TUMORIGENESIS AND NEOPLASTIC PROGRESSION

Somatic Mutations in *LRRK2* Identify a Subset of Invasive Mammary Carcinomas Associated with High Mutation Burden

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Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene are the most common cause of familial Parkinson disease. Although *LRRK2*-related Parkinson disease patients have a heightened risk of certain nonskin cancers, including breast cancer, it is unknown whether *LRRK2* somatic mutations occur and are associated with breast cancer. The objective of this study was to evaluate the occurrence of *LRRK2* somatic mutations in breast cancer and the clinicopathologic features associated with *LRRK2*-mutated tumors. Using The Cancer Genome Atlas Breast Cancer Project, somatic *LRRK2* DNA sequence information was obtained for 93 cases, of which 17 cases (18%) with 18 mutations were identified. *LRRK2*-mutated mammary carcinomas are enriched with stop-gain, truncating mutations predicted to result in loss of function; missense mutations frequently targeted the GTPase and kinase domains. Tumors displayed predominantly high-grade morphology with abundant granular eosinophilic cytoplasm, resembling mitochondria-rich apocrine-like carcinomas. Exploration of the genomic landscape of *LRRK2*-mutated carcinomas yielded frequent *TP53* deactivation and a remarkably high tumor mutation burden. More important, breast cancers with *LRRK2* mutations are associated with reduced patient survival compared with The Cancer Genome Atlas Breast Cancer Project cohort. These findings, for the first time, show that somatic *LRRK2* mutations occur frequently in breast cancer, and the high mutation burden seen in this subset of tumors suggests that *LRRK2* mutations may herald benefit from immune checkpoint inhibition. (*Am J Pathol* 2020; 190: 2478–2482; <https://doi.org/10.1016/j.ajpath.2020.08.010>)

Cancer and Parkinson disease (PD), the most common movement neurodegenerative disorder, at first glance seem pathophysiologically dissimilar. Although cancer results from an uncontrolled regenerative process, PD is characterized by neuronal cell death. Although these disease processes appear to be mechanistically contradictory, an association between PD and cancer has been established, suggesting overlap in the underlying biochemical dysfunction.¹ Studies have shown both increases and decreases in cancer incidence among PD subjects, depending on the cancer type and whether PD was familial or idiopathic.^{2–5} Interestingly, breast cancer is consistently observed to be increased among PD subjects compared with controls.

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene are the most common cause of familial PD, and like idiopathic PD, carriers of *LRRK2* mutations are at increased risk for breast cancer.^{2,6–9} Among the subset of PD patients with an *LRRK2*

mutation, cancer may arise before a PD diagnosis, suggesting that this may be the sentinel event in at least a subset of *LRRK2* mutation carriers.⁷ Despite this observation, the link between *LRRK2* mutations and breast cancer has been largely unexplored. We report, for the first time, somatic *LRRK2* mutations in breast cancer, and that this subset of tumors displays high-risk features with a high mutation burden, making them promising candidates for immune checkpoint therapy.

Materials and Methods

Clinical information and simple somatic mutations, including single-nucleotide variants and small insertions/

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deletions, from whole exome sequencing and copy number information available through The Cancer Genome Atlas (TCGA) Breast Cancer Project were downloaded from the Genomic Data Commons Data Portal. For an extensive description of the tumor variant annotation workflow performed by the Genomic Data Commons DNA-sequencing analysis pipeline, please see National Cancer Institute Genomic Data Commons (https://docs.gdc.cancer.gov/Data/Bioinformatics_Pipelines/DNA_Seq_Variant_Calling_Pipeline/#tumor-only-variant-annotation-workflow, last accessed July 10, 2020). The simple somatic mutations, single-nucleotide variants, and small insertions/deletions were subjected to the current guidelines by the American College of Medical Genetics. Briefly, *LRRK2* nonsense, frameshift, and canonical splice-site sequence variants were considered pathologically significant because all of these types of mutations lead to either a stop codon or truncated, incomplete, or typically nonfunctional protein product. The remaining variants were compared with published data or were evaluated using *in silico* analyses. SIFT, MutationTaster, and PolyPhen were used to evaluate missense variants, which were only considered pathogenic if consistently predicted deleterious by all three programs (Table 1). Those variants that did not meet these strict criteria for pathogenicity and are of unknown significance are included in Supplemental Table S1. No germ-line variants were included in the analysis.

Processed, normalized, and segmented data from Affymetrix SNP 6.0 (Applied Biosystems, Foster City, CA) arrays were used to generate masked (E.R.P.C.) copy number segment files, and numeric focal-level copy number variation values were obtained using GISTIC2 (Genomic Data Commons Copy Number Variation Analysis Pipeline).

Copy number variation with values <-0.3 were categorized as loss and values >0.3 were categorized as gain. Nonsynonymous mutation rates from 988 of 1098 cases computed by the Broad Genome Data Analysis Center using MutSigCV version 0.9 (Broad Institute, Cambridge, MA) were obtained from FireBrowse.¹⁰ The rate of nonsynonymous gene mutations was determined by the Broad Genome Data Analysis Center using MutSigCV version 0.9.

Whole slide images of diagnostic sections were downloaded from the Genomic Data Commons Data Portal and assessed by at least one breast pathologist on ImageScope. Select clinical data, follow-up times, and vital status were available for 1096 of 1098 patients. Overall survival was defined as date of diagnosis to the date of last clinical follow-up or death. Simple somatic mutations were also downloaded and analyzed from the cBio Cancer Genomics Portal.^{11,12} Statistical analysis included comparisons between the groups using the χ^2 test, *U*-test (where tests for homoscedasticity failed to demonstrate equal variances), and Mantel-Cox log-rank test.

Results

Curated clinical, mutation, and copy number information was available for 1098 of TCGA project-level breast cancer cases. Because of the large size of *LRRK2* (51 exons spanning over 148 Kb) and the stringency of gene-level curation of TCGA bioinformatics pipeline, only 93 cases with complete *LRRK2* sequence were available. A total of 28 *LRRK2* somatic variants (synonymous, nonsynonymous, and deep intronic) were identified, of which 18 were

Table 1 *LRRK2* Mutations, Predicted Protein Change, Variant Type, and Domain Affected from TCGA

Case no.	Barcode	Coding	Protein	Variant type	Domain
1	TCGA-E9-A243	c.1274T>C	p.L425P	Missense	Armadillo
2	TCGA-AN-A0AK	c.1605del	p.K535Nfs*13	Frameshift	Armadillo
3	TCGA-AC-A23H	c.2573C>G	p.S858*	Nonsense	Interdomain
4	TCGA-C8-A132	c.2765T>A	p.L922*	Nonsense	Interdomain
5	TCGA-AN-A046	c.3266A>G	p.N1089S	Missense	Leucine-rich repeat and
		c.4469C>T	p.A1490V	Missense	ROC
6	TCGA-D8-A1JP	c.3910C>T	p.L1304F	Missense	Leucine-rich repeat
7	TCGA-D8-A1X5	c.4334C>T	p.S1445F	Missense	ROC
8	TCGA-BH-A0E9	c.4514_4520del	p.I1505Rfs*16	Frameshift	ROC
9	TCGA-D8-A1XK	c.4915dup	p.R1639Kfs*13	Frameshift	COR
10	TCGA-AN-A0X0	c.5072T>C	p.I1691T	Missense	COR
11	TCGA-A0-A0J4	c.5117C>G	p.S1706*	Nonsense	COR
12	TCGA-AN-A0XU	c.5312G>C	p.R1771T	Missense	COR
13	TCGA-D8-A1XZ	c.5455G>C	p.G1819R	Missense	COR
14	TCGA-S3-AA11	c.5861C>T	p.S1954F	Missense	Kinase
15	TCGA-C8-A3M7	c.6322G>A	p.E2108K	Missense	Kinase
16	TCGA-B6-A0I8	c.7153G>A	p.G2385R	Missense	WD40
17	TCGA-AC-A3QP	c.958+1G>A	p.?	Splice site	Armadillo

*Denotes a stop codon.

COR, C-terminal of Roc; ROC, Ras of complex; TCGA, The Cancer Genome Atlas.

Table 2 Clinicopathologic Summary of Breast Cancer Patients Harboring an *LRRK2* Mutation

Case no.	Age, years	Histology	Grade	Laterality	Quadrant	pT	pN	pM	Stage ¹⁴
1	52	Ductal with apocrine features and zonal necrosis	3	Right	UIQ	T2	N0	M0	IIA
2	77	Ductal with apocrine and micropapillary features and zonal necrosis	3	Left	UOQ	T2	N0	M0	IIA
3	90	Ductal with apocrine features	3	Right	UIQ, LIQ	T2	NX	M0	IIA
4	56	Ductal with apocrine features	3	Left	NOS	T2	N1	M0	IIB
5	69	Ductal with apocrine features	3	Right	LIQ	T2	N0	M0	IIA
6	74	Ductal with clear cell features	3	Left	UIQ	T1	N0	M0	IA
7	81	Ductal with apocrine features and zonal necrosis	3	Right	UOQ, LIQ	T2	N3	MX	IIIC
8	53	Pleomorphic lobular with apocrine features	3	Right	NOS	T2	N1	M0	IIB
9	55	Ductal with prominent lymphocytic infiltrate and zonal necrosis	3	Left	LIQ	T2	N1	MX	IIB
10	59	Ductal with apocrine and cribriform features	2	Left	UOQ	T2	N1	M0	IIIA
11	41	Ductal with prominent lymphocytic infiltrate and zonal necrosis	3	Left	UOQ	T1	N0	M0	IA
12	55	Ductal with clear cell features and zonal necrosis	3	Left	UOQ	T2	N0	M0	IIA
13	82	Ductal with apocrine features, prominent lymphocytic infiltrate, and zonal necrosis	3	Right	LIQ	T1	N2	M0	IIIA
14	68	Ductal, NOS	3	Right	NOS	T2	N0	M0	IIA
15	61	Pleomorphic lobular with apocrine features	2	Left	UIQ	T4	N0	M0	IIIB
16	47	Ductal with apocrine features	3	Right	UIQ	T1	NX	M0	IA
17	80	Pleomorphic lobular with apocrine features	2	Right	NOS	T2	N1	MX	IIB

Staging information per American Joint Committee on Cancer, eighth edition.¹⁴
LIQ, lower inner quadrant; NOS, not otherwise specified; UIQ, upper inner quadrant; UOQ, upper outer quadrant.

considered potentially pathogenic in 17 cases, including 11 missense, 3 nonsense, 3 frameshift, and 1 splice-site variant (Table 1). *LRRK2* encodes a multidomain protein with an enzymatic core composed of a Ras of complex GTPase domain in tandem with a C-terminal of Roc domain and a kinase domain, which localizes to the cytoplasm and mitochondrial membrane.¹³ A large fraction of the alterations were stop-gain, inactivating mutations (41% of cases). Interestingly, missense variants commonly targeted the Ras of complex, C-terminal of Roc, and kinase domains (Table 1). A single case was characterized by the PD-associated *LRRK2* p.G2385R mutation. Cases with wild-type/polymorphic variant *LRRK2* sequences and cases with variants with insufficient evidence for pathogenicity are listed in Supplemental Tables S1 and S2.

All patients with tumors harboring *LRRK2* mutations were female, had a median age at diagnosis of 61 (range, 41 to 90) years, and most presented with stage II or III disease (82%); these characteristics were similar to the study cohort (Supplemental Table S3).¹⁴ High-grade, Nottingham grade 3, ductal and pleomorphic lobular morphologies prevailed (82% and 18%, respectively) (Table 2)¹⁴; interestingly, a granular eosinophilic cytoplasm, consistent with

mitochondrial-rich apocrine-like features, was present in 71% of *LRRK2*-mutated cases (Figure 1A and Table 2). Clinical predictive marker information was available for 15 patients with *LRRK2* mutations. Most cases were estrogen receptor–positive disease (67%), including three cases that were additionally positive for human epidermal growth factor receptor 2 (Supplemental Table S3), four cases that were triple negative, and no case that was positive for human epidermal growth factor receptor 2 in the absence of estrogen receptor expression (Supplemental Table S3). Androgen receptor expression information was not available.

To explore the genomic landscape of *LRRK2*-mutated tumors, single-nucleotide variants and copy number changes in commonly altered genes in breast cancer were assessed.¹⁵ *TP53* alterations, including stop-gain mutations and copy number losses, were the most common event (65%) (Supplemental Figure S1). Furthermore, *LRRK2*-mutated carcinomas displayed a high mutation burden compared with the remainder of the breast cancer cohort (mean, 16.6 versus 1.4 nonsilent mutations per megabase, respectively; *U*-test *P* = 0.003) (Figure 1B). In fact, the two cases with the highest tumor mutation burdens in TCGA Breast Cancer

Figure 1 Clinicopathologic features of *LRRK2*-mutated invasive mammary carcinomas. **A:** Abundant granular eosinophilic cytoplasm, with mitochondrial-rich apocrine-like features, prevailed in *LRRK2*-mutated tumors. **B:** Box plot of nonsilent mutations per megabase of DNA in tumors with *LRRK2* mutations compared with The Cancer Genome Atlas Breast Cancer Project (TCGA-BRCA) cohort, including cases with no *LRRK2* mutations or indeterminate *LRRK2* status. **C:** Kaplan-Meier overall survival (OS) stratified by *LRRK2* mutation status. Patients with tumors harboring an *LRRK2* mutation display an OS inferior to patients relative to TCGA-BRCA cohort, including cases with no *LRRK2* mutations or indeterminate *LRRK2* status, with 3-year OS of 31% (95% CI, 0.9%–74%) versus 84% (95% CI, 79%–87%), respectively. Asterisks represent extreme outliers, as defined as three times the interquartile range. Of note, breast cancer–specific survival data are not available in TCGA-BRCA cohort. $n = 16$ tumors with *LRRK2* mutations (**B**); $n = 972$ for TCGA-BRCA cohort (**B**); $n = 17$ patients with tumors harboring an *LRRK2* mutation (**C**); $n = 1079$ cases with no *LRRK2* mutations or indeterminate *LRRK2* status (**C**). Original magnification, $\times 200$ (**A**). HR, hazard ratio.

Project harbored *LRRK2* mutations. *LRRK2*-mutated carcinomas showed similarly high mutation burdens when only cases with complete *LRRK2* sequence were considered, despite the small sample size (Supplemental Figure S2). Consistent with a high-risk phenotype, subjects with *LRRK2* mutations had a statistically significant inferior overall survival, including 3-year survival rates of 31% and 84% among patients with *LRRK2* mutations and the remainder of the TCGA Breast Cancer Project, respectively, with a hazard ratio of 3.42 (95% CI, 1.08–10.80; $P = 0.036$) (Figure 1C). Similar overall survival trends were observed when *LRRK2*-sequenced cases alone were examined, albeit this study was underpowered (Supplemental Figure S3).

Discussion

We uncovered a previously unrecognized role of *LRRK2* in breast cancer, whereby tumors harboring a somatic *LRRK2* mutation may constitute a distinct clinicopathologic entity with increased tumor mutation burden and high-risk clinical behavior. Immune checkpoint inhibitors have emerged as effective oncologic therapy, leveraging adaptive immune responses, and detecting error-prone DNA repair deficiencies predicts responses to these drugs, presumably due to the production of mutation-associated neoantigens.¹⁶ As a corollary, tumor mutation burden has been used as a predictive biomarker in this therapeutic context, albeit with imperfect correlation with responses.¹⁷ Detailed biochemical studies will be necessary to dissect whether *LRRK2* alterations are causative of increased mutation burdens or a sensitive marker of *LRRK2*-independent mutagenesis. Nonetheless, the high fraction of inactivating stop-gain mutations in *LRRK2* would

suggest a mechanistic relationship, not a bystander effect, and evidence exists supporting a DNA maintenance role for *LRRK2*.^{18,19} Assessing for *LRRK2* integrity may thus identify a subset of genomically unstable breast tumors with vulnerability to immune checkpoint inhibition.

A recent study reported that PD patients with germ-line *LRRK2* p.G2019S mutations were at an increased risk for leukemia and colon cancer, suggesting that the overall baseline cancer risk may be elevated among *LRRK2* mutation carriers.⁴ Of note, a PD-associated variant, p.G2385R, was somatically detected in one breast cancer case, although the functional impact of this particular variant is still poorly understood.^{10,20,21} It will be informative to investigate whether *LRRK2* mutations occur in other primary sites, supporting a broader tumor suppressor function for *LRRK2*, and future mechanistic studies may examine a direct role in cancer pathogenesis.²²

Several PD-associated genes, including *LRRK2*, have been implicated in cell cycle control and tied to DNA integrity, which are classic tumor suppressor functions frequently targeted for inactivation in cancer.^{1,18,19} The somatic *LRRK2* variants identified herein were predicted to be loss of function, including a high proportion of stop-gain mutations, albeit biochemical functional characterizations are still necessary to substantiate the pathogenic nature of these variants. Yet, biochemical studies examining the common PD-linked p.G2019S mutation have described a gain of function,²³ and clinical trials for PD using *LRRK2* kinase inhibitors and antisense oligonucleotides are currently underway (clinicaltrials.gov, last accessed July 10, 2020). In light of our results, it may be prudent to assess the impact of *LRRK2* dysregulation on carcinogenesis as an adverse effect of *LRRK2*-directed PD therapy.

One of the limitations of our study is that of the 1098 breast cancer cases in TCGA, only a fraction had available *LRRK2* sequence information, limiting the statistical power of these results. To address this, somatic *LRRK2* pathogenic variants were identified in the cBio Cancer Genomics Portal in primary and metastatic breast cancer (Supplemental Table S4), showing some overlap with TCGA Breast Cancer Project, including another missense variant targeting leucine 425 and nonsense mutation p.S858*. The fact that stop-gain mutations and homozygous deletions are reported in this external data set additionally supports our view that *LRRK2* inactivation is a breast cancer-associated phenomenon (Supplemental Table S4). Furthermore, as a retrospective study, the findings were limited by the paucity of clinical information available for the evaluation of therapeutic outcomes. Notwithstanding these limitations, the relative frequency of *LRRK2* mutations detected is strong evidence for its biomedical and oncologic relevance. On the basis of our collective findings, the inclusion of *LRRK2* in commercial somatic sequencing panels may be warranted.

In conclusion, somatic *LRRK2* mutations are associated with breast cancer, and these findings shed light onto the mechanistic underpinnings of *LRRK2*-related neurodegeneration versus neoplastic disease. The identification of *LRRK2* mutations in breast cancer may provide an opportunity for risk stratification and new treatment paradigms.

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Supplemental Data

Supplemental material for this article can be found at <http://doi.org/10.1016/j.ajpath.2020.08.010>.

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