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ORIGINAL ARTICLE

Mutational patterns in a large cohort of parathyroid carcinomas

Chetanya Pandya[1] · Andrew V. Uzilov[1] · Jessica Costa-Guda[2,3] · Justin Bellizzi[2] · Patricia Taik[1] · Aye S. Moe[1] · Maya Strahl[1] · Karin van der Tuin[4,5] · Mark Stevenson[6] · Branca M. Cavaco[7] · Filomena Cetani[8] · Claudio Marcocci[8] · Auli Karhu[9] · Johanna Arola[10] · Camilla Schalin-Jäntti[11] · Hans Morreau[12] · Rajesh V. Thakker[6] · Eric E. Schadt[1] · Robert Sebra[1] · Shuyu D. Li[1] · Rong Chen[1] · Andrew Arnold[2]

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Abstract

Purpose A lack of targeted therapies make parathyroid carcinoma, a diagnostically challenging malignancy, difficult to treat. The rarity of this tumor type necessitates international collaboration to collect a sizable sample set for study. Prior studies have revealed the importance of driver mutations in the *CDC73* gene and identified several putative drivers/aberrant pathways including PI3K/mTOR activation and *CCND1* (cyclin D1) amplification. In this study, we sought to better understand the prevalence of putative oncogenic drivers in parathyroid carcinoma.

Methods We subjected an expanded cohort of 71 sporadic parathyroid carcinomas, fulfilling stringent WHO criteria, to next-generation DNA sequencing on a custom 16-gene targeted panel.

Results One or more variant was detected in 44 tumors (62%) and 27 (38%) had no detectable variant. Consistent with earlier studies, we detected loss-of-function *CDC73* mutations in 44% (31/70) of evaluable patients, including germline pathogenic variants in 9 patients (36 patients evaluable for somatic status as matched normal available). Notably, mutations in the PI3K/AKT/mTOR pathway were seen in 12.9% (9/70) of evaluable patients, providing further evidence of this as a key therapeutically actionable pathway in parathyroid carcinoma. Correlating genomic and clinical features revealed that patients harboring *CDC73* mutations are more likely suffer from life threatening recurrent/metastatic parathyroid carcinoma ($P = 0.024$) than those without *CDC73* variants.

Conclusions This genomic characterization of a large parathyroid carcinoma cohort improves understanding of the genomic underpinnings of this rare malignancy, provides novel evidence for genotype-phenotype correlation with recurrent/metastatic disease, and may help to provide a rational basis for individualized treatments.

Keywords Cancer · Disorders of calcium/phosphate metabolism · Parathyroid-related disorders · parathyroid carcinoma · CDC73

Introduction

Parathyroid carcinoma (PC) is a rare, life-threatening endocrine malignancy seen in less than 1% of patients with primary hyperparathyroidism. PC typically has a sporadic/nonfamilial presentation, but can also arise in the heritable hyperparathyroidism-jaw tumor syndrome (HPT-JT) and in familial isolated hyperparathyroidism due to germline mutation of the *CDC73* (formerly *HRPT2*) tumor suppressor gene. Recurrence is seen in more than 50% of patients [1–4] and PC that recurs locally or metastasizes after resection of the primary tumor is typically incurable due to progressive parathyroid hormone (PTH) mediated hypercalcemia, resulting in significant end-organ damage and high mortality [5, 6]. In such advanced cases, hypercalcemia can be partially controlled for variable durations with surgical debulking, bone resorption inhibitors, or calcimimetics. However, neither chemotherapy with traditional agents nor adjuvant radiation have proven effective against PC [7–9]. Identification of new therapies informed by insights

Rong Chen and Andrew Arnold contributed equally to this work.

Extended author information available on the last page of the article

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into PC's molecular vulnerabilities would be an important advance [6, 10].

In previous work, mutations / pathogenic variants in the *CDC73* tumor suppressor gene were identified as common drivers of PC [11–20] and associated with poorer clinical outcomes [21, 22]. However, no pharmacologic interventions targeting *CDC73* have yet been developed. Next-generation sequencing (NGS) techniques have since expanded the listing of putative or possible driver genes in this disease. For example, confirmed findings include *PI3K/MTOR* activation and *CCND1* (cyclin D1) amplification [17–19, 23] in subsets of PC, both of which carry potential therapeutic implications. However, while several genes have been implicated in PC, the rarity of this tumor type makes it difficult to determine how commonly any individual gene is involved. We sought to better understand the molecular mechanisms of oncogenesis in PC by utilizing a custom, PC-informed, targeted, NGS panel [17] to analyze an expanded cohort of PC samples.

Materials and methods

Patients and tumor specimens

We selected a cohort of patients, across multiple international sites, diagnosed with PC according to stringent clinical/pathological criteria: evidence of either local invasion into surrounding tissues, vascular invasion within or beyond the parathyroid tumor capsule, and/or distant metastasis [24]. Diagnoses of primary hyperparathyroidism were made after presentation with hypercalcemia and elevated serum PTH levels; no patient was diagnosed preclinically in a surveillance program for known/suspected carriers of germline *CDC73* mutation. Seventy-three patient-derived (surgically treated for primary hyperparathyroidism) primary, locally recurrent, or metastatic PC specimens (tumors PC001T-PC088T), including 24 previously analyzed tumor samples [17], were obtained. Peripheral blood or other uninvolved non-tumor tissue was available from 40 of the patients and provided matched germline control DNA. All samples were obtained with informed consent in concordance with Institutional Review Board approved protocols.

Immediately after surgical resection, tumor samples were either frozen in liquid nitrogen for storage at -80 °C until use (N=17), or were formalin-fixed, paraffin-embedded, sectioned, and mounted on slides, with two or three sections per tumor then grossly dissected from the slides for DNA extraction (N=59). Genomic DNA was isolated from tumor and non-tumor tissues using either proteinase K digestion followed by phenol-chloroform extraction and ethanol precipitation for frozen tissues and blood, or with the Qiagen supplementary protocol for Purification of genomic DNA from FFPE tissue using the QIAamp DNA FFPE Tissue Kit (Qiagen, Cat. No. 56404) and Deparaffinization Solution (Qiagen, Cat. No. 19093), or the GeneRead DNA FFPE kit (Qiagen, Cat. No. 180134, for formalin-fixed, paraffin-embedded tissues. For a subset of cases, total nucleic acid (undivided DNA and RNA) was isolated from formalin-fixed paraffin-embedded (FFPE) tissue cores (0.6 mm diameter and variable length) or microdissected tissue regions using a fully-automated extraction procedure [25].

Targeted panel sequencing

DNA quality control (QC), sequencing on the 16 gene ParThy panel (958 amplicons covering 97,909 bases of 356 unique genomic regions), and data analysis was performed as described previously [17]. Briefly, Qubit fluorometry (Life Technologies, Grand Island, NY) was used for DNA quantification and Agilent Bioanalyzer was used to assess DNA quality for all samples. Samples that passed quality control were used for library construction using the manufacturer's (Thermo Fisher Scientific) Ion Torrent Ampliseq library preparation protocol. After library completion and equalization, the Ion Chef was used to concentrate and load the chip using manufacturer's suggested protocols. The Torrent Chef and run conditions were set up for the ParThy cancer panel and the S5XL configuration was run by manufacturer's protocol until completion.

Variant calling and classification

Variants from targeted panel sequencing were called using the TorrentSuite variantCaller (https://github.com/iontorrent/TS) module version 5.2.2 using permissive settings (Somatic – Low-Stringency preset; all COSMIC [26] and previously observed variants [17] provided as hotspot file for force calling), exported as VCFs, and loaded into a custom MySQL database schema for analysis. Variants were annotated with SnpEff [27] using RVS [28] and filtered to include SnpEff "moderate" and "high" impact categories. If WES sequencing data were available, concordance analysis was done to ensure the two assays agreed in their somatic variant calls in genomic regions covered by both assays by design. QC statistics and chip type are listed in Supplementary Table 1.

Identification of genetic alterations

Variants observed in a tumor sample with gnomAD (release 2.0.1) [29] population allele frequency exceeding 0.5% in any ethnicity were discarded assuming that they are any combination of: contamination, a variant present but

missed in normal sample, a low-level technical artifact, or unlikely to be a cancer driver owing to common frequency in the general population. All variant calls were manually reviewed in IGV [30] and the UCSC Genome Browser [31] to inspect supporting alignment quality and alignability of the genomic region in the hg19 human genome assembly [30]. Due to the relatively sparse genome coverage of this panel & few normal diploid samples, a robust baseline for copy number variant calling could not be generated and thus, copy number status of genes on the panel could not be determined for this study.

Statistics

To determine mutual exclusivity of genetic alternations in gene pairs, one-sided Fisher's exact test was performed, and for determining correlation between clinical variables and genes two-sided Fisher's exact test was performed. Multiple hypothesis correction was performed using the Benjamini-Hochberg (also known as FDR) method to generated adjusted P-values. All calculations were performed using in-built functions in the R statistical computing software. P-value < 0.05 was considered significant.

Results

Clinical information summary

A total of 71 patients with sporadic PC, according to stringent clinical/pathological criteria (summarized in Tables 1 and 2; detailed information in Supplementary Table 2 [32, 33]), were selected. Four samples were removed from further study post-QC (Supplementary Table 1), resulting in 70 patients with evaluable specimens (71 tumors). Patient-derived tumor samples analyzed here originated from either primary (59.2%, N=42/71), locally recurrent (14.1%, N=10/71) or metastatic tumors (26.8%, N=19/71). For only one patient (PC083), paired samples were available for both primary tumor plus a recurrence/metastasis. For the 42 primary tumor samples, 11 patients developed locally recurrent disease and 12 patients developed metastatic disease.

Table 1 Characteristics of Cohort

Characteristics	Number (%) of patients (N=70)
Sequenced tumor specimen type	
Primary	42 (59.2%)
Locally recurrent	10 (14.1%)
Metastatic	19 (26.8%)
Primary disease progressed? (avail N=42)	
No	19 (45.2%)
Yes, local recurrence	11 (26.2%)
Yes, metastasis	12 (28.6%)

Patients whose tumors exhibited those overtly malignant clinical behaviors of local recurrence or distant metastasis are defined here as having "life-threatening disease".

Targeted panel sequencing

Previously, we developed an amplicon-based (Ion AmpliSeq) targeted cancer gene panel ("ParThy" panel; Supplemental Fig. 1) covering all coding exons of 16 genes implicated in PC based on our findings and the literature [17]. The genes to be included in the panel were chosen at that time based upon recurrence of variants in our discovery cohort, biological significance, and literature review. We employed the ParThy panel to study the present expanded cohort of PC samples. Briefly, DNA was extracted from all patient samples, sequenced using the ParThy panel, and the sequencing data were analyzed as described in *Materials and Methods*.

Resulting sequencing data achieved an average of 1.6×10^6 mapped reads (range = 2.3×10^4-1.0×10^7), 93.9% on-target accuracy (range = 68.4%-99.4%), 1.8×10^3 mean depth (range = 2.2×10^1-1.3×10^4) and 93.1% uniformity (range = 56.9%-97.2%) across the cohort (metrics as calculated by TorrentSuite software). A summary of per-sample sequencing QC metrics is available as Supplementary Table 1. Next, we performed variant calling and filtering (detailed in *Materials and Methods*) on the sequencing reads. Based on variant QC and manual inspection of data using IGV, we removed 4 samples from further analysis (Supplementary Table 1). For the resulting evaluable patients (N=70) in the cohort, 86 variants were observed with 20 samples having 1 or more variant (Fig. 1; Table 2). The majority of observed variants were missense (40/86, 46.5%), while the rest were truncations − 22/86 (25.6%) frameshift and 24/86 (27.9%) stop gain.

Mutational landscape in PC

Inactivation of the *CDC73* gene is the earliest discovered and the only fully established driver event for PC [34, 35]. In our cohort, we observed loss of function (stop gain or frameshift) *CDC73* variants in 31/70 (44%) patients, which is consistent with earlier studies. In 12 patients (38.7%) biallelic *CDC73* variants were found, with 4 patients harboring a inactivating germline variant plus a somatic variant and 8 having two somatic variants. In addition 5 patients carried a heterozygous germline *CDC73* variant with no second hit detected in the tumor, for a total of 9 (29.0%) patients harboring a germline inactivating variant. It is important to note our approach was not able to detect certain types of inactivating mutations such as large genomic deletions

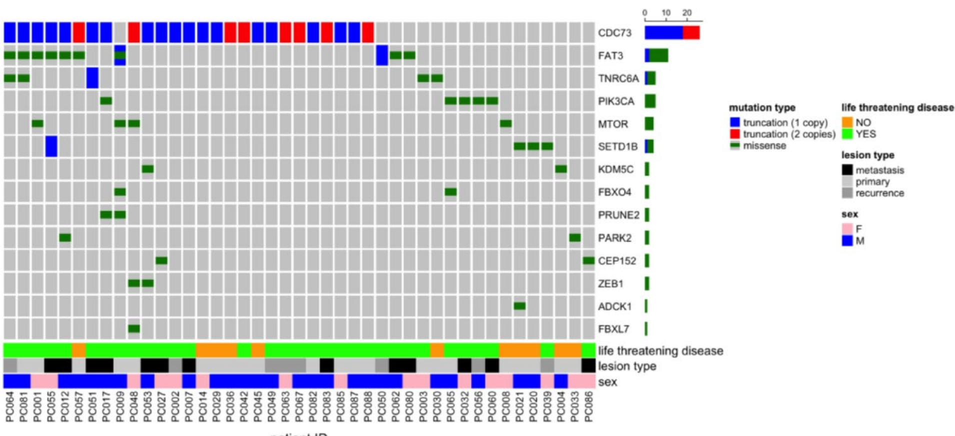

Fig. 1 Mutational landscape of PC: Custom OncoPrint/Waterfall plot [50] showing the distribution of tumor variants across patients (N=43; X-axis) in genes on the ParThy panel (N=14; Y-axis). Clinical information associated with each patient are also shown. For clarity, patients (X-axis) and genes (Y-axis) with no observed tumor mutations have not been included. Patient PC083 (sole case with both a primary and a metastasis lesion sequenced) is shown only once because mutations in the two tumors were identical

or variants in cis-regulatory or non-coding regions. All observed *CDC73* variants are detailed in Table 2.

Amongst other genes screened using the ParThy panel, we observed no sequence variants in *PCMTD1* or *CCND1*. After *CDC73*, *FAT3* (10/70, 14.3%), *TNRC6A* (5/70, 7.14%) and *PIK3CA* (5/70, 7.14%) are the top mutated genes, harboring primarily missense variants. Several genes on the panel are longer than average (>3,000 bp) which might confound this observation.

To determine oncogenic driver events in the cohort, we cross-referenced the list of observed variants with the COSMIC database v81 (Supplementary Table 3). As expected, several *CDC73* loss-of-function (LOF) variants have been observed in published studies and included in COSMIC. Importantly, four *PIK3CA* missense variants observed in our cohort are highly recurrent in COSMIC in multiple tumor types, as highlighted in Supplementary Fig. 1, providing supporting evidence for their role as drivers. Additionally, variants in *FBXO4* (N=1), *KDM5C* (N=1), *MTOR* (N=3), and *PARK2* (N=1) are also present in COSMIC. This suggests that the observed gene variants may act as potential drivers in specific subsets of PC patients.

Clinical significance of observed variants

Figure 1 shows a OncoPrint plot providing a comprehensive view of the mutational landscape of the cohort. Notably, the PI3K/AKT/mTOR pathway was altered in 12.9% (9/70) patients, primarily in tumors without *CDC73* mutations. Observed mutations in *PIK3CA* (p. K111E, p.E545K, p.E545A, and p. H1047R) all occurred in known oncogenic hotspots. *MTOR* mutations included p.T1861I, p.P1694S, and known oncogenic mutations p.L1460P and p.I1973F.

Statistical significance (p-value and odds-ratio) of disease progression with mutated genes was computed. We noted that patients with germline or somatic pathogenic *CDC73* variants were significantly more likely to suffer from life threatening recurrent/metastatic PC (p-value = 0.024, odds ratio = 3.51, CI = [1.08–12.7]). Of the 31 PC patients with *CDC73* mutations, 25 (81%) progressed to life threatening disease, compared with only 54% (21/39) of patients with no *CDC73* variant. This trend toward life-threatening disease in the *CDC73*-mutation group was similarly distributed across patients with germline vs. somatic *CDC73* mutation (8/9, 88.9% vs. 17/22, 77.3% respectively), or across those with a single allele mutation (15/19, 78.9%) vs. biallelic *CDC73* mutations (10/12, 83.3%).

Discussion

Given the dearth of effective, non-surgical therapies for PC, the identification of genetic/molecular aberrations that might serve as "actionable targets" for pharmacologic intervention in patients whose disease is no longer surgically curable remains a high priority for ongoing research. Especially important for a rare disease, international cooperation has enabled us to examine a sizeable cohort of PC samples and thereby better understand the frequency of alterations in key established and candidate driver genes [34, 35]. Most notably, our observations expand and strengthen the genetic evidence that oncogenic variants in *PIK3CA* and other PI3K/AKT/MTOR pathway genes are recurrently identified in PC and thus likely contribute to a selective advantage in the neoplastic cell. These features, and their occurrence in patients across multiple international sites, have important implications for future therapeutic interventions.

The PI3K/AKT/MTOR pathway has central roles in regulation of cell growth and survival, and cell cycle progression. Pathway members are frequently subject to mutation in human tumors. *PIK3CA* encodes the p110 alpha catalytic subunit of phosphatidylinositol 3-kinase (PI3K), which when activated, converts PIP2 to PIP3, in turn activating AKT to subsequently activate mTOR, ultimately leading to cellular growth, increased survival and angiogenesis [36]. The *PIK3CA* pathogenic variants observed in the present

Table 2 Clinical and Sequence Variant Information

Patient ID	Sex	Local recurrence	Metastasis	Life-threatening disease	Specimen/lesion that was sequenced	Specimen ID	Gene symbol	Chromosome	Position	Reference allele	Alternate allele	Amino acid change	Variant status	Allelic fraction	COSMIC ID
PC001	F	yes	yes	yes	primary	PC001T	CDC73	1	19,30,94,267	G	T	p.Glu53*	likely somatic	48.3%	
							CDC73	1	19,30,94,286	C	T	p.Ser59Phe	germline	47.2%	
							FAT3	11	9,26,13,978	G	A	p.Arg4070Gln	likely somatic	46.2%	
							MTOR	1	1,11,90,617	G	A	p.Thr1861Ile	likely somatic	5.5%	
PC002	F	yes	no	yes	normal	PC002N	no notable variants found								
					recurrence	PC002T	CDC73	1	19,30,91,415	G	T	p.Glu29*	somatic	13.7%	
PC003	F	yes	yes	yes	primary	PC003T	TNRC6A	16	2,48,02,347	C	A	p.Ser795Tyr	likely somatic	9.2%	
PC004	M	no	no	no	normal	PC004N	no notable variants found								
					primary	PC004T	KDM5C	X	5,32,24,526	C	T	p.Val1063Met	somatic	4.4%	COSM1169517
PC005	F	no	no	no	normal	PC005N	no notable variants found								
					primary	PC005T									
PC006	M	no	yes	yes	normal	PC006N	no notable variants found								
					primary	PC006T									
PC007	M	yes	yes	yes	metastasis	PC007T	CDC73	1	19,30,94,274	AC	A	p.Tyr55fs	likely somatic	34.4%	COSM26047
PC008	F	n/a	n/a	no	normal	PC008N	no notable variants found								
					primary	PC008T	MTOR	1	1,11,88,177	T	A	p.Ile1973Phe	somatic	9.1%	COSM423441
PC009	M	yes	no	yes	primary	PC009T	FAT3	11	9,20,85,687	G	A	p.Asp137Asn	likely somatic	5.4%	
							FAT3	11	9,25,31,391	C	T	p.Gln1738*	likely somatic	5.6%	
							FBXO4	5	4,19,25,487	G	A	p.Ala26Thr	likely somatic	7.1%	
							MTOR	1	1,11,99,411	G	A	p.Pro1694Ser	likely somatic	6.3%	
							PRUNE2	9	7,93,25,103	C	T	p.Arg696Lys	likely somatic	4.9%	
PC010	M	no	no	no	normal	PC010N	no notable variants found								
					primary	PC010T									
PC011	F	yes	yes	yes	metastasis	PC011T	no notable variants found								
PC012	M	yes	yes	yes	metastasis	PC012T	CDC73	1	19,30,94,272	C	G	p.Tyr54*	likely somatic	10.7%	COSM26051
							FAT3	11	9,25,77,271	A	G	p.Met3580Val	likely somatic	28.3%	
							PARK2	6	16,19,69,928	C	G	p.Gln347His	likely somatic	13.7%	COSM450871
PC013	F	no	yes	yes	normal	PC013N	no notable variants found								
					primary	PC013T									
PC014	F	no	no	no	primary	PC014T	CDC73	1	19,30,94,272	C	G	p.Tyr54*	likely somatic	99.2%	COSM26051
PC015	F	no	yes	yes	normal	PC015N	no notable variants found								
					primary	PC015T	no notable variants found								
PC017	M	no	yes	yes	normal	PC017N	CDC73	1	19,31,11,157	A	AT	p.Trp231_Arg232fs	germline	47.4%	
					metastasis	PC017T	CDC73	1	19,30,91,458	G	A	p.Trp43*	somatic	40.5%	COSM26046
							PIK3CA	3	17,89,36,091	G	A	p.Glu545Lys	somatic	39.6%	COSM763
							PRUNE2	9	7,93,22,647	C	T	p.Val1515Ile	somatic	4.6%	
PC018	M	yes	yes	yes	metastasis	PC018T	no notable variants found								
					metastasis	PC019T									
PC020	M	n/a	n/a	no	primary	PC020T	SETD1B	12	12,22,54,983	C	G	p.Asp920Glu	likely somatic	47.6%	COSM5574222
PC021	M	no	no	no	primary	PC021T	ADCK1	14	7,83,53,525	C	T	p.Thr172Met	likely somatic	47.6%	COSM2249317
							SETD1B	12	12,22,48,314	C	A	p.Ser488Tyr	likely somatic	47.2%	
PC024	F	yes	yes	yes	normal	PC024N	CDC73	1	19,31,11,145	CAG	C	p.Arg227fs	germline	43.1%	
					recurrence	PC024T	no notable variants found								
PC025	M	no	no	no	primary	PC025T	no notable variants found								

Table 2 (continued)

Patient ID	Sex	Local recurrence	Metastasis	Life-threatening disease	Specimen/lesion that was sequenced	Specimen ID	Gene symbol	Chromosome	Position	Reference allele	Alternate allele	Amino acid change	Variant status	Allelic fraction	COSMIC ID
PC026	M	yes	n/a	yes	normal	PC026N	no notable variants found								
					primary	PC026T									
PC027	F	yes	yes	yes	normal	PC027N	QC fail								
					metastasis	PC027T	CDC73	1	19,30,91,390	GA	G	p.Lys21fs	somatic	80.7%	
							CEP152	15	4,90,48,132	G	C	p.Leu1105Val	somatic	49.9%	
PC028	F	n/a	n/a	no	primary	PC028T	no notable variants found								
PC029	M	no	no	no	primary	PC029T	CDC73	1	19,30,91,417	GT	G	p.Phe30fs	likely somatic	84.4%	
PC030	M	no	no	no	primary	PC030T	CDC73	1	19,31,11,006	A	AA	p.Ile182fs	germline	34.8%	
							TNRC6A	16	2,48,18,075	C	G	p.Pro1504Ala	likely somatic	4.3%	
PC031	F	no	no	no	normal	PC031N	no notable variants found								
					primary	PC031T	no notable variants found								
PC032	F	yes	no	yes	metastasis	PC032T	PIK3CA	3	17,89,36,091	G	A	p.Glu545Lys	likely somatic	47.3%	COSM763
PC033	F	no	no	no	primary	PC033T	PARK2	6	16,22,06,909	G	A	p.Arg256Cys	likely somatic	35.2%	
PC034	F	n/a	n/a	no	primary	PC034T	no notable variants found								
PC035	M	n/a	n/a	no	primary	PC035T	no notable variants found								
PC036	M	n/a	n/a	no	primary	PC036T	CDC73	1	19,30,91,411	CG	C	p.Gly28fs	likely somatic	27.2%	COSM26069
							CDC73	1	19,31,17,027	C	T	p.Gln254*	likely somatic	36.6%	COSM4507949
PC037	M	yes	yes	yes	normal	PC037N	no notable variants found								
					recurrence	PC037T									
PC038	F	no	no	no	primary	PC038T	no notable variants found								
PC039	F	yes	n/a	yes	recurrence	PC039T	SETD1B	12	12,22,57,478	T	A	p.Val1153Glu	likely somatic	49.4%	
PC040	F	yes	yes	yes	metastasis	PC040T	no notable variants found								
PC041	F	no	no	no	normal	PC041N	no notable variants found								
					primary	PC041T									
PC042	M	yes	no	yes	normal	PC042N	no notable variants found								
					primary	PC042T	CDC73	1	19,30,91,411	CG	C	p.Gly28fs	somatic	16.5%	COSM26069
							CDC73	1	19,31,11,152	A	T	p.Arg229*	somatic	12.5%	
PC043	F	yes	yes	yes	normal	PC043N	no notable variants found								
					metastasis	PC043T									
PC044	M	no	no	no	normal	PC044N	no notable variants found								
					primary	PC044T									
PC045	M	no	no	no	normal	PC045N	no notable variants found								
					primary	PC045T	CDC73	1	19,30,91,355	C	T	p.Arg9*	somatic	37.5%	COSM26056
PC046	M	yes	no	yes	normal	PC046N	CDC73	1	19,31,17,012	AT	A	p.Ile249fs	germline	17.9%	
					primary	PC046T	no notable variants found								
PC047	F	no	no	no	normal	PC047N	no notable variants found								
					primary	PC047T									
PC048	F	yes	no	yes	normal	PC048N	no notable variants found								
					primary	PC048T	CDC73	1	19,30,91,415	G	T	p.Glu29*	somatic	19.5%	
							CDC73	1	19,31,04,668	C	CA	p.Lys125_Arg126fs	somatic	48.7%	
							FBXL7	5	1,59,36,973	G	A	p.Gly385Asp	somatic	10.3%	
							MTOR	1	1,12,17,299	A	G	p.Leu1460Pro	somatic	12.6%	COSM462618
							ZEB1	10	3,18,09,662	C	G	p.Gln467Glu	somatic	8.2%	
PC049	M	yes	no	yes	normal	PC049N	CDC73	1	19,31,11,145	C	CAG	p.Arg227_Glu228fs	germline	13.1%	
					recurrence	PC049T	CDC73	1	19,30,94,272	C	G	p.Tyr54*	somatic	29.1%	COSM26051

Table 2 (continued)

Patient ID	Sex	Local recurrence	Metastasis	Life-threatening disease	Specimen/lesion that was sequenced	Specimen ID	Gene symbol	Chromosome	Position	Reference allele	Alternate allele	Amino acid change	Variant status	Allelic fraction	COSMIC ID
PC050	M	yes	no	yes	normal	PC050N	no notable variants found								
					recurrence	PC050T	FAT3	11	9,20,86,105	T	A	p.Leu276*	somatic	16.7%	
PC051	M	yes	yes	yes	normal	PC051N	no notable variants found								
					metastasis	PC051T	CDC73	1	19,30,91,368	TC	T	p.Ile13fs	somatic	80.1%	COSM26064
							TNRC6A	16	2,48,01,018	C	G	p.Ser352*	somatic	12.2%	
PC052	M	no	no	no	normal	PC052N	no notable variants found								
					primary	PC052T									
PC053	M	no	yes	yes	normal	PC053N	no notable variants found								
					metastasis	PC053T	CDC73	1	19,30,91,352	CTGC	CGT	p.Leu8fs	somatic	17.1%	COSM26065
							KDM5C	X	5,32,31,065	C	T	p.Glu613Lys	somatic	10.1%	
							ZEB1	10	3,18,03,576	G	A	p.Glu244Lys	somatic	8.5%	
PC054	F	yes	yes	yes	normal	PC054N	no notable variants found								
					metastasis	PC054T									
PC055	F	yes	yes	yes	normal	PC055N	no notable variants found								
					metastasis	PC055T	CDC73	1	19,31,11,131	C	T	p.Arg222*	somatic	23.4%	
							FAT3	11	9,25,68,041	A	G	p.Ile3293Val	somatic	15.4%	
							SETD1B	12	12,22,60,548	CT	C	p.Leu1312fs	somatic	8.3%	
PC056	M	yes	no	yes	normal	PC056N	QC fail								
					recurrence	PC056T	PIK3CA	3	17,89,16,944	A	G	p.Lys111Glu	somatic	52.4%	COSM13570
PC057	M	no	no	no	primary	PC057T	CDC73	1	19,30,91,459	G	A	p.Trp43*	likely somatic	36.1%	COSM26046
							CDC73	1	19,31,11,159	G	A	p.Trp231*	likely somatic	33.2%	
							FAT3	11	9,25,23,182	C	T	p.Ser1470Phe	likely somatic	2.6%	
PC058	F	no	yes	yes	normal	PC058N	CDC73	1	19,31,11,152	A	T	p.Arg229*	germline	15.4%	
					primary	PC058T	QC fail								
PC059	M	yes	yes	yes	metastasis	PC059T	QC fail								
PC060	F	yes	yes	yes	metastasis	PC060T	PIK3CA	3	17,89,52,085	A	G	p.His1047Arg	likely somatic	12.2%	COSM775
PC061	F	no	no	no	primary	PC061T	no notable variants found								
PC062	M	yes	yes	yes	metastasis	PC062T	FAT3	11	9,25,31,077	C	T	p.Thr1633Met	likely somatic	27.7%	COSM2223537
PC063	F	yes	n/a	yes	recurrence	PC063T	CDC73	1	19,30,91,345	TA	T	p.Ser6fs	likely somatic	35.0%	
							CDC73	1	19,32,02,197	AC	A	p.Asp410fs	likely somatic	38.7%	
PC064	M	yes	no	yes	recurrence	PC064T	CDC73	1	19,30,91,415	G	T	p.Glu29*	likely somatic	43.5%	
							FAT3	11	9,25,32,819	G	A	p.Glu2214Lys	likely somatic	9.3%	
							TNRC6A	16	2,48,00,831	G	A	p.Gly290Ser	likely somatic	51.2%	
PC065	M	no	yes	yes	primary	PC065T	FBXO4	5	4,19,29,906	G	A	p.Arg178Gln	likely somatic	54.2%	COSM3393590
							PIK3CA	3	17,89,36,092	A	C	p.Glu545Ala	likely somatic	12.8%	COSM12458
PC066	M	no	yes	yes	primary	PC066T	no notable variants found								
PC067	M	yes	no	yes	recurrence	PC067T	CDC73	1	19,30,91,389	TGAAGGGA GAC	T	p.Val20fs	likely somatic	12.0%	
							CDC73	1	19,31,11,167	C	T	p.Arg234*	likely somatic	45.2%	COSM26077
PC080	F	yes	yes	yes	normal	PC080N	CDC73	1	19,31,11,167	C	T	p.Arg234*	germline	48.8%	COSM26077
					metastasis	PC080T	FAT3	11	9,25,31,143	C	T	p.Ala1655Val	somatic	3.6%	
PC081	M	n/a	yes	yes	normal	PC081N	no notable variants found								
					primary	PC081T	CDC73	1	19,30,94,292	T	A	p.Leu61*	somatic	77.4%	COSM1732628
							FAT3	11	9,25,65,132	C	T	p.Arg3276Trp	somatic	2.7%	
							TNRC6A	16	2,48,00,831	G	A	p.Gly290Ser	somatic	3.2%	

Table 2 (continued)

Patient ID	Sex	Local recurrence	Metastasis	Life-threatening disease	Specimen/lesion that was sequenced	Specimen ID	Gene symbol	Chromosome	Position	Reference allele	Alternate allele	Amino acid change	Variant status	Allelic fraction	COSMIC ID
PC082	M	yes	yes	yes	normal	PC082N	no notable variants found								
					primary	PC082T	CDC73	1	19,30,94,302	T	TA	p.Asn65_Asn66fs	somatic	52.0%	COSM26058
PC083	M	yes	yes	yes	normal	PC083N	no notable variants found								
					primary	PC083T	CDC73	1	19,30,94,304	A	AT	p.Asn65_Asn66fs	somatic	72.3%	COSM26058
					metastasis	PC084T	CDC73	1	19,30,94,304	A	AT	p.Asn65_Asn66fs	somatic	75.2%	COSM26058
PC085	F	yes	yes	yes	normal	PC085N	CDC73	1	19,31,04,711	C	T	p.Arg139*	germline	30.5%	
					primary	PC085T	CDC73	1	19,30,94,272	C	G	p.Tyr54*	somatic	12.1%	COSM26051
PC086	F	yes	yes	yes	normal	PC086N	no notable variants found								
					metastasis	PC086T	CEP152	15	4,90,81,074	A	G	p.Leu366Pro	somatic	6.0%	
PC087	M	n/a	yes	yes	normal	PC087N	no notable variants found								
					primary	PC087T	CDC73	1	19,30,91,355	C	T	p.Arg9*	somatic	57.5%	COSM26056
PC088	M	yes	n/a	yes	normal	PC088N	no notable variants found								
					primary	PC088T	CDC73	1	19,30,91,392	AG	A	p.Lys21fs	somatic	29.8%	
							CDC73	1	19,31,11,040	TAAGAA	T	p.Lys192fs	somatic	38.5%	

study, p.K111E, p.E545A, p.E545K and p.H1047R, are all known, activating, hot spot mutations, previously shown to be involved in other human cancers, including breast, lung, ovarian and colorectal cancers [37]. *PIK3CA* variants have been reported in other studies of PC [18, 19, 23, 38]. Two of the *MTOR* variants observed in this study, p.L1460P and p.I1973F, are also known and established pathogenic activating variants [39, 40]. Pathogenic or likely pathogenic variants have been reported in other PI3K/AKT/MTOR genes, including *PTEN* [18, 19], *TSC1* [19, 20, 38] and *TSC2* [18], suggesting the involvement of this pathway in 11.5% of PCs across the literature [18–20, 23, 38, 41, 42]. Several drugs inhibiting the PI3K/AKT/MTOR pathway are already approved for treating human cancers, with other drugs still being evaluated. For example, alpelisib, a PI3K inhibitor, is approved for the treatment of *PIK3CA*-mutated advanced breast cancer [43] and certain *MTOR* mutations, including p.I1973F, confer increased sensitivity to everolimus [44, 45], a drug approved for renal cell and other cancers. Given the availability of drugs to target this pathway, patients with advanced PC should be strongly considered for tumor sequencing, including PI3K/AKT/MTOR pathway genes, and treatment, as clinically appropriate.

Methodologically, a key advantage of using a targeted, amplicon-based panel is the ability to sequence to a significantly greater depth at lower cost compared to typically used genome- or exome-wide methods. This enables identification of variants at lower allelic fractions. Since this method requires lower DNA input, smaller tissue samples can be analyzed, or additional, multi-omic analyses can be performed on the same tumor [46], further enhancing insight into personalized therapeutic strategies. On the other hand, the present analysis was limited at its inception by the prior selection of specific genes for inclusion on the ParThy panel, plus the more general limitations of such panels for detecting larger genomic alterations and robustly detecting copy number variations. While this study is unable to speak to the potential role of some additional genes of interest, it would be worthwhile in the future to design an analogous panel whose content is informed by additional candidates [6, 47].

CCND1/cyclin D1 has long been established as a parathyroid tumor oncogene, activated by somatic gene rearrangement in a subset of common benign parathyroid adenomas [34]. More recently, it has been demonstrated that cyclin D1-driven parathyroid neoplasia, in contrast to other tumor types, depends strongly on the ability of cyclin D1 to bind to and activate its partner cdks [48], suggesting that cyclin D1-overexpressing parathyroid tumor cells may be more sensitive to alterations in cdk-mediated proliferation control, and thus may be highly responsive to cdk4/6 inhibitor therapy. Additional data have implicated cyclin D1

in parathyroid malignancies, with gene amplification being the major observed activating mechanism [49]. Specifically, using NGS we previously found *CCND1* amplification in 29% of PCs [17]. While the present study was unable to evaluate *CCND1* copy number due to the inability to obtain a robust reference for detecting somatic copy number alterations, a renewed effort to examine cyclin D1 copy number in a large set of PCs should be considered.

Finally, we observed a significant association between *CDC73* variant status and clinically-determined life-threatening disease, as described above in Results/Clinical significance of observed variants. This raises the question of whether a subset of primary parathyroid tumors, despite fulfilling currently accepted histopathologic criteria for diagnosis of PC (and generally with intact *CDC73*), may not share an equally high potential for truly malignant clinical behavior, i.e. local recurrence after primary resection or distant metastasis, with *CDC73*-mutant tumors. A prospective study would be needed to rigorously test this hypothesis, and meanwhile we consider it important for clinicians and pathologists, and authors of future studies, to specify the precise criteria used to support a diagnosis of PC in any individual case, including any evidence for clinically advanced or surgically incurable disease.

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Data availability Somatic variant calls are available publicly via COSMIC (cancer.sanger.ac.uk) under accession ID COSP53916.

Declarations

Competing Interests The authors have no competing interests to declare that are relevant to the content of this article.

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Authors and Affiliations

Chetanya Pandya[1] · Andrew V. Uzilov[1] · Jessica Costa-Guda[2,3] · Justin Bellizzi[2] · Patricia Taik[1] · Aye S. Moe[1] · Maya Strahl[1] · Karin van der Tuin[4,5] · Mark Stevenson[6] · Branca M. Cavaco[7] · Filomena Cetani[8] · Claudio Marcocci[8] · Auli Karhu[9] · Johanna Arola[10] · Camilla Schalin-Jäntti[11] · Hans Morreau[12] · Rajesh V. Thakker[6] · Eric E. Schadt[1] · Robert Sebra[1] · Shuyu D. Li[1] · Rong Chen[1] · Andrew Arnold[2]

✉ Andrew Arnold
aarnold@uchc.edu

[1] Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[2] Center for Molecular Oncology, University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, CT 06030-3101, USA

[3] Center for Regenerative Medicine and Skeletal Development, University of Connecticut School of Dental Medicine, Farmington, CT, USA

[4] Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands

[5] Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[6] Academic Endocrine Unit, Radcliffe Department of Medicine, Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), University of Oxford, Oxford, UK

[7] Molecular Endocrinology Group, Molecular Pathobiology Research Unit (UIPM), Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG), Lisboa, Portugal

[8] Department of Clinical and Experimental Medicine, Endocrine Unit, University of Pisa, Pisa, Italy

[9] Applied Tumor Genomics Research Program, Research Programs Unit, Department of Medical and Clinical Genetics, University of Helsinki, Helsinki, Finland

[10] Department of Pathology, HUSLAB, University of Helsinki, Helsinki University Hospital, Helsinki, Finland

[11] Endocrinology, Abdominal Center, Helsinki University Hospital, University of Helsinki, ENDO-ERN (European Reference Network on Rare Endocrine Conditions), Helsinki, Finland

[12] Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands