Costa-Guda. *J Transl Genet Genom* 2018;2:5
DOI: 10.20517/jtgg.2018.08

Journal of Translational Genetics and Genomics

Review

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Parathyroid carcinoma

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How to cite this article: Costa-Guda J. Parathyroid carcinoma. *J Transl Genet Genom* 2018;2:5. http://dx.doi.org/10.20517/jtgg.2018.08

Received: 30 Apr 2018 **First Decision**: 8 May 2018 **Revised**: 15 May 2018 **Accepted**: 16 May 2018 **Published**: 22 May 2018

Science Editor: David N. Cooper **Copy Editor**: Jun-Yao Li **Production Editor**: Cai-Hong Wang

Abstract

Parathyroid carcinoma is a rare but clinically-aggressive tumor. While most cases are sporadic, parathyroid cancer is overrepresented in hyperparathyroidism-jaw tumor syndrome, or rarely other heritable syndromes. Evidence suggests that sporadic parathyroid carcinomas rarely, if ever, evolve through an identifiable benign tumor intermediate. A few genes have been directly implicated in the pathogenesis of sporadic parathyroid cancer; somatic (and less common germline) mutations in the *CDC73* tumor suppressor gene are the most frequent finding and the only firmly established molecular drivers of parathyroid cancer. Alterations in other important human cancer genes, including *CCND1*/cyclin D1, *PIK3CA*, *MTOR* and *PRUNE2* have also been described in parathyroid cancer, however their abilities to drive malignant parathyroid tumorigenesis remains to be demonstrated experimentally.

Keywords: *CDC73*, cyclin D1, *PIK3CA*, hyperparathyroidism-jaw tumor syndrome

INTRODUCTION

Parathyroid cancer is a rare, but aggressive, cause of primary hyperparathyroidism, accounting for less than 1% of cases of this relatively common endocrine disorder. Parathyroid carcinoma may be suspected, prior to surgery, on the basis of clinical features. Parathyroid cancer presents equally in men and women, in contrast to the 3.5:1 female-to-male ratio seen with benign parathyroid tumors. Serum calcium levels are often markedly elevated in parathyroid cancer, with patients exhibiting renal and/or bone symptoms including nephrolithiasis, osteitis fibrosa cystica, osteoporosis and fracture. Palpable neck mass is common. While the majority of patients with parathyroid carcinoma are symptomatic, rare non-functioning parathyroid carcinomas have been reported. Histopathologic diagnosis of parathyroid cancer can be difficult and

Table 1. Hereditary parathyroid tumor predisposition syndromes

Syndrome	Gene	Parathyroid cancer	Other features	Somatic mutations in sporadic parathyroid tumors
MEN1[a]	*MEN1*	Rare	Pituitary and enteropancreatic endocrine tumors	Adenoma ~35%
	CDKN1A[b]	None reported		None reported
	CDKN2B[b]	None reported		None reported
	CDKN2C[b]	None reported		Adenoma ~1.5%
MEN4[a]	*CDKN1B*[b]	None reported		Adenoma ~5%
MEN2A	*RET*	Rare	Medullary thyroid cancer, pheochromocytoma	None reported
HPT-JT	*CDC73*	~10%-15%	Fibro-osseous jaw tumors, uterine tumors, renal lesions	Carcinoma ~77%
				Adenoma ~1.5%
NSHPT	*CASR*	None reported		None reported
FIHP	*GCM2*, others	None reported		None reported

[a]MEN1 and MEN4 are clinically indistinguishable; [b]germline mutations of *CDKN1A*, *CDKN2B*, *CDKN2C*, and *CDKN1B* have been reported in patients meeting the criteria for MEN1, however the full clinical spectrum of such patients has yet to be established. NSHPT: neonatal severe hyperparathyroidism; FIHP: familial isolated hyperparathyroidism

unequivocal diagnosis of malignancy depends on the presence of marked invasion into adjacent structures and/or distant metastasis. Features such as fibrous banding, mitotic figures and necrosis are suggestive of, but not diagnostic for, parathyroid carcinoma[1]. Historic inconsistencies in diagnostic criteria for parathyroid cancer, in addition to its rarity, have hindered efforts to understand the genetic basis of this important endocrine malignancy.

GENETIC ALTERATIONS IN PARATHYROID CANCER

A hallmark of many solid tumor malignancies is their progression from normal to malignant disease through clinically and histologically-identifiable stages of tumorigenesis, caused by incremental accumulation of acquired genetic abnormalities. Surprisingly, genetic evidence argues against such a progression for parathyroid carcinoma. Genomic and genetic alterations common in benign parathyroid adenomas, most prominently loss of chromosome 11q and accompanying mutation of MEN1, which occur in 35% of parathyroid adenomas[2-8], are rarely, if ever, seen in parathyroid cancer[3,4,8,9]. The clearly distinguishable patterns of genomic and genetic alterations present in parathyroid adenomas versus carcinomas suggests that parathyroid cancer most commonly arises *de novo*, rather than evolving from a preexisting benign adenoma[8].

Hereditary parathyroid cancer

A possible exception to the predominant process of *de novo* parathyroid carcinogenesis is that of hereditary parathyroid cancer. Primary hyperparathyroidism is a feature of several hereditary tumor-predisposition syndromes [Table 1]. While the large majority of parathyroid tumors in these syndromes are benign, rare parathyroid carcinomas have been reported in multiple endocrine neoplasia type 1 (MEN1) and type 2a (MEN2a). Somatic mutations of the causative genes, *MEN1* and *RET*, respectively do not appear to contribute to sporadic parathyroid carcinomas. A somatic mutation in *CDKN2C*/p18, which may cause a subset of cases of MEN1 or a closely related syndrome[10], has been reported in a single parathyroid carcinoma[11].

Parathyroid carcinoma is highly overrepresented in the hyperparathyroidism-jaw tumor syndrome (HPT-JT), caused by germline mutations in *CDC73* (previously called *HRPT2*). Approximately 10%-15% of parathyroid tumors in HPT-JT are malignant and affected patients have a lifetime risk of developing parathyroid cancer approaching 40%[12]. In the setting of a germline parathyroid tumor-predisposing mutation, particularly of *CDC73*, patients may occasionally develop parathyroid carcinomas that have evolved from preexisting benign or atypical adenomas. Such cases likely explain the few rare reports of apparent malignant parathyroid tumor progression.

CDC73

A large percentage of sporadic parathyroid carcinomas also harbor mutations in the *CDC73* tumor suppressor gene. A wide range of mutation frequencies (13%-100%) have been reported[13-16] across studies, likely due to inconsistencies in selection criteria. Among studies using the most stringent diagnostic criteria for parathyroid cancer, namely extracapsular invasion and/or distant metastasis, the mutation frequency is 77%[13-15]. In addition to intragenic mutations, gross deletions of *CDC73* have also been reported[17-19]. Biallelic inactivation of *CDC73* can be demonstrated in many parathyroid cancers[13-15]. A substantial subset of patients with sporadically-presenting parathyroid carcinoma possess germline *CDC73* mutations, and may represent new index cases of HPT-JT or a phenotypic variant[13,15,20,21]. Most parathyroid carcinomas also exhibit aberrant immunohistochemical staining for parafibromin, the protein product of *CDC73*; complete loss of parafibromin expression is the most common staining pattern. As the large majority of benign parathyroid tumors (except in the setting of germline *CDC73* mutation) display normal parafibromin staining, parafibromin immunohistochemistry may be considered as a diagnostic adjunct for parathyroid cancer in otherwise equivocal cases[22-24] but aberrant parafibromin staining alone is insufficient as a diagnostic marker of parathyroid carcinoma[25].

Parafibromin is a ubiquitously expressed, evolutionarily conserved 531 amino acid protein with predominantly nuclear expression. Cytoplasmic expression of parafibromin has also been described and may have functions different than nuclear parafibromin[26,27]. Parafibromin's C-terminal region contains moderate sequence similarity to yeast Cdc73p, a cell-division protein that comprises part of the polymerase-associated factor 1 complex (Paf1c). The human PAF1 complex (hPAF1C) contains homologs of most of the same subunits and shares similar functions. hPAF1C associates with RNA polymerase II during transcriptional initiation and elongation and participates in some histone modifications and posttranscriptional events, including modification of the poly (a) tail. Cdc73p homologs in higher-level organisms contain a metazoan-specific N-terminal domain, capable of directly binding β-catenin, and function in Wnt signaling, a central regulator of development and proliferation[28]. Although parafibromin's precise role in Wnt signaling, which might vary by cell type[28-30], has yet to be established, the involvement of parafibromin in canonical Wnt/β-catenin signaling provides a possible mechanism for parafibromin's tumor suppressive function(s). Activation of canonical Wnt signaling leads to β-catenin-mediated gene transcription; targets of Wnt signaling include cyclin D1, a parathyroid oncogene (described further below)[31,32]. Parafibromin can inhibit cancer cell growth and cause G1 phase arrest *in vitro*, in part through effects on cyclin D1[33,34]. Loss of Wnt pathway components APC and GSK3β[35] and accumulation of β-catenin have also been described in parathyroid cancer[36]. Cytoplasmic parafibromin interacts with cytoskeletal proteins[26] and p53 mRNA, modulating p53-mediated apoptosis[27]. Parafibromin can also interact directly with the SV40 large T antigen; cell lines expressing SV40 large T exhibit different effects on proliferation subsequent to perturbation of parafibromin levels[37], a finding which has complicated interpretation of some *in vitro* functional analyses.

Conventional and conditional transgenic mouse knockouts of *CDC73* have been developed. Homozygous germline deletion of *CDC73* is embryonic lethal and germline deletion of *CDC73* at later stages of development led to death within 20 days; increased apoptosis was observed in many tissues[38]. No parathyroid gland abnormalities were initially described in either *CDC73* knockout[38]. A later study, which followed heterozygous *CDC73* knockout mice out to 21 months, reported increased parathyroid proliferation and histologic abnormalities commonly observed in atypical parathyroid adenomas and parathyroid carcinomas in humans; frank features of parathyroid cancer, such as local invasion or distant metastasis were not described. Deletion of *CDC73* targeted to the parathyroid glands, by crossing floxed-CDC73 mice with PTH-Cre mice, resulted in similar parathyroid gland abnormalities; heterozygous and homozygous null mice were both affected[39]. Further studies are necessary to understand how loss of *CDC73* expression promotes parathyroid tumorigenesis.

Cyclin D1

CCND1, encoding cyclin D1, is a well-established oncogenic contributor to benign parathyroid adenomas and DNA amplifications or gene rearrangements have been demonstrated in a variety of tumor types. *CCND1* gene amplification[40,41] and cyclin D1 overexpression[40,42] are common in parathyroid carcinoma. Parathyroid-targeted cyclin D1 transgenic mice develop chronic biochemical hyperparathyroidism and parathyroid gland hypercellularity, but parathyroid carcinoma has not been observed[43]. These finding suggest that cyclin D1 overexpression alone may be insufficient to drive malignant parathyroid tumorigenesis. The precise mechanisms through which cyclin D1 drives tumorigenesis remain controversial. Cyclin D1's primary function is as a regulator of cell cycle progression, binding to, and activating, the cyclin-dependent kinases CDK4/CDK6, which can then phosphorylate pRB, promoting G1-S phase transition. Loss of pRB expression is also a frequent finding in parathyroid carcinomas[44,45]. Cyclin D1 levels are tightly regulated at multiple levels and dysfunction of any of these control mechanisms may contribute to tumorigenesis[46]. Cyclin D1 also has CDK-independent functions, such as a role in chromosomal stability, which may also contribute to cyclin D1's ability to drive tumorigenesis[47]. While it remains to be determined which functions of cyclin D1 are most relevant, the frequent loss of pRB expression and occasional inactivation of CDK inhibitor genes in parathyroid cancer underscore the importance of cell cycle dysregulation to the promotion of malignant parathyroid tumorigenesis.

PRUNE2

PRUNE2 has recently been identified as a likely tumor suppressor gene subject to recurrent mutation in parathyroid carcinoma[41,48]. Whole exome sequencing revealed one parathyroid carcinoma with a germline missense *PRUNE2* mutation accompanied by allelic loss[48] and two carcinomas harboring biallelic, somatic nonsense mutations[41,48]. Sanger sequencing, limited to exon 8 of *PRUNE2*, uncovered two additional somatic missense mutations. *PRUNE2* functions to suppress Ras homolog family member A (RhoA) activity, resulting in suppression of oncogenic cellular transformation, consistent with a tumor suppressive role in parathyroid carcinoma. Functional studies will be needed to determine if loss of *PRUNE2* is capable of, or sufficient to, driving malignant parathyroid tumorigenesis.

PI3K/mTOR

The phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway is an important regulator of cell cycle progression, cell growth and survival, and is frequently subject to alteration in human cancers. *PIK3CA*, encoding the p110-alpha subunit of PI3K, has been recognized as an oncogene capable of driving tumorigenesis in many types of human tumors. A heterozygous *PIK3CA* mutation, resulting in a glutamic acid to lysine change at amino acid 545 (p.E545K), was identified in a parathyroid carcinoma subjected to whole genome sequencing, but interestingly this mutation was absent from two recurrent lesions from the same patient[11]. Whole exome sequencing revealed another established activating *PIK3CA* mutation (p.K111E) in a parathyroid carcinoma[41]. Targeted sequencing revealed two additional known activating *PIK3CA* mutations, p.H1047R and p.E545A. Interestingly, across the two studies, *PIK3CA* and *CDC73* mutations were mutually exclusive, although the sample sizes were too low to determine statistical significance. Activating mutations of *MTOR*, also commonly altered in human tumors, were seen in three parathyroid carcinomas in two next-generation sequencing studies[11,41]. Functional studies are required to determine if activating mutations of the PI3K/mTOR pathway are indeed capable of driving malignant parathyroid tumorigenesis.

Additional genetic and genomic considerations

A number of studies have sought to identify regions of genomic gains and losses relevant to the pathogenesis of parathyroid carcinoma. Recurrent regions of allelic loss have been reported on chromosomes 1p, 3, 13q and 14, and recurrent regions of allelic gain on chromosomes 1q and 16[3-5,9,49]. Such regions of recurrent genomic alteration are expected to harbor important tumor suppressor genes and oncogenes, however both targeted sequencing and whole genome/exome analyses have yet to uncover commonly altered tumor suppressor genes

or oncogenes within those predicted genomic locations[11,41,44,48,50-54]. Notably, despite the high frequency of both allelic loss at the *RB1* locus on chromosome 13q[44,54-57] and loss of pRB expression[44,45], intragenic mutation of *RB1* has yet to be identified in parathyroid cancer[11,41,48,54]. Preferential amplification of mutant *CDC73* alleles has been reported, which could account, at least in part, for observed alleic gain of chromosome 1q[48]. Whole genome/exome next-generation sequence analyses have identified a number of genes that may be important to the pathogenesis of parathyroid cancer and merit further study. Recurrent mutations have been reported in *AKAP9*, a gene frequently altered in epithelial cancers, *ADCK1*, a putative kinase, *NOTCH1*, which may function as either an oncogene or tumor suppressor gene, and *ZEB1*, a transcriptional regulator of epithelial-mesenchymal transition[41]. Several mutations which were identified in only one tumor but affecting genes linked to other types of human cancer were also identified. These genes included *MLL2*, a *MEN1*-interacting tumor suppressor gene, *THRAP3*, a gene involved in regulating cyclin D1 expression, and the canonical Wnt pathway genes *APC* and *RNF43*. Several genes encoding kinases with postulated roles in cell migration and invasion, including *MAP3K11*, *JAK1* and *RIOK3*, and chromatin structure-regulating genes, including *ARID2*, *ARID4A*, *KDM5C*, *KDM4C*, *KDM4E*, *JMJD1C* and *SETD1B* were also mutated. Identification of these novel mutations is an important next step in furthering our knowledge of the molecular pathogenesis of parathyroid cancer. It remains to be determined, through further sequence analysis and functional studies, which of these mutated genes will emerge as important driver genes in parathyroid cancer.

CONCLUSION

Several important advances have been made towards the goal of understanding the molecular basis of parathyroid cancer. Observations of mutational and allelic imbalance patterns suggest that parathyroid cancer generally arises *de novo*, rather than evolving from a preexisting typical benign adenoma. Mutations in the *CDC73* tumor suppressor gene are the most common finding in malignant parathyroid carcinomas. Alterations in additional genes such as *CCND1*/CyclinD1, *PIK3CA*, *MTOR* and *PRUNE2* and others identified by next-generation sequencing methods have also been described in parathyroid cancer, however their abilities to drive malignant parathyroid tumorigenesis remains to be demonstrated experimentally. Additional genes important to the development of parathyroid carcinoma are likely to be identified and the extent and nature of their involvement will need to be carefully examined and validated with genetic and experimental-functional approaches.

DECLARATIONS

Authors' contributions

Costa-Guda J contributed solely to the paper.

Financial support and sponsorship

This work was supported in part by the Murray-Heilig Fund in Molecular Medicine.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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