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Review

Updates of Genomics and Proteomics of Parathyroid Carcinoma

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Abstract: Parathyroid carcinoma is a rare disease that needs an additional diagnostic tool and wide therapeutic options. The genomics and proteomics approach may help to find the tools to improve the prognosis of the disease by early detection and metastatic control. The findings from genomics were mainly *CDC73*, *PRUNE2*, *CCND1*, and genes related to PI3K/AKT/mTOR and Wnt pathways. *CDC73*, *PRUNE2*, and *CCND1* were closely related to each other, and *PRUNE2* and *CCND1* genes are related to expression levels of parafibromin protein, which may aid in supporting the definite diagnosis of the disease. PI3K/AKT/mTOR and Wnt pathways could be a potential therapeutic target for the disease, which needs further basket trials to prove the concept. In this review, current findings from genomics and proteomics studies in parathyroid carcinoma were reviewed.

Keywords: parathyroid; cancer; genomics; proteomics

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1. Introduction

Parathyroid carcinoma (PC) is a rare endocrine malignancy that accounts for less than 1% of parathyroid tumors [1,2], and its incidence has been increasing in Caucasian and Asian populations [2,3]. Surgical resection was the only curative treatment option. Thus, the prognosis of PC is poor in cases of local invasion or metastasis. Therefore, early diagnosis and intervention are crucial for treating patients with PC, while diagnosing PC is complicated and contentious. Since specific biochemical or clinical features are lacking, preoperative PC diagnosis is difficult. Therefore, PC is usually diagnosed postoperatively by histological examination [4]. However, histological diagnosis is often confusing unless patients present a definite local invasion or metastasis [5], and diagnostic accuracy largely depends on the pathologist's experience.

In addition, there is no effective treatment option for recurrent or metastatic PC except for surgical resection. It has been focused on controlling hypercalcemia using bisphosphonates and calcimimetics, and no chemotherapy regimen has been proven effective in clinical trials so far [6]. Therefore, in addition to improving preoperative diagnosis, effective treatment options other than surgery are needed. In line with the situation, exploring genetic and proteomic alterations can help understand the pathophysiology of PC to diagnose and treat the disease effectively. There have been some studies using genomics and a limited number of studies using the proteomics approach in PCs [7–10]. The article reviewed current findings from previous genomics and proteomics studies in PC.

2. Genetics of PC

2.1. CDC73

Germline mutation of *CDC73*, also known as *HRPT2*, is responsible for a rare autosomal dominant disorder, Hyperparathyroidism Jaw-Tumor syndrome (HPT-JT), characterized by multiple benign or malignant tumors in parathyroid, kidney, uterus, and jaw bones [11]. *CDC73* encodes a protein of 531 amino acids termed parafibromin, named due to the relationship to parathyroid and fibro-osseous lesions found in HPT-JT patients [11].

In these patients, the lifetime risk of PC is about 20%, implying a strong association between the pathophysiology and the mutation [11].

Subsequently, researchers focused on discovering *CDC73* mutations in sporadic PC patients. Somatic mutations of the *CDC73* gene have become the most established genetic alteration in PC [12]. Biallelic loss-of-function mutations of the *CDC73* tumor suppressor gene are major genetic drivers and found in 9% to 70% of sporadic PCs [13,14], while they were found in <1% of benign parathyroid adenomas [15]. The percentage of *CDC73* mutation among PC varies among studies; some reported ~70% had the mutation, while others reported only ~9% [16]. Considering the extreme rarity and different prevalence of PCs, the discordance among the studies may be due to selection bias and ethnic differences.

The *CDC73* mutations are of a missense nature due to frameshift mutations or premature truncations in conserved regions. The mutations can inactivate human polymerase-associated factor 1 (hPAF1) or nuclear localization signals (NLSs) of parafibromin. In addition to inactivating mutations, loss of heterogeneity in the *CDC73* gene locus and hypermethylation of the *CDC73* promoter region have also been found as somatic events of PCs [17,18]. In a recent whole genome sequencing study, *CDC73* mutations were found in 39% of patients, and 8% had copy number variations of *CDC73* [19].

The *CDC73* gene is ubiquitously expressed, and the encoded parafibromin is an evolutionarily conserved protein. It is a member of the hPAF regulatory complex to regulate transcriptional activity by histone-modifying and chromatic remodeling (Table 1) [20]. It has been reported to be associated with tumor-suppressive properties since most tumors with *CDC73* mutations had a loss of parafibromin expression, and functional in vitro studies showed an anti-proliferative effect of the wild-type parafibromin [21,22]. In addition, parafibromin has been reported to regulate cyclin D1.

Table 1. Major biological functions of wild-type parafibromin protein.

Protein Localization	The Function of the Protein
Nucleus	A member of the PAF1 complex, functioning as a transcriptional regulator by histone-modifying and chromatic remodeling [20] Tumor suppressor, involved in cell cycle progression by regulating cyclin D1/PRAD1 expression and the Wnt pathway, potentially downregulating β-catenin and c-Myc [21] Has a role in nuclear localization since the N-terminal of parafibromin contains a highly conserved functional monopartite nuclear localization signal (NLS) [19]
Cytoplasm	Interacts with the actin-binding proteins, actinin-2 and actinin-3, which are involved in cytoskeletal structure organization [23]

Clinically, as a confident diagnosis of PC is a challenging task, parafibromin immunohistochemistry has been suggested to help diagnose equivocal cases. In previous studies, loss of nuclear expression of parafibromin was a distinguishable feature between PC and adenoma [14], showing sensitivity and specificity of 75~90% and >90% with a kappa value of 0.9. However, there were also reports that parafibromin may not be enough to distinguish PC since only 46% of PCs showed negative staining of parafibromin [24]. The discrepancy among studies could be related to selection bias, differences in retrieval and antibodies, and different criteria for assessing reactivity. Despite these discrepancies, the loss of parafibromin nuclear staining is a useful marker that can support the diagnosis of PC in confusing cases. Additional markers for the definite diagnosis of PC-such as loss of APC expression have been suggested, although attempts to find more markers and further validation for potential markers are needed.

2.2. PRUNE2 Gene

The *PRUNE2* gene was reported to be associated with PC [10]. PRUNE2 protein is known as a tumor suppressor, suppressing Ras homolog family member An activity that

leads to inhibiting oncogenic transformation. In a recent whole exome sequencing study, 18% of PC patients had the *PRUNE2* mutation, while none of the parathyroid adenoma patients had [10], suggesting that the *PRUNE2* gene could be a potentially oncogenic gene alteration. In previous cases, somatic nonsense mutations of the *PRUNE2* gene were found along with the *CDC73* mutation, implying a synergic effect of tumor suppressors—*PRUNE2* and *CDC73*—may contribute to carcinogenesis [9]. It was previously reported that three missense mutations of the *PRUNE2* gene were likely pathogenic by inhibiting the function of the PRUNE2 protein [10]. The nonsense mutations were likely to produce a truncated PRUNE2 protein without a BNIP-2 and Cdc42GAP Homology (BCH) domain to lose control of cellular transformation by losing its tumor suppressor function. However, in another study, only 1 case among 25 PC cases harbored previously identified somatic mutations of *PRUNE2*. Therefore, further studies with whole *PRUNE2* gene sequencing on larger cases of PCs are needed to confirm the exact prevalence of the *PRUNE2* mutation.

2.3. CCND1 Gene

CCND1, which encodes cyclin D1, was reported to act as an oncogene in parathyroid adenoma through PTH-CCND1 rearrangement. It has been observed that cyclin D1 was more significantly overexpressed in parathyroid adenomas and carcinomas than in the normal parathyroid [25]. It has also been reported that mRNA and protein expression levels were higher in PCs than in adenomas [26]. In previous genomic studies, *CCND1* amplification was observed in 71–90% of PCs [9,26]. As a mechanism, it has been suggested that the loss of parafibromin may cause overexpression of cyclin D1 and thus activate cell proliferation [21]. However, interestingly, in a recent report, 80% of cases with *CCND1* amplification were mutually exclusive of *CDC73* somatic mutations, suggesting that *CCND1* amplification could be an alternative mechanism of *CDC73* inactivation to upregulate *CCND1* expression [9]. As *CCND1* overexpression is also frequently found in parathyroid adenomas, other concurrent mutations in PC may synergize and lead to a malignant phenotype.

2.4. MEN1 Gene

Multiple endocrine neoplasia 1 syndrome (MEN1) is an autosomal dominant disorder caused by mutations in the *MEN1* gene [27]. In MEN1 syndrome, 99% of cases are benign parathyroid adenomas or hyperplasia, and only 1% of them were reported as PC or atypical parathyroid adenomas [28,29]. Although somatic *MEN1* mutations are reported to be infrequent in PCs, two genomic profiling studies found genetic alterations in the *MEN1* gene in 13–31% of cases, suggesting *MEN1*-caused development of PCs as a cause of sporadic primary hyperparathyroidism may be more prevalent than initially thought [7,30]. Interestingly, unlike *CDC73*-mutated cases, all *MEN1*-mutated cases had definite single allele loss of heterogeneity (LOH) or copy number neutral LOH, implying that biallelic inactivation of the *MEN1* gene is a mandatory step for carcinogenesis [7].

2.5. PI3K/AKT/mTOR Pathway-Related Genes

The PI3K/AKT and mTOR signaling pathways are critical in cell growth and survival in physiological and pathological conditions, including cancer. Therefore, the pathway, frequently activated in various cancers, has been considered a potential therapeutic target. The pathway contributes to oncogenic transformation by regulating cell cycle progression, survival, suppression of autophagy, and senescence [31]. Activation of the pathway leads to increase cell growth, angiogenesis, and metastatic potential [32]. Clinically, it was reported that *PIK3CA* and *PTEN* mutation, which may activate the pathway, were among the top three mutated genes in a meta-analysis of 21 types of cancer [33].

In PC, genetic alterations that can activate the pathway—such as *PTEN*, *mTOR*, and *PIK3CA*—were found in 13–20% of patients [7–10], representing a major pathogenic pathway and a potential therapeutic target for PCs. In previous studies, *PIK3CA* mutations were mutually exclusive from *CDC73* mutations, suggesting that they could both be onco-

genic but act independently [9]. Further, an activated *PIK3CA* mutation without a *CDC73* mutation was reported in a PC case, consistent with other reports of mutual exclusivity of *PIK3CA* and *CDC73* mutation [8]. Moreover, *mTOR* gene mutations were found in PCs, mutually exclusive from *PIK3CA* mutations in a study, but further supporting studies are needed [9].

As the activation of the pathway could be one of the main oncogenic pathogeneses of PC, it has been suggested that modulating the axis by using PI3K/AKT/mTOR inhibitors could be helpful in the subset of patients [34]. However, PC is too rare to conduct a randomized controlled clinical trial to prove the efficacy of the inhibitors. Therefore, to overcome the rarity of the disease, as in other rare cancers, the routine evaluation of genetic alteration in PC and considering the basket trials for the disease may help improve the outcomes. 'Basket trial' means a trial design in which the targeted treatment is examined in multiple diseases with common molecular alterations. Furthermore, *PIK3CA*/*mTOR* mutations may help diagnose PC before the surgical resection, although the prevalence of the mutations in parathyroid adenomas needs to be assessed in further studies.

2.6. Wnt Signaling Pathway-Related Genes

The Wnt signaling pathway is known to regulate various cellular events, including cell proliferation, apoptosis, and survival. Aberrant activation of Wnt signaling and accumulation in the cytoplasm and nucleus plays a role in the pathogenesis of various cancer types [35]. The pathway has also been reported as a potential oncogenic pathway in PC. Although *CDC73* has been reported to regulate the Wnt signaling pathway by stabilizing β-catenin, genetic and epigenetic changes in *APC* and *RNF43* genes have been identified as another key regulator of the Wnt signaling pathway [9,36]. In a previous study of five cases of PC, all tumor tissues of five cases showed increased nonphosphorylated active β-catenin accumulation compared to adjacent normal parathyroid tissue [36]. They suggested that the activation of the Wnt pathway is likely due to a loss in expression of the *APC* gene caused by promoter DNA methylation. Inactivating somatic mutations of the *APC* gene in a study by Pandya et al. implied the importance of Wnt signaling in the carcinogenesis of parathyroid tissue, as in other cancer types [9]. *APC* is one of the members of the β-catenin destruction complex to target β-catenin for proteasomal degradation [36]. When the *APC* function is lost, β-catenin translocates into the nucleus to promote proliferation by activating S-phase regulators, including c-myc and cyclin D1. Therefore, mutations of the *APC* gene causing Wnt signaling dysregulation are well known as a first-hit mechanism and found in 10–80% of colorectal carcinomas, as well as in other cancer types [37–39].

Inactivating the mutation of the *RNF43* gene was also reported in PC, which is another key regulator of the Wnt signaling pathway [9]. *RNF43* encodes E3 ubiquitin-protein ligase that acts as a negative regulator of the pathway by mediating the ubiquitination, endocytosis, and subsequent degradation of Wnt receptor complex components Frizzled [40]. The protein acts on canonical and non-canonical Wnt signaling pathways [40]. Like the *APC* gene mutation, the *RNF43* mutation was frequently found in colorectal and endometrial carcinomas [41]. Interestingly, mutations of *RNF43* are mutually exclusive to *APC* mutations in colorectal carcinomas [41], as found in a previous study of PCs [9]. However, somatic mutations of these genes have only been reported in a small number of cases of PC. Further studies focusing on the genes related to the Wnt pathway are needed.

2.7. Other Mutations

Somatic inactivating *TERT* gene mutations were reported in sporadic PCs. The *TERT* gene encodes the telomerase catalytic subunit, which regulates transcriptional regulation, the foremost limiting step in telomerase activity [42]. In 2013, two hotspot mutations were discovered in the *TERT* promoter in over 70% of melanomas [43]. Interestingly, the same hotspot mutations were found in PC cases [7], implying the possibility of impaired telomerase activity as one of the major oncogenic pathogeneses.

AKAP9 gene encodes a member of the A-kinase anchor proteins that regulate cellular localization and function of protein kinase A. The somatic biallelic inactivation mutations were reported in 17% of PCs [9]. The biallelic inactivation implies the loss of a putative tumor suppressor activity and subsequent loss of function of protein kinase A, which may lead to parathyroid carcinogenesis.

Heterozygote somatic mutations of *ZEB1* were also reported in PCs [9]. It encodes a zinc finger transcription factor that plays a role in repressing the E-cadherin promoter and including epithelial-mesenchymal transition. The activation of the gene may promote epithelial-mesenchymal transition, tumor progression, and metastasis.

Somatic biallelic truncating mutations of the *FAT3* gene were reported in 10% of PCs, encoding a member of the atypical cadherin family [9]. Although the protein's function is yet unknown, the biallelic truncating mutations imply the loss of a putative tumor suppressor activity. Further elucidating studies are needed in *FAT3* gene mutation.

3. Proteomics of PC

Proteomic approaches are widely accepted for finding biomarkers for diagnosis and prognosis and to identify therapeutic targets for various cancers [44,45]. However, only a small number of studies have reported proteomic analysis in parathyroid diseases [46–49]. In 2011, Giusti et al. started to perform proteomic analysis on parathyroid adenomas compared to normal parathyroid tissue using two-dimensional electrophoresis and the MALDI-MS/MS technique [46]. Other researchers also investigated the proteomic profile of parathyroid hyperplasia and adenoma tissues [47,48].

However, only a few studies have reported proteomic analysis on PCs. A previous study compared proteomic profiles between five PC and five adenoma tissues using two-dimensional electrophoresis with mass spectrometry [49]. They reported 33 differentially expressed proteins associated with protein ubiquitination, cellular metabolism, and cell signaling. Specifically, they found that the UCH-L1 protein was overexpressed in PCs. It is a member of the deubiquitinase family, an enzyme involved in processing ubiquitin precursors [50]. The deubiquitinase family plays essential roles in pathways involved in carcinogenesis, including cell growth, DNA repair, and apoptosis. In previous reports, the deubiquitinase activity of UCH-L1 promoted carcinogenesis in hypoxic conditions by activating the TGFβ signaling pathway [51], which supports the recent proteomic study that the overexpression of UCH-L1 could be associated with PC. Further, a recent case reported the overexpression of UCH-L1 protein comparing PC to normal parathyroid tissue, supporting the potential importance of the UCH-L1 protein in parathyroid carcinogenesis [52].

In addition, the expression of the ANXA2 protein has been reported to be overexpressed in PCs compared to in adenomas [49]. It is a protein that binds to membrane phospholipids, dependent on extracellular calcium levels. *ANXA2* overexpression has been reported in other types of cancers, and it was correlated with the aggressiveness of the disease [53]. It was also reported to be overexpressed in parathyroid adenomas compared to normal parathyroid tissue [46].

On the other hand, circular RNAs are single-stranded, covalently closed RNA molecules. Circular RNAs have biological functions, including transcriptional regulators, interacting with proteins, and being translated into polypeptides. The expression of hsa_circRNA_0035563 was found to be increased in PCs compared to adenomas, supporting the previous findings, since a corresponding transcript of hsa_circRNA_0035563 is *ANXA2* mRNA [54]. However, since the number of studies that have investigated PC using the proteomic approach is lacking, further studies with larger datasets are needed to discover the diagnostic and prognostic proteomic markers.

4. Conclusions

PC is a rare disease that needs additional diagnostic tools and wide therapeutic options. The genomics and proteomics approach may help to find the tools to improve the prognosis of the disease by early detection and metastatic control. The findings from genomics

were mainly *CDC73*, *PRUNE2*, *CCND1*, and genes related to PI3K/AKT/mTOR and Wnt pathways. *CDC73*, *PRUNE2*, and *CCND1* are closely related to each other, and *PRUNE2* and *CCND1* genes are related to the expression levels of parafibromin protein, which may aid in supporting the definite diagnosis of the disease. PI3K/AKT/mTOR and Wnt pathways could be potential therapeutic targets for the disease, which need further basket trials to prove the concept. As both genetics and proteomics studies may give insight into finding promising targets for this rare but important disease, multicenter studies with a larger volume are needed.

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References

1. Lee, P.K.; Jarosek, S.L.; Virnig, B.A.; Evasovich, M.; Tuttle, T.M. Trends in the incidence and treatment of parathyroid cancer in the United States. *Cancer* **2007**, *109*, 1736–1741. [CrossRef]
2. Ryhänen, E.M.; Leijon, H.; Metso, S.; Eloranta, E.; Korsoff, P.; Ahtiainen, P.; Kekäläinen, P.; Tamminen, M.; Ristamäki, R.; Knutar, O.; et al. A nationwide study on parathyroid carcinoma. *Acta Oncol.* **2017**, *56*, 991–1003. [CrossRef]
3. Kong, S.H.; Kim, J.H.; Park, M.Y.; Kim, S.W.; Shin, C.S. Epidemiology and prognosis of parathyroid carcinoma: Real-world data using nationwide cohort. *J. Cancer Res. Clin. Oncol.* **2021**, *147*, 3091–3097. [CrossRef]
4. Cetani, F.; Pardi, E.; Marcocci, C. Update on parathyroid carcinoma. *J. Endocrinol. Investig.* **2016**, *39*, 595–606. [CrossRef]
5. Erickson, L.A.; Mete, O.; Juhlin, C.C.; Perren, A.; Gill, A.J. Overview of the 2022 WHO Classification of Parathyroid Tumors. *Endocr. Pathol.* **2022**, *33*, 64–89. [CrossRef]
6. Sharretts, J.M.; Kebebew, E.; Simonds, W.F. Parathyroid cancer. *Semin. Oncol.* **2010**, *37*, 580–590. [CrossRef]
7. Kang, H.; Pettinga, D.; Schubert, A.D.; Ladenson, P.W.; Ball, D.W.; Chung, J.H.; Schrock, A.B.; Madison, R.; Frampton, G.M.; Stephens, P.J.; et al. Genomic Profiling of Parathyroid Carcinoma Reveals Genomic Alterations Suggesting Benefit from Therapy. *Oncologist* **2019**, *24*, 791–797. [CrossRef]
8. Kasaian, K.; Wiseman, S.M.; Thiessen, N.; Mungall, K.L.; Corbett, R.D.; Qian, J.Q.; Nip, K.M.; He, A.; Tse, K.; Chuah, E.; et al. Complete genomic landscape of a recurring sporadic parathyroid carcinoma. *J. Pathol.* **2013**, *230*, 249–260. [CrossRef]
9. Pandya, C.; Uzilov, A.V.; Bellizzi, J.; Lau, C.Y.; Moe, A.S.; Strahl, M.; Hamou, W.; Newman, L.C.; Fink, M.Y.; Antipin, Y.; et al. Genomic profiling reveals mutational landscape in parathyroid carcinomas. *JCI Insight* **2017**, *2*, e92061. [CrossRef]
10. Yu, W.; McPherson, J.R.; Stevenson, M.; van Eijk, R.; Heng, H.L.; Newey, P.; Gan, A.; Ruano, D.; Huang, D.; Poon, S.L.; et al. Whole-exome sequencing studies of parathyroid carcinomas reveal novel PRUNE2 mutations, distinctive mutational spectra related to APOBEC-catalyzed DNA mutagenesis and mutational enrichment in kinases associated with cell migration and invasion. *J. Clin. Endocrinol. Metab.* **2015**, *100*, E360–E364. [CrossRef]
11. Cristina, E.-V.; Alberto, F. Management of familial hyperparathyroidism syndromes: MEN1, MEN2, MEN4, HPT-Jaw tumour, Familial isolated hyperparathyroidism, FHH, and neonatal severe hyperparathyroidism. *Best Pract. Res. Clin. Endocrinol. Metab.* **2018**, *32*, 861–875. [CrossRef]
12. Li, Y.; Zhang, J.; Adikaram, P.R.; Welch, J.; Guan, B.; Weinstein, L.S.; Chen, H.; Simonds, W.F. Genotype of CDC73 germline mutation determines risk of parathyroid cancer. *Endocr.-Relat. Cancer* **2020**, *27*, 483–494. [CrossRef]
13. Marcocci, C.; Cetani, F.; Rubin, M.R.; Silverberg, S.J.; Pinchera, A.; Bilezikian, J.P. Parathyroid carcinoma. *J. Bone Miner. Res.* **2008**, *23*, 1869–1880. [CrossRef]
14. Uljanovs, R.; Sinkarevs, S.; Strumfs, B.; Vidusa, L.; Merkurjeva, K.; Strumfa, I. Immunohistochemical Profile of Parathyroid Tumours: A Comprehensive Review. *Int. J. Mol. Sci.* **2022**, *23*, 6981. [CrossRef]
15. Gill, A.J.; Lim, G.; Cheung, V.K.Y.; Andrici, J.; Perry-Keene, J.L.; Paik, J.; Sioson, L.; Clarkson, A.; Sheen, A.; Luxford, C.; et al. Parafibromin-deficient (HPT-JT Type, CDC73 Mutated) Parathyroid Tumors Demonstrate Distinctive Morphologic Features. *Am. J. Surg. Pathol.* **2019**, *43*, 35–46. [CrossRef]
16. Kutahyalioglu, M.; Nguyen, H.T.; Kwatampora, L.; Clarke, C.; Silva, A.; Ibrahim, E.; Waguespack, S.G.; Cabanillas, M.E.; Jimenez, C.; Hu, M.I.; et al. Genetic profiling as a clinical tool in advanced parathyroid carcinoma. *J. Cancer Res. Clin. Oncol.* **2019**, *145*, 1977–1986. [CrossRef]
17. Cardoso, L.; Stevenson, M.; Thakker, R.V. Molecular genetics of syndromic and non-syndromic forms of parathyroid carcinoma. *Hum. Mutat.* **2017**, *38*, 1621–1648. [CrossRef]
18. Hewitt, K.M.; Sharma, P.K.; Samowitz, W.; Hobbs, M. Aberrant methylation of the HRPT2 gene in parathyroid carcinoma. *Ann. Otol. Rhinol. Laryngol.* **2007**, *116*, 928–933. [CrossRef]

19. Hu, Y.; Zhang, X.; Wang, O.; Bi, Y.; Xing, X.; Cui, M.; Wang, M.; Tao, W.; Liao, Q.; Zhao, Y. The genomic profile of parathyroid carcinoma based on whole-genome sequencing. *Int. J. Cancer* **2020**, *147*, 2446–2457. [CrossRef]
20. Newey, P.J.; Bowl, M.R.; Thakker, R.V. Parafibromin–functional insights. *J. Intern. Med.* **2009**, *266*, 84–98. [CrossRef]
21. Woodard, G.E.; Lin, L.; Zhang, J.H.; Agarwal, S.K.; Marx, S.J.; Simonds, W.F. Parafibromin, product of the hyperparathyroidism-jaw tumor syndrome gene HRPT2, regulates cyclin D1/PRAD1 expression. *Oncogene* **2005**, *24*, 1272–1276. [CrossRef]
22. Zhang, C.; Kong, D.; Tan, M.H.; Pappas, D.L., Jr.; Wang, P.F.; Chen, J.; Farber, L.; Zhang, N.; Koo, H.M.; Weinreich, M.; et al. Parafibromin inhibits cancer cell growth and causes G1 phase arrest. *Biochem. Biophys. Res. Commun.* **2006**, *350*, 17–24. [CrossRef] [PubMed]
23. Agarwal, S.K.; Simonds, W.F.; Marx, S.J. The parafibromin tumor suppressor protein interacts with actin-binding proteins actinin-2 and actinin-3. *Mol. Cancer* **2008**, *7*, 65. [CrossRef] [PubMed]
24. DeLellis, R.A. Parathyroid tumors and related disorders. *Mod. Pathol.* **2011**, *24*, S78–S93. [CrossRef]
25. Forsberg, L.; Björck, E.; Hashemi, J.; Zedenius, J.; Höög, A.; Farnebo, L.O.; Reimers, M.; Larsson, C. Distinction in gene expression profiles demonstrated in parathyroid adenomas by high-density oligoarray technology. *Eur. J. Endocrinol.* **2005**, *152*, 459–470. [CrossRef] [PubMed]
26. Zhao, L.; Sun, L.H.; Liu, D.M.; He, X.Y.; Tao, B.; Ning, G.; Liu, J.M.; Zhao, H.Y. Copy number variation in CCND1 gene is implicated in the pathogenesis of sporadic parathyroid carcinoma. *World J. Surg.* **2014**, *38*, 1730–1737. [CrossRef]
27. Chandrasekharappa, S.C.; Guru, S.C.; Manickam, P.; Olufemi, S.E.; Collins, F.S.; Emmert-Buck, M.R.; Debelenko, L.V.; Zhuang, Z.; Lubensky, I.A.; Liotta, L.A.; et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* **1997**, *276*, 404–407. [CrossRef]
28. Singh Ospina, N.; Sebo, T.J.; Thompson, G.B.; Clarke, B.L.; Young, W.F., Jr. Prevalence of parathyroid carcinoma in 348 patients with multiple endocrine neoplasia type 1—Case report and review of the literature. *Clin. Endocrinol.* **2016**, *84*, 244–249. [CrossRef]
29. Cinque, L.; Sparaneo, A.; Cetani, F.; Coco, M.; Clemente, C.; Chetta, M.; Balsamo, T.; Battista, C.; Sanpaolo, E.; Pardi, E.; et al. Novel association of MEN1 gene mutations with parathyroid carcinoma. *Oncol. Lett.* **2017**, *14*, 23–30. [CrossRef]
30. Haven, C.J.; van Puijenbroek, M.; Tan, M.H.; Teh, B.T.; Fleuren, G.J.; van Wezel, T.; Morreau, H. Identification of MEN1 and HRPT2 somatic mutations in paraffin-embedded (sporadic) parathyroid carcinomas. *Clin. Endocrinol.* **2007**, *67*, 370–376. [CrossRef]
31. Aoki, M.; Fujishita, T. Oncogenic Roles of the PI3K/AKT/mTOR Axis. *Curr. Top. Microbiol. Immunol.* **2017**, *407*, 153–189. [CrossRef]
32. Porta, C.; Paglino, C.; Mosca, A. Targeting PI3K/Akt/mTOR Signaling in Cancer. *Front. Oncol.* **2014**, *4*, 64. [CrossRef]
33. Lawrence, M.S.; Stojanov, P.; Mermel, C.H.; Robinson, J.T.; Garraway, L.A.; Golub, T.R.; Meyerson, M.; Gabriel, S.B.; Lander, E.S.; Getz, G. Discovery and saturation analysis of cancer genes across 21 tumour types. *Nature* **2014**, *505*, 495–501. [CrossRef]
34. Clarke, C.N.; Katsonis, P.; Hsu, T.K.; Koire, A.M.; Silva-Figueroa, A.; Christakis, I.; Williams, M.D.; Kutahyalioglu, M.; Kwatampora, L.; Xi, Y.; et al. Comprehensive Genomic Characterization of Parathyroid Cancer Identifies Novel Candidate Driver Mutations and Core Pathways. *J. Endocr. Soc.* **2019**, *3*, 544–559. [CrossRef]
35. Zhan, T.; Rindtorff, N.; Boutros, M. Wnt signaling in cancer. *Oncogene* **2017**, *36*, 1461–1473. [CrossRef]
36. Svedlund, J.; Aurén, M.; Sundström, M.; Dralle, H.; Akerström, G.; Björklund, P.; Westin, G. Aberrant WNT/β-catenin signaling in parathyroid carcinoma. *Mol. Cancer* **2010**, *9*, 294. [CrossRef]
37. Wachsmannova, L.; Mego, M.; Stevurkova, V.; Zajac, V.; Ciernikova, S. Novel strategies for comprehensive mutation screening of the APC gene. *Neoplasma* **2017**, *64*, 338–343. [CrossRef]
38. Liu, F.; Lu, X.; Zhou, X.; Huang, H. APC gene promoter methylation as a potential biomarker for lung cancer diagnosis: A meta-analysis. *Thorac. Cancer* **2021**, *12*, 2907–2913. [CrossRef]
39. Katoh, M. Multi-layered prevention and treatment of chronic inflammation, organ fibrosis and cancer associated with canonical WNT/β-catenin signaling activation (Review). *Int. J. Mol. Med.* **2018**, *42*, 713–725. [CrossRef]
40. Sugiura, T.; Yamaguchi, A.; Miyamoto, K. A cancer-associated RING finger protein, RNF43, is a ubiquitin ligase that interacts with a nuclear protein, HAP95. *Exp. Cell Res.* **2008**, *314*, 1519–1528. [CrossRef]
41. Giannakis, M.; Hodis, E.; Jasmine Mu, X.; Yamauchi, M.; Rosenbluh, J.; Cibulskis, K.; Saksena, G.; Lawrence, M.S.; Qian, Z.R.; Nishihara, R.; et al. RNF43 is frequently mutated in colorectal and endometrial cancers. *Nat. Genet.* **2014**, *46*, 1264–1266. [CrossRef]
42. Bell, R.J.; Rube, H.T.; Xavier-Magalhães, A.; Costa, B.M.; Mancini, A.; Song, J.S.; Costello, J.F. Understanding TERT Promoter Mutations: A Common Path to Immortality. *Mol. Cancer Res.* **2016**, *14*, 315–323. [CrossRef]
43. Horn, S.; Figl, A.; Rachakonda, P.S.; Fischer, C.; Sucker, A.; Gast, A.; Kadel, S.; Moll, I.; Nagore, E.; Hemminki, K.; et al. TERT promoter mutations in familial and sporadic melanoma. *Science* **2013**, *339*, 959–961. [CrossRef]
44. de Hoog, C.L.; Mann, M. Proteomics. *Annu. Rev. Genom. Hum Genet.* **2004**, *5*, 267–293. [CrossRef]
45. Boys, E.L.; Liu, J.; Robinson, P.J.; Reddel, R.R. Clinical applications of mass spectrometry-based proteomics in cancer: Where are we? *Proteomics* **2022**, e2200238. [CrossRef]
46. Giusti, L.; Cetani, F.; Ciregia, F.; Da Valle, Y.; Donadio, E.; Giannaccini, G.; Banti, C.; Pardi, E.; Saponaro, F.; Basolo, F.; et al. A proteomic approach to study parathyroid glands. *Mol. Biosyst.* **2011**, *7*, 687–699. [CrossRef]
47. Donadio, E.; Giusti, L.; Cetani, F.; Da Valle, Y.; Ciregia, F.; Giannaccini, G.; Pardi, E.; Saponaro, F.; Torregrossa, L.; Basolo, F.; et al. Evaluation of formalin-fixed paraffin-embedded tissues in the proteomic analysis of parathyroid glands. *Proteome Sci.* **2011**, *9*, 29. [CrossRef]

48. Varshney, S.; Bhadada, S.K.; Arya, A.K.; Sharma, S.; Behera, A.; Bhansali, A.; Rao, S.D. Changes in parathyroid proteome in patients with primary hyperparathyroidism due to sporadic parathyroid adenomas. *Clin. Endocrinol.* **2014**, *81*, 614–620. [CrossRef]
49. Ciregia, F.; Cetani, F.; Pardi, E.; Soggiu, A.; Piras, C.; Zallocco, L.; Borsari, S.; Ronci, M.; Caruso, V.; Marcocci, C.; et al. Parathyroid Carcinoma and Adenoma Co-existing in One Patient: Case Report and Comparative Proteomic Analysis. *Cancer Genom. Proteom.* **2021**, *18*, 781–796. [CrossRef]
50. Fang, Y.; Shen, X. Ubiquitin carboxyl-terminal hydrolases: Involvement in cancer progression and clinical implications. *Cancer Metastasis Rev.* **2017**, *36*, 669–682. [CrossRef]
51. Liu, S.; González-Prieto, R.; Zhang, M.; Geurink, P.P.; Kooij, R.; Iyengar, P.V.; van Dinther, M.; Bos, E.; Zhang, X.; Le Dévédec, S.E.; et al. Deubiquitinase Activity Profiling Identifies UCHL1 as a Candidate Oncoprotein That Promotes TGFβ-Induced Breast Cancer Metastasis. *Clin. Cancer Res.* **2020**, *26*, 1460–1473. [CrossRef]
52. Adam, M.A.; Untch, B.R.; Olson, J.A., Jr. Parathyroid carcinoma: Current understanding and new insights into gene expression and intraoperative parathyroid hormone kinetics. *Oncologist* **2010**, *15*, 61–72. [CrossRef]
53. Sharma, M.C. Annexin A2 (ANX A2): An emerging biomarker and potential therapeutic target for aggressive cancers. *Int. J. Cancer* **2019**, *144*, 2074–2081. [CrossRef]
54. Hu, Y.; Zhang, X.; Cui, M.; Wang, M.; Su, Z.; Liao, Q.; Zhao, Y. Circular RNA profile of parathyroid neoplasms: Analysis of co-expression networks of circular RNAs and mRNAs. *RNA Biol.* **2019**, *16*, 1228–1236. [CrossRef]