

# Parkinson's Disease and Cancer

## Insights for Pathogenesis from Epidemiology

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Epidemiological evidence suggests a reduced incidence of many common types of cancers in individuals with Parkinson's disease (PD). Parkinson's disease and cancer are two diseases that result from an excessive signaling by one of two forces driving cells to opposite directions. PD results from the excessive death of dopaminergic neurons in the substantia nigra pars compacta (SNc) in the brain, while uncontrolled growth is the key property of cancer. Parkinson's disease is a complex disorder, probably due in most of the cases to the interaction of environment and genes. Many genes responsible for familial forms of PD are supposed to have a supportive role in regulating or maintaining the cell cycle, a fact that allows us to assume their interaction in tumorigenesis. Understanding the nature of these processes may help researchers find new and more efficacious therapeutic approaches for both diseases.

**Key words:** Parkinson's disease; cancer; epidemiology; genetics; risk factors

### Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease. PD is associated with a selective loss of dopaminergic neurons in the nigrostriatal pathway of the brain, and pathologically it is characterized by the presence of Lewy bodies whose primary structural component is alpha-synuclein. Clinical manifestations include motor abnormalities (tremor, rigidity, slowness, balance problems), autonomic disturbances, and nonmotor symptoms (depression and cognitive impairment).

The cause of PD is still unknown. Only in a minority of cases is PD determined by major gene mutations, while in most cases, nongenetic

factors probably interacting with susceptibility genes play the most important role.

Many environmental risk factors for PD have been proposed on the basis of presumed pathogenetic mechanisms of the disease. The first evidence suggesting that PD might be the consequence of environmental toxin goes back to 1983, when several people developed a parkinsonian syndrome after intravenous injection of drugs contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP was successively demonstrated to selectively damage dopaminergic cells in the substantia nigra and therefore came the hypothesis that exposure to environmental toxins was possibly one of the causes of PD.<sup>1</sup>

Cigarette smoking and coffee consumption are among the most studied risk factors for PD. Consistent results across epidemiological studies have been obtained showing a reduced risk of PD among cigarette smokers and coffee drinkers.<sup>2</sup> PD risk is increased in men

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compared to women, and a protective role of estrogens has been hypothesized.<sup>3-5</sup> So far, however, literature investigating this topic is not yet definitive. Other factors have been investigated (antioxidants, fat and fatty acids, dietary iron) but results of the studies have been not yet convincing.<sup>6</sup>

In recent years, the discovery of several causative monogenetic mutations determined an increase in the interest of the scientific community in PD. These mutations, however, explain only a small proportion of all PD, while approximately 90% of cases are still considered sporadic. Therefore, the pathogenetic mechanisms underlying the selective dopaminergic cell loss in PD are still not understood. Mitochondrial dysfunction, oxidative stress, and protein mishandling seem to play a central role in PD pathogenesis,<sup>7</sup> and these processes, in sporadic PD, might be induced by nongenetic factors, probably interacting with susceptibility genes. The need to search for nongenetic causes is still striking in order to further understand the pathogenesis of PD and develop effective therapeutic strategies.

In the last two decades it has increasingly been suggested that PD patients are in some way protected from cancer. Some epidemiological evidence suggests in fact a low incidence of many common types of cancers in individuals with PD.

In this article, we will first describe epidemiological studies supporting the inverse association between cancer and PD, and then we will focus on possible explanations for the inverse association.

## **Cancer and Parkinson's Disease**

### **Epidemiological Studies**

Evidence in favor of the inverse association between PD and cancer goes back to mid 1900s, when it was pointed that "for reasons as yet unclear, cancer is phenomenally rare in paralysis agitans."<sup>8</sup> Later a significant reduced

risk of death for cancer among PD patients was reported.<sup>9</sup>

Recently epidemiologists approached the study of the association between cancer and PD in two different ways. Cancer and PD are chronic disorders with a long time interval between the onset of pathogenic alterations and clinical manifestations. As the association between PD and cancer might have several explanations, it is methodologically important to define, in order to estimate a cause-effect relationship, if cancer happens before or after PD onset. While in the case of onset of cancer before PD the best study design is a case-control study, a cohort design is the best method to estimate the incidence of cancer in previously diagnosed PD patients. Therefore, this review will gather results of studies stratified by those who looked at cancer occurrence before PD onset (Table 1) and those who estimated cancer incidence in PD patients (Table 2).

### **Cancer Preceding PD Onset**

Only four studies looked at the frequency of cancer preceding PD onset. The first study was conducted in Rochester, Minnesota.<sup>10</sup> This was a population-based case-control study performed using the medical records linkage system of the Rochester Epidemiology Project. One-hundred ninety-six PD incident cases during the period 1976–1995 were matched by age and gender to a general population control. Overall frequency of cancer was lower in cases (19.4%) than in controls (23.5%). The inverse association was stronger in women and in individuals younger than 71 years of age. Though none of the associations reached the statistical significance, bladder and breast cancer were less frequent among cases, while prostate cancer was more common among controls.

The second case-control study, chronologically, was based on prevalent PD cases.<sup>11</sup> Starting from a sample of 368 individuals complaining of parkinsonian signs, the authors included in the study a sample of 222 PD individuals. In fact, excluded from the original sample were those individuals not satisfying PD criteria

**TABLE 1. Prior Studies on the Association Between Cancer and Parkinson's Disease Before PD Onset**

Study	Study population	PD definition	Cancer definition	Overall cancer risk	Other results
Elbaz, '02	Population-based database	Medical records	Medical records	Lower cancer frequency among cases (19.4%) than in controls (23.5%) (OR 0.79, 0.49–1.27)	Suggestive trends in analyses stratified by sex and age at PD onset; bladder and breast cancer were less common in cases than in controls, while PD patients had twice the risk of controls of prostate cancer
D'Amelio, '04	Hospital-based case-control study	Validated epidemiological criteria; PD diagnoses confirmed by two neurologists	Medical records; structured questionnaire	Lower cancer frequency among cases (6.8%) than in controls (12.6%) (OR 0.4, 0.2–0.7)	Risk of cancer was decreased only for PD women, also benign tumors were considered
Olsen, '06	Study cohort identified from a National Hospital Register	ICD code; not validated	Cancer registry	Increased frequency of malignant melanoma and skin carcinoma in PD patients	Decreased frequency of smoking-related cancers (larynx, lung, bladder)
Driver, '07a	Physicians Health Study	Self-report and validation of the diagnosis through analysis of medical records	Same as PD diagnosis	Lower cancer frequency among cases (13.1%) than in controls (14.8%) (OR 0.83, 0.57–1.21)	Smoking had a significant effect on the relationship between cancer and PD. Risk for smoking-related cancers in PD patients who smoked was decreased (OR 0.32; 0.11–0.89), while in those who did not smoke was increased (OR 6.85; 0.83–56.39)

SIR = standardized incidence ratio.

**TABLE 2. Prior Studies on the Incidence of Cancer in Parkinson's Disease Patients**

Study	Study population	PD definition	Cancer definition	Overall cancer risk	Other results and comments
Janson, '85	Hospital-based	Not specified; neurologist diagnosed	Abstracted from medical records.	Cancer risk was significantly decreased only for men (RR 0.4; $P < 0.005$ )	No reference group; number of cases of malignant melanoma was higher than expected
Moller, '95	Danish Hospital Register	ICD codes	Cancer registry.	Overall incidence of cancer was lower than expected (RR 0.88; 0.8, 1.0)	While RR were reduced for lung (0.29) and bladder cancers (0.42), they were increased for melanoma (1.96)
Minami, '00	PD patients were identified through an epidemiological survey	Hospital register	Cancer registry	Both sex combined: SIR 0.83; 0.46, 1.37	Risk of breast cancer in women was higher among cases compare to referent subjects (SIR 5.49; 1.10, 16.03)
Olsen, '04	Study cohort identified from a National Hospital Register	ICD code; not validated	Cancer registry	SIR 0.88; 95% CI 0.8, 0.9	Significant increased risk were seen for melanoma (1.95), nonmelanocytic skin (1.25) and breast cancers (1.24)
Elbaz, '05	Population-based database	Medical records	Medical records	Cancer risk was higher among cases than in referent subjects (RR 1.64; 1.15, 2.35)	Risk was significant for nonmelanoma skin cancer (RR 1.76; 1.07, 2.89). Smoking-related cancers were less common among PD cases (RR 0.77; 0.29, 2.03)
Driver, '07b	Physicians Health Study	Self-report and validation of the diagnosis through analysis of medical records	Same as PD diagnosis	Decreased incidence of most cancer in patients with PD (RR 0.85; 0.59, 1.22)	Increased risk of malignant melanoma (RR 6.15; 1.77, 21.37); they confirmed an interaction between smoking and relationship of PD to smoking-related cancers

(110 patients), those with a Mini-Mental State Examination (MMSE) score lower than 24 (25 patients), and 11 persons refusing to participate in the study. Cases were then matched by age and gender to 222 PD free individuals. The frequency of cancer preceding PD onset was significantly lower among PD patients (6.8%) compared to controls (12.6%). Also, this study found a decreased significant risk of cancer only for women and, though based on small numbers, in spite of an overall reduced risk of cancer in PD patients, breast cancer was twice more common among cases than in controls.

The third study observed an increased significant prevalence of malignant melanoma and skin carcinoma prior to the first hospital contact for PD,<sup>12</sup> with an overall odds ratios of 1.4 (95% CI 1.0–2.0) and 1.3 (95% CI 1.1–1.4), respectively. On the contrary, a reduced prevalence of cancers at smoking-related sites in patients before their first hospital contact for Parkinson's disease was observed. Findings of this study supported previous observation of an increased risk of melanoma prior to PD diagnosis observed by Elbaz *et al.* (OR 1.5; 95% CI 0.3–9.0), weakening the hypothesis that skin cancers might be caused by PD treatment. For the authors the finding of a decreased prevalence of smoking-related cancers preceding Parkinson's disease was consistent with the well-known higher risk of Parkinson's disease among nonsmokers.

Finally, the most recent study<sup>13</sup> used data from the Physician's Health Study (PHS), enrolling 22,071 male physicians. The authors identified 487 PD incident cases and matched them to 487 controls. They then evaluated a history of cancer prior to the index date that was confirmed by medical record review. Also this study observed a decrease, though not significant, frequency of cancer of any type preceding the diagnosis of PD.

### **Cancer after PD Onset**

Studies estimating cancer incidence in PD patients are more abundant. The first study

used data from two separate surveys and calculated the expected incidence rates for malignancies in a sample of 406 PD patients with PD.<sup>14</sup>

Cancer incidence was about one-third that of the general population. Relative risk of cancer increased after the onset of PD and after the treatment was started, but it was still half that of the general population. Thyroid cancer in females (3 cases) and melanomas (2 cases) were significantly more common in PD patients than expected.

Using three computerized registries in Denmark<sup>15</sup> a cohort of 7046 patients with PD, located from three computerized Danish registries, were matched to the Danish cancer registry and the Danish registry of deaths. Cancer incidence in PD patients (observed number of cases) was compared to the expected number of cancer cases. A significantly lower risk of cancer was observed for PD patients (relative risk [RR] 0.88). In particular, PD patients had a lower risk of smoking-related cancer (lung and bladder), while they showed a two-fold increased risk of malignant melanoma.

A prognosis study of 246 PD patients<sup>16</sup> identified in an epidemiological survey on the number of patients treated for intractable neurological diseases reported a lower, though not significant, decreased risk of cancer in both genders. However, risk of breast cancer was 5.5 times higher in PD patients compared to the general population.

A significant increased risk of breast cancer was also observed in a Danish study,<sup>17</sup> which observed also a twofold increased risk for malignant melanomas and a slight increased incidence of nonmelanocytic skin cancers. Overall, smoking-related cancers were less common in PD patients. Interestingly, as already reported by other authors, risk for melanoma skin cancer decreased gradually with increasing periods of follow-up, making less likely a role of levodopa treatment in melanoma development.

Incidence of cancer<sup>18</sup> was ascertained in an historical cohort of PD patients. Risk of cancer was higher among PD patients than in

the general population (RR 1.6; 95% CI 1.2–2.4), but most cancer risk was attributable to melanoma skin cancer (RR 1.8; 95% CI 1.1–1.9). The estimate of the effect of the cumulative dose of levodopa was specifically calculated and no evidence for a dose-effect relation was observed.

In the last study<sup>19</sup> 487 incident cases of PD without cancer preceding PD onset were identified and matched to PD-free individuals. Consistent with previous studies individuals with PD had a lower cancer risk. PD patients had in particular less lung (RR 0.3), colorectal (RR 0.54), and bladder (RR 0.68) malignancies. Among the studies described, this was the one with the highest significant risk for melanoma skin cancer (RR 6.15). However, smoking status significantly modified the relationship between PD and smoking-related cancers, suggesting a gene–environment interaction. PD patients who smoked were in fact at a reduced risk for smoking-related cancers (RR 0.33), whereas nonsmoker PD patients were at increased risk (RR 1.8).

## Discussion

Case-control studies and large prospective studies reported a suggestive decreased frequency of smoking and nonsmoking related cancers among patients with PD. Though most cancers appear to be less common, a few cancer types, including melanomas, thyroid, and breast cancer, have been reported to occur with increased rates in PD patients.

Ultraviolet radiation (UVR) exposure and individual phenotype are well-known major etiologic risk factors for cutaneous melanoma.<sup>20</sup> PD patients might have higher risk of melanoma skin cancer because of high solar exposure due to other risk factors for PD (i.e., rural living, farming). The association between Parkinson's disease and melanoma could be explained by the association between farming and/or rural living, both conditions gen-

erally associated with higher solar exposure, and PD. However, it seems unlikely that PD patients are individuals who significantly spend more time than the general population in the sunlight.

Other possible explanations consider the common embryonic origin of melanocytes and neurons. Levodopa is a substrate for the synthesis of melanin, and though according to some authors increased rate of melanoma in PD patients is unrelated to levodopa treatment,<sup>21</sup> one of the most recent hypotheses linked these malignancies to the levodopa in genetic-susceptible individuals,<sup>22</sup> suggesting again a gene–environment interaction.

Breast cancer is also more frequent in PD patients than in the general population. Ascertainment bias must be considered, as individuals with PD are more likely to seek medical care and receive a diagnostic investigation than individuals without PD. This statement is also supported by the contrasting result of an inverse association between breast cancer and PD when tumors are diagnosed before PD onset.<sup>10</sup>

While we could have doubts about the predisposition for PD patients to develop some cancers, we are also more prone to believe to the inverse association between malignancies and PD.

The risk that a tumor is underdiagnosed in PD patients is very low. On the contrary, as it has already been suggested, patients with PD are more likely to see a medical doctor and as a result they would have higher risk to be diagnosed with a second disease.

PD is due to neurodegeneration of dopaminergic neurons of the substantia nigra, and it is just the process leading to cell death that might explain the relationship between PD and cancer.

The discovery of gene mutations associated with familial parkinsonian disorders and understanding their role in cell survival and cell death may unravel the relationship between these two disorders.

**TABLE 3.** Familial Forms of PD

Type	Loci	Gene	Inheritance
PARK1	4q21-23	$\alpha$ -synuclein	AD
PARK2	6q25.20-27	parkin	AR
PARK3	2p13	unknown	AD
PARK4	4q21-23	$\alpha$ -synuclein	AD
PARK5	4p14	UCH-L1	AD
PARK6	1p35-36	PINK1	AR
PARK7	1p36	DJ-1	AR
PARK8	12p11.2-q13.1	LRRK2	AD
PARK9	1p36	ATP13A2	AR
PARK10	1p32	unknown	SP
PARK11	2q36-37	unknown	AD
PARK12	Xq21-25	unknown	SP
PARK13	2p13	Omi/HtrA2	AD?

AD = autosomal dominant; AR = autosomal recessive; S = sporadic

### Familial Forms of Parkinson's Disease

Thirteen chromosome loci (Table 3) linked to familial forms of PD have been until now identified. As PARK1 and PARK4 represent the same locus, the number of the familial forms is 12.

PARK1- and PARK4-linked PD is an autosomal dominant one, caused by mutations of the alpha-synuclein gene (SNCA); PARK1 is caused by missense mutations and PARK4 by multiplications of SNCA.

Alpha-synuclein was found to be widely expressed both in a variety of brain tumors<sup>23,24</sup> such as medulloblastoma, neuroblastoma, pineoblastoma, and ganglioma, as well as in peripheral cancers, including ovarian and breast cancers.<sup>25</sup> Recently, alpha-synuclein-overexpressing cells transfected to human osteosarcoma MG63 cell line<sup>26</sup> exhibited distinct features of differentiated osteoblastic phenotype. In alpha-synuclein-overexpressing cells, proteasome and kinase C activity were significantly decreased, while activity of lysosome was upregulated. Taken together these results suggest that the stimulatory effect of alpha-synuclein on tumor differentiation may be

attributed to downregulation of proteasome, which is further modulated by alterations of various factors, such as protein kinase C signaling pathway and a autophagy-lysosomal degradation system. It has been hypothesized that PD-related molecules might converge to regulate the activity of ubiquitin proteasome system (UPS) in tumor differentiation.

Parkin (PARK2) is the most common cause of inherited PD,<sup>27-29</sup> accounting for up to 49% of familial recessive early-onset PD cases. The parkin gene is characterized by a large 1.4-Mb genomic structure covering more than 40% of the 6q25-q27 chromosomal region,<sup>30</sup> which frequently undergoes deletions in a wide spectrum of human neoplasms, such as hepatocellular carcinoma,<sup>31</sup> ovarian and breast cancer,<sup>32</sup> and hematological neoplasm.<sup>33</sup>

The deregulation of the parkin gene, observed in various human cancers, suggest that the parkin gene is important in tumorigenesis.

In particular, parkin gene may play an important role in the development of mammary and ovarian tumors.<sup>34</sup> In this study DNA from 20 malignant breast tumors, 20 ovarian tumors, and corresponding nontumor tissues were genotyped. The analysis revealed deletions at the 6q25-q27 locus in 55% of cases analyzed. Subsequently, analysis of parkin gene expression in a variety of human cancers, including malignant ovarian and breast tumors, revealed the reduction of lack of transcript in approximately 70% of the samples examined.

The authors concluded suggesting that parkin is a strong candidate tumor suppressor gene (TSG), located at human chromosome 6q25-q27, and that its reduced expression and inactivation by hemizygous or homozygous deletion may play an important role in ovarian and breast carcinogenesis and other human tumors.

Later, the histological spectrum of tumors in which the candidate TSG parkin is genetically altered was expanded also to non-small-cell lung cancer.<sup>35</sup>

Recently,<sup>36</sup> a parkin<sup>-/-</sup> mouse lacking exon 3 of the parkin gene showed hepatocyte proliferation and developed macroscopic hepatic tumors with the characteristics of hepatocellular carcinoma. Microarray analyses revealed that parkin deficiency caused the alteration of gene expression profiles in the liver. Among them, endogenous follistatin is commonly upregulated in both nontumorous and tumorous liver tissues of parkin-deficient mice. Parkin deficiency resulted in suppression of caspase activation and made hepatocytes resistant to apoptosis in a follistatin-dependent manner. These results suggested that parkin deficiency caused enhanced hepatocyte proliferation and resistance to apoptosis, resulting in hepatic tumor development. The finding that parkin-deficient mice are susceptible to hepatocarcinogenesis provided the evidence that parkin is indeed a tumor suppressor gene.

Although this finding suggests that parkin is a TSG, it is not clear whether mutations in the gene, found in patients with PARK2, results in increased risk of cancer.

PARK5-linked PD is an autosomal dominant PD. The disease gene was reported as ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1).<sup>37</sup> UCH-L1 is an enzyme that cleaves carboxy-terminal peptide bond of polyubiquitine chains. Thus, UCH-L1 is an ubiquitin-recycling enzyme. UCH-L1 is a neuron-specific enzyme and is one of the most abundant proteins in the brain, but also presents in neuroendocrine cells in the lung.

Human lung cancers, in fact, frequently overexpress the ubiquitin carboxyterminal hydrolase UCHL1.<sup>38</sup> Aberrant DNA methylation is associated with many types of human cancers. A microarray analysis for genes whose expression was induced by treatment of human colon cancer cells with a demethylating agent<sup>39</sup> showed an upregulation and overexpression of seven known genes. Among these was the UCHL1 gene. UCHL1 silencing was observed in 11 of 12 human colorectal cancer cell lines, and its methylation was detected

in 8 of 17 primary colorectal cancers. Further, UCHL1 silencing was observed in 6 of 13 ovarian cancer cell lines, and its methylation was detected in 1 of 17 primary ovarian cancers. These results showed that UCHL1 is inactivated in human colorectal and ovarian cancers by its promoter methylation, suggesting that disturbance of cellular ubiquitin levels is present. Regarding the ubiquitin-proteasome system, to which UCHL1 belongs, its important roles in various cellular processes, such as cell cycle, apoptosis, and intracellular signaling, and its disturbances in cancer development are well recognized.<sup>40,41</sup>

PARK7-linked PD is another young onset PD. The disease gene was identified as DJ-1.<sup>42</sup> The size of DJ-1 is 24 kb with 8 exons encoding a protein consisting of 189 amino acids. PARK7-linked PD is very rare, and the function of DJ-1 protein is not well known. DJ-1 is a cytoplasmic protein that can translocate into the mitochondria. It has a strong antioxidative property.<sup>43</sup> Downregulation of endogenous DJ-1 protein of neuronal cell line was reported to enhance the cell death induced by oxidative stress.<sup>44</sup> DJ-1 protein expression is increased upon oxidative stress induced by paraquat.<sup>45</sup> As nigral neurons are exposed to high oxidative stress owing to the presence of dopamine, DJ-1 may be act as a strong antioxidative protein.

DJ-1 has been identified as a novel suppressor of PTEN (phosphatase and tensin homolog, a human gene that acts as a tumor suppressor gene).<sup>46,47</sup> It seems to play a role in human tumorigenesis and also to be a useful prognostic marker for cancer. Breast cancer patients have elevated levels of serum DJ-1 and circulating anti-DJ-1 autoantibodies.<sup>48</sup> Moreover it is increased in primary non-small-cell lung carcinoma samples.<sup>49</sup>

Mutations in the PTEN-induced putative kinase (PINK1, of the PARK6 locus) have been recently identified in individuals with PD.<sup>50,51</sup>

PARK6-linked PD is another form of young onset autosomal recessive PD. PINK1 has eight exons and cDNA spans 1.8 kb. It encodes a



protein with 581 amino acids. The protein is ubiquitously expressed including brain and systemic organs. Interestingly, it is a mitochondrial protein located in the matrix and the intermembrane space.

PINK1 have been shown to regulate cell death and/or the cell cycle, and several lines of evidence imply that malfunction of a shared biochemical pathway may lead to PD or cancer. PINK1 in fact encodes a kinase that is down-regulated in the absence of PTEN.<sup>52</sup>

Tough premature—as the most common domain encoded by cancer genes is the protein-kinase domain<sup>53</sup>—mutations in the leucine-rich-repeat kinase 2 gene (LRRK2 of the PARK8 locus) recently identified in individuals with PD could also influence cell-cycle control.<sup>54</sup> PARK8-linked PD is now believed to be the most common form of autosomal dominant familial PD. Function of LRRK2 is not well-known, but alterations of LRRK2 protein-reducing kinase activity corresponded to a reduced neuronal toxicity.<sup>55</sup>

## Conclusions

In this review we summarized results of epidemiological studies showing an overall reduced risk of cancer in patients with Parkinson's disease compared to that of general population. Whereas the risk of most cancers is reduced in PD patients, melanomas and breast cancers seem to occur more frequently in the PD population compared to controls. Cancer risk reduction cannot be attributed solely to the well-known reduced smoking habit of PD patients, as not only do smoking-related cancers, but also nonsmoking-related cancers appear to be less frequent in PD patients.

The explanation of this peculiar finding might be related to the involvement of common genes in both the diseases. PD-linked genes influencing cell-cycle control and predisposing individuals either to develop Parkinson's disease or a specific cancer provide in fact a biological basis for results of epidemiological studies.

Health or disease states are determined for all individuals by interactions between genes and environment. How the environment modifies gene expression and how this can incline an individual to develop a disease needs to be explored in a productive way, one that considers exposure to known risk factors in genetically predisposed individuals. Future epidemiological studies will benefit from study designs that verify not only if specific types of cancers are more closely associated with PD, but in particular if they are associated with specific familial forms of PD. This will provide insights into the function of genes associated with Parkinson's disease, characterize biological pathways, and be important for the development of therapies directed to the cure of neurodegenerative diseases and malignancies.

## Conflicts of Interest

The authors declare no conflicts of interest.

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