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RESEARCH ARTICLE

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Germline sequence analysis of *RABL3* in a large series of pancreatic ductal adenocarcinoma patients reveals no evidence of deleterious variants

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with a 5-year survival rate of less than 10%. Individuals with a pathogenic germline variant in a pancreatic cancer susceptibility gene are at an increased risk of developing pancreatic cancer. Understanding the inherited genetic basis of pancreatic tumor development provides a unique opportunity to improve patient care and outcomes. For example, relatives of a patients with PDAC who have a pathogenic germline variant in a pancreatic cancer susceptibility gene are eligible for disease surveillance where cancers may be detected early, and 5-year survival greatly improved. Furthermore, for some patients with PDAC and a pathogenic germline variant in a pancreatic cancer susceptibility gene, their tumors may be susceptible to specific anti-cancer therapies. Recently, *RABL3* was identified as a pancreatic cancer susceptibility gene. To validate these findings and inform clinical translation, we determined the prevalence of deleterious *RABL3* variants in a large cohort of 1037 patients with PDAC that had undergone either whole genome or whole exome germline sequencing. We identified two synonymous variants and four missense variants classified as variants of unknown significance. We found no pathogenic *RABL3* variants, indicating that the maximum prevalence of such variants in patients with PDAC is less than 0.36% (minor allele frequency 0, 97.5% one-sided confidence interval: 0-0.0036). This finding has important implications for germline genetic testing of patients with PDAC.

Nicholas J. Roberts and Robert C. Grant contributed equally and share co-first authorship.

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KEYWORDS
Cancer, Inherited, Pancreas, RABL3, Variants

1 | INTRODUCTION

Up to 10% of newly diagnosed patients with PDAC have a family history of pancreatic cancer.[1] These aggregation of PDAC in these families can be due to inherited genetic variants, environmental factors, or stochastic effects. Inherited causes; however, are an important cause of this familial aggregation, with up to 20% of newly diagnosed patients with familial pancreatic cancer having an identifiable pathogenic germline variant in a pancreatic cancer susceptibility gene, most frequently in *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, and *PALB2*.[2] However, it is clear that many inherited cases of pancreatic cancer remain unexplained by our current knowledge.

In addition to patients with a family history, pathogenic germline variants in pancreatic cancer susceptibility genes have also been found in 5%-10% of patients with PDAC without a family history and 2.9% of patients with surgically resected intraductal papillary mucinous neoplasms, a pancreatic cancer precursor lesion, unselected for a family history of pancreatic cancer.[3-6] These studies indicate an inherited disease etiology for a larger number of patents than was previously appreciated.

Knowing whether a patient with PDAC carriers a pathogenic germline variant in a pancreatic cancer susceptibility gene has important implications for the clinical management of the patient and their biological relatives. Specifically, patients with PDAC and a pathogenic germline variant in *BRCA1*, *BRCA2*, or *PALB2*, may have better outcomes when treated with poly(ADP ribose) polymerase inhibitors or platinum containing chemotherapeutic agents due to somatic loss of homology directed DNA repair.[7,8] Similarly, patients with PDAC and a pathogenic germline mutation in *MLH1*, *MSH2*, *MSH6*, or *PMS2*, have tumors that are deficient in DNA mismatch repair and are exquisitely sensitive to PD-1 blockade.[9] Furthermore, family members with pathogenic germline variants in a pancreatic cancer susceptibility genes are eligible for clinical surveillance to detect pancreatic and other cancers early when surgical intervention may be curative.[10] These advances in our understanding of the role of inherited factors in pancreatic cancer risk, as well as the treatment implications of such findings, were the driving forces behind updated National Comprehensive Cancer Network Clinical Practice Guidelines to consider germline genetic testing in all patients with PDAC.[11] Because of the significance of carrying a pathogenic variant in a pancreatic cancer susceptibility gene, several studies have used next generation sequencing approaches to identify novel susceptibility genes with some success, including *ATM*, *CPA1*, and *CPB1*.[12-14] Recently, *RABL3* was identified as a potential pancreatic cancer susceptibility gene after a functionally deleterious *RABL3* germline variant was identified in a single family with multiple affected members and found to segregate with disease.[15] However, additional pancreatic cancer patients with pathogenic germline *RABL3* variants have not yet been reported. Thus, the utility of including *RABL3* as part of multi-gene panel testing for pancreatic cancer patients and their relatives remains unclear. Therefore, to replicate the initial finding and better understand the contribution of *RABL3* variants to pancreatic cancer risk, we examined the coding region of the *RABL3* gene in the germline of 1037 patients with PDAC, over 600 of which had familial pancreatic cancer, and determined the prevalence of pathogenic *RABL3* variants.[13,16,17]

2 | MATERIALS AND METHODS

2.1 | ETHICS STATEMENT

This analysis was reviewed and approved by the Institutional Review Board at the Johns Hopkins University and the Research Ethics Board at the University of Toronto.

2.2 | Patients with PDAC

One thousand and thirty-seven patients with pathologically confirmed PDAC and either germline whole genome or whole exome germline sequence data were included in this study and were previously described.[13,16,17] The first cohort included patients with familial pancreatic cancer, that is the patient was in a kindred in which there were at least two first-degree relatives with pancreatic cancer, and germline whole genome sequence data. Patients with familial pancreatic cancer were enrolled in the National Familial Pancreas Tumor Registry (NFPTR) at Johns Hopkins and familial pancreatic cancer registries at Mount Sinai Hospital, as well as other sites.[13] The second cohort included patients with either familial pancreatic cancer or sporadic PDAC and either germline whole exome or whole genome sequence data, analyzed as part of the Ontario Institute for Cancer Research PanCuRx Translational Research Initiative.[16,17] We excluded the following patient samples from our analysis: (a) duplicate patient samples in the combined cohort such that patients were included only once for analysis, (b) patients of non-European Ancestry, and (c) patient samples from Dana-Farber Cancer Institute to avoid inclusion of patients already reported by Nissim et al.[15]

2.3 | Sequencing and bioinformatic analysis

We re-analyzed all exome and genome sequencing data through a harmonized bioinformatic pipeline. Sequencing reads were aligned to the human reference (hg19) genome using Burrows-Wheeler Aligner version 0.7.12.[18] Variants were called using the HaplotypeCaller,

CombineGVCFs, and GenotypeGVCF functionalities of the Genome Analysis Tool Kit version 3.5.0.[19]

2.4 | Variant annotation and classification

Germline variants, including single base substitutions and small insertions and deletions (INDELs), in the *RABL3* coding region were extracted and annotated with transcript information and protein functional consequence using the Reference Sequence Database (RefSeq), minor allele frequency (MAF) form the population-based variation database gnomAD ((v.2.1.1.1 [non-cancer]), and clinical significance in ClinVar using ANNOVAR.[20-23] We classified *RABL3* variants as either benign, variant of unknown significance (VUS), or pathogenic using our previous published criteria based on the American College of Medical Genetics (ACMG) variant classification guidelines.[6,24] Briefly, variants with MAF>0.005 were classified as benign. Nonsynonymous variants or in-frame insertions or deletions (INDELs), with a MAF ≤0.005 and not reported as pathogenic in ClinVar, were classified as VUS. Nonsense variants, frameshift INDELs, or splicing variants (±1 or ± 2 position of adjacent intronic sequence) with a MAF ≤0.005, as well as nonsynonymous variants or in-frame indels with a MAF ≤0.005 reported to be pathogenic in ClinVar, were classified as deleterious.

2.5 | Statistical analysis

STATA v.13 (StataCorp LLC, College Station, TX) was used for all statistical analyses. The confidence interval for deleterious *RABL3* variants in patients was calculated using a binomial distribution. Variant association analysis used the European (non-Finnish) population in the gnomAD database (v.2.1.1.1 [non-cancer]) as a control group and was conducted using a Fisher's exact test. $P < .05$ was considered significant.[19]

3 | RESULTS

We included 1037 patients with PDAC in this study. The demographics of the patients are presented in Table 1. Germline whole genome sequence data was available for 532 (51.3%) patients and whole exome sequence data available for 505 (48.7%) patients.[13,16,17] Overall, 601 (58.0%) patients had a family history consistent with familial pancreatic cancer. 499 (48.1%) patients were male, 442 (42.6%) patients were female, and for 96 (9.3%) patients, sex was not reported. The median age group of patients at diagnosis was 60-69 years.

We identified six unique coding variants in *RABL3* in this cohort of 1037 patients (Table 2). These included 2 benign synonymous variants and 4 missense VUS classified using ACMG variant classification guidelines.[24] We did not identify any deleterious *RABL3* variants. Comparison to the European (non-Finnish) population in the gnomAD database showed that all *RABL3* variants identified in our patient cohort were rare in the general population (MAF ≤0.00808). Thus, in our series of over 1000 patients with PDAC, the prevalence of deleterious *RABL3* variants was 0 (97.5% one-sided confidence interval: 0-0.0036).

TABLE 1 Demographics of patients with pancreatic ductal adenocarcinoma included in study

Characteristic[a]	Number	Percent (%)
Type of sequencing		
Whole genome	532	51.3
Whole exome	505	48.7
Family history		
FPC	601	58.0
non-FPC	307	29.6
Not reported	129	12.4
Age (years)		
<40	8	0.8
40-49	57	5.5
50-59	196	18.9
60–69	310	29.9
70-79	280	27.0
80+	84	8.1
Not reported	102	9.8
Sex		
Male	499	48.1
Female	442	42.6
Not reported	96	9.3

[a]FPC, familial pancreatic cancer.

4 | DISCUSSION

Understanding the genetic basis of susceptibility to PDAC has important consequences both for patients and their relatives. Germline genetic testing identifies patients with apparently pathogenic variants or VUS in genes associated with either high, moderate, or no increased risk of cancer. Such findings are the source of significant clinical uncertainty in the management of patients.[25] Therefore, validation of cancer-associated variants and genes in independent patient cohorts is essential to determine the utility of germline testing.

The recent study by Nissim et al reported *RABL3* as a putative pancreatic cancer susceptibility gene.[15] Specifically, a functionally defective nonsense variant (g.chr3:120449574_G > T; p.S36X) was found to segregate with two individuals with PDAC in a single family. By contrast, we did not identify any deleterious *RABL3* variants in our large cohort of patients with PDAC. In addition to the p.S36X variant, Nissim *et al* also reported an excess of a rare *RABL3* missense variant (g.chr3:120413055_C > T; p.R184Q) in The Cancer Genome Atlas

TABLE 2 *RABL3* variants identified in patients with pancreatic ductal adenocarcinoma

Variant	Functional consequence	Transcript	Protein	SNP identifier	Classification	MAF gnomAD	Allele count gnomAD	Allele number gnomAD	Allele frequency patients with PDAC	Allele count patients with PDAC	Allele number patients with PDAC
g.chr3:120417330_A > G	Synonymous	c.T474C	p.H158H	rs61758778	Benign	0.00808	954	118 076	0.00386	8	2074
g.chr3:120428634_G > A	Synonymous	c.C261T	p.S87S	rs35389318	Benign	0.00682	796	116 760	0.00530	11	2074
g.chr3:120413055_C > T	Nonsynonymous	c.G551A	p.R184Q	rs61756477	VUS	0.00135	159	117 926	0.00193	4	2074
g.chr3:120424944_C > G	Nonsynonymous	cG286C	p.D96H	rs564912172	VUS	0.00001	1	102 678	0.00048	1	2074
g.chr3:120424950_C > T	Nonsynonymous	c.G280A	p.V94I	rs755345084	VUS	0.00002	2	118 012	0.00048	1	2074
g.chr3:120449569_T > C	Nonsynonymous	c.A112G	p.T38A	NA	VUS	0.00000	0	102 686	0.00048	1	2074

Note: Genomic co-ordinates use hg19 version of human genome. *RABL3* transcript accession number: NM_173825; *RABL3* protein accession number: NP_776186; gnomAD v.2.1.1 (non-cancer) for the European (non-Finnish) population.
Abbreviations: NA, not applicable; MAF, minor allele frequency; VUS, variant of unknown significance.

(TCGA) exome sequenced samples compared to the non-TCGA cohort in the Exome Aggregation Consortium (ExAC) database. While this variant was observed at a frequency of 0.19% in our dataset, this was not statistically significantly higher than the frequency observed in non-cancer cases in gnomAD (Table 2; 0.13%, $P = .36$). Our findings are in agreement with a recently published report that did not identify the p.S36X and p.R194Q variants in 66 patients with pancreatic cancer.[26]

Our study has a few limitations. Firstly, as the true prevalence of *RABL3* deleterious variants in patients with PDAC is likely to be <0.0036, studies incorporating additional cases are necessary to determine whether deleterious *RABL3* variants are associated, but only rarely, with risk of PDAC. Secondly, we assessed only coding variants in *RABL3* as their functional consequence could be interpreted. Non-coding and structural variants in *RABL3* could potentially play an as-of-yet unappreciated role in susceptibility to PDAC.

In conclusion, we found no deleterious *RABL3* variants in our large series of patients with PDAC, over half of which were from kindreds with familial pancreatic cancer and therefore more likely to harbor high-risk germline variants. Therefore, until further studies are conducted to better understand the role of *RABL3* as a pancreatic cancer susceptibility gene, including the validation of its association with pancreatic cancer risk, the inclusion of *RABL3* in routine genetic testing for patients with PDAC is premature.

Familial Pancreatic Cancer Genome Sequencing Project (FPC-GSP) Investigators

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Data used in this article were obtained from the FPC-GSP (www.familialpancreaticcancer.org). Thereby, the FPC-GSP investigators contributed to the design and implementation of FPC-GSP and/or provided data. They did not participate in analysis or writing of this report. The FPC-GSP project was generously supported by Dennis Troper and Susan Wojcicki, the Lustgarten Foundation for Pancreatic Cancer Research, the Sol Goldman Pancreatic Cancer Research Center, the Virginia and D.K. Ludwig Fund for Cancer Research, the Michael Rolfe Foundation, the Joseph C. Monastra Foundation, the Gerald O. Mann Charitable Foundation, the Ladies Auxiliary to the Veterans of Foreign Wars, the friends and family of Roger L. Kerns Sr., the Weston Garfield Foundation, the NIH Specialized Programs of Research Excellence P30CA006973, P50CA62924 and P50CA102701, and NIH grants K99-CA190889, R01-CA57345, R01-CA97075, R01-CA154823, and R01-DK060694.

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AUTHOR CONTRIBUTIONS

Nicholas J. Roberts, Robert C. Grant, Steven Gallinger, Alison P. Klein planned and designed study. Nicholas J. Roberts, Robert C. Grant, Steven Gallinger, Alison P. Klein conducted experiments and generated sequence data. Nicholas J. Roberts, Robert C. Grant, Steven Gallinger, Alison P. Klein analyzed data. Nicholas J. Roberts, Robert C. Grant, Steven Gallinger, Alison P. Klein wrote the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

This study used previously published germline whole genome and whole exome sequences from patients with PDAC - see article text for details.

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