Physiol. Res. 72 (Suppl. 4): S357-S363, 2023 *https://doi.org/10.33549/physiolres.935253*

REVIEW

Molecular Genetic Aspects of Sporadic Multiglandular Primary Hyperparathyroidism

Josef VČELÁK[1,3], Zora ŠERKOVÁ[2], Kateřina ZAJÍČKOVÁ[1,3]

[1]Institute of Endocrinology, Prague, Czech Republic, [2]2nd Faculty of Medicine, Motol University Hospital, Prague, Czech Republic, [3]First Faculty of Medicine Charles University, Czech Republic

Received October 12, 2023
Accepted November 27, 2023

Summary

Multiglandular primary hyperparathyroidism (MGD) represents a rare form of primary hyperparathyroidism (PHPT). MGD is associated with hereditary PHPT, but the sporadic MGD is more common and affects a similar patient profile as single gland parathyroid disease (SGD). The distinction between SGD and MGD is of great clinical importance, especially for the strategy of parathyroidectomy. Based on the limited knowledge available, MGD is likely to be a genetically heterogeneous disease resulting from the interaction of germline and somatic DNA mutations together with epigenetic alterations. Furthermore, these events may combine and occur independently in parathyroid tumors within the same individual with MGD. Gene expression profiling has shown that SGD and MGD may represent distinct entities in parathyroid tumorigenesis. We are waiting for studies to analyze exactly which genes are different in SGD and MGD in order to identify potential biomarkers that can distinguish between the two forms of the disease.

Key words

Multiglandular primary hyperparathyroidism • Somatic and germline mutations • Candidate genes • Epigenetics • MEN1

Corresponding author

Katerina Zajickova, Institute of Endocrinology, Narodni 8, Praha 1, 116 94, Czech Republic. E-mail: kzajickova@endo.cz

Introduction

Primary hyperparathyroidism (PHPT) occurs most often sporadically in an individual with no known family history of parathyroid disease due to autonomous secretion of parathyroid hormone (PTH) by one of the parathyroid glands (SGD - single gland parathyroid disease). Adenoma is the most common histopathological basis of PHPT. The typical patient is a postmenopausal woman aged 60-65 years [1]. The increase in the incidence of PHPT after menopause suggests that ageing with reduced estrogen levels are likely to be involved in the pathogenesis of the disease [2,3].

More rarely, in about 15-20 %, autonomous PTH secretion may occur in more than one parathyroid gland, in which case it is called multiglandular form of PHPT (MGD – multigland parathyroid disease [4]. Multiglandular parathyroid involvement is usually associated with hereditary PHPT. According to some authors, the sporadic form of MGD predominates in 2/3 of MGD cases with a similar patient profile as SGD [5]. According to the 5th WHO classification of endocrine tumors, the term germline susceptibility-driven multi-glandular parathyroid neoplasia is recommended for MGD [6]. The new WHO terminology for MGD thus suggests that changes at the germline DNA level could probably also be responsible for the sporadic form of MGD. As MGD represents a rare form of PHPT, the role of low frequency, low penetrance germline variants may be involved in the pathogenesis of the disease. Although sporadic MGD occurs at an older age than the hereditary form of the disease it is one of the indications for consultation with a clinical geneticist in patients with

PHPT because the role of genetic factors could not be completely excluded.

The distinction between SGD and MGD is of great clinical importance, especially for the strategy of parathyroidectomy. Modern focused approaches may not lead to disease resolution in the case of unrecognized MGD [4]. Currently, there is no clinical or biochemical parameter that reliably distinguishes SGD and MGD. Therefore, attention is turning to the study of pathogenic mechanisms, including genetic factors, the identification of which could lead to new diagnostic and therapeutic options.

Most studies have analyzed the genetic background between parathyroid gland (PG) adenomas and carcinomas, between adenomas and parathyroid hyperplasia, or between sporadic and hereditary (familial) forms of PHPT [7,8]. Studies that have specifically investigated genetic factors between SGD and MGD are very few.

Clonality studies of parathyroid adenomas (PAs) indicate that sporadic PHPT likely has a genetically heterogeneous background. Shi et al. [9] showed that up to 46 % of PAs are polyclonal. Patients with polyclonal PAs did not differ from patients with monoclonal PAs in clinical parameters, but were more likely to have a multiglandular form of the disease (OR 4.1, $p\leq 0{,}039$). The fact that almost half of parathyroid tumours are polyclonal may indicate that independent somatic genetic events are very likely to play a role in the pathogenesis of sporadic PHPT.

In the sporadic form of the disease, we expect changes mainly in somatic DNA in the parathyroid tissue. Surprisingly, in addition to somatic mutations, germline mutations in key regulatory genes responsible for the hereditary form of the disease have also been found in patients with sporadic PHPT. Park et al. [5] showed that in PHPT factors associated with a positive germline DNA genetic testing result included in 76.9 % subjects in addition to age less than 40 years and a positive family history, a recurrent or multiglandular form of the disease ($p\leq 0.010$).

In the sporadic form of PHPT, mutations in somatic DNA are infrequently found in genes whose germline mutations are responsible for parathyroid proliferation in hereditary forms of the disease. These genes include the gene for menin, cyclin D1, cyclin dependent kinases, Calcium-sensing receptor (CaSR) and Glial cells missing homolog 2 (GCM2). Most studies have focused on their role in hereditary forms of PHPT, less frequently in sporadic adenoma [7,8]. There is very little data on whether, for example, the frequency of their somatic mutations differs between SGD and MGD.

Most often, in 30-40 %, somatic mutations are found in the menin gene (*MEN1*, OMIM 613733) in sporadic PA adenomas [10]. These can be either intragenic biallelic mutations (12-21 %) or deletions of larger DNA regions which is more common mechanism (25-40 %) [11]. Loss of heterozygosity (LOH) at the 11q13 locus is required for PG proliferation, leading to impaired tumour suppressor function of menin. A mouse model with menin knock-out in PG tissue confirms that *MEN1* gene is a major driver of parathyroid tumorigenesis [12]. Menin does not act directly on DNA as a transcription factor, but is likely part of a larger complex of transcription factors, of which more than 50 are currently known [13]. Interactions of menin with other proteins go beyond the PG, playing a role in a variety of cancers (e.g., mixed leukemia fusion protein) [14]. Although menin is expressed in every cell of the human body, there is a specific group of menin-associated tumors, as is known primarily in hereditary syndromes. Why tumor formation is restricted to certain tissues is unknown.

The second most common gene whose increased expression has been found in sporadic PA is cyclin D1 (*CCND1*, OMIM 168461) [8]. This event is present in about 18-40 %. The *CCND1* gene product, the cyclin D1 protein, stimulates the cell cycle [15]. Cyclin D1 was originally identified as a fusion gene with the promoter region of the PTH gene at the pericentromeric inversion on chromosome 11 (*PTH-CCND1*). This variant is found in about 8 % of PAs [16]. Other, as yet unknown, mechanisms are probably involved in the increased expression of *CCND1* in PG tissue. It is suspected that they involve copy number alterations and chromosomal rearrangements. Analysis of parathyroid carcinomas has shown that amplifications of larger DNA regions also containing the gene for cyclin D1 are more often responsible for the increased expression than the *CCND1* somatic mutations [17,18].

The action of cyclin D1 is inhibited, and thus controlled, by cyclin dependent kinase inhibitors (CDKI) [8]. CDKI inactivation causes proliferation of parathyroid tissue [19]. Germline mutations in the *CDKN1B* gene (OMIM 600778), a member of the *CDKI* gene family, cause MEN4 syndrome [20]. Somatic inactivation of *CDKN1B* in combination with a germline mutation in the menin gene has been found in pancreatic islet tumours,

suggesting a common tumorigenic pathway between the two genes [21]. Although somatic mutations in *CDKI* genes have been associated with breast cancer and lymphoproliferative disorders, their somatic mutations have been rarely found in sporadic PAs [22,23]. Their inactivation may occur epigenetically. Methylation of *CDKI* promoters, leading to gene silencing, has been found in both PA and parathyroid carcinoma [18,24].

Although CaSR expression is reduced in PA, somatic mutations in the *CASR* gene (OMIM 601199) have not been found [8,18,25]. CaSR expression may be silenced through epigenetic mechanisms. Singh et al. [26] showed that methylation of the promoter and histone 3 of the *CASR* gene are responsible for the reduced CaSR expression in PA. So-called adhesion molecules such as filamin A and Yes-associated protein may also play a role [27].

Inactivating germline mutations in the *GCM2* gene (OMIM 603716) lead to hereditary hypoparathyroidism [8]. Activating mutations, on the other hand, are responsible for familial isolated hyperparathyroidism (FIH) [28]. Compared to the sporadic form of PHPT, patients with FIH and germline activating mutations in *GCM2* had significantly higher PTH levels and more frequent multiglandular involvement (78 % vs 14.3 % in subjects without *GCM2* mutation, $p<0.001$) [29]. In a cohort of patients with sporadic MGD, the presence of Y282D (rs61734277) activation variability was identified in 11 % [30]. Identification of Y282D prior to surgery would indicate an increased risk of MGD, which could modify the surgical approach. However, variations in the gene for GCM2 have low penetrance and their presence may not be associated with the development of hyperparathyroidism, which complicates the introduction of *GCM2* genotyping into the clinical practice [31]. Although GCM2 is a key transcriptional regulatory factor for parathyroid development, somatic mutations in *GCM2* are rarely found in PA [32].

Somatic or even germline mutations are found in many other genes with tumor oncogene or tumor suppressor functions (e.g. *POT1, HIC1, ASXL3*) [7,8]. However, their mutations have only been identified in a few PA. It is, therefore, questionable whether these variants are involved in the development of PA on a population scale.

The genes whose activation leads to parathyroid carcinoma are not identical to the genes whose activation is responsible for benign PG proliferation. A Finland-based national retrospective study reported no evidence of malignant transformation of the original parathyroid adenoma in patients with a history of PA between years 2000 and 2011 [33]. Menin mutations are found predominantly in PA, whereas mutations in *CDC73, TERT, RET* and retinoblastoma gene are found in parathyroid carcinomas [17,18]. PT carcinoma has probably different genetic signature and arises as a distinct entity de novo, not in the setting of PG adenoma or hyperplasia. On the other hand, whole genome sequencing on blood-tumor pairs from patients with sporadic PA has identified the Y54X (rs121434265) mutation in the *CDC73* gene, which was previously associated with PC, in 6.8 % PA samples [34].

The study of hereditary forms of PHPT has contributed to the elucidation of a number of key regulatory loops in calcium-phosphate metabolism. However, a number of factors remain unknown. In pedigrees of patients with familial isolated PHPT, the genetic basis of the disease has been identified in only about 10-20 %. Thus, in the remaining 80 % of families, the genetic basis of the disease has yet to be uncovered. As shown by recent genome-wide association study, PHPT-associated loci were also identified outside the known parathyroid proliferation driver genes [35]. In a Scottish cohort of PHPT patients, four genes with as yet unknown function were identified (*SOX9, SLITRK5, LPAR3*, and *BCDIN3D-AS1*). Moreover, the study showed some quantitative relationship between the number of risk alleles and the likelihood of PHPT. Population genetics thus extends the knowledge gained from the study of monogenic forms of PHPT.

To the best of our knowledge, the study by Dwight et al. [36] was the only study to analyze genetic factors in pairs of parathyroid tumors within the same individual with multiglandular hyperparathyroidism. LOH, comparative genomic hybridization and *MEN1* mutation analysis showed that independent genetic events were associated with the development of a subset of these parathyroid tumors. These events differed in paired parathyroid glands from the same individual. Whether the genetic changes were random or due to the involvement of other factors such as low frequency germline mutations, germline mosaicism, epigenetic silencing of *CaSR* or altered concentration of calcium and phosphorus remains unknown.

Two studies using gene expression profiling in PG from patients with PHPT have attempted to differentiate between SGD and MGD. The study by

Morrison et al. [37] showed distinct expression profiles between the two forms of PHPT. Whereas SGD showed over- and under-expression of a number of genes involved in DNA repair and cell cycle progression, MGD showed over-expression of a number of genes related to central nervous system development and disease. Although the number of samples examined in the study was limited, these findings may indicate that MGD is a distinct entity from adenoma in PHPT.

A different transcription profile between sporadic adenoma and multiglandular form of PHPT has been confirmed by cDNA microarray in the study by Velazquez et al. [38]. The number of differentially expressed genes compared to normal parathyroid tissue was higher in MGD than in adenomas, which could indicate a more genetically heterogeneous background in MGD. Genes for Hook1, TBXA2R and FHIT had increased expression in MGD compared to adenoma (SGD). In contrast, genes for prostaglandin synthase and EGFR, for example, had increased expression in adenomas and decreased expression in MGD.

Compared to other malignancies, PHPT does not have an abnormal global DNA methylation profile. Targeted methylation of regulatory DNA regions occurs more commonly in PHPT [39]. Methylation of the promoter of the cell cycle inhibitor gene *RASFF1A* has been found in most PA [40]. The same epigenetic mechanism was also found in pancreatic neuroendocrine tumors in individuals with MEN1 [41]. Hypermethylation of the *APC* gene promoter was also found in PA [40]. The APC protein is an inhibitor of beta catenin which is a component of the Wnt cascade [42]. The Wnt signaling is involved in colorectal cancerogeneis. Not only promoter methylation, but also reduced acetylation of histones in the promoter region led to the reduced expression of the transcription factor PAX1 in PA [43].

In addition to methylation of gene regulatory regions and histone modification, non-coding RNAs have been studied with respect to genetic expression. The different expression profile of miRNAs between PA and parathyroid carcinoma tissues has been shown in a number of studies [44,45]. The work of Mizamtsidi [46] showed a different PG expression of miRNA30e between SGD and MGD. Patients with sporadic MGD had higher miRNA30e tissue expression levels than patients with a single adenoma. However, it was not possible to distinguish the two groups on the basis of genomic DNA variations encoding miRNA30e what would help discerning SGD and MGD prior to surgery. miRNA30e interacts with a number of genes involved in tumorigenesis. Which of these genes plays a role in sporadic PHPT is not yet known.

Sporadic MGD is associated with polyclonality, different mRNA and miRNA transcription profiles and a higher probability of identifying a germline mutation. MGD is likely to be a genetically heterogeneous disease resulting from the interaction of germline and somatic DNA mutations together with epigenetic alterations. Furthermore, these events may combine and occur independently in parathyroid tumors within the same individual in MGD. Gene expression profiling has shown that SGD and MGD may represent distinct entities in parathyroid tumorigenesis. We are waiting for studies to analyze exactly which genes are different in SGD and MGD in order to identify potential biomarkers that can distinguish between the two forms of the disease.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

Supported by Ministry of Health, Czech Republic - conceptual development of research organization (Institute of Endocrinology - EÚ, 00023761)

References

1. Bilezikian JP, Khan AA, Silverberg SJ, Fuleihan GE, Marcocci C, Minisola S, Perrier N, Sitges-Serra A, Thakker RV, Guyatt G, Mannstadt M, Potts JT, Clarke BL, Brandi ML, International Workshop on Primary H. Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop. J Bone Miner Res 2022;37:2293-2314. https://doi.org/10.1002/jbmr.4677, https://doi.org/10.1002/jbmr.4670
2. Griebeler ML, Kearns AE, Ryu E, Hathcock MA, Melton LJ, 3rd, Wermers RA. Secular trends in the incidence of primary hyperparathyroidism over five decades (1965-2010). Bone 2015;73:1-7. https://doi.org/10.1016/j.bone.2014.12.003

3. Haglund F, Ma R, Huss M, Sulaiman L, Lu M, Nilsson IL, Hoog A, Juhlin CC, Hartman J, Larsson C. Evidence of a functional estrogen receptor in parathyroid adenomas. J Clin Endocrinol Metab 2012;97:4631-4639. https://doi.org/10.1210/jc.2012-2484
4. Barczynski M, Branstrom R, Dionigi G, Mihai R. Sporadic multiple parathyroid gland disease--a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbecks Arch Surg 2015;400:887-905. https://doi.org/10.1007/s00423-015-1348-1
5. Park HS, Lee YH, Hong N, Won D, Rhee Y. Germline Mutations Related to Primary Hyperparathyroidism Identified by Next-Generation Sequencing. Front Endocrinol (Lausanne) 2022;13:853171. https://doi.org/10.3389/fendo.2022.853171
6. Erickson LA, Mete O, Juhlin CC, Perren A, Gill AJ. Overview of the 2022 WHO Classification of Parathyroid Tumors. Endocr Pathol 2022;33:64-89. https://doi.org/10.1007/s12022-022-09709-1
7. Brewer K, Costa-Guda J, Arnold A. Molecular genetic insights into sporadic primary hyperparathyroidism. Endocr Relat Cancer 2019;26:R53-R72. https://doi.org/10.1530/ERC-18-0304
8. Jha S, Simonds WF. Molecular and Clinical Spectrum of Primary Hyperparathyroidism. Endocr Rev 2023;44:779-818. https://doi.org/10.1210/endrev/bnad009
9. Shi Y, Azimzadeh P, Jamingal S, Wentworth S, Ferlitch J, Koh J, Balenga N, Olson JA, Jr. Polyclonal origin of parathyroid tumors is common and is associated with multiple gland disease in primary hyperparathyroidism. Surgery 2018;163:9-14. https://doi.org/10.1016/j.surg.2017.04.038
10. Alvelos MI, Vinagre J, Fonseca E, Barbosa E, Teixeira-Gomes J, Sobrinho-Simoes M, Soares P. MEN1 intragenic deletions may represent the most prevalent somatic event in sporadic primary hyperparathyroidism. Eur J Endocrinol 2013;168:119-128. https://doi.org/10.1530/EJE-12-0327
11. Cromer MK, Starker LF, Choi M, Udelsman R, Nelson-Williams C, Lifton RP, Carling T. Identification of somatic mutations in parathyroid tumors using whole-exome sequencing. J Clin Endocrinol Metab 2012;97:E1774-1781. https://doi.org/10.1210/jc.2012-1743
12. Libutti SK, Crabtree JS, Lorang D, Burns AL, Mazzanti C, Hewitt SM, O'Connor S, Ward JM, Emmert-Buck MR, Remaley A, Miller M, Turner E, Alexander HR, Arnold A, Marx SJ, Collins FS, Spiegel AM. Parathyroid gland-specific deletion of the mouse Men1 gene results in parathyroid neoplasia and hypercalcemic hyperparathyroidism. Cancer Res 2003;63:8022-8028.
13. Huang J, Gurung B, Wan B, Matkar S, Veniaminova NA, Wan K, Merchant JL, Hua X, Lei M. The same pocket in menin binds both MLL and JUND but has opposite effects on transcription. Nature 2012;482:542-546. https://doi.org/10.1038/nature10806
14. Yokoyama A, Somervaille TC, Smith KS, Rozenblatt-Rosen O, Meyerson M, Cleary ML. The menin tumor suppressor protein is an essential oncogenic cofactor for MLL-associated leukemogenesis. Cell 2005;123:207-218. https://doi.org/10.1016/j.cell.2005.09.025
15. Arnold A, Kim HG, Gaz RD, Eddy RL, Fukushima Y, Byers MG, Shows TB, Kronenberg HM. Molecular cloning and chromosomal mapping of DNA rearranged with the parathyroid hormone gene in a parathyroid adenoma. J Clin Invest 1989;83:2034-2040. https://doi.org/10.1172/JCI114114
16. Hsi ED, Zukerberg LR, Yang WI, Arnold A. Cyclin D1/PRAD1 expression in parathyroid adenomas: an immunohistochemical study. J Clin Endocrinol Metab 1996;81:1736-1739. https://doi.org/10.1210/jcem.81.5.8626826, https://doi.org/10.1210/jc.81.5.1736
17. Pandya C, Uzilov AV, Bellizzi J, Lau CY, Moe AS, Strahl M, Hamou W, Newman LC, Fink MY, Antipin Y, Yu W, Stevenson M, Cavaco BM, Teh BT, Thakker RV, Morreau H, Schadt EE, Sebra R, Li SD, Arnold A, Chen R. Genomic profiling reveals mutational landscape in parathyroid carcinomas. JCI Insight 2017;2:e92061. https://doi.org/10.1172/jci.insight.92061
18. Marini F, Giusti F, Iantomasi T, Brandi ML. Parathyroid Tumors: Molecular Signatures. Int J Mol Sci 2021;22. https://doi.org/10.3390/ijms222011206
19. Costa-Guda J, Soong CP, Parekh VI, Agarwal SK, Arnold A. Germline and somatic mutations in cyclin-dependent kinase inhibitor genes CDKN1A, CDKN2B, and CDKN2C in sporadic parathyroid adenomas. Horm Cancer 2013;4:301-307. https://doi.org/10.1007/s12672-013-0147-9

20. Alevizaki M, Stratakis CA. Multiple endocrine neoplasias: advances and challenges for the future. J Intern Med 2009;266:1-4. https://doi.org/10.1111/j.1365-2796.2009.02108.x
21. Karnik SK, Hughes CM, Gu X, Rozenblatt-Rosen O, McLean GW, Xiong Y, Meyerson M, Kim SK. Menin regulates pancreatic islet growth by promoting histone methylation and expression of genes encoding p27Kip1 and p18INK4c. Proc Natl Acad Sci U S A 2005;102:14659-14664. https://doi.org/10.1073/pnas.0503484102
22. Borsari S, Pardi E, Pellegata NS, Lee M, Saponaro F, Torregrossa L, Basolo F, Paltrinieri E, Zatelli MC, Materazzi G, Miccoli P, Marcocci C, Cetani F. Loss of p27 expression is associated with MEN1 gene mutations in sporadic parathyroid adenomas. Endocrine 2017;55:386-397. https://doi.org/10.1007/s12020-016-0941-6
23. Pappa V, Papageorgiou S, Papageorgiou E, Panani A, Boutou E, Tsirigotis P, Dervenoulas J, Economopoulos T, Raptis S. A novel p27 gene mutation in a case of unclassified myeloproliferative disorder. Leuk Res 2005;29:229-231. https://doi.org/10.1016/j.leukres.2004.06.007
24. Starker LF, Svedlund J, Udelsman R, Dralle H, Akerstrom G, Westin G, Lifton RP, Bjorklund P, Carling T. The DNA methylome of benign and malignant parathyroid tumors. Genes Chromosomes Cancer 2011;50:735-745. https://doi.org/10.1002/gcc.20895
25. Corbetta S, Mantovani G, Lania A, Borgato S, Vicentini L, Beretta E, Faglia G, Di Blasio AM, Spada A. Calcium-sensing receptor expression and signalling in human parathyroid adenomas and primary hyperplasia. Clin Endocrinol (Oxf) 2000;52:339-348. https://doi.org/10.1046/j.1365-2265.2000.00933.x
26. Singh P, Bhadada SK, Dahiya D, Arya AK, Saikia UN, Sachdeva N, Kaur J, Brandi ML, Rao SD. Reduced calcium sensing receptor (CaSR) expression is epigenetically deregulated in parathyroid adenomas. J Clin Endocrinol Metab 2020;105:3015-3024. https://doi.org/10.1210/clinem/dgaa419
27. Balenga N, Azimzadeh P, Hogue JA, Staats PN, Shi Y, Koh J, Dressman H, Olson JA, Jr. Orphan Adhesion GPCR GPR64/ADGRG2 is overexpressed in parathyroid tumors and attenuates calcium-sensing receptor-mediated signaling. J Bone Miner Res 2017;32:654-666. https://doi.org/10.1002/jbmr.3023
28. Guan B, Welch JM, Sapp JC, Ling H, Li Y, Johnston JJ, Kebebew E, Biesecker LG, Simonds WF, Marx SJ, Agarwal SK. GCM2-Activating Mutations in Familial Isolated Hyperparathyroidism. Am J Hum Genet 2016;99:1034-1044. https://doi.org/10.1016/j.ajhg.2016.08.018
29. El Lakis M, Nockel P, Guan B, Agarwal S, Welch J, Simonds WF, Marx S, Li Y, Nilubol N, Patel D, Yang L, Merkel R, Kebebew E. Familial isolated primary hyperparathyroidism associated with germline GCM2 mutations is more aggressive and has a lesser rate of biochemical cure. Surgery 2018;163:31-34. https://doi.org/10.1016/j.surg.2017.04.027
30. Vincze S, Peters NV, Kuo CL, Brown TC, Korah R, Murtha TD, Bellizzi J, Riccardi A, Parham K, Carling T, Costa-Guda J, Arnold A. GCM2 Variants in Familial and Multiglandular Primary Hyperparathyroidism. J Clin Endocrinol Metab 2022;107:e2021-e2026. https://doi.org/10.1210/clinem/dgab929
31. Canaff L, Guarnieri V, Kim Y, Wong BYL, Nolin-Lapalme A, Cole DEC, Minisola S, Eller-Vainicher C, Cetani F, Repaci A, Turchetti D, Corbetta S, Scillitani A, Goltzman D. Novel Glial Cells Missing-2 (GCM2) variants in parathyroid disorders. Eur J Endocrinol 2022;186:351-366. https://doi.org/10.1530/EJE-21-0433
32. Mannstadt M, Holick E, Zhao W, Juppner H. Mutational analysis of GCMB, a parathyroid-specific transcription factor, in parathyroid adenoma of primary hyperparathyroidism. J Endocrinol 2011;210:165-171. https://doi.org/10.1530/JOE-10-0247
33. Ryhanen EM, Leijon H, Metso S, Eloranta E, Korsoff P, Ahtiainen P, Kekalainen P, Tamminen M, Ristamaki R, Knutar O, Loyttyniemi E, Niskanen L, Vaisanen M, Heiskanen I, Valimaki MJ, Laakso M, Haglund C, Arola J, Schalin-Jantti C. A nationwide study on parathyroid carcinoma. Acta Oncol 2017;56:991-1003. https://doi.org/10.1080/0284186X.2017.1306103
34. Tao X, Xu T, Lin X, Xu S, Fan Y, Guo B, Deng X, Jiao Q, Chen L, Wei Z, Chen C, Yang W, Zhang Z, Yu X, Yue H. Genomic Profiling Reveals the Variant Landscape of Sporadic Parathyroid Adenomas in Chinese Population. J Clin Endocrinol Metab 2023;108:1768-1775. https://doi.org/10.1210/clinem/dgad002
35. Soto-Pedre E, Newey PJ, Srinivasan S, Siddiqui MK, Palmer CNA, Leese GP. Identification of 4 New Loci Associated With Primary Hyperparathyroidism (PHPT) and a Polygenic Risk Score for PHPT. J Clin Endocrinol Metab 2022;107:3302-3308. https://doi.org/10.1210/clinem/dgac527

36. Dwight T, Nelson AE, Theodosopoulos G, Richardson AL, Learoyd DL, Philips J, Delbridge L, Zedenius J, Teh BT, Larsson C, Marsh DJ, Robinson BG. Independent genetic events associated with the development of multiple parathyroid tumors in patients with primary hyperparathyroidism. Am J Pathol 2002;161:1299-1306. https://doi.org/10.1016/S0002-9440(10)64406-9
37. Morrison C, Farrar W, Kneile J, Williams N, Liu-Stratton Y, Bakaletz A, Aldred MA, Eng C. Molecular classification of parathyroid neoplasia by gene expression profiling. Am J Pathol 2004;165:565-576. https://doi.org/10.1016/S0002-9440(10)63321-4
38. Velazquez-Fernandez D, Laurell C, Saqui-Salces M, Pantoja JP, Candanedo-Gonzalez F, Reza-Albarran A, Gamboa-Dominguez A, Herrera MF. Differential RNA expression profile by cDNA microarray in sporadic primary hyperparathyroidism (pHPT): primary parathyroid hyperplasia versus adenoma. World J Surg 2006;30:705-713. https://doi.org/10.1007/s00268-005-0708-3
39. Sulaiman L, Juhlin CC, Nilsson IL, Fotouhi O, Larsson C, Hashemi J. Global and gene-specific promoter methylation analysis in primary hyperparathyroidism. Epigenetics 2013;8:646-655. https://doi.org/10.4161/epi.24823
40. Juhlin CC, Kiss NB, Villablanca A, Haglund F, Nordenstrom J, Hoog A, Larsson C. Frequent promoter hypermethylation of the APC and RASSF1A tumour suppressors in parathyroid tumours. PLoS One 2010;5:e9472. https://doi.org/10.1371/journal.pone.0009472
41. Conemans EB, Lodewijk L, Moelans CB, Offerhaus GJA, Pieterman CRC, Morsink FH, Dekkers OM, de Herder WW, Hermus AR, van der Horst-Schrivers AN, Drent ML, Bisschop PH, Havekes B, Brosens LAA, Dreijerink KMA, Borel Rinkes IHM, Timmers HTM, Valk GD, Vriens MR. DNA methylation profiling in MEN1-related pancreatic neuroendocrine tumors reveals a potential epigenetic target for treatment. Eur J Endocrinol 2018;179:153-160. https://doi.org/10.1530/EJE-18-0195
42. Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. Oncogene 2017;36:1461-1473. https://doi.org/10.1038/onc.2016.304
43. Singh P, Bhadada SK, Arya AK, Saikia UN, Sachdeva N, Dahiya D, Kaur J, Brandi ML, Rao SD. Aberrant Epigenetic Alteration of PAX1 Expression Contributes to Parathyroid Tumorigenesis. J Clin Endocrinol Metab 2022;107:e783-e792. https://doi.org/10.1210/clinem/dgab626
44. Verdelli C, Forno I, Vaira V, Corbetta S. MicroRNA deregulation in parathyroid tumours suggests an embryonic signature. J Endocrinol Invest 2015;38:383-388. https://doi.org/10.1007/s40618-014-0234-y
45. Corbetta S, Vaira V, Guarnieri V, Scillitani A, Eller-Vainicher C, Ferrero S, Vicentini L, Chiodini I, Bisceglia M, Beck-Peccoz P, Bosari S, Spada A. Differential expression of microRNAs in human parathyroid carcinomas compared with normal parathyroid tissue. Endocr Relat Cancer 2010;17:135-146. https://doi.org/10.1677/ERC-09-0134
46. Mizamtsidi M, Nastos K, Palazzo F, Constantinides V, Dina R, Farenden M, Mastorakos G, Vassiliou I, Gazouli M. Association Between hsa-miR-30e Polymorphisms and Sporadic Primary Hyperparathyroidism Risk. In Vivo 2019;33:1263-1269. https://doi.org/10.21873/invivo.11598