RESEARCH ARTICLE

Prognostic and Biological Roles of Parkinson's Disease-Associated Genes in Cancer

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ABSTRACT: Background: Increasing evidence suggests significant associations between Parkinson's disease (PD) and cancer risks, with epidemiological studies revealing a complex relationship. PD patients exhibit lower risks of lung, genitourinary, and gastrointestinal cancers but higher risks of melanoma and brain cancers. Despite these observations, the underlying mechanisms between PD and cancers are poorly understood.
Objectives: We aimed to identify molecular signatures underlying this complex connection by assessing transcriptional associations between PD-related genes, patient survival, and the cancer-specific co-expression networks in which these genes are involved.
Methods: To explore this, we analyzed transcriptomic data from 18 cancer types in the TCGA dataset (n = 6088) and 16 cancer types in the DepMap dataset (n = 682). We focused on seven genes causally implicated in PD (*SNCA*, *PINK1*, *LRRK2*, *PRKN*/*PARK2*, *PARK7*, *GBA1*, and *ATP13A2*) and conducted in silico analyses, to evaluate their associations with survival and correlation with genes, pathways, and response to drugs in the context of cancer.
Results: Our findings revealed that the expression levels of the genes correlated with overall survival in a cancer-specific manner, often influenced by the TP53 genetic status. These genes were also associated with key cancer hallmarks such as genomic instability and cell proliferation.
Conclusions: This study suggests that PD and cancer may be connected through shared biological pathways, some overlapping with cancer hallmarks, and highlights the need for future mechanistic and functional studies to clarify the role of PD genes in cancer biology. © 2025 International Parkinson and Movement Disorder Society.

Key Words: cancer; molecular pathways; Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by motor symptoms, as well as a range of non-motor symptoms including cognitive impairment, mood disorders, and autonomic dysfunction.[1] Traditionally, PD has been associated with the degeneration of dopaminergic neurons in the substantia nigra,[2] but emerging evidence suggests that it could also be linked to other pathological processes that might influence the risk of other diseases, including cancer.[3]

Epidemiological studies investigating the link between PD and cancer generally report an inverse relationship[4]: individuals with PD tend to have a lower overall risk of developing cancer, and cancer patients show a reduced risk of developing PD. This association may partly reflect a lower incidence of smoking-related cancers (eg, lung, bladder, and colorectal) among people with PD, likely due to the lower prevalence of smoking in this population, possibly driven by the putative protective effect of smoking against PD.[5] The biological basis remains debated, but one leading hypothesis is that nicotine may protect dopaminergic neurons.[6,7] However, positive correlations between PD and certain cancers, including melanoma, skin, breast, brain, and prostate

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cancers, have also been documented,[4,8,9] sometimes with confounding results.[10] Among these possible correlations, the positive association between PD and melanoma seems to be the most established.[11] This link is observed for melanomas developing both prior to and following a PD diagnosis, suggesting that antiparkinsonian medications are unlikely to be the underlying cause.[12] Common genetic factors could explain this association, as people with a familial history of melanoma had an increased risk for PD. This was recently confirmed by using genome-wide association study (GWAS) data from two PD and six cancer consortia.[13]

Most PD cases are sporadic, with only about 10%–15% having a positive family history.[14] More than 200 genes have been associated to PD, but rare pathogenic variants in genes such as *SNCA, LRRK2, PRKN, PINK1, DJ-1, ATP13A2*, and *GBA1* are the most established contributors to PD pathogenesis, particularly in familial and early-onset forms.[15-17] The most significant genetic risk factors for PD are mutations in the *GBA1* gene, which encodes the lysosomal enzyme glucocerebrosidase, essential for glycosphingolipid homeostasis.[18] Clinically, PD associated with *GBA1* mutations mirrors sporadic PD but typically manifests earlier.[18,19] However, GBA1 is not currently considered a monogenic cause of PD. Not all carriers do develop the disease, indicating that additional genetic or environmental modifiers influence the penetrance and disease expression.[19] Mutations in *SNCA* (*PARK1/4*, alpha-synuclein) and *LRRK2* (*PARK8*, leucine-rich repeat kinase 2 [LRRK2]) cause autosomal dominant PD. Meanwhile, mutations in *PRKN* (*PARK2*, Parkin), *PINK1* (*PARK6*, PTEN-induced putative kinase 1), *PARK7* (DJ-1, parkinsonism associated deglycase), and *ATP13A2* (*PARK9*, ATPase type 13A2) lead to autosomal recessive forms.[20] Importantly, these PD-related genes also participate in cellular pathways commonly dysregulated in cancer. Alpha-synuclein modulates the tumor suppressor *TP53*.[21] PINK1 interacts with PTEN, a well-known tumor suppressor frequently mutated in human cancers.[22] *PRKN/PARK2* encodes for an E3 ubiquitin ligase involved in mitophagy, genomic stability, and tumorigenesis.[22,23] *DJ-1* is implicated in oxidative stress responses and may act as an oncogene.[24] *LRRK2*, while primarily studied in the context of neurodegeneration, may regulate *TP53*.[25] Low expression of *GBA1* is associated with increased metastatic potential in liver cancer cells.[26] *SNCA*, *LRKK2*, *PRKN/PARK2*, *PINK1*, and *PARK7* also play roles in the DNA damage response and the maintenance of genomic stability.[25,27-30]

These mechanistic overlaps may suggest that inverse or cancer-specific associations seen in epidemiological studies may stem from shared cellular processes, such as mitochondrial dysfunction, DNA damage response, oxidative stress, and autophagy, rather than lifestyle or treatment effects alone. Understanding how PD genes may affect cancer biology will require deeper investigation into their underlying molecular mechanisms.

By leveraging data from The Cancer Genome Atlas (TCGA)[31] and the DepMap datasets,[32] this study aimed to elucidate the expression patterns of *GBA1, SNCA*, *LRKK2*, *PRKN/PARK2*, *PINK1*, and *PARK7* across different cancer types, assess their association with patient survival, and unveil the biological co-expression networks they are involved in. Understanding these patterns may reveal novel insights into the bidirectional relationship between PD and cancer, shedding light on shared pathophysiological pathways and guide future mechanistic and functional studies.

Methods

Datasets

TCGA Dataset Analysis

The Cancer Genome Atlas (TCGA) pan-cancer dataset was obtained from the GDC Data Portal, specifically utilizing the files EBPlusPlusAdjustPANCAN_IlluminaHiSeq_RNASeqV2.geneExp.tsv and clinical_PANCAN_patient_with_followup.tsv. This dataset initially comprised 11,069 samples spanning 32 distinct cancer types. After excluding 737 non-tumoral samples, the final cohort for analysis consisted of 10,332 samples.

For downstream analyses, genes were retained if they exhibited an average expression level of log10(FPKM + 1) greater than 0.5 and a standard deviation exceeding 0.2 in at least one cancer type, resulting in a filtered set of 17,646 genes.

The expression levels of *SNCA, PINK1, LRRK2, PRKN/PARK2, PARK7, GBA1*, and *ATP13A2* were correlated with those of all other genes using Spearman correlation, as implemented in the R Stats Package (v.3.5.0).

Additionally, *TP53* mutation and copy number alteration (CNA) data, also downloaded from the GDC portal, were utilized to classify samples into wild-type (WT) and mutant (MUT) groups, as well as to delineate functionally distinct subgroups according to the criteria outlined in Callari et al.[33]

DepMap Dataset Analysis

CRISPR knockout, gene expression, proteomic, and drug response data for SNCA, PINK1, LRRK2, PRKN/PARK2, PARK7, GBA1, and ATP13A2 and other genes were downloaded from the Dependency Map (DepMap) initiative. Specifically, we obtained the following files: from version 21Q1 – CCLE_expression.tsv, protein_quant_current_normalized.csv, sanger-dose–response.csv, and sample_info.csv; and from PRISM Repurposing 19Q4 – primary-screen-replicate-collapsed-logfold-change.csv. To ensure adequate

representation, only cancer types with at least two cell lines in the gene expression dataset were retained. Cell lines annotated as "Engineered" or "Fibroblast" were excluded. After filtering, gene expression data were available for 1320 cell lines across 28 cancer types, and drug response data were available for 692 cell lines representing 22 cancer types. For each cancer type, we correlated the area under the drug response curve (AUC)—which ranges from 0 (high sensitivity) to 1 (resistance)—with the expression of SNCA, PINK1, LRRK2, PRKN/PARK2, PARK7, GBA1, and ATP13A2. Spearman correlation analyses were performed only on drugs tested in at least 10 cell lines per cancer type, with a minimum of two cell lines classified as sensitive (AUC < 0.8) and two as resistant (AUC > 0.8).

Data Analysis

Correlation Analysis

All statistical analyses were conducted in R (v.4.4.1; platform: x86_64-apple-darwin17.0, macOS Monterey 12.3). Associations between pairs of continuous variables (eg, gene expression levels) were quantified using Spearman's correlation analysis. *P*-values were computed with the *cor.test* function and adjusted for multiple comparisons using the Benjamini–Hochberg correction using the *p.adjust* function.

A correlation threshold of 0.6 was used. As shown in Fig. S5, where each plot displays the Benjamini–Hochberg adjusted *P*-values as a function of the corresponding correlation coefficients, all gene pairs above this threshold are statistically significant. This indicates that high correlation consistently corresponds to strong statistical significance.

Unsupervised Analysis

Cancer types were clustered based on the correlation profiles of *SNCA, PINK1, LRRK2, PRKN/PARK2, PARK7, GBA1*, and *ATP13A2* expression. Clustering was performed using the ConsensusClusterPlus method[34], implementing the K-means algorithm with Euclidean distance as the similarity metric.

Gene Set Enrichment Analysis (GSEA)

A custom list of gene sets was assembled as follows. The HALLMARK gene set collection (v.7.1) was obtained from MSigDB,[35] and gene sets related to the PANTHER classification system[36] were downloaded from https://maayanlab.cloud/Harmonizome/dataset/PANTHER+Pathways.

Correlation-ranked genes were then subjected to GSEA using the gsea function from the phenoTest R/Bioconductor package (v.1.28.0). Gene sets with a false discovery rate (FDR) below 0.1% and an absolute normalized enrichment score (NES) greater than 2.3 in at least one cancer type were considered significant and reported. Additionally, in analyses stratified by *TP53* status, gene sets displaying an absolute delta NES (ie, the difference in NES between *TP53* mutant and WT tumors) exceeding 0.6 were deemed significant.

Survival Analysis

Overall survival (OS) was evaluated using univariate and multivariate Cox regression[37,38] analyses implemented in the survival (v.3.1) R/Bioconductor package. Analyses were performed only when at least 10 events (deaths) were observed within a given cancer type subset.[39,40] For multivariate models, at least three of the following four covariates—tumor size, lymph node status, metastatic status, and AURKA gene expression—needed to be available in a minimum of 20 patients. A significance threshold of $P < 0.05$ was applied.

Gene expression levels for *SNCA, PINK1, LRRK2, PRKN/PARK2, PARK7, GBA1*, and *ATP13A2* were dichotomized into high and low groups using the median expression within each cancer type as the cutoff.

Hazard ratios (HRs) were calculated from the Cox regression coefficients to quantify the relative risk associated with gene expression. An HR below 1 indicates a decreased risk relative to the reference group, an HR above 1 indicates an increased risk, and an HR of 1 denotes no difference in risk.

Results

Expression Patterns of PD Genes in Cancer

To elucidate the relevance of PD genes in cancer, we began by evaluating the expression of seven PD-associated genes, firmly linked to PD predisposition and with known molecular connections to cancer-related pathways (*SNCA, PINK1, LRRK2, PRKN/PARK2, PARK7, GBA1*, and *ATP13A2*), across 18 distinct cancer types using transcriptomic data from the TCGA Pan-Cancer cohort. The cancers were selected from the available 32 to represent cancer types previously linked to PD through epidemiological studies: lung, genitourinary, gastrointestinal, melanoma, and brain tumors. Our analysis revealed substantial variability in gene expression levels across different tumor types, as shown in Figure 1A. Notably, certain cancers, including glioblastoma multiforme (GBM), lower grade glioma (LGG), uveal melanoma (UVM), and skin cutaneous melanoma (SKCM), consistently exhibited higher expression levels of the PD-related genes. This was particularly evident for *SNCA, ATP13A2*, and *GBA1*. Interestingly, not all PD-related genes followed the same expression patterns. For instance, *LRRK2* displayed the highest expression in prostate

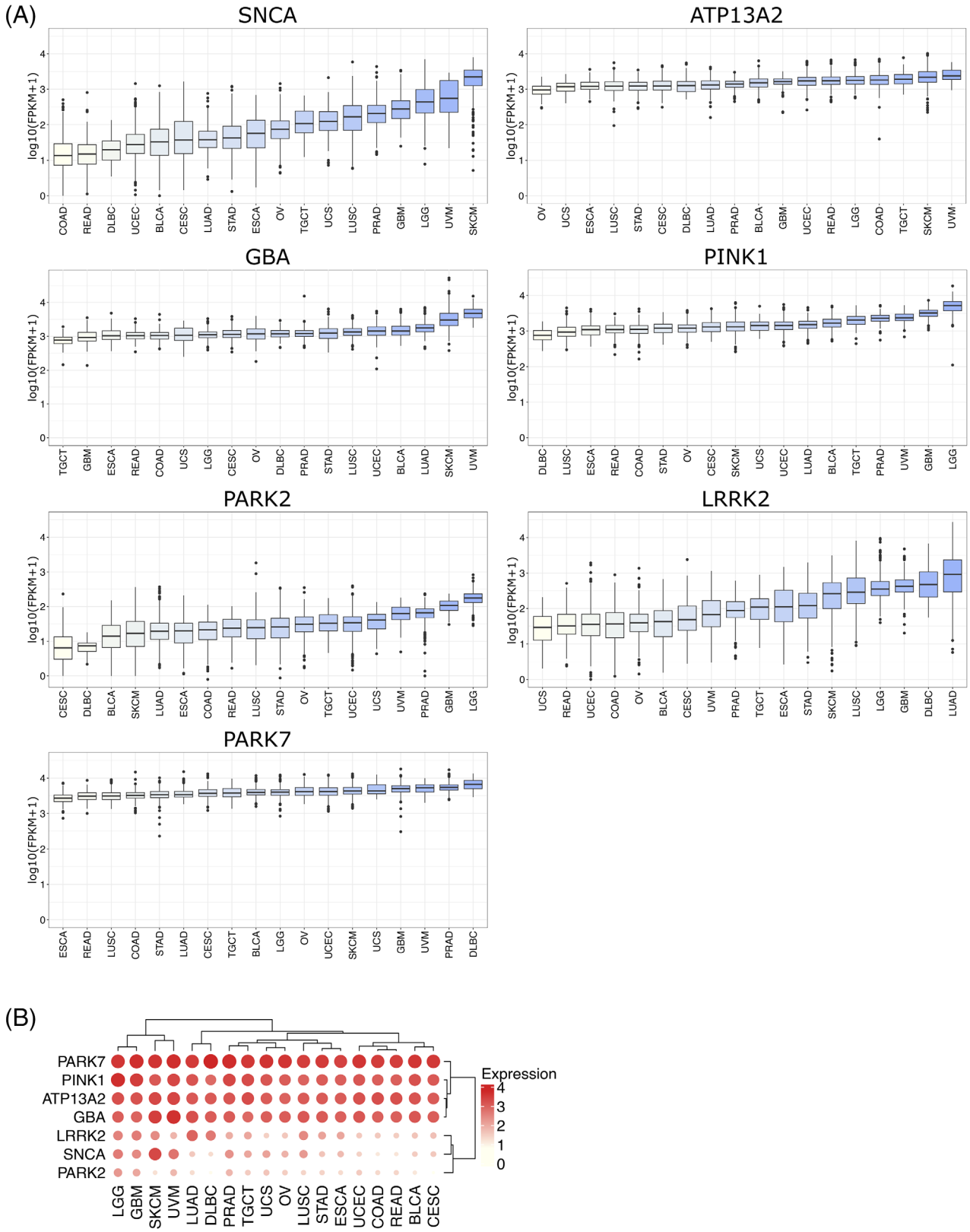

FIG. 1. (A) Pan-cancer evaluation of Parkinson's disease-related genes' expression and transcriptional associations obtained by mining The Cancer Genome Atlas (TCGA) dataset. (B) Correlation expression (log10(FPKM +)) among SNCA, PINK1, LRRK2, PRKN/PARK2, PARK7, GBA1, and ATP13A2. [Color figure can be viewed at wileyonlinelibrary.com]

adenocarcinoma (PRAD) and lung adenocarcinoma (LUAD), while *PARK7* showed the highest expression in diffuse large B-cell lymphoma (DLBC) and LUAD. In contrast, cancers such as esophageal carcinoma (ESCA) and colon adenocarcinoma (COAD) demonstrated relatively low expression levels for most of the genes, potentially reflecting a less pronounced role of PD-associated pathways in these tumor types. We next compared the expression of the genes to each other and found that unsupervised clustering of their correlation patterns identified distinct cancer groups (Fig. 1b). Notably, LGG, GBM, SKCM, and UVM formed a cluster characterized by higher expression levels of these genes. These findings, together with epidemiological evidence, suggest a potential role for PD-related genes in these cancers and deserve further investigation into their tumor-specific functions through in silico analyses and targeted mechanistic studies in vitro and in vivo.

PD Gene Association with Survival in Skin and Brain Cancers

Considering the observed expression patterns, we next investigated in silico the correlation between the expressions of *SNCA, PINK1, LRRK2, PRKN/PARK2, PARK7, GBA1*, and *ATP13A2* and OS in UVM, SKCM, GBM, and LGG. For this, we used univariate and multivariate Cox regression analyses (Table 1). Models were adjusted for clinical covariates (eg, tumor size, nodal status, metastasis, AURKA expression[33]), with additional inclusion of age and cytolytic score (CYT)[41], in LGG and SKCM since both were significantly associated with survival in these two cancer types (Fig. S1). In univariate analysis, high expression of ATP13A2 and SNCA was linked to worse prognosis in SKCM, while LRRK2 was associated with poor outcomes in LGG. Conversely, better prognosis was seen with high *SNCA* and *ATP13A2* in UVM, *LRRK2* in SKCM, *PARK2* in LGG, and *PINK1* in UVM. Multivariate analysis largely confirmed these trends, though *SNCA* lost significance in UVM, and *ATP13A2* and *PINK1* were instead linked to worse prognosis in LGG. Given *TP53*'s role in cancer, we stratified survival by *TP53* status, *TP53* wild-type (WT) or *TP53* mutated (MUT). In SKCM (*TP53*-WT), high *SNCA* and *ATP13A2* remained associated with worse prognosis, while LRRK2 was favorable in univariate analysis. In LGG (*TP53*-WT), *LRRK2* predicted worse outcomes in both models, while *PARK2* was favorable in univariate analysis. In GBM, *LRRK2* was linked to better prognosis, whereas *TP53* mutation itself predicted poorer outcomes in multivariate analysis. In *TP53*-MUT tumors, *LRRK2* showed favorable associations in LGG univariate analysis. In *TP53*-MUT SKCM, high *SNCA, ATP13A2, LRRK2*, and *PINK1* expression were linked to improved survival in multivariate models. In GBM, high *SNCA* and *PARK2* were also favorable. *ATP13A2* showed strong prognostic value in *TP53*-WT (HR = 1.7990, $P = 0.0158$) in both analyses, and in *TP53*-MUT multivariate only. *SNCA* followed a similar trend but was additionally associated with worse prognosis in *TP53*-MUT GBM.

Survival Curves Analysis

Kaplan–Meier survival curves were generated to visually assess the association between gene expression levels and patient outcomes. In UVM, the expression levels of *SNCA*, *PINK1*, and *ATP13A2* showed significant correlations with survival (Fig. S2A), while no significant associations were observed for the other four genes. In SKCM, *LRRK2* expression was positively correlated with OS, with higher expression linked to better prognosis ($P = 1e^{-4}$). In contrast, higher expression levels of *SNCA* and *ATP13A2* were associated with poorer outcomes ($P = 0.02$ for both) (Fig. S2b). No significant survival differences were found for the remaining genes. In UVM, *TP53* stratification did not reveal any significant survival differences for *SNCA*, *LRRK2*, or *ATP13A2*. In SKCM, stratification uncovered associations with survival for *SNCA, LRRK2*, and *ATP13A2*, but only in the *TP53*-WT subgroup (Fig. S3). No significant associations were found in the *TP53*-MUT group. To better capture the complexity of *TP53* mutations in cancer, we further stratified *TP53* status into truncating/homozygous loss (TRUNC/HOMODEL) and inframe/missense (INFRAME/MISSENSE) categories. We lacked sufficient data on TP53 copy number status, so it could not be included in our analysis (Tables S1 and S2). However, within the TRUNC/HOMODEL and INFRAME/MISSENSE subgroups, we did not observe any significant trends (Fig. S3). We next examined correlations in brain tumors. In LGG, high *PINK1* expression was associated with improved OS ($P = 0.04$) (Fig. S4A). No significant data were obtained when stratifying for TP53. Low *LRRK2* expression was strongly associated with better OS ($P = 5e^{-7}$), and this trend was consistent across both *TP53* WT and MUT subgroups. Interestingly, an opposite trend was observed in the TP53 INFRAME/MISSENSE subgroup, where high *LRRK2* expression was significantly associated with better survival. High *PRKN/PARK2* expression was associated with improved OS ($P = 0.001$), particularly in *TP53*-WT LGG cases ($P = 1e^{-4}$), but this association was not observed in *TP53*-MUT cases. A similar pattern was noted for *ATP13A2*, which correlated with better OS in *TP53*-WT LGG ($P = 0.001$) (Fig. S4A). Interestingly, however, high ATP13A2 correlated with better survival in TP53 TRUNC/HOMODEL. In GBM, low *PARK7* expression was modestly associated with better survival, and this trend was more pronounced in the *TP53*-WT subgroup

TABLE 1 *Univariate and multivariate Cox survival analysis for each cancer type in all samples and stratified by P53 status*

		All – univariate			All – multivariate			*TP53*-WT – univariate			*TP53*-WT – multivariate			*TP53*-MUT – univariate			*TP53*-MUT – multivariate		
Gene	**Cancer**	**n.uni**	**uni. hr**	**uni. pval**	**n. multi**	**multi.hr**	**multi. pval**	**n. uni. wt**	**uni. hr. wt**	**uni. pval. wt**	**n. multi. wt**	**multi. hr.wt**	**multi. pval. wt**	**n. uni. mut**	**uni. hr. mut**	**uni. pval. mut**	**n. multi. mut**	**multi.hr.mut**	**multi. pval. mut**
SNCA	UVM	80.00	0.24	0.03	55.00	0.00	1.00	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	SKCM	356.00	1.79	0.00	270.00	1.54	0.05	292.00	2.02	0.00	219.00	2.59	0.00	64.00	1.09	0.84	51.00	1641477.36	0.00
	GBM	157.00	1.00	1.00	157.00	1.09	0.75	100.00	1.02	0.93	100.00	1.28	0.27	57.00	0.89	0.71	57.00	8.41	0.00
	LGG	520.00	0.70	0.08	520.00	0.75	0.15	260.00	0.61	0.06	260.00	0.78	0.48	260.00	0.72	0.28	260.00	0.7	0.43
ATP13A2	UVM	80.00	0.29	0.04	55.00	0.00	1.00	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	SKCM	356.00	1.54	0.02	270.00	2.87	0.00	292.00	1.51	0.05	219.00	2.49	0.00	64.00	1.64	0.26	51.00	5.86	0.01
	GBM	157.00	1.19	0.34	157.00	1.06	0.80	100.00	1.04	0.85	100.00	0.64	0.05	57.00	1.47	0.24	57.00	1.19	0.62
	LGG	520.00	1.06	0.76	520.00	1.59	0.02	260.00	2.41	0.00	260.00	3.48	0.00	260.00	1.26	0.44	260.00	0.75	0.35
LRRK2	UVM	80.00	0.43	0.17	55.00	0.00	1.00	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	SKCM	356.00	0.53	0.00	270.00	0.5	0.01	292.00	0.52	0.00	219.00	0.71	0.15	64.00	1.22	0.65	51.00	28.06	0.00
	GBM	157.00	0.85	0.37	157.00	0.8	0.50	100.00	0.76	0.21	100.00	0.44	0.00	57.00	1.02	0.96	57.00	1.15	0.69
	LGG	520.00	2.83	0.00	520.00	3.12	0.00	260.00	2.77	0.00	260.00	5.05	0.00	260.00	2.76	0.00	260.00	1.3	0.37
PARK2	UVM	80.00	0.54	0.28	55.00	0.0	1.00	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	SKCM	356.00	1.00	0.98	270.00	0.8	0.42	292.00	0.96	0.84	219.00	0.97	0.88	64.00	1.22	0.65	51.00	20829842915 6508113179127 157083105298 988576861293 4629434923 5639812096.00	0.75
	GBM	157.00	1.20	0.30	157.00	1.15	0.55	100.00	1.16	0.51	100.00	1.54	0.05	57.00	1.14	0.69	57.00	0.3	0.00
	LGG	520.00	0.54	0.00	520.00	0.5	0.00	260.00	0.35	0.00	260.00	0.72	0.47	260.00	0.79	0.44	260.00	1.2	0.47
PINK1	UVM	80.00	0.23	0.03	> 1e3	2502301466 459317 248.00	1.00	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	SKCM	356.00	1.07	0.70	270.00	1.00	0.99	292.00	1.12	0.58	219.00	0.98	0.94	64.00	1.25	0.61	51.00	6.0	0.00
	GBM	157.00	1.21	0.29	157.00	1.4	0.19	100.00	1.03	0.88	100.00	1.08	0.74	57.00	1.15	0.65	57.00	0.57	0.09
	LGG	520.00	0.66	0.04	520.00	1.7	0.01	260.00	0.80	0.41	260.00	1.96	0.07	260.00	0.79	0.46	260.00	1.66	0.11

Abbreviations: WT, wild-type; MUT, mutated; uveal melanoma (UVM); skin cutaneous melanoma (SKCM); glioblastoma multiforme (GBM); lower grade glioma (LGG).

(Fig. S4B). No significant data were obtained for the other genes.

Gene and Pathway Correlation Analysis for PD Genes in Skin and Brain Cancer

To further investigate the molecular mechanisms underlying these associations, we analyzed the correlation between the expression levels of *PINK1*, *SNCA*, *LRRK2*, and *ATP13A2* and all other expressed genes within each of the four cancer types (UVM, SKCM, LGG, and GBM). Each cancer type was analyzed independently, and no cross-cancer comparisons were performed. We set an absolute correlation threshold at 0.6, and the statistical significance of the correlation was evaluated and corrected for multiple testing (Fig. S5). The resulting ranked gene lists were used as input for GSEA to identify biological processes and pathways either positively or negatively associated with gene expression. Genesets with FDR < 0.1% and absolute NES > 2.3 in at least one cancer type were considered significant and reported in Fig. 2. We found that PINK1 expression was generally negatively associated with pathways related to DNA repair, DNA replication, and cell cycle regulation (including G2M checkpoint, DNA replication, E2F targets, and MYC targets V2) (Fig. 2). This was driven by negative correlations with genes such as RAD51-associated protein 1, polo-like kinase 4 (PLK4), and *BRCA2* (Fig. S6 and Table S3). For *SNCA*, both GBM and LGG showed similar correlation patterns, again highlighting negative associations with DNA repair and cell cycle pathways. These findings are supported by negative correlations with genes such as the proto-oncogene *RAF1* and *CYC1* (Fig. S6; Table S5), a gene linked to tumor growth.[42] We also performed network analysis, which revealed consistent negative correlations between *SNCA* and multiple DNA repair genes across SKCM, UVM, GBM, and LGG (Fig. S7). In contrast, *SNCA* expression was positively associated with metabolic pathways, particularly fatty acid metabolism and oxidative phosphorylation. *LRRK2* expression showed similar negative correlations with cell cycle and DNA metabolism pathways (Fig. S6; Table S4). *ATP13A2* was also mainly negatively associated with cell cycle pathways, as

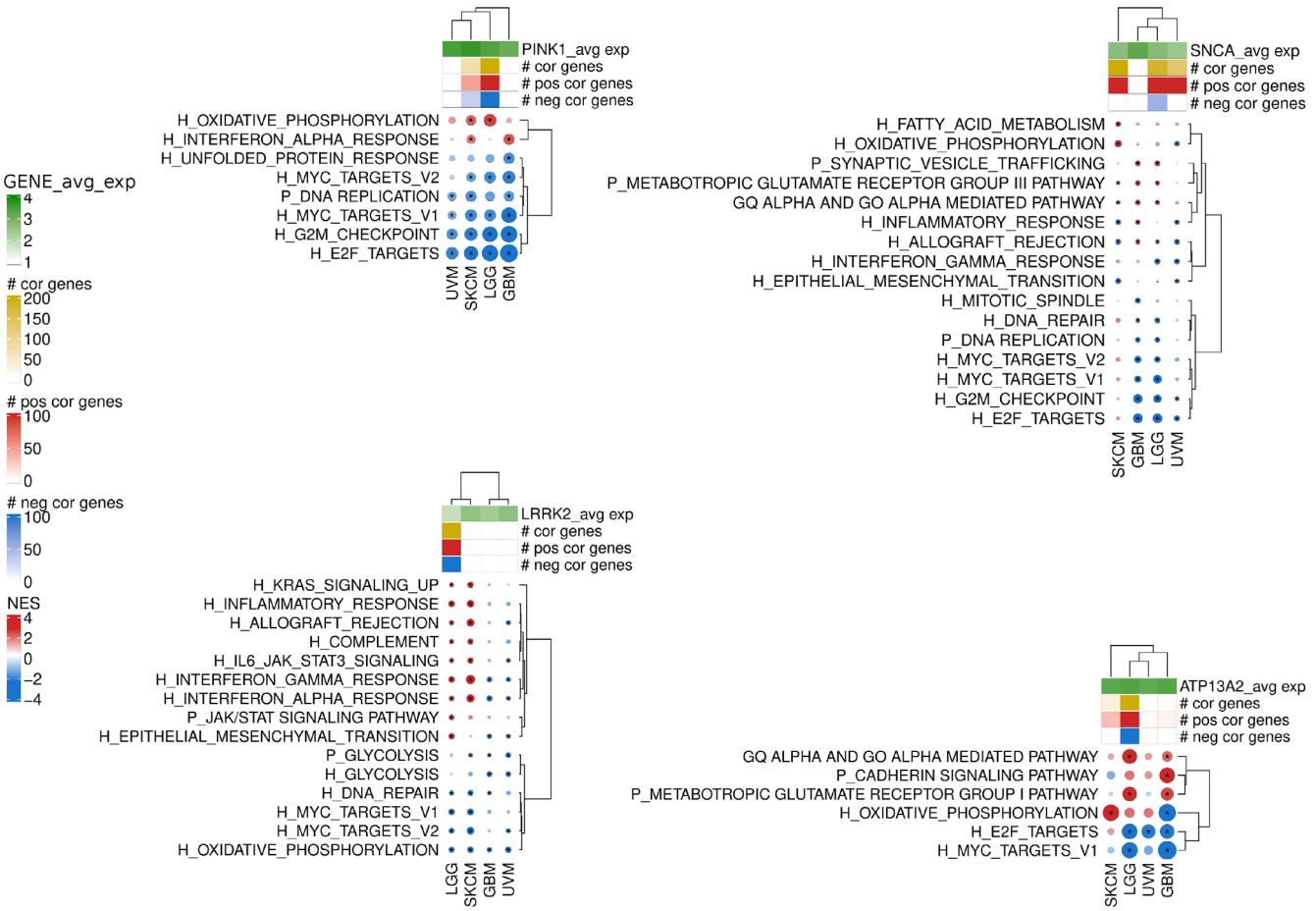

FIG. 2. Gene set enrichment analysis (GSEA) on the genes ranked according to their correlation with PINK1, SNCA, LRRK2, and ATP13A2 expression in each cancer type. A negative normalized enrichment score (NES) means down-regulation of the gene set for high Parkinson's disease-related genes' expression and vice versa for positive NES. An asterisk "*" indicates statistical significance. [Color figure can be viewed at wileyonlinelibrary.com]

indicated by correlations with genes such as *CDKN1B*[43] (Fig. S6; Table S6). Pathways related to oxidative phosphorylation and fatty acid metabolism were consistently enriched across multiple PD-related genes and cancer types, suggesting a potential link between PD-associated mitochondrial dysfunction and altered cancer metabolism. This was further supported by positive correlations with mitochondrial genes such as *ABCB6* and *MRPS11*. Finally, we did not find the expression of the seven genes to change in *TP53*-WT and *TP53*-MUT tumors (Fig. S8).

PD Genes Association to Cancer Drugs Response

Next, leveraging the DEPMAP transcriptomic dataset, we analyzed the expression patterns of *PINK1, SNCA, LRRK2*, and *ATP13A2* in tissue-specific cancer cell lines. Drug–gene associations were quantified by computing Spearman correlation coefficients between gene expression levels and drug response. This analysis revealed distinct expression patterns for these PD-associated genes and confirmed our TCGA findings: on average, their expression was higher in nervous system- and skin-derived cells (Fig. 3A). We then examined the CRISPR-based DEPMAP dataset to assess the impact of gene knockout (KO) of *PINK1, SNCA, LRRK2*, and *ATP13A2* on cell viability. In general, the KO effects on viability were modest and tended to be negative, except for *SNCA*, which showed a more pronounced impact (Fig. 3B). To explore potential therapeutic implications, we analyzed drug response profiles associated with the KO of these genes. After data filtering (see Methods), we evaluated a panel of 121 drugs in cell lines derived from three cancer types: skin, central nervous system (CNS), and peripheral nervous system (PNS) (Fig. 4). The observed drug–gene interactions involved multiple drug classes and were largely cancer-type specific. Notably, ERBB inhibitors, targeting pathways involved in cell growth, showed a general positive correlation with *SNCA*, *PINK1*, and *ATP13A2* expression. A similar trend was observed with chemotherapeutic agents.

Discussion

By leveraging TCGA data, we explored expression patterns, survival associations, and TP53 interactions, revealing the complex roles of PD-related genes in cancer.

Prognostic Implications

PD-associated genes showed elevated expression in GBM, LGG, UVM, and SKCM - cancers previously linked to PD - and were low in ESCA and COAD, indicating cancer-type specificity. Survival analyses revealed context-dependent prognostic roles: for example, *SNCA, PINK1*, and *ATP13A2* were associated with better outcomes in UVM but poorer survival in SKCM. Notably, *PINK1, LRRK2*, and *PRKN* were prognostic only in *TP53*-WT LGG, consistent with their involvement in DNA repair and apoptosis. These findings suggest that PD-related genes, including *SNCA, ATP13A2, LRRK2*, and *PARK2*, may act as modulators of cancer progression in a tumor- and *TP53*-status–dependent manner. Their differential expression and prognostic value highlight potential for biomarker development, particularly in gliomas and melanoma, where they could support risk stratification and guide therapeutic decisions.

TP53-Dependent Mechanisms

Given *TP53*'s role in cell cycle control and genomic stability, the observed negative correlations between PD gene expression and cell cycle/DNA repair pathways may be modulated by *TP53* status. Survival stratification supports this, and elevated p53 activity in PD models suggests it may act as a molecular hub linking neurodegeneration and cancer. This relationship also extends to Alzheimer's disease (AD), where *MAPT* (tau) and p53 are reciprocally regulated.[44]

Tumor-Suppressive Phenotypes

We often observed negative correlations between PD gene expression and cell cycle pathways, indicating a potential tumor-suppressive function. This was most evident in UVM, where high *PINK1, SNCA*, and *ATP13A2* expression was associated with downregulation of DNA metabolism and better survival, suggesting reduced proliferation and improved genomic stability.

Shared Mechanisms between Neurodegeneration and Cancer

Neurodegeneration and cancer, though seemingly opposing, one marked by cell loss, the other by unchecked growth, share key molecular mechanisms, including oxidative stress, inflammation, and genomic instability.[45] Our pathway analysis showed that PD-related genes (eg, *SNCA, LRRK2, PINK1*) negatively correlate with DNA repair and cell cycle pathways in brain and skin tumors. Genomic instability may serve as an aging-related modifier linking both diseases. Similar patterns are seen in AD and Huntington's disease.[46] Notably, neurons in PD and AD can aberrantly re-enter the cell cycle.[47] These

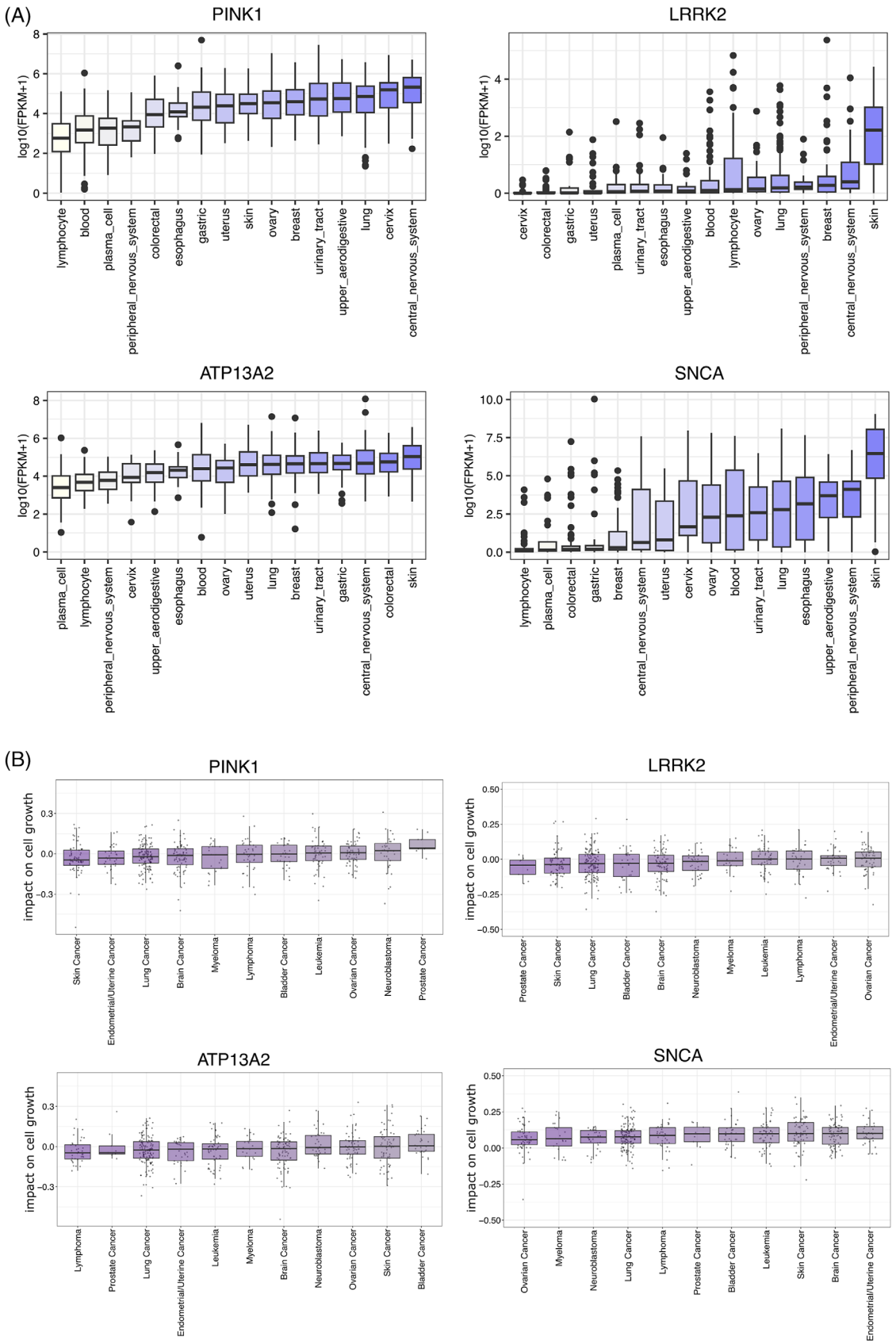

FIG. 3. (A) Parkinson's disease (PD)-related genes' expression in the DEPMAP cell line dataset according to the cancer type. (B) Cell viability after PD-related genes knockout in the CRISPR DEPMAP dataset. Viability scores are normalized such that nonessential genes have a median score of 0 and independently identified common essentials have a median score of −1. [Color figure can be viewed at wileyonlinelibrary.com]

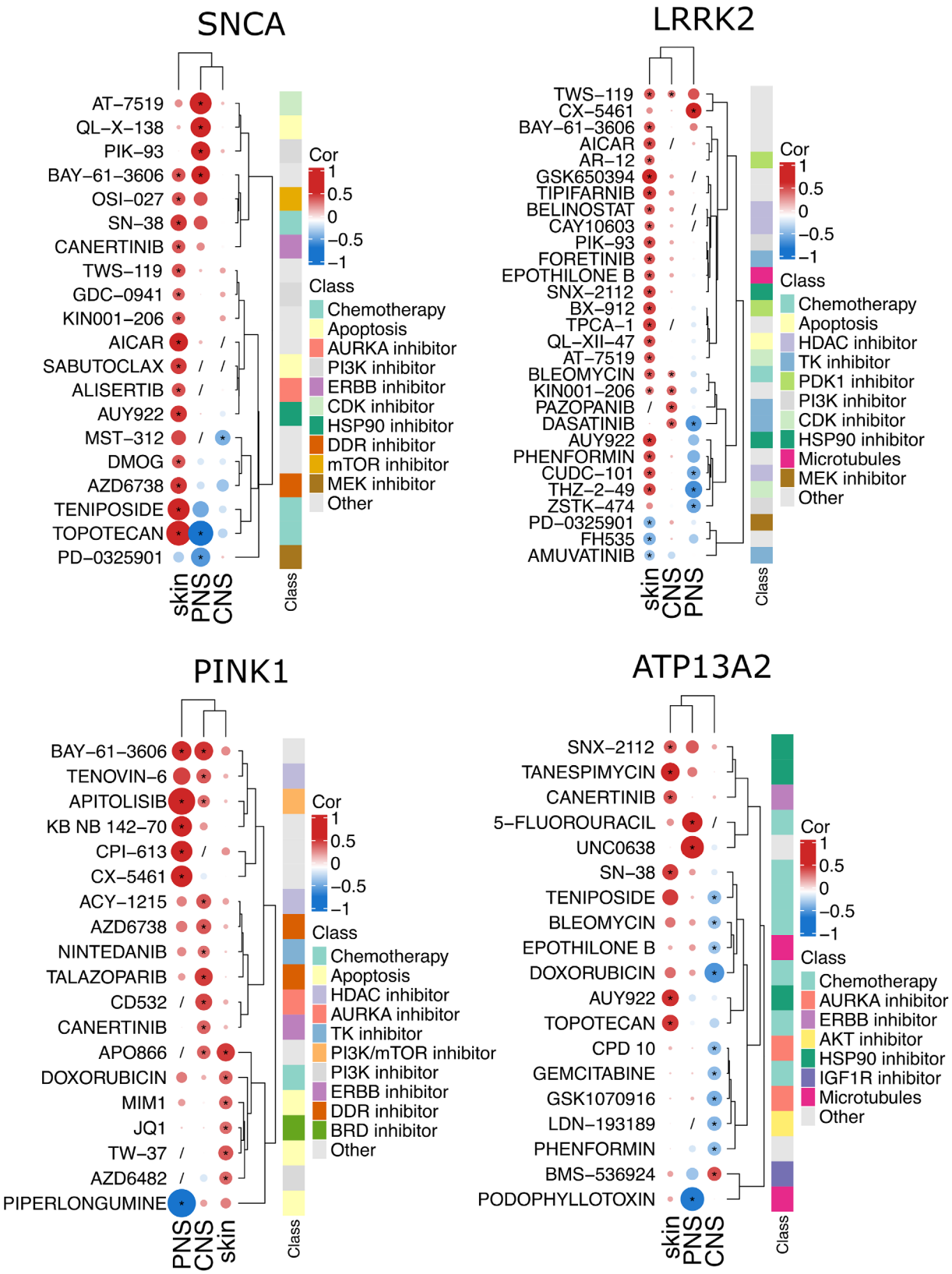

FIG. 4. Heatmap summarizing the correlations between Parkinson's disease-related genes' expression with drug response quantified as area under the drug response curve (AUC). An asterisk "*" indicates statistical significance. [Color figure can be viewed at wileyonlinelibrary.com]

associations highlight the need for mechanistic studies into shared processes.

Study Limitations

Our analyses were mainly carried out using the TCGA dataset that has some limitations. We were not able to integrate germline variant data with gene expression profiles, which limits our ability to distinguish whether observed transcriptomic alterations are driven by inherited genetic risk or somatic tumor-specific changes, due to the lack of germline data. Future studies incorporating genomic sequencing data could help clarify the relationship between PD-associated germline variants and gene expression in cancer. Moreover, the TCGA does not provide non-cancer controls in the same numbers as cancer samples, thus this constrains our ability to determine whether the expression patterns of PD-related genes are specific to tumor biology or reflect broader tissue-specific expression trends. Finally, our findings are based on observational data and lack experimental validation, which limits causal inferences about the functional roles of these genes in cancer progression. Despite these constraints, our analyses provide novel insights into the context-dependent effects of PD-related genes in cancer, particularly in relation to TP53 status and tumor survival, and lay the groundwork for more mechanistic investigations.

Conclusions

Overall, our analysis underscores the complex and context-dependent roles of PD-related genes in cancer biology, revealing significant associations with survival, cancer hallmarks, and the interplay with *TP53* status. Future research should focus on mechanistic studies to unravel the intricate interactions between these pathways, with the goal of developing treatments that address the overlapping biology of these two conditions.

Author Roles: (1) Research Project: A. Conception, B. Organization, C. Analysis; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Approval; (4) Supervision.
S.F.: 1C, 2B, 2C, 3B.
F.M.: 1C, 3B.
L.C.: 1A, 1B, 1C, 2A, 2C, 3A, 3B, 4A.
M.C.: 2C, 3B, 4A.
All authors: 2C, 3B.

Data Availability Statement

The data and codes that support the findings of this study are available from the corresponding author upon reasonable request.

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