC1R* variants [30, 83], other studies failed to replicate these findings [24, 26, 28, 55]. Analyses focused on single variants in other melanoma risk genes have also failed to yield consistent associations with PD [19, 28, 56]. Multi-variant analyses have thus far reported a lack of genetic association as well. For example, a melanoma genetic risk score—calculated by aggregating the effect of melanoma genome-wide association study (GWAS)-significant ($P < 5 \times 10^{-8}$) loci included in the GWAS catalog [89] as of 2012—was not significantly associated with PD [65]. Similarly, no evidence for an association between GWAS-significant melanoma loci and PD is observed in a more recent multi-variant, Mendelian randomization study [66]. In contrast, genes associated with Mendelian forms of PD have been identified to be somatically mutated in melanoma lesions [37, 40, 48]. There may also exist an enrichment of Mendelian PD gene germline variants in individuals with melanoma [37], though this requires replication. Nevertheless, over 90% of individuals with PD do not have mutations in any known Mendelian PD genes [1] and thus variants in Mendelian PD genes are unlikely to fully explain any genetic correlation between melanoma and PD.

The genetic risk architecture underlying complex diseases like PD and melanoma is mediated by many common genetic variants of small effect size, most of which do not demonstrate GWAS-significant associations given current study sample sizes [8]. Analyses which only include GWAS-significant loci are not expected to fully represent the genetic architecture of these complex diseases and thus may lead to false-negative genetic overlap results. Recently, statistical methods that aggregate all loci from disease-specific GWAS summary statistic datasets in a linkage disequilibrium (LD)-informed manner have been developed to better model these polygenic architectures [11]. These aggregated signals can be leveraged to estimate the genetic correlation between different diseases [11, 54], even at the level of gene expression in specific tissues [35, 57] or across tissues [38]. Here, we apply these novel methods to GWAS summary statistics derived from the largest currently available studies of melanoma [45], PD [13, 63, 64], and other neurodegenerative diseases [25, 44] to investigate whether there exists specific genetic architecture overlap between melanoma and PD.

Methods

GWAS summary statistics

We obtained the largest available, European genetic ancestry, case–control, GWAS summary statistic data for melanoma (Law 2015 [45]) and three independent studies of PD (Nalls 2014 [64]; Chang 2017 [13]; Nalls 2019 [63]) as well as two negative control comparator neurodegenerative diseases: Alzheimer disease (Kunkle 2019 [44]) and frontotemporal dementia (Ferrari 2014 [25]). The summary statistics for these datasets included *P* value, effect allele, number of individuals or studies, and standard error for every genetic variant reported in each study. All individual studies contributing to the GWAS summary statistic datasets used in the current analysis received approval from the pertinent institutional review boards or ethics committees, and all participants gave informed consent. Additional details for each dataset are included below and in the individual study articles [13, 25, 44, 45, 63, 64].

Melanoma: Law 2015

We obtained summary statistics for the GWAS meta-analyses for melanoma risk from the melanoma consortium (https://genomel.org/). These data were published in Law et al., Nature Genetics, 2015 [45]. This dataset includes melanoma-association results for 9,469,417 genotyped and imputed variants derived from 12,814 pathologically confirmed melanoma cases and 23,203 controls of European ancestry.

Parkinson disease: Nalls 2014

We obtained PD risk summary statistic data from PDGENE (http://www.pdgene.org/). This dataset was published in Nalls et al., Nature Genetics, 2014 [64] and Lill et al., PLoS Genetics 2012 [50]. The summary statistic data we obtained did not include any 23andMe participants and thus the dataset includes PD-association results for 7,799,580 genotyped and imputed variants derived from 9,581 PD cases—mostly diagnosed, but some self-reported—and 33,245 controls of European ancestry. This dataset only included the number of studies, and not the number of individuals, supporting the association results for each variant. Consequently, we only included variants supported by at least 12 of 13 studies in downstream analyses.

Parkinson disease: Chang 2017

We obtained Parkinson disease (PD) risk summary statistic data from 23andMe, Inc., a personal genetics company (https://research.23andme.com/dataset-access/). These data were published in Chang et al., Nature Genetics, 2017 [13]. This dataset includes PD-association results for 12,896,220 genotyped and imputed variants derived from 6,476 self-reported PD cases and 302,042 controls of European ancestry. This dataset excludes any 23andMe participants included in the Nalls 2014 study.

Parkinson disease: Nalls 2019

We obtained PD risk summary statistic data from the IPDGC (https://pdgenetics.org/). This dataset was published in Nalls et al., The Lancet Neurology, 2019 [63]. The summary statistic data we obtained did not include any 23andMe data or Nalls 2014 data and thus include PD-association results for 17,510,617 genotyped and imputed variants derived from 33,674 PD cases—diagnosed and UKB proxy cases, that is individuals with a first-degree relative to PD—and 449,056 controls of European ancestry.

Alzheimer disease: Kunkle 2019

We downloaded stage 1 meta-analysis Alzheimer Disease (AD) risk GWAS summary statistic data from NIAGADS (National Institute on Aging Genetics of Alzheimer Disease Data Storage Site) website: https://www.niagads.org/datasets/ng00075 (#NG00075). These data were generated by the International Genomics of Alzheimer Project and published in Kunkle et al., Nature Genetics, 2019 [44]. The stage 1 meta-analysis dataset includes AD-association results for 11,480,632 genotyped and imputed variants derived from 21,982 AD cases and 41,944 cognitively normal controls of European ancestry.

Frontotemporal Dementia: Ferrari 2014

We obtained discovery phase frontotemporal dementia (FTD) risk GWAS summary statistic data from the International Frontotemporal Dementia Genomics Consortium (IFGC, https://ifgcsite.wordpress.com/data-access/). These data were generated by the IFGC and published in Ferrari et al., Lancet Neurology, 2014 [25]. The discovery phase dataset includes FTD-association results for 6,026,385 variants derived from 2154 individuals with FTD and 4,308 control of European ancestry.

Meta-analyzing PD GWAS datasets

We used METAL software [90] to perform an inverse-variance-weighted meta-analysis of the three independent PD GWAS summary statistics. We refer to this meta-analyzed PD dataset in the text, tables, and figures as METAPD (49,731 cases and 784,343 controls).

Standardization and filtering of GWAS summary statistics

We standardized all summary statistics prior to polygenic analyses. We first confirmed the genome build to be GRCh37 and then annotated variants with dbSNP v151 rs-identifiers and gnomAD [41] non-Finnish European (NFE) allele frequencies using ANNOVAR software (2018 Apr 16) [88]. We only included bi-allelic variants with rs-identifiers and in instances where multiple variants shared the same rs-identifiers, we selected the variant that was supported by the largest number of studies and/or the greatest sample size. Finally, we processed and filtered summary statistics using the munge_sumstats.py tool provided with Linkage Disequilibrium Score Regression Software (LDSC) [11]. This processing and filtering removed variants with an effect allele frequency of less than 0.05 in the gnomAD NFE population, variants with strand ambiguous alleles, variants supported by a low sample size or effective sample ($N_{eff} = 4/(1/N_{cases} + 1/N_{controls})$) for the meta-analysis [90], and variants that were not reported in the HapMap3 study [31]. The number of variants overlapping across all processed GWAS summary statistic datasets analyzed in the present study is presented in Table 1.

Estimating genetic overlap by GNOVA

We calculated genetic overlap using GNOVA software [54]. GNOVA estimates genetic covariance based on all the genetic variants shared between two GWAS summary statistic datasets. In brief, the summary statistic z scores observed for each variant are multiplied and their product is regressed against the LD score for that variant,

Table 1 Number of overlapping variants in processed GWAS summary statistic datasets

Dataset	Melanoma Law 2015	PD Nalls 2014	PD Chang 2017	PD Nalls 2019	METAPD	AD Kunkle 2019	FTD Ferrari 2014
Law 2015	1,038,973	–	–	–	–	–	–
Nalls 2014	997,418	1,015,955	–	–	–	–	–
Chang 2017	1,038,516	1,015,498	1,075,906	–	–	–	–
Nalls 2019	1,007,785	983,012	1,033,569	1,034,607	–	–	–
METAPD	1,007,521	983,023	1,032,819	1,033,287	1,033,303	–	–
Kunkle 2019	1,038,796	1,015,849	1,075,582	1,034,409	1,033,126	1,077,308	–
Ferrari 2014	979,084	973,381	993,831	961,697	961,512	994,078	994,337

All GWAS summary statistic datasets were standardized and filtered using the same pipeline. We annotated all variants with dbSNP v151 rs-identifiers and gnomAD non-Finnish European (NFE) allele frequencies. We filtered variants as to only include bi-allelic variants with rs-identifiers and further removed variants with an effect allele frequency less than 0.05, variants with strand ambiguous alleles, variants with limited support, i.e., those supported by a low sample or study number, and variants that were not reported in the HapMap3 study. Presented are the numbers of variants overlapping between each dataset. METAPD is an inverse-variance-weighted meta-analysis of the three independent Parkinson disease summary statistic datasets

PD Parkinson disease, *AD* Alzheimer disease, *FTD* frontotemporal dementia

with the LD score being calculated based on the external 1000 genomes project CEU population [84]. Genetic covariance is then estimated based on all shared variants using the method of moments and a block-wise jackknife approach as described in the GNOVA manuscript [54]. GNOVA further provides an estimate of genetic correlation based on this calculated genetic covariance and the estimated GWAS variant-based heritabilities. As with LD score regression [11], GNOVA is able to statistically correct for any sample overlap between two different sets of GWAS summary statistics. In addition, GNOVA produces unbounded genetic correlation estimates which may be greater than one for traits which are highly genetically correlated. GNOVA provides greater statistical power and higher estimation accuracy for genetic correlations than LD score regression, especially when the correlations are moderate [54], as is expected for melanoma and PD. We ran GNOVA software on the processed GWAS summary statistics using default parameters and the 1000 Genomes [84] European population-derived reference data provided with the software. Given we test the genetic correlation of melanoma against PD, AD, and FTD, we use a Bonferroni-corrected significance threshold of $P < 1.67 \times 10^{-02}$ (0.05/3) for our primary analysis. We also ran annotation-stratified analyses using the minor allele frequency quartile and chromosome annotations provided with GNOVA software as well as the aforementioned reference data and parameters. In the text, we present genetic correlations, 95% confidence intervals, and *P* values that have been corrected for sample overlap by GNOVA.

Disease-inferred gene expression overlap analyses

We investigated whether the genetic overlap between PD and melanoma was mediated by shared regulation of gene expression. To do this, we generated tissue-specific, disease-inferred gene expression profiles from the processed GWAS summary statistics using FUSION/TWAS software with the default parameters [35]. FUSION/TWAS imputes gene expression using *cis* expression quantitative trait loci (eQTL) data derived from reference panels of paired genotype and tissue-specific gene expression data. As gene expression is imputed based on disease-specific GWAS summary statistics, FUSION/TWAS identifies disease-inferred gene expression profiles with tissue-level resolution. For this study, we used eQTL weights based on the 48 tissue Genotype-Tissue Expression (GTEx) [34] version 7 (v7) reference panel provided with FUSION/TWAS to generate all disease-inferred gene expression profiles. We tested for overlap or correlation between the disease-inferred gene expression using RHOGE software [57], providing the effective sample size [90] for each dataset and only including those FUSION/TWAS results that were at least nominally ($P < 0.05$) associated with each disease as per the default RHOGE parameters. RHOGE provides an estimate of the genetic correlation between two traits that can be attributed to eQTLs as represented by the different trait-inferred gene expression profiles. We exclude the major histocompatibility complex (MHC) region from disease-inferred gene expression overlap analyses due to its complex LD structure

[35, 57]. To consider an overlap as significant, we used a Bonferroni-corrected threshold: $P < 1.04 \times 10^{-03}$ (0.05/48 tissues) and present uncorrected *P* values and 95% confidence intervals in the text.

Highlighting genes underlying disease-inferred gene expression overlap

We used UTMOST software [38] to generate single-tissue, disease-inferred gene expression, and then aggregated them into a summary metric representing cross-tissue, eGene-disease associations. eGenes are those genes whose expressions are influenced by a least one *cis* disease-associated genetic variant [93]. For this analysis, we generated the single-tissue disease-inferred results based on the processed GWAS summary statistics and the 44 tissue GTEx v6 reference panel provided with UTMOST, using default parameters. We similarly generated the cross-tissue summary metric using default parameters. The UTMOST cross-tissue test summary metric represents the maximum one-sided likelihood ratio test statistic for an eGene being associated with the disease, with larger test statistics indicating greater support for an association. This summary metric does not include any indicator of uncertainty. We identified transcriptome-wide significant, cross-tissue, eGene-disease associations using a false discovery rate (FDR) threshold of 0.05, that is five expected false discoveries per 100 reported. We compared PD and melanoma UTMOST summary metric eGene results for the disease-specific GWAS summary statistics to identify eGenes that were independently associated with both diseases.

Investigating differential expression of highlighted eGenes in PD brain tissues

To investigate whether the eGenes we identified as being independently associated with both melanoma and PD demonstrated differential expression in PD, we downloaded publicly available, normalized microarray gene expression data derived from substantia nigra brain tissues donated by individuals with and without PD. These datasets were deposited in the Gene Expression Omnibus (GEO) under the accession codes: GDS2821 [47] and GDS3129 [22, 62]. The GDS2821 dataset includes Affymetrix Human Genome U133 Plus 2.0 array data collected from 16 individuals with neuropathologically confirmed PD and nine aged individuals with no history or pathological diagnosis of neurologic or psychiatric disease [47]. The GDS3129 dataset includes Affymetrix Human Genome U133B array data derived from 15 samples of medial substantia nigra and nine samples of lateral substantia nigra from individuals with neuropathologically confirmed PD as well as eight samples of medial substantia nigra and seven samples of lateral substantia nigra from control individuals without neurodegenerative disease pathology [22, 62]. We extracted the normalized expression levels of *GPATCH8*, *MYO9A*, *PIEZO1*, *SOX6*, *TRAPPC2L*, *ZNF341*, and *ZNF778* genes and compared the expression between controls using a Mann–Whitney test using Graphpad Prism 8.0.

Results

Polygenic analysis reveals specific genetic overlap between melanoma and PD

Prior to cross-disease analyses, we first confirmed that the three independent PD datasets demonstrated positive and significant genetic correlation with each other (genetic correlation range 0.94–1.07, Table 2) using GNOVA software. Following this confirmation and method validation, we proceeded to analyze for potential genetic correlations between melanoma, PD, and the comparator neurodegenerative disease datasets.

We identified a significant and positive genetic correlation between melanoma and the meta-analyzed PD dataset (genetic correlation 0.17, 95% CI 0.10–0.24; $P = 4.09 \times 10^{-06}$, Table 3). This result was not driven by any specific PD dataset, but all three independent datasets contributed to the association ($P < 0.05$; genetic correlation range 0.14–0.25, Fig. 1 and Table 4). We further investigated the genetic correlation between melanoma and the meta-analyzed PD dataset by stratifying it to the level of minor allele frequency and chromosome annotations. Consistent with the polygenic nature of these diseases, we found their genetic correlation to be most highly enriched in those genetic variants annotated as being in the top quartile of minor allele frequency (Supplementary Table 1, online resource). We also found the genetic correlation between melanoma and the meta-analyzed PD dataset to be enriched in chromosomes 1, 2, 8, 11, 16, and 17 (Supplementary Table 2, online resource).

We found no shared genetic architecture between melanoma and Alzheimer disease (genetic correlation −0.02, 95% CI −0.11 to 0.07; $P = 0.73$, Table 3) nor between melanoma and Frontotemporal dementia (genetic correlation −0.13, 95% CI −0.37 to 0.12; $P = 0.32$, Table 3). We similarly did not observe any significant correlation between the meta-analyzed PD dataset and AD (Table 3), although one of the individual PD studies showed nominal correlation with AD (Nalls 2014: genetic correlation: −0.22, 95% CI −0.22 to 0.00, $P = 4.94 \times 10^{-02}$; Table 4). We did identify a positive and significant genetic correlation between the meta-analyzed PD dataset and FTD (genetic correlation: 0.27, 95% CI 0.07–0.47; $P = 8.43 \times 10^{-03}$, Table 3), but this appeared to be primarily driven by one of the individual PD studies

Table 2 GNOVA genetic correlation results for independent Parkinson disease datasets

Parkinson disease dataset	Nalls2014	Chang2017	Nalls2019	METAPD
Nalls2014 $n_{Case}=9581$ $n_{Control}=33{,}245$	–	–	–	–
Chang2017 $n_{Case}=6476$ $n_{Control}=302{,}042$	0.95 [0.77, 1.12] (**4.16×10^{-26}**)	–	–	–
Nalls2019 $n_{Case}=33{,}674$ $n_{Control}=449{,}056$	1.07 [0.90, 1.25] (**7.91×10^{-34}**)	0.94 [0.80, 1.09] (**1.43×10^{-36}**)	–	–
METAPD $n_{Case}=49{,}731$ $n_{Control}=784{,}343$	1.00 [0.83, 1.18] (**1.04×10^{-28}**)	0.71 [0.56, 0.86] (**8.09×10^{-21}**)	1.06 [0.91, 1.21] (**6.10×10^{-42}**)	–

We estimated the genetic correlation between the independent Parkinson disease datasets using GNOVA software. All correlation estimates, 95% confidence intervals—presented in square brackets—and *P* values—presented in parentheses—are corrected for any potential sample overlap. GNOVA genetic correlation estimates are unbounded and thus may be greater than 1. METAPD is an inverse-variance-weighted meta-analysis of the three independent Parkinson disease summary statistic datasets

P values in bold denotes significant associations

Table 3 GNOVA genetic correlation results for meta-analyzed Parkinson disease, melanoma, and comparator neurodegenerative diseases GWAS summary statistic datasets

Summary statistic dataset	Melanoma Law2015	PD METAPD	AD Kunkle2019	FTD Ferrari2014
Melanoma Law2015 $n_{Case}=12{,}814$ $n_{Control}=23{,}203$	–	–	–	–
PD METAPD $n_{Case}=49{,}731$ $n_{Control}=784{,}343$	0.17 [0.10, 0.24] (**4.09×10^{-06}**)	–	–	–
AD Kunkle2019 $n_{Case}=21{,}982$ $n_{Control}=41{,}944$	−0.02 [−0.11, 0.07] (0.73)	0.01 [−0.06, 0.09] (0.71)	–	–
FTD Ferrari2014 $n_{Case}=2154$ $n_{Control}=4308$	−0.13 [−0.37, 0.12] (0.32)	0.27 [0.07, 0.47] (**8.43×10^{-03}**)	0.22 [−0.05, 0.49] (0.11)	–

We estimated the genetic correlation between diseases using processed disease-specific GWAS summary statistic datasets and GNOVA software. All correlation estimates, 95% confidence intervals—presented in square brackets—and *P* values—presented in parentheses—are corrected for any potential sample overlap. METAPD is an inverse-variance-weighted meta-analysis of the three independent Parkinson disease summary statistic datasets

P values in bold denotes significant associations

PD Parkinson disease, *AD* Alzheimer disease, *FTD* frontotemporal dementia

(Table 4). Together these results demonstrate a consistent, positive and significant genetic correlation between melanoma and PD but not between melanoma and FTD or AD.

PD and melanoma disease-inferred gene expression overlaps across tissues

To investigate whether melanoma and PD-associated risk variants regulated the expression of the same genes, we generated disease-inferred, tissue-specific gene expression profiles from the processed melanoma and METAPD GWAS

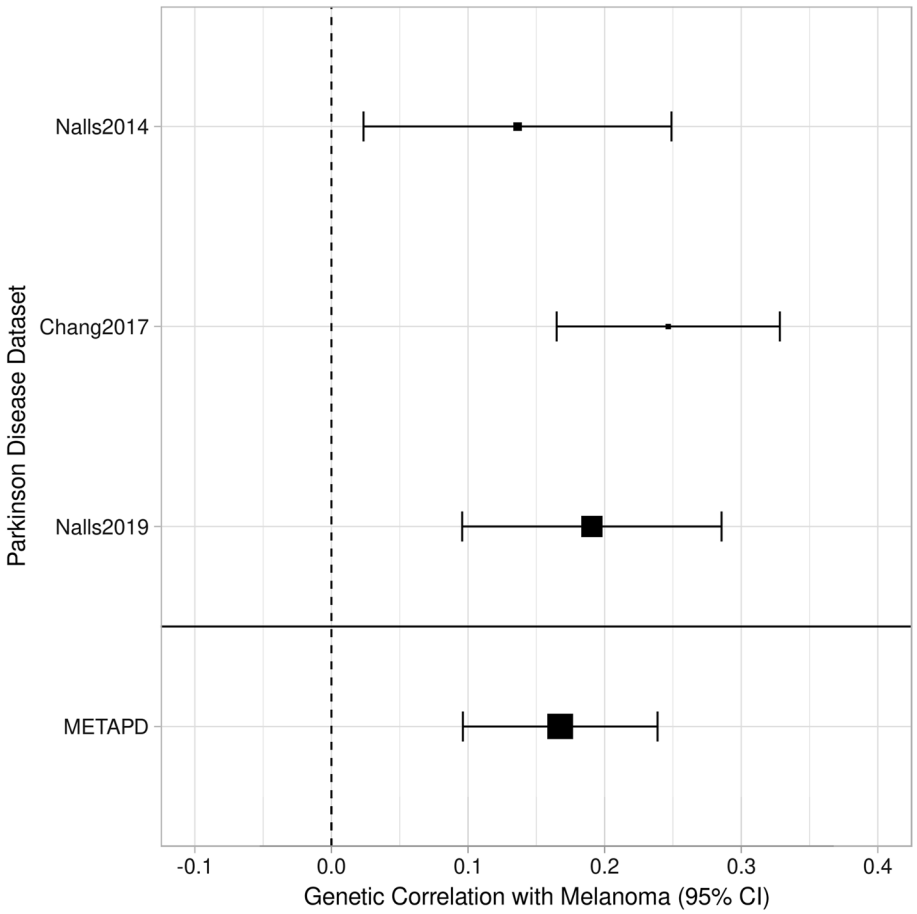

Fig. 1 GNOVA genetic correlation results for Parkinson disease and melanoma GWAS summary statistic datasets. Forest plot of genetic correlation between melanoma and the individual and meta-analyzed Parkinson disease datasets (Tables 3, 4). Box size indicates the effective sample size ($N_{eff} = 4/(1/N_{cases} + 1/N_{controls})$). The three independent PD datasets are Nalls 2014 (Nalls et al. [64]); Chang 2017 (Chang et al. [13]); Nalls 2019 (Nalls et al. [63]). METAPD is an inverse-variance-weighted meta-analysis of the three independent Parkinson disease summary statistic datasets

Table 4 GNOVA genetic correlation results for independent Parkinson disease, melanoma, and comparator neurodegenerative diseases GWAS summary statistic datasets

Summary statistic dataset	Melanoma Law2015 $n_{Case} = 12{,}814$ $n_{Control} = 23{,}203$	AD Kunkle2019 $n_{Case} = 21{,}982$ $n_{Control} = 41{,}944$	FTD Ferrari2014 $n_{Case} = 2154$ $n_{Control} = 4308$
PD Nalls2014 $n_{Case} = 9581$ $n_{Control} = 33{,}245$	0.14 [0.02, 0.25] (**1.79×10^{-02}**)	−0.11 [−0.22, 0.00] (4.94×10^{-02})	0.27 [−0.06, 0.60] (0.10)
PD Chang2017 $n_{Case} = 6476$ $n_{Control} = 302{,}042$	0.25 [0.16, 0.33] (**3.31×10^{-09}**)	−0.01 [−0.11, 0.09] (0.87)	−0.16 [−0.45, 0.12] (0.26)
PD Nalls2019 $n_{Case} = 33{,}674$ $n_{Control} = 449{,}056$	0.19 [0.10, 0.29] (**8.28×10^{-05}**)	0.05 [−0.04, 0.14] (0.27)	0.40 [0.14, 0.66] (**2.78×10^{-03}**)

We estimated the genetic correlation between diseases using processed disease-specific GWAS summary statistic datasets and GNOVA software. All correlation estimates, 95% confidence intervals—presented in square brackets—and *P* values—presented in parentheses—are corrected for any potential sample overlap

P values in bold denotes significant associations

PD Parkinson disease, *AD* Alzheimer disease, *FTD* frontotemporal dementia

summary statistic datasets via FUSION/TWAS software [35]. We further investigated for overlap between the different disease-inferred gene expression profiles using RHOGE software [57].

We identified a positive and significant overlap between the PD- and melanoma-inferred gene expression profiles in a joint analysis of the 48 tissues included in the GTEx v7 reference panel provided with the FUSION/TWAS software (disease-inferred gene expression correlation: 0.14, 95% CI 0.06–0.22; P: 7.87×10^{-04}). Analyzing the PD- and melanoma-inferred gene expression correlation in each of the reference panel tissues individually, we observed positive overlap in 44 tissues (disease-inferred gene expression correlation median: 0.25, IQR: 0.13, Fig. 2 and Table 5), but only a statistically significant overlap in the suprapubic, non-sun-exposed, skin tissue (disease-inferred gene expression correlation: 0.37, 95% CI 0.17–0.57; P: 7.58×10^{-04}). Eleven additional tissues demonstrated positive and nominal (Fig. 2 and Table 5) the PD- and melanoma-inferred gene expression overlap including spleen (disease-inferred gene expression correlation: 0.40, 95% CI 0.13–0.66; P: 5.49×10^{-03}), minor salivary gland (disease-inferred gene expression correlation: 0.45, 95% CI 0.15–0.75; P: 7.49×10^{-03}), heart atrial appendage (disease-inferred gene expression

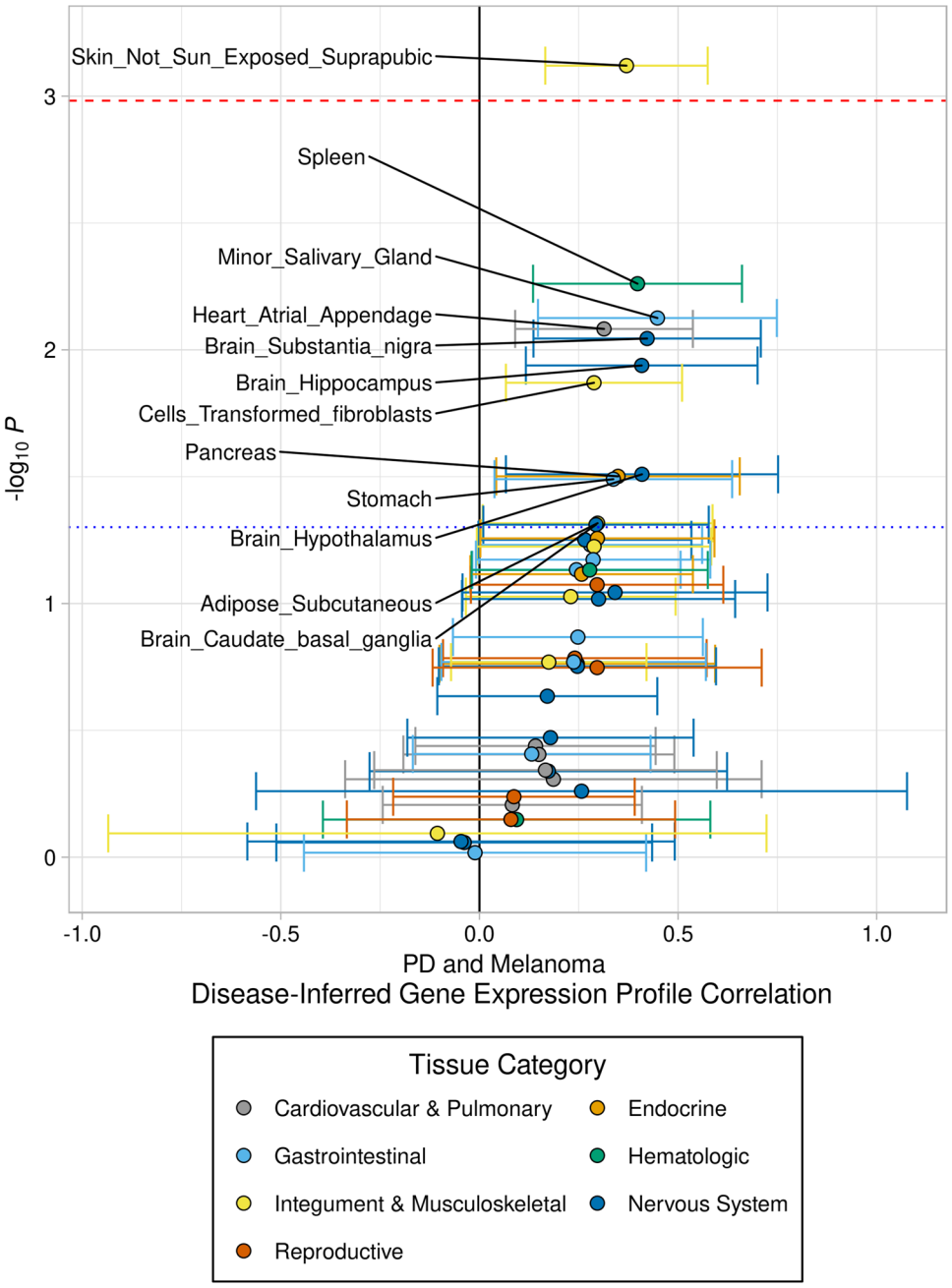

Fig. 2 Parkinson disease (PD) and melanoma tissue-specific, disease-inferred gene expression profile correlation. PD and melanoma disease-inferred gene expression profile correlation at the level of 48 specific tissues included in the GTEx v7 reference panel (Table 5). Disease-inferred gene expression profiles were generated from the processed melanoma and METAPD summary statistics using FUSION/TWAS software and correlation between these profiles was estimated using RHOGE software. METAPD is an inverse-variance-weighted meta-analysis of the three independent Parkinson disease summary statistic datasets. The red dashed line demarks the multiple test corrected P threshold of 1.04×10^{-03} (0.05/48), while the blue dotted line demarks the nominal threshold, $P=0.05$

Table 5 Disease-inferred gene expression profile overlap between melanoma and PD in GTEx v7 reference panel tissues

GTEx v7 tissue	Number of samples in tissue reference panel	Melanoma vs. METAPD	
		ρ_{GE}	*P* value
Adipose subcutaneous	385	0.30 [0.01, 0.59]	4.82×10^{-02}
Adipose visceral omentum	313	0.23 [−0.03, 0.49]	9.39×10^{-02}
Adrenal gland	175	0.25 [−0.10, 0.59]	1.73×10^{-01}
Artery aorta	267	0.14 [−0.16, 0.44]	3.64×10^{-01}
Artery coronary	152	0.19 [−0.34, 0.71]	4.93×10^{-01}
Artery tibial	388	0.15 [−0.19, 0.49]	3.93×10^{-01}
Brain amygdala	88	0.25 [−0.10, 0.60]	1.77×10^{-01}
Brain anterior cingulate cortex BA24	109	0.17 [−0.28, 0.62]	4.58×10^{-01}
Brain caudate basal ganglia	144	0.29 [0.01, 0.58]	4.89×10^{-02}
Brain cerebellar hemisphere	125	0.18 [−0.18, 0.54]	3.38×10^{-01}
Brain cerebellum	154	0.17 [−0.11, 0.45]	2.32×10^{-01}
Brain cortex	136	−0.04 [−0.51, 0.43]	8.75×10^{-01}
Brain frontal cortex BA9	118	−0.05 [−0.58, 0.49]	8.67×10^{-01}
Brain hippocampus	111	0.41 [0.12, 0.70]	1.15×10^{-02}
Brain hypothalamus	108	0.41 [0.07, 0.75]	3.09×10^{-02}
Brain nucleus accumbens basal ganglia	130	0.34 [−0.04, 0.73]	9.04×10^{-02}
Brain putamen basal ganglia	111	0.30 [−0.04, 0.64]	9.60×10^{-02}
Brain spinal cord cervical c-1	83	0.26 [−0.56, 1.08]	5.49×10^{-01}
Brain substantia nigra	80	0.42 [0.14, 0.71]	9.02×10^{-03}
Breast mammary tissue	251	0.24 [−0.09, 0.57]	1.64×10^{-01}
Cells EBV-transformed lymphocytes	117	0.09 [-0.39, 0.58]	7.11×10^{-01}
Cells transformed fibroblasts	300	0.29 [0.07, 0.51]	1.35×10^{-02}
Colon sigmoid	203	−0.01 [−0.44, 0.42]	9.60×10^{-01}
Colon transverse	246	0.24 [−0.10, 0.57]	1.70×10^{-01}
Esophagus gastroesophageal junction	213	0.28 [−0.00, 0.56]	5.88×10^{-02}
Esophagus mucosa	358	0.13 [−0.17, 0.43]	3.92×10^{-01}
Esophagus muscularis	335	0.24 [−0.02, 0.51]	7.36×10^{-02}
Heart atrial appendage	264	0.31 [0.09, 0.54]	8.27×10^{-03}
Heart left ventricle	272	0.08 [−0.24, 0.41]	6.22×10^{-01}
Liver	153	0.25 [−0.07, 0.56]	1.36×10^{-01}
Lung	383	0.17 [−0.27, 0.60]	4.54×10^{-01}
Minor salivary gland	85	0.45 [0.15, 0.75]	7.49×10^{-03}
Muscle skeletal	491	0.17 [−0.07, 0.42]	1.70×10^{-01}
Nerve tibial	361	0.27 [−0.00, 0.53]	5.61×10^{-02}
Ovary	122	0.30 [−0.12, 0.71]	1.79×10^{-01}
Pancreas	220	0.35 [0.04, 0.66]	3.15×10^{-02}
Pituitary	157	0.30 [0.00, 0.59]	5.54×10^{-02}
Prostate	132	0.08 [−0.33, 0.49]	7.10×10^{-01}
Skin not sun exposed suprapubic	335	0.37 [0.17, 0.57]	7.58×10^{-04}
Skin sun exposed lower leg	414	0.29 [−0.01, 0.58]	5.96×10^{-02}
Small intestine terminal ileum	122	0.29 [−0.01, 0.58]	6.71×10^{-02}
Spleen	146	0.40 [0.13, 0.66]	5.49×10^{-03}
Stomach	237	0.34 [0.04, 0.64]	3.23×10^{-02}
Testis	225	0.09 [−0.22, 0.39]	5.78×10^{-01}
Thyroid	399	0.26 [−0.02, 0.54]	7.66×10^{-02}
Uterus	101	0.30 [−0.02, 0.61]	8.43×10^{-02}
Vagina	106	−0.11 [−0.93, 0.72]	8.05×10^{-01}
Whole Blood	369	0.28 [−0.02, 0.57]	7.38×10^{-02}

We generated disease-inferred gene expression profiles based on standardized and processed GWAS summary statistics using FUSION/TWAS software and the Genotype-Tissue Expression Project (GTEx) v7 reference panel. We further compared the overlap of these disease-inferred gene expression profiles using RHOGE software. METAPD is an inverse-variance-weighted meta-analysis of the three independent Parkinson disease summary statistic datasets

PD Parkinson disease, ρ_{GE} correlation coefficient for inferred transcriptomic overlap, *BA* Brodmann area

correlation: 0.31, 95% CI 0.09–0.54; *P*: 8.27×10^{-03}) brain substantia nigra (disease-inferred gene expression correlation: 0.42, 95% CI 0.14–0.71; *P*: 9.02×10^{-03}), and brain caudate nucleus (disease-inferred gene expression correlation: 0.29, 95% CI 0.01–0.58; *P*: 4.89×10^{-02}).

To highlight genes whose expression was commonly regulated by PD and melanoma risk variants, we generated cross-tissue, summary metric eGene-disease associations using UTMOST [38] software. Applying UTMOST to the METAPD GWAS summary statistics, we identified 606 eGenes significantly associated with PD (Supplementary Table 3, online resource), including genes in previously reported PD-associated loci [50, 64], such as *MAPT* (*P:* 1.28×10^{-04}). In the melanoma dataset, we identified 168 significantly associated eGenes (Supplementary Table 4, online resource) including those reported in a previous TWAS study [92], such as *MAFF* (*P:* 1.28×10^{-12}). Comparing the two sets of cross-tissue summary metric results, we identify seven eGene-disease associations that passed the FDR threshold for both PD and melanoma: *GPATCH8, MYO9A*, *PIEZO1, SOX6, TRAPPC2L*, *ZNF341*, and *ZNF778* (Fig. 3 and Table 6). In addition, we found evidence for differential expression between individuals with and without neuropathologically confirmed PD for five of these seven eGenes in publicly available substantia nigra microarray datasets (Supplementary Fig. 1A–O, online resource). Together, these results suggest that some component of the genetic correlation between melanoma and PD may be

Table 6 Cross-tissue eGene-disease associations for melanoma and PD

Gene	Melanoma UTMOST cross-tissue		PD UTMOST cross-tissue	
	Test metric	*P*	Test metric	***P***
GPATCH8	9.27	8.33×10^{-05}	9.18	9.17×10^{-05}
MYO9A	10.10	2.41×10^{-05}	6.47	1.01×10^{-03}
PIEZO1	176.52	2.74×10^{-11}	9.29	5.65×10^{-05}
SOX6	9.02	1.30×10^{-04}	9.77	5.97×10^{-05}
TRAPPC2L	690.56	2.36×10^{-11}	9.27	8.47×10^{-05}
ZNF341	8.42	1.67×10^{-04}	6.57	1.19×10^{-03}
ZNF778	219.82	2.55×10^{-11}	6.07	1.47×10^{-03}

We inferred cross-tissue, eGene-disease associations based on standardized and processed melanoma and METAPD GWAS summary statistics using UTMOST software and the Genotype-Tissue Expression Project (GTEx) v6 reference panel. METAPD is an inverse-variance-weighted meta-analysis of the three independent Parkinson disease (PD) summary statistic datasets

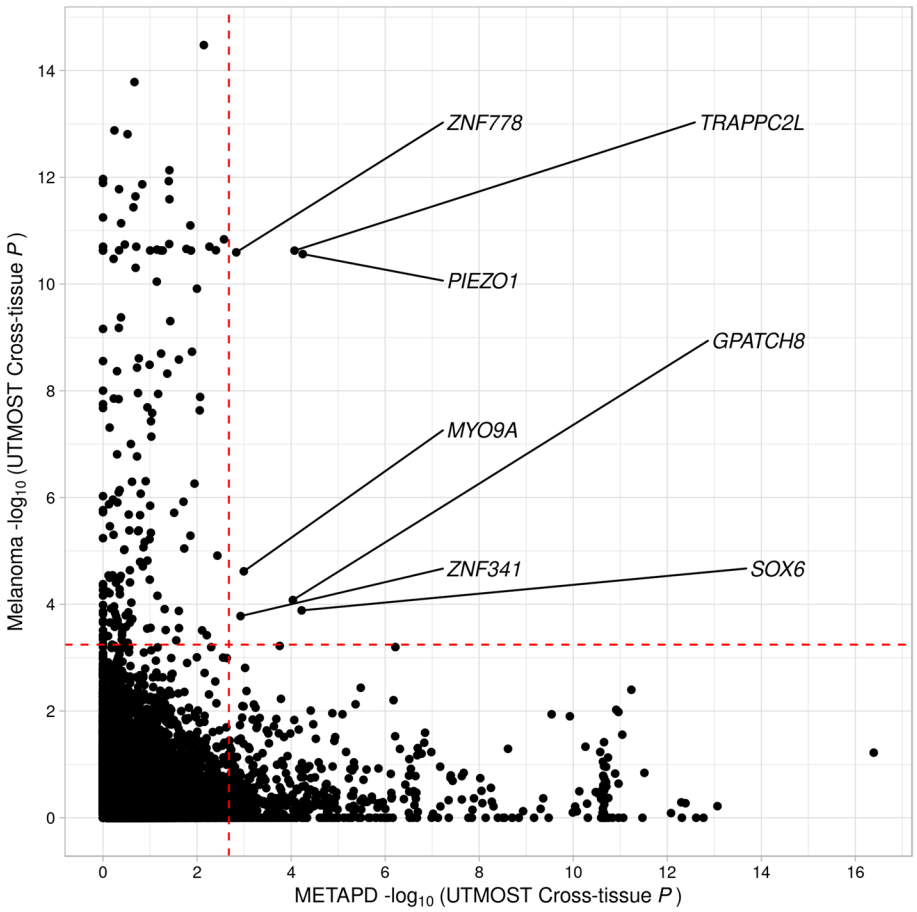

Fig. 3 Cross-tissue eGenes associated with both Parkinson disease (PD) and melanoma. Conjunction plot of the cross-tissue PD and melanoma eGene -$\log_{10}$ *P* values. We generated cross-tissue eGene-disease results (Supplementary Tables 3, 4, online resource) from the processed melanoma and METAPD summary statistics using UTMOST software. METAPD is an inverse-variance-weighted meta-analysis of the three independent Parkinson disease summary statistic datasets. The red dashed lines demark the false discovery rate (FDR) threshold of 0.05. Labels and lines indicate eGenes associated with both PD and melanoma under the FDR threshold

mediated by the shared regulation of gene expression across tissues.

Discussion

In this study, we have identified a positive and significant genetic correlation between melanoma and PD by leveraging the largest available GWAS summary statistic datasets and recent advances in polygenic complex trait modeling [11, 54] (Tables 3, 4). Our results support the findings of several epidemiologic studies of shared—individual and familial—risk [5, 17, 21, 27, 29, 36, 42, 53, 67, 68, 81, 87, 91] between the two diseases. We also demonstrate no evidence for shared genetic overlap between melanoma and two negative comparison neurodegenerative diseases: AD and FTD (Table 3), suggesting specificity.

Our results of positive genetic correlations between melanoma and PD stand in contrast to negative results from several other genetic studies including single-variant analyses [24, 26, 28, 55, 65, 66] and multi-variant analyses [65, 66]. Both melanoma and PD are complex diseases with inherently polygenic risk architectures. Consequently, efforts to identify shared genetic architecture at the single-variant level are likely underpowered, especially given the moderate epidemiologic and genetic, correlation between melanoma and PD. This is especially true given the fact that the GWAS results analyzed for such single-variant level investigations are themselves currently underpowered. For example, a power analysis reported in the largest PD GWAS to date (Nalls 2019) suggests that an adequately powered PD GWAS would require the inclusion of approximately 99,000 PD cases—more than double their current PD case sample size [63]. Consequently, our current knowledge regarding the genetic architectures of PD and melanoma is hardly comprehensive and larger GWAS may reveal shared individual risk loci between these diseases in the future. Similarly, previous multi-variant genetic analyses investigating melanoma and PD have focused specifically on GWAS-significant loci and thus can be expected to have missed a substantial proportion of the genetic architecture [8] underlying these complex diseases. Genetic correlation methods that consider linkage disequilibrium structure and incorporate all common variants are better powered to detect genetic overlap, especially given current GWAS sample sizes, as we demonstrate here for melanoma and PD.

The classification and ascertainment of participants were different between the three independent PD datasets included in the present study; however, they all demonstrate positive and significant genetic overlap with each other (Table 2). While this overlap does not guarantee specificity of the represented genetic architecture [12], the fact we observe all three independent PD studies to demonstrate positive and significant genetic overlap with melanoma (Fig. 1 and Table 4) bolsters confidence in our results. Importantly, although the PD and melanoma genetic correlation point estimates for the three individual PD studies appear different, their 95% confidence intervals overlap which indicates that the effect size estimates are not significantly different (Fig. 1 and Table 4). The genetic overlap between the independent PD datasets supported their meta-analysis, and the genetic correlation between the meta-analyzed PD dataset and melanoma provided the most precise estimate (genetic correlation: 0.17, 95% CI 0.10–0.24; $P = 4.09 \times 10^{-06}$; Fig. 1 and Tables 3, 4). Further increases in precision may result from incorporating additional independent GWAS summary statistic datasets and thus our analyses should be repeated as these become available for both melanoma and PD. Similarly, our FTD genetic correlation results should be interpreted with caution as the current sample size is at least one order of magnitude smaller than the other disease datasets. For example, among the individual PD datasets, we only observe a positive genetic correlation between FTD and Nalls 2019. Parkinsonism has been observed in about 20% on individuals with FTD [2, 7], and this result may suggest that individuals with FTD with parkinsonism were included among the UKB-proxy cases in the Nalls 2019 dataset. Alternatively, a positive genetic correlation between FTD and the other PD datasets may be observed from the use of a larger FTD GWAS summary statistic dataset. Thus, our analyses should be repeated as larger GWAS summary statistic datasets become available.

We infer disease-associated gene expression profiles [35] using melanoma and meta-analyzed PD GWAS summary statistics and investigate for their overlap at the level of tissues [57] and genes [38] to provide bioinformatically driven biological context to our melanoma and PD genetic correlation results. We identify significant cross-tissue overlap (disease-inferred gene expression correlation: 0.14, 95% CI 0.06–0.22; P: 7.87×10^{-04}) and significant individual tissue overlap in suprapubic non-sun-exposed skin (disease-inferred gene expression correlation: 0.37, 95% CI 0.17–0.57; P: 7.58×10^{-04}). We also observe positive, nominal disease-inferred gene expression correlation in peripheral tissues with PD relevance like the heart atrial appendage (disease-inferred gene expression correlation: 0.31, $P < 0.05$, Table 5)—which may reflect the cardiac sympathetic denervation associated with PD [32, 82]—or the minor salivary glands (disease-inferred gene expression correlation: 0.45, $P < 0.05$, Table 5)—which have been reported in some, but not all, studies as containing alpha syncline aggregates in the context of PD [46, 85]. In terms of PD-relevant brain tissues, we observe positive, nominal disease-inferred gene expression correlation in the substantia nigra and basal ganglia caudate nucleus (disease-inferred gene expression correlation: 0.42 and 0.29, respectively; $P < 0.05$, Fig. 2 and

Table 5). Importantly, the available GTEx v7 inferred gene expression reference model for brain tissues is based on substantially fewer samples than most peripheral tissues, for example the brain substantia nigra reference is derived from 80 donors compared to 335 donors for the suprapubic skin reference (Table 5). Consequently, our disease-inferred gene expression risk profile overlap analyses should be repeated as larger reference panels become available. Similarly, another limitation of the GTEx dataset is the inclusion of tissues from individuals with extended post-mortem intervals. As this can be expected to result in an underrepresentation of short-lived transcripts in the inferred gene expression reference panels, our analyses should be repeated, as reference panels based on the tissues from individuals with shorter post-mortem intervals become available.

We identify seven cross-tissue, eGene-disease associations passing the FDR threshold for both melanoma and PD (Fig. 3 and Table 6), most of which are located on the chromosomes which we identified as being enriched for the genetic correlation between these two diseases. Importantly, the UTMOST software currently only provides a compatible reference panel based on the GTEx v6 release which is derived from fewer donor samples per tissue compared to GTEx v7 release. In addition, the GTEx v6 reference panel does not include four tissues—brain substantia nigra, brain spinal cervical spinal cord, brain amygdala, and minor salivary gland—which we observed to demonstrate positive disease-inferred gene expression overlap for melanoma and PD (Table 5). Additional eGenes may pass the FDR threshold for both PD and melanoma in analyses based on the larger GTEx v7 reference panel. Thus, our analyses should be repeated when this or other larger reference panels become available for UTMOST. Nevertheless, using the smaller GTEx v6 reference panel we identify seven genes that may be commonly regulated by melanoma and PD-associated variants under the FDR threshold (Fig. 3 and Table 6), including *PIEZO1* (Melanoma *P*: 2.74×10^{-11}; METAPD *P*: 5.65×10^{-05}); *TRAPPC2L* (Melanoma *P*: 2.36×10^{-11}; METAPD *P*: 8.47×10^{-05}); and *SOX6* (Melanoma *P*: 1.30×10^{-04}; METAPD *P*: 5.97×10^{-05}).

PIEZO1 encodes a recently described mechanosensitive cation channel [15] with several biological functions including human T cell activation [52], direction of lineage choice in human neural stem cells [71], and mediating the age-related loss of function of oligodendrocyte progenitor cells [79]. *PIEZO1* is expressed in the neurons of the human substantia nigra [20, 76] and is also ubiquitously expressed in human enteric neurons [58], both neuronal types impacted by PD [10, 43]. Interestingly, the expression of *PIEZO2*—*PIEZO1*'s paralog—is regulated by putatively melanocyte-derived dopamine signaling in mouse primary sensory neurons [69] but whether this regulation is relevant for *PIEZO1* is currently unknown. Similarly, a role for *PIEZO1* in melanoma remains largely unexplored though *PIEZO1* has been identified to contribute to the migration of invasive melanoma cells [39].

TRAPPC2L is a component of transport protein particle (TRAPP) complexes which function in intracellular vesicle-mediated transport and autophagy [60, 61, 78]. This gene is expressed in human substantia nigra neurons [20] and a homozygous missense variant in it causes a neurodevelopmental disorder characterized by progressive encephalopathy and episodic rhabdomyolysis [60]. The intergenic variant rs12921479—which is an eQTL for *TRAPPC2L* in the brain [34, 74]—was reported to be associated with PD (*P:* 9.31×10^{-07}) in an autopsy-confirmed cohort of PD [3], but is only nominally associated with PD in our meta-analyzed PD dataset (*P:* 1.01×10^{-02}). A role for *TRAPPC2L* in melanoma remains to be explored.

SOX6 is a transcription factor which was recently identified as a determinant of substantia nigra neuron development and maintenance [70]. Its expression was observed to localize to pigmented and tyrosine hydroxylase positive neurons but not to pigment-negative neurons within the substantia nigra [70]. In addition, *SOX6* expression was diminished in the substantia nigra of individuals with PD and deletion of *SOX6* in mice was observed to decrease dopamine levels and innervation in the striatum [70], a brain region that is also impacted in PD [9]. In a separate study, a large deletion in *SOX6* was identified in a patient with global developmental delay and progressive parkinsonian symptoms including rest tremor [77]. Interestingly, *SOX6* has been identified as a determinant of gastric dopaminergic neuron development [59], which may suggest a role for this gene in the enteric nervous system dysfunction and pathology observed in PD. *SOX6* may also have a role in melanoma. In a cancer cell line expression study, *SOX6* was found to be highly expressed in melanoma cells but was not detectable in eight other cancers [86]. Additionally, *SOX6* was identified as a candidate melanoma driver gene [72] in a screen and *SOX6* may be a melanoma stem cell marker [51].

While we observe evidence for differential expression between neuropathologically confirmed PD and controls for *PIEZO1*, *TRAPPC2L*, and *SOX6* in at least one substantia nigra microarray dataset, these results should be interpreted with caution. Neurodegenerative diseases like PD are characterized by dramatic changes in cell-type proportions [49] which will impact differential expression results. Thus, the PD-associated differential expression of the eGenes highlighted in this study should be confirmed in larger, RNA-sequencing-based datasets—as these become available—to allow for the inclusion of important covariates like cell-type proportions, sex, age of death, and RNA quality among others. Nevertheless, the fact we observe differential expression of *SOX6* in the same direction as previously published [70] is reassuring.

Investigating for differential expression of the eGenes highlighted in this study in the context of melanoma is challenging given our focus on the risk of developing melanoma. Nevertheless, a recent GTEx v8-based multi-tissue TWAS resource (phenomexcan.org) [73] provides some evidence for a link between the eGenes we highlight and melanoma-associated pigmentation traits included in the UK Biobank study. For example, *PIEZO1* is associated with red hair ($P: \sim 0$), ease of skin tanning ($P: 3.74 \times 10^{-175}$), and skin colour ($P: 3.41 \times 10^{-121}$); *TRAPPC2L* is associated with red hair ($P: 3.28 \times 10^{-181}$), ease of skin tanning ($P: 1.06 \times 10^{-71}$), and skin colour ($P: 6.24 \times 10^{-55}$); and *SOX6* is associated with ease of skin tanning ($P: 1.40 \times 10^{-13}$), skin colour ($P: 1.55 \times 10^{-11}$), and childhood sunburn occasions ($P: 3.92 \times 10^{-11}$).

Together, these results support a biologically plausible role for *PIEZO1*, *TRAPPCL2*, and *SOX6* in the genetic correlation between melanoma and PD, but these findings require confirmation and further investigation with future experimental work.

PD and melanoma are clinically heterogenous diseases [16, 18] for which spatiotemporal environmental exposures are relevant [14, 16] and may be necessary, in addition to innate genetic susceptibility, for the development of sporadic disease. Consequently, the moderate genetic correlation we observe should not be interpreted as suggesting that these diseases will always be co-morbid. However, our results of replicable and significant genetic correlation, regardless of the magnitude of effect, do suggest that these two very different diseases share common biological pathways. Thus, even if only a minority of individuals with PD ultimately develop melanoma, understanding the genetic correlation between these disease at the molecular level—for example, if and how the regulation of *PIEZO1, TRAPPC2L*, and *SOX6* and their related biological pathways contribute to PD etiopathogenesis—may provide mechanistic insight that is generalizable to all individuals with PD. Our results support such future research efforts.

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Compliance with ethical standards

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