Parkinson disease (*PARK*) genes are somatically mutated in cutaneous melanoma

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ABSTRACT

Objective: To assess whether Parkinson disease (PD) genes are somatically mutated in cutaneous melanoma (CM) tissue, because CM occurs in patients with PD at higher rates than in the general population and PD is more common than expected in CM cohorts.

Methods: We cross-referenced somatic mutations in metastatic CM detected by whole-exome sequencing with the 15 known PD (*PARK*) genes. We computed the empirical distribution of the sum of mutations in each gene (Smut) and of the number of tissue samples in which a given gene was mutated at least once (SSampl) for each of the analyzable genes, determined the 90th and 95th percentiles of the empirical distributions of these sums, and verified the location of *PARK* genes in these distributions. Identical analyses were applied to adenocarcinoma of lung (ADENOCA-LUNG) and squamous cell carcinoma of lung (SQUAMCA-LUNG). We also analyzed the distribution of the number of mutated *PARK* genes in CM samples vs the 2 lung cancers.

Results: Somatic CM mutation analysis (n = 246) detected 315,914 mutations in 18,758 genes. Somatic CM mutations were found in 14 of 15 *PARK* genes. Forty-eight percent of CM samples carried ≥1 *PARK* mutation and 25% carried multiple *PARK* mutations. *PARK8* mutations occurred above the 95th percentile of the empirical distribution for SMut and SSampl. Significantly more CM samples harbored multiple *PARK* gene mutations compared with SQUAMCA-LUNG ($p = 0.0026$) and with ADENOCA-LUNG ($p < 0.0001$).

Conclusions: The overrepresentation of somatic *PARK* mutations in CM suggests shared dysregulated pathways for CM and PD. ***Neurol Genet* 2016;2:e70; doi: 10.1212/NXG.0000000000000070**

GLOSSARY

ADENOCA-LUNG = adenocarcinoma of lung; **CM** = cutaneous melanoma; **PD** = Parkinson disease; **SNCA** = alpha-synuclein gene; **SNPs** = single-nucleotide polymorphisms; **SQUAMCA-LUNG** = squamous cell carcinoma of lung.

Epidemiologic evidence shows that cutaneous melanoma (CM) occurs 1.5–3.5 times more frequently among patients with Parkinson disease (PD) than in the general population.[1] The CM-PD co-occurrence is also reported for first- and second-degree relatives of PD and CM patients.[2–4] Alterations in the activity of melanin synthesis enzymes, impaired autophagy, and/or genetic predisposition for both diseases have been suggested as possible mechanisms.[5] Although the risk for PD and for CM is higher in individuals with red hair color,[6] an *MC1R* variant, a main genetic determinant of skin and hair color (R160W**MC1R* -rs1805008), was reported to be associated with PD.[7] It is of interest to note that some familial PD genes (*PARK* genes) play a role in regulating or maintaining the cell cycle, a key component in the malignant transformation process.[8] Some *PARK* genes are tumor suppressors (e.g., *PARK2-PRKN-PARKIN*) and

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others are oncogenes (e.g., *PARK7-DJ1*).[8,9] In this context, one plausible explanation underlying the CM-PD co-occurrence could be genes involved in both processes that co-segregate or are in linkage disequilibrium with each other. A study testing this notion reported no shared PD-related single-nucleotide polymorphisms (SNPs) in 2,297 melanoma cases and 6,651 controls.[10] Moreover, no association was shown when cross-referencing 360 pigmentation or melanoma SNPs in 5,333 PD cases and 12,019 controls.[11]

Given the negative findings summarized above in cross-referencing germline DNA of CM and PD patients, we hypothesized that *PARK* genes may preferentially be mutated somatically in CM. The present study tested this notion.

METHODS

***PARK* genes.** To define PD predisposition genes and loci, OMIM (http://www.ncbi.nlm.nih.gov/omim) was searched with the words "Parkinson disease" and "genes" and "locus/loci."

Data formatting. The somatic CM mutation data used in this article merged melanoma exome/genome sequencing from different sources as described elsewhere.[12,13] All mutational data from 6 different whole-exome/genome sources were collated from 4 published studies[14–17] and unpublished data. The data were formatted so that all positional data were mapped to the same genome build. In this case, any data that were on hg18 were lifted over to hg19 using the Lift Genome Annotations tool available from UCSC (http://genome.ucsc.edu/cgi-bin/hgLiftOver, UC Santa Cruz Software, The Regents of the University of California, Santa Cruz, CA). In some cases, as data were merged, it became necessary to eliminate redundant information. For instance, with some samples, both a tumor and a cell line derived from it were sequenced and the overwhelming majority of mutations were shared. This is also true in the case of samples that were sequenced in more than one study[15] and for multiple metastases extracted from the same patient in another study.[17] When removing these duplicates and redundancies, all mutations were retained at a count of one and the sample name was merged into a single entry. This step was taken to ensure that the number of recurrent positions was not inflated in later analysis. Once the list of mutations was established, the positional data and changes were formatted to an oncotator input format and annotated using the web-based version of oncotator (http://www.broadinstitute.org/oncotator, Cambridge, MA). The next step taken was to remove any samples that were listed as acral, mucosal, or uveal melanoma subtypes, to ensure focusing on CM. In the final step, any samples in the initial publication that did not include a matched normal genotype were also removed.

The data were arranged in a table, where the rows represent genes and the columns are CM tissue samples. The entries are the number of somatic mutations per each combination of gene and tissue sample.

The list of somatic mutations was sorted by gene name. The somatic CM mutation platform was cross-referenced with the list of the defined *PARK* genes and loci (PARK1 to PARK20).

To assess CM-related specificity of the findings, identical analyses were performed for adenocarcinoma of lung (ADENOCA-LUNG) and squamous cell carcinoma of lung (SQUAMCA-LUNG), based on data derived from the COSMIC database (studies COSU417 and COSU418).[18] The data format of the CM mutation data set was compatible with the COSMIC data sets. Splice variants are annotated in COSMIC and are used if a mutation arises in a region that maps to the coding domain of a gene and the predicted protein is different.[18] No ethical approval was required for this study.

Statistical analysis. The statistical analysis was performed in 2 steps. As an initial step, we analyzed each gene individually, and in the second step, we analyzed the *PARK* genes combined as a group.

***Analysis by each* PARK *gene individually*.** The question of interest was whether single *PARK* genes harbor a relatively high number of somatic mutations, when compared with other genes in CM tissue. To answer this question, 2 measures were defined: (1) the sum of mutations in each gene (Smut) and (2) the number of tissue samples in which a given gene was mutated at least once (SSampl). (Note that the difference between SMut and SSampl is that in SSampl, each sample is counted at most once.)

Analysis was performed by the following steps: (1) computation of the empirical distributions for SMut and SSampl for all analyzable genes, (2) determination of the percentiles (75th, 90th, and 95th) of the empirical distribution, and (3) determination of the location of the known *PARK* genes in the above empirical distributions.

For comparison, and to ensure CM specificity of the findings, identical analyses were applied for ADENOCA-LUNG and SQUAMCA-LUNG in COSMIC data sets of studies COSU417 and COSU418.[18] Lung carcinomas were chosen as control tissues because the number of somatic mutations in lung cancer is roughly similar to that of CM (12–13/megabase in lung vs 10–18/megabase in CM).[19–21]

***Analysis of the 15* PARK *genes combined as a group*.** Because some samples harbored mutations in more than 1 *PARK* gene, we analyzed the distribution of the number of mutated *PARK* genes in CM using 2 methods:

1. We compared the distribution of the number of mutated *PARK* genes in CM samples with the distribution in ADENOCA-LUNG and in SQUAMCA-LUNG samples using the Kolmogorov-Smirnov test.
2. Here, the question of interest was how often the 15 *PARK* genes are mutated as a group, relative to a randomly chosen group of 15 genes.

Using a bootstrap-like procedure, we generated the empirical distributions of the variables of interest (SMut, SSampl), aggregated over the 15 *PARK* genes. The aggregated variables are denoted by SMutGroup, which is the total number of mutations of the 15 *PARK* genes as a group in all samples, and SSamplGroup, which is the number of samples in which at least one gene from the group was mutated. The procedure was performed as follows:

1. Randomly select a group of 15 genes.
2. Compute SMutGroup and SSamplGroup for the selected group.
3. Repeat steps 1 and 2, ten thousand times.
4. Obtain the empirical distributions of SMutGroup and SSamplGroup.

We note that the 15 *PARK* genes were excluded from the pool of genes (18,758 − 15 = 18,743 genes). The same analysis was applied to each of the 3 cancer types.

Once the empirical distributions of these variables were generated for random gene groups, we verified the locations of the group of 15 *PARK* genes in these distributions, for SMutGroup and SSamplGroup and for each cancer type.

Statistical analyses used SAS (9.2 version) and MATLAB (r2014a version).

RESULTS **Analysis by each *PARK* gene individually.** A total of 15 *PARK* genes and 20 *PARK*-associated loci were identified (table 1, first column). Somatic CM analysis resulted in 315,914 mutations in 18,758 genes by whole-exome sequencing in 246 metastatic CM tissue samples.[12] Fourteen of the 15 *PARK* genes were mutated in CM tissues. Table 1 summarizes the observed number of mutations and the number of samples harboring *PARK* gene mutations and the percentiles of the empirical distribution of mutations. As shown in the table, *PARK8* (shown as straight bold numbers) was mutated in CM, as counted by Smut, 55 times, thus being above the 95th percentile of the empirical distribution (which is 49 times) and in SSampl = 40 CM samples, again above 36, the 95th percentile of number of samples with mutations.

Three additional *PARK* genes (*PARK2*, *PARK18*, and *PARK20*, shown in table 1 as italic bold numbers) were mutated above the 90th percentile of the empirical distributions of SMut and SSampl.

Somatic *PARK* mutations were also detected in lung cancer tissue samples. Figure 1 summarizes *PARK* genes found above the 90th percentile of the empirical distribution of tissue samples (SSampl) in CM, ADENOCA-LUNG, and SQUAMCA-LUNG, and table 1 depicts the distributions of *PARK* gene mutations for the SMut and SSampl variables in the 3 cancer types.

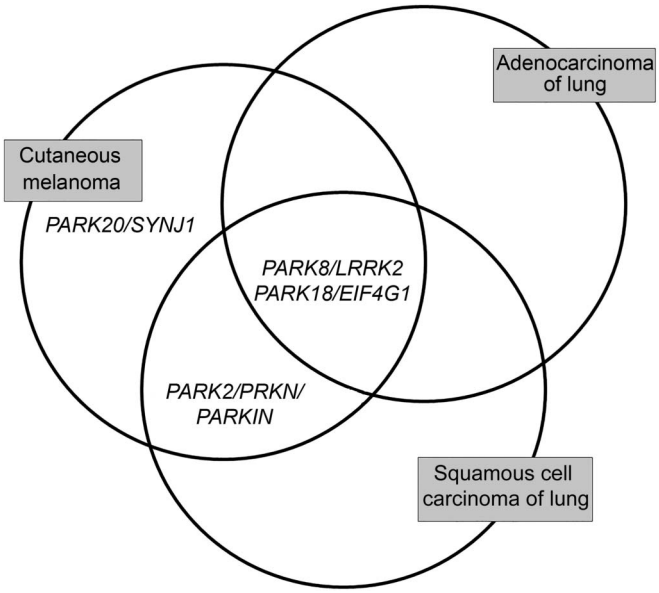
Analysis of the 15 *PARK* genes as a group. Overall, 48% of CM samples had a mutation in at least 1 *PARK* gene and 25% had mutations in multiple *PARK* genes

Table 1 ***PARK*** **mutations in cutaneous melanoma, adenocarcinoma, and squamous cell carcinoma of lung**

		CM		ADENOCA-LUNG		SQUAMCA-LUNG	
No. of mutations		324,462		130,523		80,136	
No. of samples		246		307		177	
Empirical percentile		SMut	SSampl	SMut	SSampl	SMut	SSampl
95th		49	36	26	19	14	11
90th		33	27	16	13	10	8
75th		18	16	8	7	5	5
Observed		CM		ADENOCA-LUNG		SQUAMCA-LUNG	
Locus	Gene	n	n (%)	n	n (%)	n	n (%)
PARK1/4	*SNCA*	2	2 (0.8)	5	5 (1.6)	0	0
PARK2	*PRKN*	***39***	***31 (12.6)***	16	13 (4.2)	***11***	***10 (5.6)***
PARK5	*UCHL1*	9	9 (3.6)	2	2 (0.7)	0	0
PARK6	*PINK1*	0	0	1	1 (0.3)	3	3 (1.6)
PARK7	*DJ1*	4	4 (1.6)	0	0	1	1 (0.6)
PARK8	*LRRK2*	**55**	**40 (16.2)**	***23***	***16 (5.2)***	**29**	**27 (15.3)**
PARK9	*ATP13A2*	21	18 (7.3)	6	6 (2.0)	2	2 (1.1)
PARK11	*GIGYF2*	24	21 (8.5)	11	6 (2.0)	7	4 (2.3)
PARK13	*HTRA2*	4	4 (1.6)	2	2 (0.7)	3	3 (1.7)
PARK14	*PLA2G6*	20	17 (6.9)	4	4 (1.3)	5	5 (2.8)
PARK15	*FBX07*	11	11 (4.5)	6	3 (1.0)	4	2 (1.1)
PARK17	*VPS35*	17	16 (6.5)	2	2 (0.7)	7	7 (4.0)
PARK18	*EIF4G1*	***37***	***31 (12.6)***	***20***	***15 (4.8)***	***13***	***10 (5.7)***
PARK19	*DNAJC6*	27	22 (8.9)	10	10 (3.2)	8	8 (4.5)
PARK20	*SYNJ1*	***32***	***28 (11.4)***	14	7 (2.3)	***14***	7 (4.0)

Abbreviations: ADENOCA-LUNG = adenocarcinoma of lung; CM = cutaneous melanoma; Smut = Sum of mutations in each gene; SQUAMCA-LUNG = squamous cell carcinoma of lung; SSampl = number of tissue samples in which a given gene is mutated at least once.
Figures above the 95th empirical percentile are shown in straight bold characters. The figures above the 90th percentile are shown as italic bold characters.

Figure 1 ***PARK* genes observed above the 90th percentile**



Venn diagram summarizing mutated *PARK* genes observed above the 90th percentile of the empirical distribution in melanoma, adenocarcinoma, and squamous cell carcinoma of lung.

(2–8 mutated genes) (table 2). Samples with mutations in multiple *PARK* genes (2–5 mutated genes) were found in only 6% of ADENOCA-LUNG and in 7% of SQUAMCA-LUNG samples. Comparison of the distribution of the number of mutated *PARK* genes in the 3 cancer types is shown in table 2. Significantly more CM samples harbored multiple *PARK* gene mutations compared with SQUAMCA-LUNG ($p = 0.0026$) and with ADENOCA-LUNG ($p < 0.0001$) (Kolmogorov-Smirnov test). This finding was significant after Bonferroni correction for multiple comparisons (required p value $<0.025 = 0.05/2$).

Table 2 **Number of samples with mutations in *i* mutated *PARK* genes, *i* = 1,…,8, by cancer type**

No. of mutated *PARK* genes	CM samples with mutations, n (%)	ADENOCA-LUNG samples with mutations, n (%)	SQUAMCA-LUNG samples with mutations, n (%)
1	57 (23)	54 (18)	59 (34)
2	29 (12)	13 (4)	9 (5)
3	13 (5)	4 (1)	1 (1)
4	7 (3)	0	1 (1)
5	6 (2)	0	1 (1)
6	2 (1)	0	0
7	2 (1)	0	0
8	2 (1)	0	0
Total no. of samples	246	307	177
Samples with ≥2 *PARK* mutations, n (%)	61 (25)	17 (6)	12 (7)

Abbreviations: ADENOCA-LUNG = adenocarcinoma of lung; CM = cutaneous melanoma; SQUAMCA-LUNG = squamous cell carcinoma of lung.

The number of samples carrying diverse combinations of multiple *PARK* gene mutations in CM samples is depicted in table 3. The higher frequencies of some of the combinations in CM samples (in particular, those involving *PARK2*, *PARK8*, *PARK18*, and *PARK20*, table 3) vs the paucity of such samples in ADENOCA-LUNG (table e-1 at Neurology.org/ng) and SQUAMCA-LUNG (table e-2) are clearly notable.

To further study the *PARK* genes as a group, we used the bootstrap-like permutation method (see "Statistical analysis"). The results plotted as histograms are shown in figure 2, A–C: SMutGroup (upper panel) and SSamplGroup (lower panel). SMutGroup and SSamplGroup of *PARK* genes shown as the vertical lines appearing to be located in the upper end of the distribution of genes in CM (figure 2A) and SQUAMCA-LUNG (figure 2C) and not for ADENOCA-LUNG (figure 2B). For CM (figure 2A), the location of SMutGroup for the 15 *PARK* genes as a group was at the 83.5th percentile and that of SSamplGroup was at the 90.8th percentile. For SQUAMCA-LUNG (figure 2C), the location of SMutGroup was at the 92.8th percentile and that of SSamplGroup was at the 94.1th percentile. For ADENOCA-LUNG (figure 2B), the respective sums were located at the 76.3rd percentile for SMutGroup and at the 60.8th percentile for SSamplGroup.

DISCUSSION In the present study, we observed that genes associated with PD predisposition (*PARK* genes) are somatically mutated above random occurrence in CM. This overrepresentation suggests shared dysregulated functional pathways between CM and PD. It is possible that the co-occurrence of mutations in multiple *PARK* genes has a cumulative contribution beyond the influence of a single gene dysfunction.

The most commonly mutated *PARK* gene observed herein in CM (~15% of tumors) was *PARK*8 or *LRRK2*, a gene that accounts for the most common autosomal dominant form in PD.[22] LRRK2, leucine-rich repeat kinase 2, is a large protein displaying dual enzymatic functions, a protein kinase effector domain, and a ras-oncogene like GTPase domain, in addition to multiple protein interaction domains.[23] The G2019S missense mutation, the most common *LRRK2* germline mutation in PD, results in gain of function.[23] A previous study reported that *LRRK2* is overexpressed in papillary renal and thyroid cancers.[24] Downregulation of *LRRK2* in cultured renal and thyroid cancer cells compromised MET activation and reduced downstream signaling, suggesting that LRRK2 and MET cooperate in controlling tumor growth.[24]

Table 3 Frequencies of combinations of *PARK* gene mutations in cutaneous melanoma (246 samples)

PARK gene	*PARK2*	*PARK8*	*PARK18*	*PARK20*	*PARK1/4*	*PARK5*	*PARK6*	*PARK7*	*PARK9*	*PARK11*	*PARK13*	*PARK14*	*PARK15*	*PARK17*
PARK2														
PARK8	9													
PARK18	10	11												
PARK20	8	7	7											
PARK1/4		1	1	3										
PARK5	2	4	3	3	1									
PARK6														
PARK7	2	1	1	1	2									
PARK9	4	8	4	3	1			1						
PARK11	4	4	6	5		3			3					
PARK13		3	2	2		1			1					
PARK14	7	8	9	4		2		1	2	3				
PARK15	4	2	4	2	1	1		1	2	2		3		
PARK17	6	6	4	5	1	1		2	3	3		5	3	
PARK19	5	6	6	7	1	2		1	4	2	1	5	4	

The first row and first column depict the 15 *PARK* genes, while the cells represent the joint frequencies (number of samples with these mutations). The first 4 rows (and columns) depict the 4 most frequently mutated *PARK* genes.

Patients with Ashkenazi-Jewish PD, who carry the germline *G2019S*LRRK2* mutation, were reportedly at higher risk for developing mainly hormone-related cancers, breast and prostate, but not for melanoma or any skin cancer compared with PD patients who do not carry this mutation.[25–27] It is of interest to note that a new bioinformatics tool used for detecting somatic activating mutations identified the *LRRK2* locus as a possible oncogene, albeit analyzed only in nonskin cancers, and not CM.[28]

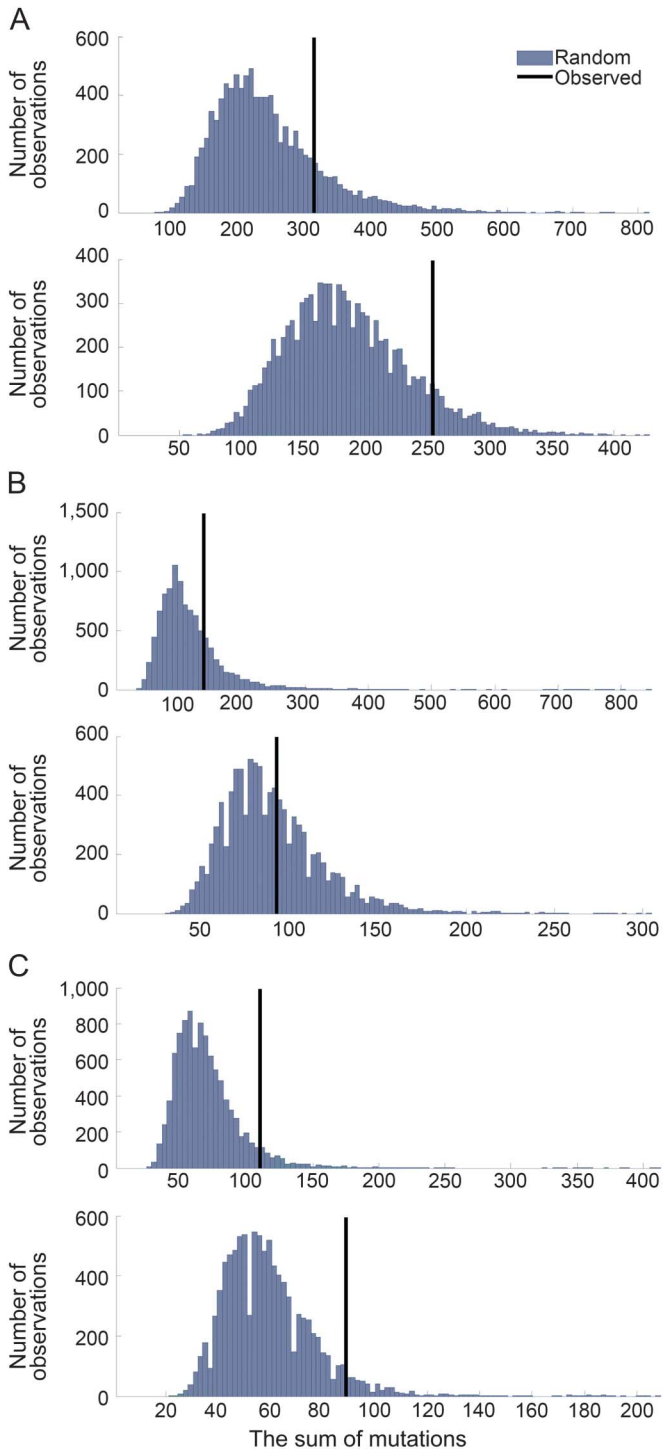
The second most commonly mutated gene in our study was *PARK2* encoding for parkin, an ubiquitin ligase 3. *PARK2*-inactivating germline mutations underlie the most common form of autosomal recessive early-onset PD.[22] Several studies have shown that *PARK2* is a potential tumor suppressor, inactivated in many cancers including glioblastoma, renal cell carcinoma, colon, lung, and pancreatic cancers.[9,29,30] Germline *PARK2*-inactivating mutations were recently reported to be more frequently encountered in a CM cohort than in controls (odds ratio = 4.93).[31] Furthermore, parkin was underexpressed in melanocytes whereas reexpression of parkin in melanoma cell lines resulted in reduction of cell proliferation rates.[31] In that study, 43% of primary and 66% of metastatic CM cell lines harbored an inactivating *PARK2* mutation.[31]

The third most frequently mutated gene in CM in the present study was *PARK18* or *EIF4G1*.[32] EIF4G1 is a member of the translation initiation complex eIF4F and plays a central role in eIF4F complex formation.[33] The effect of eIF4G1 mutations on cap complex assembly and initiation of protein synthesis remains currently unknown. Notably, *LRRK2* is involved in protein translation and cross-talks with elongations factors, one of which is encoded by *EIF4G1*.[33] The possible association of this gene with carcinogenesis is indirectly inferred from abnormal expression patterns in cancers such as SQUAMCA-LUNG, inflammatory breast cancer, and nasopharyngeal cancer.[34,35]

The fourth most commonly mutated gene somatically in CM is *PARK20* or *SYNJ1*, a gene whose biallelic mutations are associated with an uncommon form of autosomal recessive PD.[22] Recently, functional protein-protein interactions of *EIF4G1* with *SYNJ1* were reported.[36] *SYNJ1* has not been shown to be involved in cancer pathogenesis, but its homolog, *SYNJ2*, was reportedly overexpressed in breast cancer.[37]

One caveat to these results and the putative specificity of *PARK* genes targeted somatically in CM is the fact that CM displays much higher somatic mutation rates than other cancer types: somatic mutation frequency per megabase is 2 in ovarian cancer, 3–4 in breast cancer, vs 10–18 in CM.[19–21] To account for these different mutation rates, we chose to compute the relative location of *PARK* genes in CM, in comparison with the empirical distributions of the plethora of mutations in CM itself and were able to dissect *PARK* genes mutated above these distributions. In addition, we chose lung cancer, which has the closest mutation load (12–13/megabase) to CM as control tumor tissue[19–21] and showed that CM has significantly more mutated *PARK* genes compared with ADENOCA-LUNG and SQUAMCA-LUNG.

Figure 2 **Empirical distributions of the sums of mutations in groups of 15 genes in cutaneous melanoma, adenocarcinoma of lung, and squamous cell carcinoma of lung**



Histograms of the empirical distributions of the sums of mutations in groups of 15 genes, generated by randomly selecting 10,000 groups of 15 genes in (A) cutaneous melanoma, (B) adenocarcinoma of lung, and (C) squamous cell carcinoma of lung (SMutGroup—upper panel, SSamplGroup—lower panel). X axis: the sum of mutations; Y axis: number of observations. The vertical lines depict the locations of the sums of mutations (SMutGroup) in the *PARK* genes.

The strength of our study is its approach focusing on all *PARK* genes and in the use of big data. There are inherent weaknesses that should be acknowledged. Our study relies exclusively on bioinformatics findings, and there is no assignment of the somatic sequence variants as pathogenic or nonpathogenic and there are no experimental data to prove (or disprove) the possible mechanisms of association of genetic variants with phenotypes. Additional concerns involve the use of stringent statistical nonparametric analysis that may only be able to detect high odds and omit moderate contributions of single genes or subsets and thus may leave true associations undetected.

The present study focused only on *PARK* genes that are somatically mutated in CM. Yet, the possible functional and genetic intersections between CM and PD are, in all likelihood, more complex. Notably, the reported list of somatic CM mutations encompasses several genes that are functionally associated with PD.[20] For example, the alpha-synuclein gene (*SNCA*) is associated with 2 autosomal dominant inherited forms of PD (PARK1 and PARK4).[22] SNCA accumulates in neurons and forms the main component of the Lewy bodies, the pathologic hallmark of familial and sporadic PD.[22] *SNCA* is highly expressed in both primary and metastatic melanoma tissues, but not in nonmelanocytic cells.[38] Another example is *PLA2G6* (*PARK14*), a gene related to nevus count, whose germline mutations cause familial PD[39] and whose variability has been associated with increased risk for developing melanoma.[20]

A common denominator between the cells affected in CM and PD is their shared neural crest origin. The initiation of CM malignant transformation process occurs presumably early in life and is associated in a number of cases with sunburn episodes during early childhood.[40] It may be speculated that melanocytes derived from neuroectodermal stem cells with a germline "PD genotype" may be more prone to UV-induced mutations, increasing the likelihood of acquiring "driver" mutations during early childhood. This may be suggestive of some "genomic instability" that ultimately predisposes to PD and CM.

The present study highlights an association between somatic PD-related gene mutations and CM. Although the functional consequences of the mutations observed in shared genes in both diseases remain to be elucidated, our observation suggests shared pathways and offers one plausible explanation for the observed CM-PD relationship.

AUTHOR CONTRIBUTIONS

Rivka Inzelberg: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Yardena Samuels: drafting/revising the manuscript, study concept or design, analysis or

interpretation of data, acquisition of data. Esther Azizi: drafting/revising the manuscript, study concept or design. Nouar Qutob: drafting/revising the manuscript, acquisition of data. Lilah Inzelberg: drafting/revising the manuscript, analysis or interpretation of data. Edna Schechtman: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Eytan Domany: drafting/revising the manuscript, analysis or interpretation of data. Eitan Friedman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

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DISCLOSURE

Dr. Eytan Domany has served on the editorial board of *BMC Bioinformatics Journal of Statistical Mechanics: Theory and Experiment*, holds a patent for Serologic diagnosis of pemphigus vulgaris, has received research support from the Leir Charitable Foundation, has received royalty payments for Technology invention (Immunarray Co.), and holds stocks/stock options in Immunarray. The other authors report no disclosures. Go to Neurology.org/ng for full disclosure forms.

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